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Cardiorespiratory Fitness in Pediatric Renal Transplant Recipients

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Abstract

Background—The impact of body size, fat-free mass (FFM) and fat mass (FM) on cardiorespiratory fitness in pediatric renal transplant recipients (TX) has not been established. Study objectives were to assess maximal oxygen consumption (VO_{2max}) in TX and controls, adjusted for body composition, and to identify risk factors for reduced fitness in TX.

Methods—Cycle ergometry and DXA were obtained in 50 TX and 70 controls, ages 8 to 21 yr. Control recruitment was targeted to include obese subjects with body mass index (BMI) Z-scores comparable to TX. Allometric regression models were utilized.

Results—TX had significantly lower height Z-scores ($p < 0.001$) and comparable BMI Z-scores. VO_{2max} per body weight (ml/kg/min) and per FFM (ml/kgFFM/min) did not differ between groups. However, VO_{2max} was 13% lower (95% CI 18, 8; $p < 0.001$) in TX, compared with controls, adjusted for FM, FFM, sex and race. Greater FFM, lower FM, non-black race, and male sex were independently associated with greater VO_{2max}. Within TX, hemoglobin levels were positively associated with VO_{2max} ($p = 0.04$) and sirolimus use was associated with lower VO_{2max} ($p < 0.01$).

Conclusions—TX had significant VO_{2max} deficits that were not captured by conventional measures (ml/kg/min). Greater FM was an independent risk factor for low VO_{2max}. Lower fitness in TX may be related to sirolimus effects on skeletal muscle.

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Author Contributions

C.B. Sethna participated in performance of the research, data analysis, and writing of the paper.

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M.G. McBride participated in performance of the research and writing of the paper.

J. Shults participated in data analysis.

S.M. Paridon participated in research design.

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Keywords

Pediatric kidney transplant; exercise; fitness

Introduction

Young adults with a history of renal transplantation during childhood and adolescence have a greater than ten fold risk of cardiovascular death compared to the general population (1). Although research has focused on minimizing traditional cardiovascular risk factors such as hypertension and obesity, little attention has been paid to the role of physical inactivity and reduced cardiorespiratory fitness in this population. In healthy persons, it is well documented that improvements in aerobic fitness ameliorate many cardiovascular risk factors and decrease overall cardiovascular mortality (2-5). Therefore, further study of cardiorespiratory fitness in this high-risk population is of paramount importance.

Aerobic fitness is defined as the capacity to deliver oxygen to working skeletal muscles and the ability of muscles to utilize oxygen through the process of aerobic metabolism (6). The point at which the body reaches its limit for maximal utilization of oxygen is termed maximal oxygen consumption ($\text{VO}_{2\text{max}}$). $\text{VO}_{2\text{max}}$ is the best single measure of aerobic capacity (6), and is measured in milliliters of oxygen consumed per minute (ml/min).

One of the greatest challenges in the interpretation of $\text{VO}_{2\text{max}}$ is normalizing the results for differences in body size and body composition (7-10). This is especially important in pediatric renal transplantation which is frequently complicated by poor growth and obesity (11). Traditionally, $\text{VO}_{2\text{max}}$ is divided by body mass (ml/kg/min) to facilitate comparisons across body sizes. The published normal reference data for $\text{VO}_{2\text{max}}$ in children are based on age or body size [body surface area (BSA) or weight](12-14). The use of such ratios to adjust $\text{VO}_{2\text{max}}$ for differences in body size assumes that $\text{VO}_{2\text{max}}$ and body size are isometrically related – that is, $\text{VO}_{2\text{max}}$ increases as a linear function of body size; this assumption is not however correct (8). In contrast, allometric scaling techniques, employing log-transformed regression models in children and adults, have consistently shown that $\text{VO}_{2\text{max}}$ increases as a function of body weight to the 0.60 to 0.75 power (e.g. ml/kg^{0.60}/min) (8). Therefore, the expression of traditional measures of $\text{VO}_{2\text{max}}$ (ml/kg/min) will result in systematic underestimation of fitness in heavier individuals and overestimation in lighter subjects. Furthermore, scaling $\text{VO}_{2\text{max}}$ to fat-free mass (FFM) rather than total body weight provides better estimates of fitness since the metabolically active body cell mass is pertinent to the expression of oxygen consumption. A study in normal weight children demonstrated that log transformed regression models for $\text{VO}_{2\text{max}}$ relative to FFM eliminated the effect of body size (15).

The primary objective of this study was to assess aerobic fitness as measured by maximal oxygen consumption ($\text{VO}_{2\text{max}}$) in renal transplant recipients relative to body size and body composition, compared with healthy controls. An additional objective was to identify risk factors for a lower level of aerobic fitness in renal transplant recipients.

