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Pretransplant Physical Activity Predicts All-Cause Mortality in Kidney Transplant Recipients

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Key Words
Kidney transplantation · Mortality · Physical activity

Abstract
Background: Low physical activity (PA) has been associated with higher rates of cardiovascular disease (CVD) and mortality in the general population. Despite the benefits of kidney transplantation, kidney transplant recipients (KTRs) remain at elevated risk for CVD and mortality compared to individuals without kidney disease. ***Methods:*** A prospective cohort of 507 adult KTRs from three academic centers completed the Physical Activity Scale for the Elderly (PASE) at transplantation. PASE scores were divided into tertiles. ***Results:*** PA was lower with older age, history of CVD, smoking, and diabetes. During the median 8-year follow-up period, 128 individuals died, among whom 101 had a functioning allograft. In multivariable Cox regression for all-cause mortality, greater PA was strongly associated with better survival (HR: 0.52 for most active vs. inactive tertiles, 95% CI: 0.31–0.87, p = 0.01). Secondary analyses, in which (1) death with a functioning graft was the primary outcome, and (2) PASE scores were converted to the metabolic equivalent of task, revealed similar results. We did not find an association between change of PA after transplantation and mortality. ***Conclusions:*** PA at the time of kidney transplantation is a strong predictor of all-cause mortality and death with graft function. Evaluation of PA level among kidney transplant candidates may be a useful method to risk-stratify patients for survival after kidney transplantation. Kidney transplant candidates and recipients should also be encouraged to be physically active.

Introduction

Compared to chronic dialysis, kidney transplantation substantially decreases the risk of death and cardiovascular disease (CVD) events, and improves quality of life for most individuals with end-stage kidney disease (ESKD). Given the scarcity of kidney allografts, there is increasing interest in identifying patient characteristics before transplantation that predict posttransplant survival, as well as matching projected survival of kidney transplant candidates to projected allograft survival. Studies of diverse populations suggest that physical activity (PA) independently predicts mortality. Greater PA may directly improve overall health and cardiovascular fitness through improvements in blood pressure, lipids, insulin sensitivity, and systemic inflammation.

Kidney transplant recipients (KTRs) have fourfold increases in pooled nonfatal and fatal CVD incidence when

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compared to the general population [1]. This markedly elevated risk of CVD has been attributed to diverse pathological changes associated with advancing kidney disease, including hypertension, left ventricular hypertrophy, anemia, coronary calcification, and endothelial dysfunction [2].

Most studies of PA in the ESKD population have involved dialysis populations, while a few have focused on PA levels among KTRs. In a small study, 32 KTRs self-reported their PA at 1, 3, 6, 12, and 60 months [3]. KTRs had PA similar to elderly individuals in the general population, and PA levels increased approximately 30% of their baseline by 1 year after transplantation.

The aims of this study were to (1) assess pretransplant PA in a prospective cohort of incident and racially diverse KTRs, (2) identify predictors of pretransplant PA, (3) evaluate changes in PA after transplantation, and (4) determine the association between pretransplant PA with all-cause mortality and death with graft function.

Materials and Methods

We conducted a prospective cohort study of KTRs, who were recruited during their initial transplant hospitalization or shortly following their transplant. Recipients of multiorgan transplants were excluded, except for kidney-pancreas recipients. The primary outcome was mortality and the primary exposure was pretransplant PA.

Institutional review board approval was obtained. Informed written consent was collected from all participants.

Physical Activity

Pretransplant PA was measured using the Physical Activity Scale for the Elderly (PASE) questionnaire in recipients recruited between August 2000 and June 2004. The PASE is a 10-item instrument which assesses PA in the domains of leisure, household, and work activities, and takes 5 min to complete. Respondents were instructed to report their PA level for the prior week. Though originally designed for individuals over 65 years of age and developed with reference to accelerometer data [4], the PASE has been validated in cohorts of nonelderly, chronically ill, and sedentary individuals, as well as patients with ESKD [4, 5]. The PASE score has also been correlated with physiological measurements such as VO_2 [6]. The PASE score is computed by multiplying the duration of time spent in each activity in hours per day over a 7-day period by the respective weights and summing the scores of all activities. Because PASE scores were not normally distributed, we empirically divided recipients into tertiles of PASE scores. We also evaluated PASE as a continuous variable and as the natural log of the PASE score.

