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Low Physical Activity and Risk of Cardiovascular and All-Cause Mortality in Renal Transplant Recipients

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Summary

Background and objectives Low physical activity (PA) is a risk factor for mortality in the general population. This is largely unexplored in renal transplant recipients (RTRs). We studied whether PA is associated with cardiovascular and all-cause mortality in a prospective cohort of RTR.

Design, setting, participants, & measurements Between 2001 and 2003, 540 RTRs were studied (age, 51 ± 12 years; 54% male). PA was assessed using validated questionnaires (Tecumseh Occupational Activity Questionnaire and the Minnesota Leisure Time Physical Activity Questionnaire). Cardiovascular and all-cause mortality were recorded until August 2007.

Results Independent of age, PA was inversely associated with metabolic syndrome, history of cardiovascular disease, fasting insulin, and triglyceride concentration, and positively associated with kidney function and 24-hour urinary creatinine excretion (*i.e.*, muscle mass). During follow-up for 5.3 years (range, 4.7 to 5.7 years), 81 RTRs died, with 37 cardiovascular deaths. Cardiovascular mortality was 11.7, 7.2, and 1.7%, respectively, according to gender-stratified tertiles of PA ($P = 0.001$). All-cause mortality was 24.4, 15.0, and 5.6% according to these tertiles ($P < 0.001$). In Cox regression analyses, adjustment for potential confounders including history of cardiovascular disease, muscle mass, and traditional risk factors for cardiovascular disease did not materially change these associations.

Conclusions Low PA is strongly associated with increased risk for cardiovascular and all-cause mortality in RTRs. Intervention studies are necessary to investigate whether PA improves long-term survival after renal transplantation.

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Introduction

The incidence and prevalence of cardiovascular disease (CVD) are estimated to be four to six times higher in renal transplant recipients (RTRs) than in the general population (1,2). Classical CVD risk factors such as dyslipidemia, hypertension, and obesity, which commonly coexist as the metabolic syndrome (MS), contribute to this excess in CVD (3,4). Other factors more specific for transplantation, such as use of immunosuppressive drugs and muscle wasting, might also be relevant to this high-risk profile. However, the influence of physical activity (PA) on CVD and mortality is largely unexplored.

In the general population, PA is associated with a lower prevalence and incidence of cardiovascular (CV) risk factors, including hypertension, type 2 diabetes mellitus, obesity, and dyslipidemia (5,6). It has also been established that low PA predicts CVD and mortality in the general population (5,7,8).

In advanced chronic kidney disease (CKD), PA levels are low and remain low after renal transplantation (9,10). Most RTRs enhance their level of PA slightly

immediately after transplantation, although compared with the general population, cardiorespiratory fitness in RTRs remains low (11). These low levels of PA can be explained by several factors. Muscle strength is impaired in RTRs compared with controls (10). Use of corticosteroids as immunosuppressive therapy and impaired renal function may contribute to an altered body composition, characterized by higher fat and lower muscle mass (12). Additionally, disuse of muscle by lack of PA can result in muscle atrophy (13), which is a risk factor for mortality in both RTRs and the general population (12,14).

It is not known whether low levels of PA are related to risk factors for CVD in RTRs. Likewise, it is not known whether low PA in RTRs translates into increased risk for CV and all-cause mortality.

We aimed to study cross-sectionally whether PA level is associated with CV risk factors and MS in RTRs. We further aimed to prospectively investigate in these patients whether PA is associated with CV and all-cause mortality. Finally, we sought to analyze whether these associations are independent of muscle

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mass as apparent from 24-hour urinary creatinine excretion.

Materials and Methods

Design and Subjects

In this prospective cohort study, all RTRs who visited the outpatient clinic at the University Medical Centre Groningen between August 2001 and July 2003 were invited to participate. Eligible for participation were all adult RTRs with transplant duration >1 year and with functioning allograft at time of invitation. The group that did sign informed consent was comparable with the group that did not sign informed consent with respect to age, gender, body mass index, serum creatinine, creatinine clearance, and proteinuria. In patients with fever or other signs of infection (*e.g.*, complaints of upper respiratory tract infection or urinary tract infection), baseline visits were postponed until symptoms had resolved. Patients with overt congestive heart failure and patients diagnosed with cancer other than cured skin cancer were not considered eligible for the study. Data on PA were available in 547 patients; 7 patients with amputations were excluded because of the possible incapability of being physically active. Full details on the study design have been previously reported (15). The Institutional Review Board approved the study protocol (METc 2001/039).