Methods

Study Subjects

Renal transplant recipients and healthy control subjects were enrolled in this cross-sectional study from November 2005 through February 2008. Renal transplant recipients, ages 8-21 years, who were greater than 6 months after transplantation with stable renal function for three months were eligible. Children with cognitive impairment or orthopedic complications

that limited their ability to perform the exercise protocol, as well as those with significant cardiac or pulmonary co-morbidity (such as restrictive lung disease secondary to obstructive uropathy) were excluded. Of a total of 160 transplant recipients, 110 were eligible to participate in the study. Of the eligible subjects, 50 subjects were enrolled and 11 transplant recipients declined to participate in the study. Healthy control subjects were recruited from general pediatric practices in Philadelphia and the surrounding community. Recruitment of healthy controls targeted overweight and obese children in order to achieve comparable distributions of body mass index (BMI, kg/m²) Z-scores in the transplant recipients and controls. Control subjects with chronic diseases or medications known to affect growth or body composition were excluded. All subjects had to be greater than 130 cm in height (minimum height required to perform cycle ergometry) and weigh less than 135 kg to meet dual-energy x-ray absorptiometry (DXA) scanner requirements. This study protocol was approved by the Institutional Review Board of The Children's Hospital of Philadelphia. Informed consent was obtained directly from study participants older than 18 years, and assent along with parental consent from participants less than 18 years of age.

Subject Characteristics

Medical charts of the transplant recipients were reviewed for information regarding primary renal diagnosis, age at transplant, donor source, pre-transplant dialysis duration, interval since transplant, current medications and prior medications following transplantation. Laboratory data collected on the day of exercise testing included serum creatinine, phosphorus and hemoglobin levels. Glomerular filtration rate (eGFR) was estimated using the Schwartz formula (16).

Anthropometry and Maturation

Height was measured to the nearest 0.1 cm with a stadiometer (Holtain, Crymych, UK) and weight to the nearest 0.1 kg with a digital scale (Scaletronix, White Plains, NY). The stage of pubertal development was determined using a validated self-assessment questionnaire (17) and classified according to the method of Tanner (18). Study participants and their parents were asked to categorize the participant's race according to the National Institute of Health categories.

DXA Scans

DXA scans of the whole body were performed using a Delphi/Discovery (Hologic, Bedford, MA) densitometer with a fan beam in the array mode. All scans were analyzed using software version 12.3. The scans were analyzed to generate estimates of whole body FFM (kg) and fat mass (FM, kg).

Exercise Testing

Subjects were exercised to maximal volition using an electronically braked cycle ergometer (SensorMedics, Yorba Linda, CA). The protocol consisted of three minutes of pedaling in an unloaded state followed by a ramp increase in work rate (Watts) to maximal exercise. The steepness of the ramp protocol was determined by subject weight and designed to achieve predicted peak work rate in 10 to 12 minutes of cycling time (6). A 12-lead ECG (Marquette Case-8000, Milwaukee, WI) was obtained at rest in the supine, sitting, and standing position. Cardiac rhythm was monitored continuously throughout the study. Blood pressure was measured at rest and every three minutes during exercise and recovery by auscultation. Systemic arterial oxygen saturation (SaO₂) was monitored continuously during exercise by pulse oximetry.

Metabolic data were obtained throughout the exercise study and for the first two minutes of recovery on a breath-by-breath basis using a metabolic cart (SensorMedics V29, Yorba Linda, CA). The primary outcome variable measured was VO_{2max} . The respiratory exchange ratio (RER), defined as CO_2 produced divided by O_2 consumed, was calculated at peak exercise to assess effort. RER values greater than 1.10 were considered adequate for maximal effort (19).

Statistical Analysis

Descriptive analyses included means, standard deviation (SD), median and interquartile ranges of continuous variables and distributions of categorical variables. Differences in means were assessed using Student's t-test, or the Wilcoxon Rank Sum test if the data were not normally distributed. Differences in proportions were assessed using the chi-square test. A p-value of < 0.05 was considered statistically significant, and two-sided tests of hypotheses were used throughout. The SPSS 15.0 (SPSS Inc., Chicago, IL) statistical package was used in the analysis.

Age- and sex-specific Z-scores (standard deviation scores) for height, weight and BMI were calculated using National Center for Health Statistics 2000 Center for Disease Control growth data (20). Obesity was defined as a BMI greater than the 95th percentile for age and sex (21). Blood pressure index was calculated by dividing the blood pressure of the subject by the age, sex and height specific 95th percentiles for systolic and diastolic blood pressures (22,23).

Correlations between VO_{2max} and anthropometric measures were evaluated by Pearson correlation analysis, or Spearman rank correlation for non-normally distributed data. Variables with P values < 0.1 on univariate analysis were tested in log-transformed multivariate linear regression models to determine which measurement or combination of measurements explained the greatest proportion of the variability in VO_{2max} in healthy control subjects. All models were adjusted for sex, race (black versus all others) and for Tanner stage of pubertal maturation (stage 1 through 3 as the referent group with an indicator variable for Tanner stages 4 and 5). Subsequently, a dummy variable was added to the model in order to compare VO_{2max} in transplant recipients to that of controls, adjusted for the significant body composition and demographic factors. The independent effect of transplantation in the models is presented as the adjusted ratio of the outcome in transplant recipients divided by the outcome in controls. The adjusted ratios and 95% confidence intervals (C.I.) were calculated as exponentiated estimates of the regression coefficients for the transplant dummy variable. Tests for interactions between variables were performed using multiplicative interaction terms.