In additional secondary analysis using established methods, we calculated metabolic equivalents of task using the responses from the PASE questionnaire [7]. A subset of recipients had a second questionnaire completed a year after transplantation.

Delayed Graft Function and Mortality

Delayed graft function was defined as the need for dialysis during the first week after transplantation. Mortality was assessed through medical records and through the Social Security Death Index. Survival time was defined as time from transplant to death in years or March 31, 2011. Death with graft function survival time was defined as time from transplant to death in years or March 31, 2011 with censoring on date of allograft failure.

Statistical Analysis

All data analyses were performed using Stata Version 10.1 (Stata Corp., College Station, Tex., USA). Since PASE scores were not normally distributed, we created tertiles of PA, stratified by gender as per other reports [8]. We determined associations between PASE tertile and other participant attributes using ANOVA for continuous variables or χ^2 for categorical variables. In addition, we report total PASE scores categorized as limited (<50.0), low (50.1–200.0), and high (>200.0) PA to allow comparisons with previously reported PASE results based on cross-sectional studies [9]. We evaluated the change of PA after transplantation using previously described methods [10].

Kaplan-Meier survival analysis was used to evaluate mortality and death with graft function based on PASE score tertile. Significance was evaluated using the log-rank test.

Multivariable Cox proportional hazard models were used to evaluate risk factors associated with mortality and death with graft function. Both unadjusted and adjusted models were used to identify factors that were predictive of mortality events in multivariate models with PASE score. Appropriate diagnostics were performed to ensure that the proportionality assumption was not violated in the implementation of the Cox model. We selected a priori variables that had been previously associated with survival as well as considered covariates with $p < 0.20$ in univariate models for inclusion in the survival analyses. Covariates that were considered included recipient and donor age, race, gender, education, income, transplant type (deceased vs. living donor), HDL, triglycerides, Apo A1, BMI, history of smoking, CVD, diabetes, and ESKD vintage. Income was not entered into the final multivariable models due to underreporting.

A small proportion of patients had missing data (smoking history: n = 25, dialysis vintage: n = 17, BMI: n = 14, delayed graft function: n = 2). In order to explore the potential for bias due to nondifferential missing data, we performed secondary analyses using the multiple imputation by chained equations (MICE) procedure, and using sensitivity analyses. A total of 10 imputed datasets were created. Results were similar to those presented with all the nonmissing data in table 1.

Results

Five hundred and fifteen recipients completed the PASE questionnaire within 2 weeks of transplantation. The median time from transplant to questionnaire completion was 3 days. Due to missing data, eight PASE scores could not be calculated. Therefore, the cohort was comprised of 507 recipients with complete questionnaires.