Endpoints of the study

The primary endpoints of the study were recipient CV and all-cause mortality. The continuous surveillance system of the outpatient program ensures up-to-date information on patient status and cause of death. CV and all-cause mortality was recorded until August 2007. We contacted general practitioners or referring nephrologists in case the status of a patient was unknown. Cause of death was obtained by linking the number of the death certificate to the primary cause of death as coded by a physician from the Central Bureau of Statistics. Causes of death were coded according to the International Classification of Diseases, 9th revision (ICD-9) (16). CV death was defined as deaths in which the principal cause of death was cardiovascular in nature, using ICD-9 codes 410 to 447.

Renal Transplant Characteristics

The Groningen Renal Transplant Database contains information about all renal transplantations that have been performed at the University Medical Centre Groningen since 1986, including dialysis history. Relevant transplant characteristics, such as age and gender, were taken from this database. Current medication was extracted from the medical record. Presence of amputations, smoking status, and CVD history were obtained using a self-report questionnaire. CVD history was considered positive if participants had a myocardial infarction, transient ischemic attack, or cerebrovascular accident.

PA

PA data were estimated using the Tecumseh Occupational Activity Questionnaire (TOAQ) and the Minnesota Leisure Time Physical Activity Questionnaire (MLTPAQ). These questionnaires, taken by interview with trained re-

search assistants, estimate the total amount of PA over the past 12 months. The TOAQ measures frequency, intensity, and duration of a maximum of three occupation-related activities within the previous 12 months. PAs associated with transportation to work are also included. The TOAQ is an acceptable measure of occupational PA energy expenditure and has been widely used (17). The MLTPAQ measures leisure time physical activities, including household activities, over the previous 12 months. Both questionnaires have been extensively validated against the Caltrac accelerometer, a PA record, and the doubly labeled water method (18,19).

A combination of these two questionnaires was used to estimate PA levels by using metabolic equivalents of task (MET) (20,21). These questionnaires can be combined because they measure both intensity and duration of the activity, which allows calculation summary scores in MET-minutes per day (MET-min/d). MET-minutes are calculated by multiplying the intensity (indicated by the MET-score) and the duration spent on that activity (measured in minutes). The MET-score can be derived from tables (the Compendium of Physical Activities) (22) that indicate the intensity of the activity relative to resting. MET-minutes spent on PA refer to the energy that is spent on activities, over and above existing levels of resting energy expenditure. Thus, if no notable PA is performed, PA will be scored as 0 MET-min/d. This does not imply that there is no energy expenditure, because resting energy expenditure is not taken into account in the calculation of PA. The combination of these questionnaires covers the whole of physical activities during the day. A MET is a multiple of daytime resting energy expenditure expressed in multiples of 3.5 ml O₂/kg per minute consumed, approximately equaling the energy expenditure of an average adult at rest, sitting quietly in a chair (18,22). For example, 1 MET is the rate of energy expenditure while at rest, whereas normal walking corresponds to a MET-score of 3.5 and brisk walking to a MET-score of 5. If one would perform 1 hour of brisk walking per day as a single activity, the total MET-min/d for PA would be $60 \times 5 = 300$ MET-min/d. This means that during 1 hour of brisk walking, five times more energy is spent than during 1 hour of resting.

In addition, it was assessed how many RTRs fulfilled the most recent PA guideline (23). According to this guideline, adults should do 2.5 h/wk of moderate-intensity PA, which equals 30 minutes of moderate PA per day, for 5 d/wk. Because moderate PA corresponds to a MET-score of 5 (brisk walking or mid-tempo cycling are typical examples), the guidelines correspond to $30 \times 5 = 150$ MET-min/d for 5 d/wk.

Measurements and Definitions

Body mass index was determined as a measure of overall obesity. Waist circumference was measured on bare skin midway between the iliac crest and the 10th rib. Muscle mass was estimated by 24-hour urinary creatinine excretion as described earlier (14). Twenty-four-hour urinary creatinine excretion is considered a reliable measure of muscle mass even in patients with advanced renal failure, in elderly people, and in patients with wasting conditions (24–26). Blood was drawn after an overnight fasting

period, which included no intake of medication, including anti-hypertensive drugs and blood glucose-lowering medication. BP was measured after a 6-minute rest in supine position as the average of three automated measurements at 1-minute intervals (Omron M4; Omron Europe).

Total cholesterol was determined using the cholesterol oxidase-phenol aminophenazone method (MEGA AU 510; Merck Diagnostica, Darmstadt, Germany), and serum triglycerides were determined with the glycerol-3-phosphate oxidase-phenol aminophenazone method. HDL-cholesterol was determined with the cholesterol oxidase-phenol aminophenazone method on a Technikon RA-1000 (Bayer Diagnostics, Mijdrecht, The Netherlands), and LDL-cholesterol was calculated using the Friedewald formula (21). Plasma glucose was determined by the glucose-oxidase method (YSI 2300 Stat plus; Yellow Springs). Serum high sensitive C-reactive protein (hsCRP) was assessed with a high sensitivity CRP ELISA assay. Serum and urine creatinine concentration were analyzed with a photometric modification with the Jaffé method. Creatinine clearance was calculated from 24-hour urinary creatinine excretion and serum creatinine. Total urinary protein concentration was analyzed using the Biuret reaction (MEGA AU 510; Merck Diagnostica), and proteinuria was defined as urinary protein excretion >0.5 g/24 h.