A secondary aim of the study was to determine potential transplant risk factors for lower level of fitness (VO_{2max}). The risk factors were tested in the multivariable regression model in transplant recipients only. These included diagnosis (congenital vs. others), pre-emptive transplant, duration of end stage renal disease (ESRD), time since transplant, eGFR, hemoglobin, serum phosphorus, and medications.

Results

Subject Characteristics

Fifty pediatric renal transplant recipients and 70 healthy control subjects were enrolled in the study (Table 1). The male predominance in the renal transplant group is consistent with the demographics of ESRD in childhood (24). A greater proportion of the control subjects were black ($p = 0.01$), consistent with the demographics in the recruitment population. As compared with the controls, renal transplant recipients had significantly lower height Z-

scores ($p < 0.001$) and a smaller proportion were pubertal ($p = 0.001$). Consistent with their shorter stature, body weight was significantly lower in the transplant recipients, compared with controls. However, BMI Z-scores and the proportion that were obese were comparable between groups. Transplant recipients had significantly lower whole body FFM compared to controls ($p = 0.02$). However, log transformed regression models demonstrated that whole body FFM was not significantly lower in transplant recipients compared with controls (ratio 0.99, 95% C.I. 0.93 to 1.05, $p = 0.88$), adjusted for height, race, pubertal stage and sex. Similarly, whole body fat mass was not significantly greater in the transplant recipients compared with controls (ratio 1.15, 95% C.I. 0.90 to 1.49, $p = 0.25$), adjusted for height, race, pubertal stage and sex.

The medical histories of the renal transplant recipients are summarized in Table 2. eGFR ranged from 24.7 to 183.2 ml/min/1.73 m². Only 4 subjects had eGFR less than 50 ml/min/1.73 m². Of the 50 transplant recipients, 10% had hemoglobin levels below the normal range for age and four were on treatment with erythropoietin at the time of the study. All were on prednisone; dosages ranged from 2.5 mg to 10 mg daily or every other day. Ten renal transplant recipients had a history of treatment with growth hormone prior to transplantation; none were treated with growth hormone following transplantation. The percentages of concurrent medications are summarized in the Table.

Exercise Outcomes

The results of the exercise testing are summarized in Table 3. Both groups achieved maximal effort on exercise testing, average RER > 1.10 . The control group reached a higher peak heart rate than the transplant recipients, 96% and 93% of predicted, respectively. Transplant recipients had a higher diastolic blood pressure index compared to controls during rest ($p = 0.01$) and peak exercise ($p = 0.01$). Absolute $\text{VO}_{2\text{max}}$ (L/min) was significantly lower in the transplant group as compared to the control group ($p < 0.01$). However, no significant differences were detected between transplant recipients and controls when $\text{VO}_{2\text{max}}$ was divided by body weight (ml/kg/min) or fat free mass (ml/kgFFM/min). There was no significant difference in $\text{VO}_{2\text{max}}$ in transplant recipients based on chronic kidney disease stage.

The relationships between $\text{VO}_{2\text{max}}$ and anthropometric measures were examined. The significant univariate relationship between log $\text{VO}_{2\text{max}}$ (ml/min) and log body weight ($\beta = 0.72$, 95% CI: 0.59 to 0.85; $R = 0.71$, $p < 0.001$) is illustrated in Figure 1; the slope is significantly less than 1.0, illustrating the need for allometric scaling techniques. The stronger correlation between log $\text{VO}_{2\text{max}}$ and log FFM ($\beta = 0.87$, 95% CI: 0.78 to 0.97; $R = 0.86$, $p < 0.001$) is illustrated in Figure 2. Other potential confounders of $\text{VO}_{2\text{max}}$ with $p < 0.1$ in univariate analyses were entered in a log transformed multivariate linear regression model of $\text{VO}_{2\text{max}}$ within the control subjects only. In the final model ($R^2 = 0.87$), FFM was independently associated with greater $\text{VO}_{2\text{max}}$, while FM, female sex, and black race were independently associated with lower $\text{VO}_{2\text{max}}$. Pubertal stage was not associated with $\text{VO}_{2\text{max}}$.

Transplant recipients were subsequently added to the above model (Table 4). Ratios for each covariate were calculated as exponentiated estimates of the regression coefficients, adjusted for other covariates in the model. $\text{VO}_{2\text{max}}$, adjusted for FFM, FM, gender and race, was significantly lower in transplant recipients, compared with healthy controls. The adjusted ratio for $\text{VO}_{2\text{max}}$ in the transplant recipients compared with that in the controls was 0.87 (95% C.I. 0.83 to 0.92, $p < 0.001$), indicating that $\text{VO}_{2\text{max}}$ was, on average, 13% lower in the transplant recipients. Although there were insufficient numbers of control subjects to generate age and sex specific Z-scores (standard deviation scores) for the VO_2 measures in the renal transplant recipients, the effect size was estimated by comparing the standardized

residuals from the regression models in the renal transplant recipients and the controls. The standardized residuals differed by 0.72 (95% C.I. 0.38, 1.07; $p < 0.0001$) suggesting that the VO_2 levels were 0.72 SD lower in transplant recipients, compared with controls, adjusted for body composition, race and gender.