Table 1. Recipient characteristics by PA gender-stratified tertiles

	n[1]	Inactive	n[1]	Moderate	n[1]	Active	p
Mean age, years	169	51.4 ± 13.1	166	47.3 ± 12.7	172	44.8 ± 11.6	<0.001
Mean BMI	157	27.9 ± 5.8	158	27.3 ± 5.7	154	26.8 ± 6.5	0.33
African American	169	58 (34.3)	166	58 (34.9)	172	45 (26.2)	0.15
Male	169	103 (61.0)	166	102 (61.4)	172	104 (60.5)	0.98
College-educated	156	60 (38.5)	154	47 (30.5)	167	74 (44.3)	0.04
Married	156	98 (62.8)	156	102 (65.4)	167	103 (61.7)	0.78
Income USD >40,000	121	59 (48.8)	115	55 (47.8)	129	63 (48.8)	0.99
Living donor transplant	169	55 (32.5)	166	64 (38.6)	172	68 (39.5)	0.35
CVD	160	52 (32.7)	157	46 (29.3)	168	42 (25)	0.31
Diabetes	169	71 (42)	166	48 (28.9)	172	40 (23.3)	0.001
Hypertension	165	157 (95.2)	162	158 (97.5)	172	161 (93.6)	0.23
Ever smoked	158	85 (53.8)	157	83 (52.9)	167	69 (41.3)	0.04
Prior dialysis	162	137 (84.6)	162	132 (81.5)	166	137 (82.5)	0.76
Graft failure	169	23 (13.6)	166	26 (15.7)	172	17 (9.9)	0.28
HDL ≥40, mg/dl	91	38 (41.8)	98	47 (48)	102	53 (52)	0.36
HDL, mg/dl	91	43.5 ± 20.3	98	41.6 ± 13.9	102	42.5 ± 13.0	0.72
LDL, mg/dl	86	93.1 ± 38.1	92	92.0 ± 34.1	100	99.4 ± 32.8	0.29
Total cholesterol, mg/dl	91	169.0 ± 50.2	98	169.1 ± 41.4	102	172.9 ± 41.2	0.77
Triglycerides, mg/dl	91	167.5 ± 118.7	98	178.9 ± 131.8	102	153.8 ± 84.7	0.29
Creatinine at transplant, mg/dl	158	7.97 ± 3.41	153	8.01 ± 3.02	157	8.70 ± 3.39	0.09

Values in parentheses represent percentages.
[1] Total numbers may vary due to missing data.

Table 1 describes the characteristics of recipients according to PASE score tertile. The majority of the cohort was male (61.0%), non-African American (68.2%), and received deceased donor transplants (63.1%). The mean (±SD) age was 47.8 ± 12.8 years. Kidney disease was most commonly attributed to hypertension (67.3%), diabetes (27.1%), and polycystic kidney disease (14.3%). Over one third of the participants had a history of cardiovascular events pretransplant and 31.4% had diabetes.

PA Score

Figure 1 displays the distribution of the PASE scores. The median PASE score was 92.7, with a range of 0–415.96 (25–75th interquartile range: 58.6–141) and a mean of 105.3 ± 70.2. The average PASE score was 103.3 ± 71.5 for men and 108.3 ± 68.1 for women. Recipients with higher scores were younger, less likely to have diabetes, and less likely to smoke. Using the activity category, 20% of recipients were in the limited category while the majority was in the low category (70.2%). Only 9.6% were in the high activity category.

With regard to leisure activity, 14.6% reported participating in light sports and 18.7% reported endurance training at least once per week. About a third of the recipients reported volunteering or working outside of the home at least part-time. There were no significant gender differences in the work (17.3 vs. 19.0, p = 0.59), leisure (24.3 vs. 21.5, p = 0.36), and household subscores (61.8

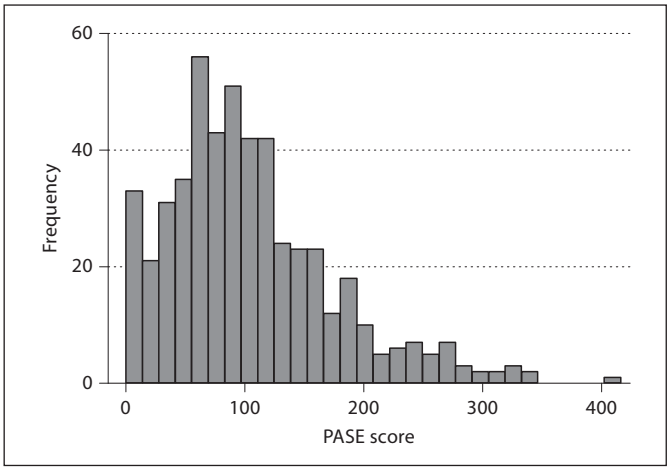

Fig. 1. Distribution of PASE scores in the kidney transplant cohort.