In this study, MS was defined by the definition of the National Cholesterol Education Program Expert Panel (27). Recently, the American Diabetes Association (ADA) lowered the cut-off point for impaired fasting glucose to ≥ 5.6 mmol/L (28). For our analysis of the prevalence of MS, we used this ADA cut-off point. Diabetes was defined according to the guidelines of the ADA as a fasting plasma glucose ≥ 7.0 mmol/L or the use of anti-diabetic medication (29).

Statistical Analyses

Data were analyzed with SPSS version 16.0 (SPSS, Chicago, IL) and GraphPad Prism version 4.03 (GraphPad Software, San Diego, CA). Normally distributed variables are expressed as mean \pm SD, whereas skewed distributed variables are given as median (25th to 75th percentile); percentages were used to summarize categorical variables. Log transformation was used for variables with a skewed distribution. Hazard ratios are reported with 95% confidence interval.

Recipient-related characteristics were analyzed separately for tertiles of PA level; predicted values are shown adjusted for age. ANOVA or Kruskal-Wallis test was used to compare means for continuous variables, with χ^2 for categorical variables. To analyze whether PA is associated with mortality, we first performed a Kaplan-Meier analyses with a log-rank test.

Multivariate Cox regression analyses were performed to study whether PA is independently associated with CV and all-cause mortality. For these analyses MET-minutes per day were first log transformed to achieve a normal distribution and entered in the model as a continuous variable. In multivariate Cox regression analyses, we first adjusted for recipient age, gender (model 2), and history of CV events (model 3). In addition to the adjustments for age, gender, and history of CV events, we performed ad-

justment for insulin concentration, systolic BP, waist circumference, triglycerides, smoking, and hsCRP (model 4). Similarly, we adjusted for Framingham risk score factors (model 5), creatinine clearance and urinary protein excretion (model 6), and 24-hour urinary creatinine excretion (model 7).

We also studied potential interactions between PA and 24-hour urinary creatinine excretion as a measure for muscle mass.

Results

A total of 540 RTRs were studied (mean age, 51 ± 12 years; 54% men). Baseline characteristics according to gender-stratified tertiles of PA of the RTRs are shown in Table 1. Because PA was strongly inversely associated with age, we also adjusted the gender-stratified baseline characteristics for age. Median values of PA over the tertiles were 4 [0 to 27], 115 [75 to 218], and 378 [234 to 514] MET-min/d, respectively. Median PA levels for women and men separately were 69 [4 to 171] MET-min/d in women and 204 [56 to 396] MET-min/d ($P < 0.001$) in men. With regard to the guidelines for minimum requirements of PA, 260 (48%) of RTRs were not meeting the criteria, and 79 (14.6%) were completely inactive, with a PA score of 0 MET-min/d.

Independent of its relation to age, PA was inversely associated with history of CVD, insulin concentration, triglycerides, and hsCRP. Also independent of age, PA was positively associated with creatinine clearance and urinary creatinine excretion. Of the total of 540 patients, 364 (64.0%) fulfilled the criteria for MS. Prevalence of MS decreased from 135 (75%) to 118 (65.5%) and 111 (61.7%) according to increasing tertiles of PA ($P = 0.007$).

During follow-up for 5.3 [4.7 to 5.7] years, 81 recipients died, with 37 deaths being CV in origin. Incidence of CV death significantly decreased according to increasing tertiles of PA, with respective numbers of 21 (11.7%), 13 (7.2%), and 3 (1.7%) ($P < 0.001$; Figure 1A). A similar association was present for all-cause mortality, with numbers of 50 (27.8%), 39 (21.7%), and 30 (16.7%) according to increasing tertiles, respectively ($P < 0.001$; Figure 1B). RTRs with moderate PA levels (second tertile) already had a lower risk for CV and all-cause mortality than inactive RTRs (first tertile).