VO_{2max} in black subjects (transplants and controls) was 12% lower compared with all other subjects (ratio 0.88, 95% C.I. 0.84 to 0.93, $p < 0.001$). VO_{2max} in female subjects (transplants and controls) was 10% lower compared with male subjects (ratio 0.90, 95% C.I. 0.84 to 0.95, $p = 0.001$). The values for fat free mass and fat mass were log transformed. Therefore, VO_{2max} *increases* as a function of fat free mass to the power of 0.923, and VO_{2max} *decreases* as a function of fat mass to the power of 0.093. Tests for interaction between transplant status and race, gender or FFM were not significant. Specifically, the VO_{2max} deficits in the transplant recipients compared with controls were of comparable magnitude within the black and non-black subjects (ratios of 0.86 and 0.84, respectively).

Transplant Risk Factors

Each one-unit increase in hemoglobin was associated with a five percent greater VO_{2max} in the transplant recipients (ratio = 1.05, 95% C.I. 1.01 to 1.09, $p = 0.04$), adjusted for sex, race, FM and FFM. Sirolimus use was associated with a lower VO_{2max} (ratio = 0.87, 95% C.I. 0.80 to 0.95, $p < 0.01$), adjusted for sex, race, FM, and FFM. The effect of sirolimus persisted after adjustment for hemoglobin in the model. There was no difference in prednisone dose between those on sirolimus (0.0787 mg/kg/day) vs. those not on sirolimus (0.0626 mg/kg/day, $p = 0.105$). None of the other transplant covariates described in Table 2 were significant, independent determinants of VO_{2max} .

Discussion

Using allometric scaling techniques, we found that cardiorespiratory fitness in children and adolescents with renal transplants was reduced by an average of 13% when compared to healthy controls, after adjusting for race, sex, FM, and FFM. Assuming that VO_2 is at the 50th percentile in the controls (standard deviation score = 0) on average, these data would indicate that the transplant recipients are at the 24th percentile (standard deviation score = -0.72) on average. This reduction likely represents a clinically significant increase in the number of renal transplant recipients below the normal range relative to body composition, race and gender. This VO_{2max} deficit in transplant recipients was not captured by conventional ratios, dividing VO_{2max} by weight or FFM (Table 3). This was likely due to overestimation of cardiorespiratory fitness in the transplant recipients using the ratio method because they were smaller (lower weight and FFM) than the controls. As such, the use of ratios to express the nonlinear relationship between body weight and VO_{2max} leads to several types of statistical error and misinterpretations. Log-linear regression (allometric) analyses in adults have demonstrated that scaled expressions of VO_{2max} are more appropriate. VO_{2max} in adults increases as body mass raised to the 0.6 - 0.75 power (e.g. ml/kg^{0.75}/min) (8). Our results illustrate similar relations in children and adolescents.

To our knowledge, this is the first study in pediatric transplant recipients to include measures of body composition in an allometric analysis of VO_{2max} relative to body size in comparison to control subjects. Earlier studies comparing VO_{2max} in pediatric renal transplant recipients to controls (25, 26) or reference data (27-29) have yielded a broad range of VO_{2max} deficits in renal transplant recipients. Different approaches to calculate VO_{2max} utilizing ratios were carried out in these reports. Our data demonstrated a slope of 0.72 for log VO_2 max relative to log body weight, consistent with adult studies (8). Therefore, we submit that our analysis of VO_{2max} using allometric regression models

instead of conventional ratios more accurately adjusts VO_{2max} for differences in body size and composition between transplant recipients and controls.

Furthermore, no prior studies of pediatric renal transplant recipients utilized measures of FFM in their assessments of cardiorespiratory fitness. FFM has been found to be the best single predictor of VO_{2max} (10, 30, 31). Three previous studies obtained DXA scans in transplant recipients (27, 29, 32), however, body composition measures were not analyzed with respect to VO_{2max} . Weaver et al. included estimates of FFM that were derived from predictor equations for FFM based on height and weight that may not be appropriate in children with ESRD (26). Our analyses that incorporate DXA measures of whole body FM and FFM in transplant recipients and controls confirmed the strong, positive association between FFM and VO_{2max} , and also demonstrated an additional, independent adverse effect of greater adiposity (FM). Given that transplant recipients have a high incidence of obesity following transplant (33), their cardiorespiratory fitness may be compromised further by increasing adiposity.

Our findings highlight the importance of adjusting for race in the renal transplant population. No other pediatric transplant studies reported associations between race and VO_{2max} . Our results confirm prior reports in healthy children of lower VO_{2max} in black children versus white children (34-37). Factors such as physical activity level, body composition and hematologic profile may account for the racial differences in VO_{2max} (34). However, our study demonstrated racial differences independent of body composition. Furthermore, the high proportion of black subjects in the control group may have contributed to the lack of difference in VO_{2max} between the transplant group and controls when using conventional ratios.

The recruitment of controls targeted overweight and obese children in order to achieve sufficiently overlapping distributions of body weight, FM and FFM compared with the transplant recipients. Given that conventional ratio measures of VO_{2max} (ml/kg/min) result in an underestimation of fitness in larger individuals (greater absolute body weight), these measures may result in an underestimation of VO_{2max} in obese transplant recipients compared with non-obese controls. In contrast, if predominantly overweight and obese transplant recipients weigh less than the non-obese controls due to shorter stature, the ratio measures may result in an overestimation of VO_{2max} . Given that transplant recipients have lower height Z-scores and greater BMI Z-score than the general population, it is important to use a control population that allows for adjustment for these variable effects of body size and composition.