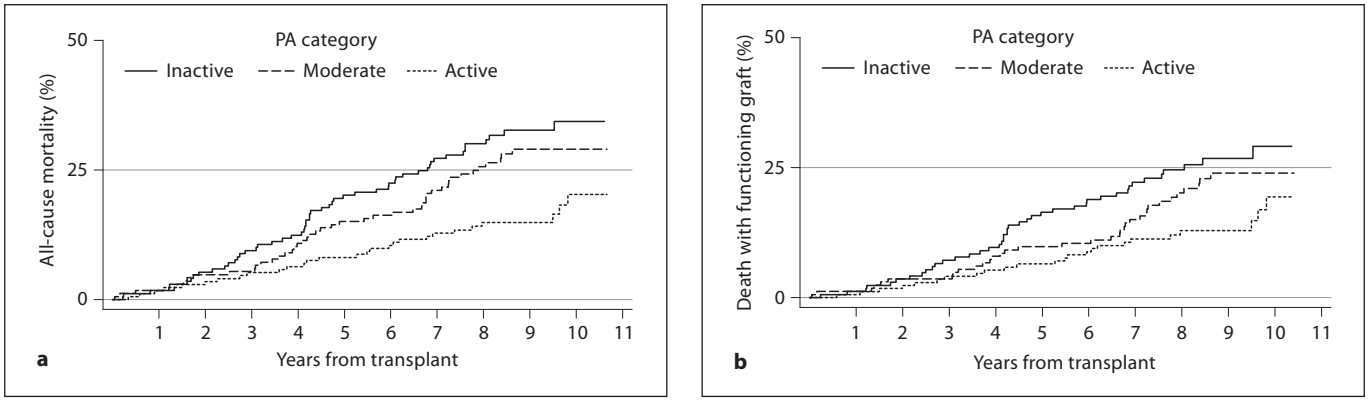

Fig. 2. a Kaplan-Meier curves of all-cause mortality according to gender-stratified tertiles of PA (p = 0.002). **b** Kaplan-Meier curves of death with a functioning graft according to gender-stratified tertiles of PA (p = 0.02).

vs. 67.8, p = 0.12) between men and women (online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000334732).

PA and Mortality

Median follow-up from transplantation was 8.4 years (interquartile range: 7.2–9.6), with a total of 3,990 person-years of observation. There were 128 deaths during the study period; among these, 101 of the deceased had functioning grafts. PASE scores were significantly higher among recipients who survived versus those who died (111.7 ± 71.6 vs. 86.1 ± 62.0, $p < 0.001$). Longer survival was also associated with younger age (46.0 ± 12.7 vs. 53.1 ± 11.0 years, $p < 0.001$) and shorter ESKD vintage (2.64 ± 3.3 vs. 4.5 ± 5.5 years, $p < 0.001$). In addition, recipients who survived were less likely to have diabetes (26.4 vs. 46.1%, $p < 0.001$), CVD (24.9 vs. 42%, $p < 0.001$), and a smoking history (44.5 vs. 63.8%, $p < 0.001$), and were more likely to have an income USD >40,000/year (82.5 vs. 67.6%, p = 0.001). Recipients who survived were less likely to have deceased donor transplants (60.2 vs. 71.9%, p = 0.02). There were no differences in BMI, race, and sex between the recipients who survived and those who expired.

There was also a graded association between activity category and death. In the limited category 36.3% of recipients died, while in the low category it was 23.3% and in the high category it was 16.3% (p = 0.01).