Results of univariate and multivariate Cox regression analyses for associations of PA as a log-transformed continuous variable with CV and all-cause mortality are presented in Table 2. In univariate analyses, low PA strongly predicted CV and all-cause mortality in RTRs (model 1). These associations slightly weakened after adjustment for age and gender (model 2). The same was true for adjustment for history of CVD (model 3) and components of MS, smoking, fasting insulin concentration, and hsCRP (model 4). In model 5, adjustments were made for Framingham risk score factors (30) (BP, LDL-cholesterol, HDL-cholesterol, smoking, and presence of diabetes). Further adjustment for renal function, urinary protein excretion, and 24-hour urinary creatinine excretion as a measure of muscle mass (models 6 and 7) did not materially change hazard ratios. If analyses were repeated with either censoring at the moment of return to dialysis of all RTRs who returned to dialysis during follow-up ($n = 38$) or exclusion of these

	Tertiles of Physical Activity ^a			P
	Inactive (n = 180)	Moderate (n = 180)	Active (n = 180)	
Table 1. Baseline characteristics according to tertiles of physical activity				
General characteristics				
age (years)	56.1 ± 11.0	51.6 ± 11.8	46.0 ± 11.5	<0.001
smoking, n (%)	48 (26)	33 (18)	38 (21)	0.2
MS, n (%)	135 (75)	118 (70)	111 (62)	0.007
Cardiovascular disease				
myocardial infarction, n (%)	21 (12)	13 (7)	9 (5)	0.06
transient ischemic attack/cerebrovascular accident, n (%)	17 (10)	9 (5)	6 (3)	0.05
Body composition				
body mass index (kg/m ²)	26.3 ± 4	25.8 ± 4	26.0 ± 4	0.7
waist circumference in women (cm)	96.6 ± 14	93.2 ± 14	92.4 ± 14	0.1
waist circumference in men (cm)	100.4 ± 12	98.2 ± 12	100.3 ± 12	0.4
urinary creatinine excretion (mmol/24 h)	10.7 [10.3 to 1.2]	11.4 [10.9 to 11.9]	12.5 [11.9 to 13.1]	<0.001
Blood pressure				
systolic BP (mmHg)	150 ± 22	157 ± 22	151 ± 23	0.003
diastolic BP (mmHg)	89 ± 10	92 ± 10	90 ± 10	0.04
anti-hypertensive medication, n (%)	164 (91)	149 (83)	158 (88)	0.08
use of ACE inhibitor, n (%)	65 (36)	50 (28)	70 (39)	0.09
use of β-blocker, n (%)	119 (66)	108 (60)	108 (60)	0.5
Lipids and inflammation				
total cholesterol (mmol/L)	5.65 ± 1.1	5.59 ± 1.1	5.61 ± 1.1	0.89
HDL-cholesterol (mmol/L)	1.06 ± 0.34	1.12 ± 0.32	1.12 ± 0.34	0.13
LDL-cholesterol (mmol/L)	3.6 ± 1.0	3.5 ± 1.0	3.6 ± 1.0	0.7
triglycerides (mmol/L)	2.0 [1.9 to 2.1]	2.0 [1.8 to 2.1]	1.8 [1.6 to 1.9]	0.05
hsCRP (mg/L)	2.5 [2.2 to 2.8]	1.9 [1.7 to 2.1]	1.8 [1.6 to 2.0]	0.05
Glucose homeostasis				
glucose (mmol/L)	5.0 ± 1.4	4.8 ± 1.4	4.8 ± 1.4	0.4
insulin (μmol/L)	12.7 [11.7 to 13.8]	11.2 [10.3 to 12.1]	10.2 [9.4 to 11.1]	0.001
diabetes mellitus, n (%)	36 (20)	31 (17)	27 (15)	0.4
Renal function				
serum creatinine (μmol/L)	141.6 [135 to 149]	137.1 [131 to 144]	136.5 [130 to 143]	0.6
creatinine clearance (ml/min)	53.1 [50 to 56]	57.8 [55 to 61]	63.4 [60 to 67]	<0.001
urinary protein excretion (g/24 h)	0.36 [0.3 to 0.4]	0.35 [0.3 to 0.4]	0.32 [0.3 to 0.4]	0.8
proteinuria ≥ 0.5 g/24 h, n (%)	50 (28)	52 (29)	50 (28)	0.9
Data are represented as mean ± SD or median [95% confidence interval]. Differences were tested by ANOVA or Kruskal-Wallis test for continuous variables and with χ^2 for categorical variables. ACE inhibitor, angiotensin converting enzyme inhibitor.				
^a Tertiles of PA are stratified for gender and values are adjusted for age.				

RTRs, results of univariate and multivariate analyses remained materially unchanged.

In multivariate Cox regression analyses, no interaction between urinary creatinine excretion and PA was found.

Discussion

This study showed that low PA levels are strongly associated with CV and all-cause mortality in RTRs. To our knowledge, this is the first study to report on PA level and CV and all-cause mortality in these patients. This is consistent with earlier findings in dialysis, CKD, and the general population (8,9,31). Furthermore, it shows low levels of PA are positively associated with CVD risk factors in RTRs. Independent of age, PA was inversely associated with history of CVD, presence of MS, fasting insulin concentration, and triglycerides, and positively associated with kidney function and 24-hour urinary creatinine excretion (as a measure of muscle mass).