The mechanism of decreased fitness in the pediatric renal transplant population is likely multi-factorial. Studies in adults have implicated skeletal muscle weakness due to residual effects of renal failure on neuromuscular structure and function (38), prednisone effects on skeletal muscle structure and function (39-41), decreased oxygen transport capacity in anemia (42), ventricular dysfunction (43), and sedentary lifestyle (43). Evidence documenting the risk factors for low fitness in pediatric renal transplant recipients is sparse. Weaver et al. found that diastolic dysfunction was an independent predictor of lower VO_{2max} in a group of children with chronic kidney disease and renal transplant recipients. In agreement with Krull et al., our study showed that hemoglobin was positively associated with VO_{2max} although published results are conflicting (28, 29). Our results confirm previous studies demonstrating no significant relationship between VO_{2max} and duration of dialysis or time since transplant (28, 29). We also found no relationship between VO_{2max} and underlying renal disease, pre-emptive transplant, treatment with blood pressure medication, eGFR or serum phosphorus level.

A novel finding of this study is that sirolimus use was associated with lower fitness in renal transplant recipients. Animal studies have shown that activation of the mammalian target of rapamycin (mTOR) signaling pathway is vital in the regulation of skeletal muscle size through an increase in protein synthesis (44). Sirolimus inhibits the ability of mTOR to phosphorylate its downstream targets, resulting in decreased cell growth and dysregulation of cell cycle proliferation and cell cycle progression. Treatment with sirolimus in two week old rat pups resulted in a 40% reduction in hind leg muscle mass. Treatment at four weeks of age resulted in a 20-25% reduction and, interestingly, sirolimus had no effect on muscle mass of young adult rats (10-12 weeks) (44). Another murine study demonstrated that muscle hypertrophy in response to altered mechanical loading is blocked by sirolimus (45). These data suggest that sirolimus inhibits skeletal muscle growth and hypertrophy; however, in our study, we saw an association between sirolimus and VO_{2max} even after adjustment for FFM. Currently, there are no published reports on the effects of sirolimus on muscle mass or metabolism in humans or the relationship of sirolimus with VO_{2max} .

The present study is limited by the cross-sectional design and heterogeneity of the transplant population. The difficulty in measuring residual confounding factors such as the complexity of ESRD course, past medical histories and fluctuating values of covariates (e.g. recent rejection episode) is also a limitation. Additionally, transplant recipients who agreed to participate in the study may be more fit or more interested in physical activity than those who declined to participate. However, since lower fitness was found, such a bias would lead to an underestimation of the difference. Given the small control group, we could not fully adjust for differences in maturation and body composition, but our study has more concurrent controls than any prior study. Our study also lacked a measure of physical activity in cases and controls, such as accelerometry, which has been shown to have a positive association with VO_{2max} in healthy children (46). Despite the aforementioned limitations, we believe that our conclusions remain valid. And, our study is strengthened by the use of allometric scaling techniques, DXA measures of body composition and concurrent controls with specific attention to race and obesity.

CONCLUSION

Our findings illustrate the importance of the consideration of race and body size and composition in the assessment of cardiorespiratory fitness in pediatric transplant recipients. Our results also highlight the independent relation between greater adiposity and lower cardiorespiratory fitness. Future prospective longitudinal studies are needed that include accelerometric measures of physical activity, assessment of cardiovascular disease, including diastolic dysfunction, and measures of concurrent medication exposures. Decreased cardiorespiratory fitness is a cardiovascular risk factor and post-transplant care should include Interventions to improve physical functioning of pediatric renal transplant recipients.

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References

1. Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. *J Am Soc Nephrol*. 1998; 9(12 Suppl):S16–23. [PubMed: 11443763]