Table 2 depicts the multivariable models. Model 1 was adjusted for demographic variables and Model 2 was additionally adjusted for comorbidities. The highest PASE tertile (active group) had significantly longer survival after multivariable adjustment for demographic and clinical attributes as well as comorbidities. In our analysis by PASE score tertile, increasing age [lower tertile = reference; middle tertile = HR: 2.6 (1.4–4.8), p = 0.002; higher tertile = HR: 3.5 (1.9–6.2), $p < 0.001$], diabetes [HR: 1.7 (1.1–2.5), p = 0.01], and ESKD vintage [1st quartile (lower) = reference; 2nd quartile = HR: 1.5 (0.82–2.9), p = 0.18; 3rd quartile = HR: 2.1 (1.2–3.8), p = 0.02; 4th quartile (high) = HR: 3.3 (1.8–6.1), $p < 0.001$] were also significantly associated with all-cause mortality. Delayed graft function was marginally associated with mortality [HR: 1.68 (0.99–2.8), p = 0.05].

Sensitivity analyses revealed similar results when the primary exposure was the PASE score as a continuous measure or as the natural log of the PASE score, and when the primary exposure was metabolic equivalent of task.

Figure 2a represents the Kaplan-Meier estimates of cumulative overall mortality for kidney recipients by gender-stratified PASE score tertile ($p < 0.01$). Figure 2b represents the Kaplan-Meier estimates of cumulative overall death with graft function stratified by PASE score tertile (p = 0.02).

In a subset of participants (n = 291) with HDL measurements on the date of transplant, an HDL level ≥40 mg/dl was also predictive of improved survival [HR: 0.45 (0.25–0.82), p = 0.01]. The relationship between PA and mortality was unchanged.

Change in PA

Follow-up measurements were available in 290 recipients a median of 11.1 months after the first questionnaires. The recipients with a follow-up questionnaire data had similar baseline PASE scores compared to those without it (median: 91 vs. 93.6, p = 0.82). While most characteristics were similar to the complete cohort, those with a follow-up

Table 2. Association of PA with all-cause mortality and death with functioning graft

PA measure	Unadjusted (n = 507)			Model 1[1] (n = 507)			Model 2[2] (n = 454)		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
All-cause mortality (n = 128)									
METS[3]	0.91	0.87–0.96	<0.001	0.93	0.88–0.97	0.002	0.94	0.88–0.99	0.02
PASE score[3]	0.95	0.92–0.97	<0.001	0.96	0.93–0.99	0.005	0.96	0.92–0.99	0.005
log PASE	0.89	0.80–0.99	0.04	0.89	0.80–0.99	0.04	0.88	0.78–0.99	0.04
PASE tertile									
Inactive	ref.			ref.			ref.		
Moderate	0.81	0.55–1.20	0.31	0.91	0.61–1.36	0.65	0.87	0.56–1.35	0.53
Active	0.45	0.29–0.72	0.001	0.53	0.33–0.84	0.01	0.52	0.31–0.87	0.01
Death with functioning graft (n = 101)									
METS[3]	0.92	0.87	0.97 0.003	0.93	0.88	0.98 0.01	0.94	0.89	1.01 0.07
PASE score[3]	0.95	0.92	0.98 0.002	0.96	0.93	0.99 0.01	0.95	0.92	0.99 0.01
log PASE	0.90	0.79	1.02 0.09	0.89	0.78	1.02 0.08	0.87	0.76	0.996 0.046
PASE tertile									
Inactive	ref.			ref.			ref.		
Moderate	0.79	0.50	1.24 0.30	0.87	0.54	1.36 0.53	0.82	0.50	1.35 0.44
Active	0.49	0.30	0.82 0.01	0.55	0.33	0.93 0.03	0.54	0.30	0.97 0.04

METS = Metabolic equivalent of task.
[1] Model 1: adjusted for age, race, and gender.
[2] Model 2: also adjusted for diabetes, dialysis vintage, smoking history, BMI, and delayed graft function.
[3] Every 10-unit change.

questionnaire were more likely to be women (42.7 vs. 34.1, p = 0.05) and less likely to have a college education (33.8 vs. 44, p = 0.02). There was no change in activity category in most recipients (64.8%). However, 19.7% had increased their activity by at least one category, and 15.5% had decreased their activity by at least one category.