We anticipated that a potential association of PA with mortality could depend on risk factors for CVD, MS, or smoking status. We found, however, that the association of PA with mortality was not substantially affected by adjustments for history of CV events, insulin concentrations,

components of the MS, or Framingham risk score factors. The same holds for adjustments for renal function, despite differences in creatinine clearance over the tertiles. Another anticipated confounder was the effect of muscle mass, as reflected by 24-hour creatinine excretion, on the association between PA and mortality. In a previous study, we showed that muscle mass (as measured by 24-hour creatinine excretion) is associated with mortality in RTRs (12). Therefore, we speculated that low PA is associated with low muscle mass and thereby with higher mortality. Indeed, we now found that RTRs with higher PA also had higher 24-hour creatinine excretion (*i.e.*, larger muscle mass). However, on multivariate analyses, PA was associated with CV and all-cause mortality independent of 24-hour creatinine excretion. Based on the association between PA and mortality, it is tempting to speculate that improvement of PA levels could contribute to improved survival in RTRs.

PA may modulate CVD risk in several ways. Several clinical studies in the general population showed that PA lowers BP (32), improves body composition (33), lowers triglycerides (34), and improves glucose tolerance and insulin sensitivity (35,36). PA could modulate components of

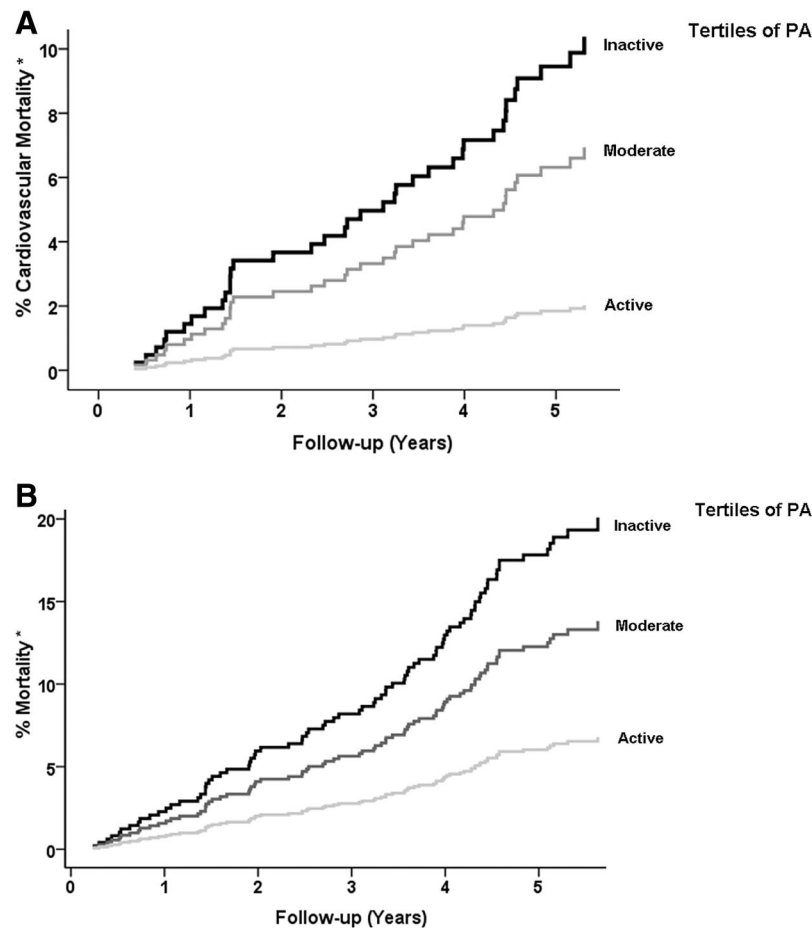


Figure 1. | (A) Kaplan-Meier curves of cardiovascular mortality according to gender-stratified tertiles of PA. *Adjusted for age ($P < 0.001$). (B) Kaplan-Meier curves of mortality according to gender-stratified tertiles of PA. *Adjusted for age ($P < 0.001$).

Model	Cardiovascular Mortality ($n = 37$)		All-Cause Mortality ($n = 81$)	
	HR [95% CI]	P	HR [95% CI]	P
1	0.51 [0.39 to 0.67]	<0.001	0.58 [0.48 to 0.70]	<0.001
2	0.56 [0.41 to 0.76]	<0.001	0.67 [0.54 to 0.83]	<0.001
3	0.58 [0.42 to 0.79]	0.001	0.69 [0.55 to 0.85]	0.001
4	0.61 [0.44 to 0.84]	0.003	0.70 [0.57 to 0.88]	0.002
5	0.58 [0.42 to 0.80]	0.001	0.70 [0.56 to 0.87]	0.001
6	0.62 [0.45 to 0.85]	0.003	0.76 [0.61 to 0.95]	0.02
7	0.62 [0.45 to 0.86]	0.004	0.75 [0.60 to 0.94]	0.01