2. Blair SN, Kohl HW 3rd, Paffenbarger RS Jr, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA*. 1989; 262(17): 2395–2401. [PubMed: 2795824]
3. Carnethon MR, Gidding SS, Nehgme R, Sidney S, Jacobs DR Jr, Liu K. Cardiorespiratory fitness in young adulthood and the development of cardiovascular disease risk factors. *JAMA*. 2003; 290(23): 3092–3100. [PubMed: 14679272]
4. Ekelund LG, Haskell WL, Johnson JL, Whaley FS, Criqui MH, Sheps DS. Physical fitness as a predictor of cardiovascular mortality in asymptomatic North American men. The Lipid Research Clinics Mortality Follow-up Study. *N Engl J Med*. 1988; 319(21):1379–1384. [PubMed: 3185648]
5. Mora S, Redberg RF, Cui Y, Whiteman MK, Flaws JA, Sharrett AR, et al. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the lipid research clinics prevalence study. *JAMA*. 2003; 290(12):1600–1607. [PubMed: 14506119]
6. Rowland, TW. Pediatric laboratory exercise testing : clinical guidelines. Champaign, IL: Human Kinetics Publishers; 1992.
7. Beunen GP, Rogers DM, Woynarowska B, Malina RM. Longitudinal study of ontogenetic allometry of oxygen uptake in boys and girls grouped by maturity status. *Ann Hum Biol*. 1997; 24(1):33–43. [PubMed: 9022904]
8. Buresh R, Berg K. Scaling oxygen uptake to body size and several practical applications. *J Strength Cond Res*. 2002; 16(3):461–465. [PubMed: 12173964]
9. Rogers DM, Olson BL, Wilmore JH. Scaling for the VO₂-to-body size relationship among children and adults. *J Appl Physiol*. 1995; 79(3):958–967. [PubMed: 8567540]
10. Toth MJ, Goran MI, Ades PA, Howard DB, Poehlman ET. Examination of data normalization procedures for expressing peak VO₂ data. *J Appl Physiol*. 1993; 75(5):2288–2292. [PubMed: 7695668]
11. Hanevold CD, Ho PL, Talley L, Mitsnefes MM. Obesity and renal transplant outcome: a report of the North American Pediatric Renal Transplant Cooperative Study. *Pediatrics*. 2005; 115(2):352–356. [PubMed: 15687444]
12. Cooper DM, Weiler-Ravell D, Whipp BJ, Wasserman K. Aerobic parameters of exercise as a function of body size during growth in children. *J Appl Physiol*. 1984; 56(3):628–634. [PubMed: 6706770]
13. Nagle FJ, Hagberg J, Kamei S. Maximal O₂ uptake of boys and girls -- ages 14--17. *Eur J Appl Physiol Occup Physiol*. 1977; 36(2):75–80. [PubMed: 837914]
14. Washington RL, van Gundy JC, Cohen C, Sondheimer HM, Wolfe RR. Normal aerobic and anaerobic exercise data for North American school-age children. *J Pediatr*. 1988; 112(2):223–233. [PubMed: 3339503]
15. Janz KF, Burns TL, Witt JD, Mahoney LT. Longitudinal analysis of scaling VO₂ for differences in body size during puberty: the Muscatine Study. *Med Sci Sports Exerc*. 1998; 30(9):1436–1444. [PubMed: 9741614]
16. Schwartz GJ, Feld LG, Langford DJ. A simple estimate of glomerular filtration rate in full-term infants during the first year of life. *J Pediatr*. 1984; 104(6):849–854. [PubMed: 6726515]
17. Morris N, Udry J. Validation of a self-administered instrument to assess stage of adolescent development. *Journal of Youth and Adolescence*. 1980; 9(3):271–280.
18. Tanner, JM. Assessment of skeletal maturity and prediction of adult height (TW2 method). London ; New York: Academic Press; 1975.
19. Paridon SM, Alpert BS, Boas SR, Cabrera ME, Caldarera LL, Daniels SR, et al. Clinical stress testing in the pediatric age group: a statement from the American Heart Association Council on Cardiovascular Disease in the Young, Committee on Atherosclerosis, Hypertension, and Obesity in Youth. *Circulation*. 2006; 113(15):1905–1920. [PubMed: 16567564]
20. Ogden CL, Kuczmarski RJ, Flegal KM, Mei Z, Guo S, Wei R, et al. Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. *Pediatrics*. 2002; 109(1):45–60. [PubMed: 11773541]
21. Krebs NF, Jacobson MS. Prevention of pediatric overweight and obesity. *Pediatrics*. 2003; 112(2): 424–430. [PubMed: 12897303]

22. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004; 114(2 Suppl):555–576. 4th Report. [PubMed: 15286277]
23. Sorof JM, Cardwell G, Franco K, Portman RJ. Ambulatory blood pressure and left ventricular mass index in hypertensive children. *Hypertension*. 2002; 39:903–908. [PubMed: 11967247]
24. Smith JM, Stablein DM, Munoz R, Hebert D, McDonald RA. Contributions of the Transplant Registry: The 2006 Annual Report of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS). *Pediatr Transplant*. 2007; 11(4):366–373. [PubMed: 17493215]
25. Bonzel KE, Wildi B, Weiss M, Scharer K. Spiroergometric performance of children and adolescents with chronic renal failure. *Pediatr Nephrol*. 1991; 5(1):22–28. [PubMed: 2025532]
26. Weaver DJ Jr, Kimball TR, Knilans T, Mays W, Knecht SK, Gerdes YM, et al. Decreased maximal aerobic capacity in pediatric chronic kidney disease. *J Am Soc Nephrol*. 2008; 19(3): 624–630. [PubMed: 18184856]
27. Krasnoff JB, Mathias R, Rosenthal P, Painter PL. The comprehensive assessment of physical fitness in children following kidney and liver transplantation. *Transplantation*. 2006; 82(2):211–217. [PubMed: 16858284]
28. Krull F, Schulze-Neick I, Hatopp A, Offner G, Brodehl J. Exercise capacity and blood pressure response in children and adolescents after renal transplantation. *Acta Paediatr*. 1994; 83(12):1296–1302. [PubMed: 7734874]
29. Painter P, Krasnoff J, Mathias R. Exercise capacity and physical fitness in pediatric dialysis and kidney transplant patients. *Pediatr Nephrol*. 2007; 22(7):1030–1039. [PubMed: 17372771]
30. Batterham AM, Vanderburgh PM, Mahar MT, Jackson AS. Modeling the influence of body size on V(O₂) peak: effects of model choice and body composition. *J Appl Physiol*. 1999; 87(4):1317–1325. [PubMed: 10517758]
31. Vanderburgh PM, Katch FI. Ratio scaling of VO₂max penalizes women with larger percent body fat, not lean body mass. *Med Sci Sports Exerc*. 1996; 28(9):1204–1208. [PubMed: 8883011]
32. Feber J, Dupuis JM, Chapuis F, Braillon P, Jocteur-Monrozier D, Daudet G, et al. Body composition and physical performance in children after renal transplantation. *Nephron*. 1997; 75(1):13–19. [PubMed: 9031264]
33. Mitsnefes MM, Khoury P, McEnery PT. Body mass index and allograft function in pediatric renal transplantation. *Pediatr Nephrol*. 2002; 17(7):535–539. [PubMed: 12172770]
34. Andreacci JL, Robertson RJ, Dube JJ, Aaron DJ, Balasekaran G, Arslanian SA. Comparison of maximal oxygen consumption between black and white prepubertal and pubertal children. *Pediatr Res*. 2004; 56(5):706–713. [PubMed: 15319460]
35. Gutin B, Islam S, Manos T, Cucuzzo N, Smith C, Stachura ME. Relation of percentage of body fat and maximal aerobic capacity to risk factors for atherosclerosis and diabetes in black and white seven- to eleven-year-old children. *J Pediatr*. 1994; 125(6 Pt 1):847–852. [PubMed: 7996354]
36. Pivarnik JM, Fulton JE, Taylor WC, Snider SA. Aerobic capacity in black adolescent girls. *Res Q Exerc Sport*. 1993; 64(2):202–207. [PubMed: 8341843]
37. Trowbridge CA, Gower BA, Nagy TR, Hunter GR, Treuth MS, Goran MI. Maximal aerobic capacity in African-American and Caucasian prepubertal children. *Am J Physiol*. 1997; 273(4 Pt 1):E809–814. [PubMed: 9357812]
38. Diesel W, Emms M, Knight BK, Noakes TD, Swanepoel CR, van Zyl Smit R, et al. Morphologic features of the myopathy associated with chronic renal failure. *Am J Kidney Dis*. 1993; 22(5):677–684. [PubMed: 8238013]
39. Horber FF, Hoppeler H, Herren D, Claassen H, Howald H, Gerber C, et al. Altered skeletal muscle ultrastructure in renal transplant patients on prednisone. *Kidney Int*. 1986; 30(3):411–416. [PubMed: 3537448]
40. Horber FF, Scheidegger JR, Grunig BE, Frey FJ. Thigh muscle mass and function in patients treated with glucocorticoids. *Eur J Clin Invest*. 1985; 15(6):302–307. [PubMed: 3938399]
41. Topp KS, Painter PL, Walcott S, Krasnoff JB, Adey D, Sakkas GK, et al. Alterations in skeletal muscle structure are minimized with steroid withdrawal after renal transplantation. *Transplantation*. 2003; 76(4):667–673. [PubMed: 12973106]

42. Painter P, Messer-Rehak D, Hanson P, Zimmerman SW, Glass NR. Exercise capacity in hemodialysis, CAPD, and renal transplant patients. *Nephron*. 1986; 42(1):47–51. [PubMed: 3510400]
43. Painter P. Exercise after renal transplantation. *Adv Ren Replace Ther*. 1999; 6(2):159–164. [PubMed: 10230883]
44. Bodine SC. mTOR signaling and the molecular adaptation to resistance exercise. *Med Sci Sports Exerc*. 2006; 38(11):1950–1957. [PubMed: 17095929]
45. Bodine SC, Stitt TN, Gonzalez M, Kline WO, Stover GL, Bauerlein R, et al. Akt/mTOR pathway is a crucial regulator of skeletal muscle hypertrophy and can prevent muscle atrophy in vivo. *Nat Cell Biol*. 2001; 3(11):1014–1019. [PubMed: 11715023]
46. LeMura LM, Andreacci J, Carlonas R, Klebez JM, Chelland S. Evaluation of physical activity measured via accelerometry in rural fourth-grade children. *Percept Mot Skills*. 2000; 90(1):329–337. [PubMed: 10769919]

Figure 1. Association between log transformed maximal oxygen consumption (VO₂max) and log transformed body weight in renal transplant recipients and control subjects
 $R = 0.71$, $\beta = 0.72$, $p < 0.001$

Figure 2. Association between log transformed maximal oxygen consumption (VO₂max) and log transformed fat free mass in renal transplant recipients and control subjects
 $R = 0.86$, $\beta = 0.87$ $p < 0.001$