We evaluated change in score using several measures. While 42.4% of the recipients had an increase in score of 20, only 16.2% increased it by 70 which is 1 SD of the PASE score. The mean PASE score difference for the cohort was 6.2 (range: –247 to 222.7). We did not find any association between change in PASE score (percentage change or absolute difference) and mortality adjusted for the variables in our full mortality model.

Discussion

This study reveals that KTRs engage in modest levels of PA at the time of transplantation. Higher PA at the time of kidney transplantation was significantly linked to decreased mortality and death with graft function independent of other established predictors of mortality. During the first year after transplantation, there were modest improvements in PA. Our study therefore extends the association of PA with all-cause mortality to incident KTRs in an ethnically diverse cohort. We did not find an association between change of PA after transplantation and mortality.

Despite having a wide age range, the recipients in our cohort had PASE scores that were similar to those previously described in the elderly. The PASE scores of the recipients by gender correspond to the PASE scores of 70- to 75-year-old men and 65- to 69-year-old women in the general population. The PASE scores obtained were slightly higher than previously described for a cohort of 39 prevalent dialysis patients (105.3 ± 70.2 vs. 90.3 ± 76.8) likely reflecting their transplant eligibility [6].

Confirming prior studies, age, diabetes, and ESKD vintage were significantly associated with mortality [11–13]. The strong relationship between PA and mortality in our study confirms recent studies of physical function among KTRs. Pretransplantation physical functioning, as revealed by the physical function subscale of the Medical Outcomes Study Short-Form 36 questionnaire, was found to be a significant predictor of hospitalization and death among 366 incident dialysis patients who received a transplant within 24 months of starting dialysis [14].

In a retrospective study of 402 recipients, Yango et al. [15] found that pretransplant inactivity predicted recipient survival. Recently, Zelle et al. [8] using a different PA questionnaire found a strong association between low PA and all-cause mortality in prevalent KTRs who were transplanted at least a year earlier.

Our findings have important clinical implications. Sedentary lifestyle is associated with increased risk of CVD mortality among individuals with hypertension and diabetes [16–19]. PA is a modifiable risk factor for death. Exercise programs have been shown to improve survival as well as improve glycemic and blood pressure control [20, 21]. In the kidney transplant population, exercise interventions have been shown to increase peak oxygen intake and muscle strength [22]. The benefits of exercise in kidney replacement therapy participants were notable in physiological parameters, such as VO_2 maximum which increased during a 6-month aerobic exercise program and peak exercise heart rate which decreased from a mean 158.6 ± 21 to 150.5 ± 22.7 in KTRs [23].

Collectively, these findings suggest that the level of PA should be evaluated among kidney transplant candidates and recipients. Counseling kidney transplant candidates and recipients to increase the level of PA could have important health benefits and potentially increase their survival.

Inferences about the impact of changes in PA on the risk of mortality should be made with caution. While it is possible that we were unable to contact the more active participants for follow-up, there was no difference in baseline PA between those that completed a second questionnaire and those without it. One small study of 32 adults noted a 30% improvement from baseline at 1 year, but no further improvement up to 5 years after transplantation [3].

While our study involved a prospectively followed, large, racially diverse cohort of incident KTRs with long follow-up, this study has limitations including selection bias. KTRs who agreed to participate in the study may not have had equivalent PA compared to individuals who declined participation. Residual confounding is also likely due to inadequate adjustment for unmeasured covariates.

In conclusion, we demonstrated a strong association between low pretransplant PA and increased risk of mortality after transplantation. Clinical exercise intervention trials are needed to determine if training programs pre- or posttransplant improve mortality outcomes. Evaluation of PA level may be beneficial during the evaluation of candidates for kidney transplantation, and patients listed for transplantation should be encouraged to exercise.

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Disclosure Statement

None of the authors have any conflicts of interest to declare.

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