Model 1: Crude model of physical activity as a continuous variable (log-MET-min/day). Model 2: model 1 + adjustment for age and gender. Model 3: model 2 + adjustment for history of cardiovascular events. Model 4: model 3 + adjustment for insulin concentration, systolic BP, waist circumference, triglycerides, smoking, and hsCRP. Model 5: model 3 + adjustment for Framingham risk score factors (BP, LDL-cholesterol, HDL-cholesterol, smoking, presence of diabetes). Model 6: model 5 + adjustment for creatinine clearance and urinary protein excretion. Model 7: model 5 + adjustment for 24-hour urinary creatinine excretion. HR, hazard ratio; CI, confidence interval.

the MS in RTRs in the same way as in the general population, which is supported by our data. Most RTRs gain substantial weight after transplantation, mainly because of an increase in fat mass (37). Inactivity is strongly associated

with obesity, and consequently, with the accumulation of visceral fat (38). Both visceral fat and physical inactivity itself are associated with the activation of inflammatory pathways (39), which in turn is involved in the cascade of

atherosclerosis and insulin resistance (40,41). The factors above could partially explain the modulating effect of PA on CVD risk.

Another mechanism that could elucidate the cardioprotective effects of exercise is vascular adaptation. Physical inactivity could lead to endothelial dysfunction in part by reduced activity of vascular nitric oxide, an established precursor to the atherosclerosis process (42,43). Exercise training has been shown to increase nitric oxide production, angiogenesis, and arteriogenesis and reduce vascular oxidative stress; this could represent the response to exercise that protects against CVD (43,44).

In our study, median energy expenditure attributable to PA was 115 MET-min/d, with values of 69 MET-min/d for women and 204 MET-min/d for men. Richardson *et al.* (18) measured a mean energy expenditure of about 410 MET-min/d in healthy subjects using the MLTPAQ, which only measures leisure time physical activity. Thus, compared with healthy subjects, RTRs have low PA levels in our study, which is in line with two other studies in which RTRs had lower levels of PA compared with healthy subjects (45,46). A 5-year follow-up study showed that most RTRs spontaneously became more active after transplantation, which was associated with a better quality of life (46). Although PA levels increase after transplantation, they often remain relatively low (45,47).

There could be several reasons for the low levels of PA in RTRs. Exercise capacity is approximately 30% lower in RTRs than in controls (10). The main determinants of exercise capacity in RTRs are skeletal muscle strength and PA level (47). It is difficult to determine whether low PA levels are caused by low muscle mass or the other way around. Before transplant, muscle mass is frequently low as a consequence of muscle wasting associated with ESRD and chronic hemodialysis (48). Metabolic acidosis and chronic inflammation contribute to the process of muscle protein degradation (48). After transplantation, chronic exposure to corticosteroids can contribute to decreased muscle mass. In line with this, we found in an earlier study that cumulative prednisolone dose was inversely related to muscle mass as reflected by 24-hour urinary creatinine excretion (12). Thus, a primary lack in muscle mass may impair RTRs in their capacity to exert PA. However, use of corticosteroids has been shown to not limit the potential to build muscle mass and exercise capacity (47). It has also been shown that disuse of muscle because of a lack of PA can adversely affect muscle mass (13). It is therefore obvious that to restore and maintain muscle mass after transplantation, regular PA is needed. Another reason for inactivity may also be uncertainty about being capable of being (and being allowed to be) physically active, with fear of injuring the graft playing a role in this uncertainty.

Exercise studies in RTRs have indicated that exercise training results in an improved exercise capacity, increased muscle strength, improved BP control and bone remodeling, and higher levels of self-reported physical functioning (11,47). These results show that exercise training in RTRs can be effective and feasible. Our results suggest that exercise training may benefit RTRs in terms of better survival. In regular care after transplan-

tation, exercise training is not yet incorporated. Further research is needed to study the role of PA intervention after renal transplantation in the prevention and treatment of CV risk factors, physical functioning, and long-term outcome.

The strength of our study is its prospective design. RTRs in this study were closely monitored by regular check-up in our clinic, which allows for extensive information gathering on patient status. A limitation of our study is that we used questionnaires to measure PA. However, the questionnaires have been validated (17–19), and the RTRs were interviewed by trained research assistants. Recall bias and social desirability bias where the participants could tend to report high volumes of PA are unfortunately unavoidable and could influence internal validation. Validation studies have shown that questionnaires may be effective in classifying people into broad categories of PA (*e.g.*, inactive, moderate, and active) but are less appropriate for quantifying absolute energy expenditure (49). Therefore, the focus in this study is not on absolute MET scores of PA but on the ranking based on these scores. It is tempting to speculate that stimulation of PA will improve outcome after transplantation. This study is, however, observational in design and not an intervention study; thus, hard conclusions on causality can not be drawn. We can not exclude a more general effect of a more healthy lifestyle, but our data support that PA contributes to a healthy lifestyle pattern in RTRs.