Table 1

Characteristics of renal transplant recipients and healthy controls

Characteristic	Transplant N = 50	Controls N = 70	p value
N (%) or Mean $\pm$ SD (Range)			
Age (years)	14.5 $\pm$ 3.0	14.9 $\pm$ 3.7	0.61
Range	(8.5 to 20)	(8.1 to 21.9)	
Male	35 (70%)	28 (40%)	0.001
Black race	15 (30%)	40 (57%)	0.01
Tanner stage 4-5	25 (50%)	55 (79%)	0.001
Body weight (kg)	58.0 $\pm$ 21.5	66.2 $\pm$ 20.4	0.049
Range	(31.0 to 126.7)	(25.4 to 126.7)	
Weight Z-score	0.5 $\pm$ 1.7	1.1 $\pm$ 1.2	0.02
Height (cm)	153.2 $\pm$ 14.5	160.4 $\pm$ 13.0	<0.01
Range	(126.2 to 182.3)	(129.1 to 182.4)	
Height Z-score	-1.0 $\pm$ 1.2	0.2 $\pm$ 1.0	<0.001
BMI (kg/m ²)	24.1 $\pm$ 6.0	25.4 $\pm$ 6.2	0.34
Range	(14.7 to 43.2)	(14.9 to 44.4)	
BMI Z-score	0.9 $\pm$ 1.2	1.0 $\pm$ 1.1	0.54
Fat-Free Mass (kg)	37.0 $\pm$ 13.0	42.5 $\pm$ 12.8	0.02
Range	(20.5 to 76.1)	(17.2 to 72.4)	
Fat mass (kg)	16.1 $\pm$ 10.2	17.8 $\pm$ 10.5	0.40
Range	(3.6 to 57.5)	(3.6 to 51.5)	
Obese	17 (34%)	26 (37%)	0.72

BMI, body mass index

Table 2

Disease characteristics of renal transplant recipients

Characteristic	N= 50
N (%) or Median and inter-quartile range (25%-75%)	
Diagnosis:	
FSGS	9 (18%)
Congenital renal disease	25 (50%)
Other glomerular disease	6 (12%)
Other	10 (20%)
Duration of ESRD (months)	39.2 (24.0-92.4)
Age at transplant (years)	11.1 (6.7-15.1)
Duration since transplant (months)	26.3 (16.2-72.5)
Living related donor	24 (48%)
History of dialysis	29 (58%)
Duration of dialysis (months)	9.8 (3.5-21.8)
eGFR (ml/min/1.73 m ²)	87.2 (73.4-96.3)
eGFR ≥90 ml/min/1.73 m ²	20 (40%)
eGFR 60 -89 ml/min/1.73 m ²	18 (36%)
eGFR 30-59 ml/min/1.73 m ²	3 (6%)
eGFR 15 -29 ml/min/1.73 m ²	1 (2%)
Hemoglobin (g/dl)	12.6 (11.9-13.4)
Serum phosphorus (g/dl)	4.3 (3.8-4.8)
Current Medications	
Antihypertensive	21 (42%)
Calcineurin inhibitor	43 (86%)
Sirolimus	18 (36%)
Mycophenolate mofetil	20 (40%)
Cyclosporine	2 (4%)
Azathioprine	7 (14)
Prednisone, mean daily dose	50 (100%), 0.069 mg/kg/day

FSGS, focal segmental glomerulosclerosis; ESRD, end stage renal disease; eGFR, estimated glomerular filtration rate

Table 3

Exercise outcomes in renal transplant recipients and control subjects

Characteristic	Transplant N = 50	Controls N = 70	p value
Peak heart rate	186 ± 16	191 ± 12	0.04
RER	1.18 ± 0.08	1.20 ± 0.09	0.35
Resting SBP index	0.92 ± 0.10	0.89 ± 0.10	0.12
Peak SBP index	1.28 ± 0.18	1.29 ± 0.19	0.73
Resting DBP index	0.96 ± 0.15	0.90 ± 0.09	0.01
Peak DBP index	0.88 ± 0.12	0.83 ± 0.09	0.01
Change in BP	44 ± 17	51 ± 19	0.06
VO _{2max} (L/min)	1.7 ± 0.6	2.0 ± 0.6	< 0.01
VO _{2max} (ml/kg/min)	29.6 ± 7.7	31.5 ± 7.8	0.20
VO _{2max} (ml/kgFFM/min)	45.5 ± 8.8	47.7 ± 8.0	0.14

RER, respiratory exchange ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; VO_{2max}, maximal oxygen consumption; FFM, fat free mass.

Table 4Multiple linear regression analysis of predictors of maximal oxygen consumption (log VO_{2max})

	β	95% Confidence Interval	p value
Renal transplant (vs. controls)	-0.136	-0.192 to -0.079	p < 0.001
Black race (vs. non-black)	-0.128	-0.179 to -0.077	p < 0.001
Female sex (vs. male sex)	-0.109	-0.170 to -0.048	p = 0.001
Fat free mass	0.923	0.822 to 1.024	p < 0.001
Fat mass	-0.093	-0.144 to -.042	p < 0.001
Constant	-2.144		

$R^2 = 0.84$. Model is described by $VO_{2max} = \exp [-2.144 + (-0.128 * \text{Race}) + (-0.109 * \text{Sex}) + (-0.136 * \text{Renal Transplant})] * \text{Fat Free Mass}^{0.923} * \text{Fat Mass}^{-0.093}$.

VO_{2max}, fat free mass and fat mass were log transformed.