In summary, low PA is an independent risk factor for CV and all-cause mortality in RTRs. Our data suggest that increased PA might have a CV survival benefit for RTRs. Given the four to six times increased CV mortality in RTRs, there is great potential for mortality reduction by exercise participation in these patients.

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Disclosures

None.

References

- Oterdoom LH, de Vries AP, van Ree RM, Gansevoort RT, van Son WJ, van der Heide JJ, Navis G, de Jong PE, Gans RO, Bakker SJ: N-terminal pro-B-type natriuretic peptide and mortality in renal transplant recipients versus the general population. *Transplantation* 87: 1562–1570, 2009
- Aakhus S, Dahl K, Wideroe TE: Cardiovascular disease in stable renal transplant patients in Norway: Morbidity and mortality during a 5-yr follow-up *Clin Transplant* 18: 596–604, 2004
- Ojo AO: Cardiovascular complications after renal transplantation and their prevention. *Transplantation* 82: 603–611, 2006
- Hjeltnes J, Hartmann A, Midtvedt K, Aakhus S, Stenstrom J, Morkrid L, Egeland T, Tordarson H, Fauchald P: Metabolic cardiovascular syndrome after renal transplantation. *Nephrol Dial Transplant* 16: 1047–1052, 2001
- Leitzmann MF, Park Y, Blair A, Ballard-Barbash R, Mouw T, Hollenbeck A, Schatzkin A: Physical activity recommenda-

- tions and decreased risk of mortality. *Arch Intern Med* 167: 2453–2460, 2007
6. Jennings G, Nelson L, Nestel P, Esler M, Korner P, Burton D, Bazelmans J: The effects of changes in physical activity on major cardiovascular risk factors, hemodynamics, sympathetic function, and glucose utilization in man: A controlled study of four levels of activity. *Circulation* 73: 30–40, 1986
 7. Hu FB, Stampfer MJ, Colditz GA, Ascherio A, Rexrode KM, Willett WC, Manson JE: Physical activity and risk of stroke in women. *JAMA* 283: 2961–2967, 2000
 8. Paffenbarger RS Jr, Hyde RT, Wing AL, Lee IM, Jung DL, Kampert JB: The association of changes in physical-activity level and other lifestyle characteristics with mortality among men. *N Engl J Med* 328: 538–545, 1993
 9. Beddhu S, Baird BC, Zitterkoph J, Neilson J, Greene T: Physical activity and mortality in chronic kidney disease (NHANES III). *Clin J Am Soc Nephrol* 4: 1901–1906, 2009
 10. van den Ham EC, Kooman JP, Schols AM, Nieman FH, Does JD, Franssen FM, Akkermans MA, Janssen PP, van Hooff JP: Similarities in skeletal muscle strength and exercise capacity between renal transplant and hemodialysis patients. *Am J Transplant* 5: 1957–1965, 2005
 11. Painter PL, Hector L, Ray K, Lynes L, Dibble S, Paul SM, Tomlanovich SL, Ascher NL: A randomized trial of exercise training after renal transplantation. *Transplantation* 74: 42–48, 2002
 12. Oterdoom LH, van Ree RM, de Vries AP, Gansevoort RT, Schouten JP, van Son WJ, Homan van der Heide JJ, Navis G, de Jong PE, Gans RO, Bakker SJ: Urinary creatinine excretion reflecting muscle mass is a predictor of mortality and graft loss in renal transplant recipients. *Transplantation* 86: 391–398, 2008
 13. Little JP, Phillips SM: Resistance exercise and nutrition to counteract muscle wasting. *Appl Physiol Nutr Metab* 34: 817–828, 2009
 14. Oterdoom LH, Gansevoort RT, Schouten JP, de Jong PE, Gans RO, Bakker SJ: Urinary creatinine excretion, an indirect measure of muscle mass, is an independent predictor of cardiovascular disease and mortality in the general population *Atherosclerosis* 207: 534–540, 2009
 15. van Ree RM, de Vries AP, Oterdoom LH, The TH, Gansevoort RT, Homan van der Heide JJ, van Son WJ, Ploeg RJ, de Jong PE, Gans RO, Bakker SJ: Abdominal obesity and smoking are important determinants of C-reactive protein in renal transplant recipients *Nephrol Dial Transplant* 20: 2524–2531, 2005
 16. Zelle DM, Corpeleijn E, van Ree RM, Stolk RP, van der Veer E, Gans RO, Homan van der Heide JJ, Navis G, Bakker SJ: Markers of the hepatic component of the metabolic syndrome as predictors of mortality in renal transplant recipients *Am J Transplant* 10: 106–114, 2010
 17. Jacobs DR Jr, Ainsworth BE, Hartman TJ, Leon AS: A simultaneous evaluation of 10 commonly used physical activity questionnaires. *Med Sci Sports Exerc* 25: 81–91, 1993
 18. Richardson MT, Leon AS, Jacobs DR Jr, Ainsworth BE, Serfass R: Comprehensive evaluation of the Minnesota Leisure Time Physical Activity Questionnaire. *J Clin Epidemiol* 47: 271–281, 1994
 19. Folsom AR, Jacobs DR Jr, Caspersen CJ, Gomez-Marín O, Knudsen J: Test-retest reliability of the Minnesota Leisure Time Physical Activity Questionnaire. *J Chronic Dis* 39: 505–511, 1986
 20. Conway JM, Irwin ML, Ainsworth BE: Estimating energy expenditure from the Minnesota Leisure Time Physical Activity and Tecumseh Occupational Activity questionnaires: A doubly labeled water validation. *J Clin Epidemiol* 55: 392–399, 2002
 21. Montoye HJ, Kemper HCG, Saris WHM, Washburn RA: *Measuring Physical Activity and Energy Expenditure*, Champaign, IL, Human Kinetics, 1996
 22. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr, Schmitz KH, Emplaincourt PO, Jacobs DR Jr, Leon AS: Compendium of physical activities: An update of activity codes and MET intensities. *Med Sci Sports Exerc* 32: S498–S504, 2000
 23. Oja P, Bull FC, Fogelholm M, Martin BW: Physical activity recommendations for health: What should Europe do? *BMC Public Health* 10: 10, 2010
 24. Beddhu S, Pappas LM, Ramkumar N, Samore M: Effects of body size and body composition on survival in hemodialysis patients *J Am Soc Nephrol* 14: 2366–2372, 2003
 25. Proctor DN, O'Brien PC, Atkinson EJ, Nair KS: Comparison of techniques to estimate total body skeletal muscle mass in people of different age groups. *Am J Physiol* 277: E489–E495, 1999
 26. Heymsfield SB, Arteaga C, McManus C, Smith J, Moffitt S: Measurement of muscle mass in humans: Validity of the 24-hour urinary creatinine method. *Am J Clin Nutr* 37: 478–494, 1983
 27. National Cholesterol Education Program (NCEP): Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 106: 3143–3421, 2002
 28. American Diabetes Association: Diagnosis and classification of diabetes mellitus. *Diabetes Care* 31[Suppl 1]: S55–S60, 2008
 29. American Diabetes Association: Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 26[Suppl 1]: S5–S20, 2003
 30. Anderson KM, Wilson PW, Odell PM, Kannel WB: An updated coronary risk profile: A statement for health professionals. *Circulation* 83: 356–362, 1991
 31. Stack AG, Molony DA, Rives T, Tyson J, Murthy BV: Association of physical activity with mortality in the US dialysis population. *Am J Kidney Dis* 45: 690–701, 2005
 32. Hagberg JM, Park JJ, Brown MD: The role of exercise training in the treatment of hypertension: An update. *Sports Med* 30: 193–206, 2000
 33. Wood PD, Stefanick ML, Williams PT, Haskell WL: The effects on plasma lipoproteins of a prudent weight-reducing diet, with or without exercise, in overweight men and women. *N Engl J Med* 325: 461–466, 1991
 34. Slentz CA, Houmard JA, Johnson JL, Bateman LA, Tanner CJ, McCartney JS, Duscha BD, Kraus WE: Inactivity, exercise training and detraining, and plasma lipoproteins STRRIDE: A randomized, controlled study of exercise intensity and amount. *J Appl Physiol* 103: 432–442, 2007
 35. Sato Y, Nagasaki M, Nakai N, Fushimi T: Physical exercise improves glucose metabolism in lifestyle-related diseases. *Exp Biol Med (Maywood)* 228: 1208–1212, 2003
 36. Koivisto VA, Yki-Jarvinen H, DeFronzo RA: Physical training and insulin sensitivity. *Diabetes Metab Rev* 1: 445–481, 1986
 37. van den Ham EC, Kooman JP, Christiaans MH, Leunissen KM, van Hooff JP: Posttransplantation weight gain is predominantly due to an increase in body fat mass. *Transplantation* 70: 241–242, 2000
 38. Olsen RH, Krogh-Madsen R, Thomsen C, Booth FW, Pedersen BK: Metabolic responses to reduced daily steps in healthy nonexercising men. *JAMA* 299: 1261–1263, 2008
 39. Pedersen BK: The disease of physical inactivity and the role of myokines in muscle-fat cross talk. *J Physiol* 587: 5559–5568, 2009
 40. Handschin C, Spiegelman BM: The role of exercise and PGC1alpha in inflammation and chronic disease. *Nature* 454: 463–469, 2008
 41. Febbraio MA: Exercise and inflammation. *J Appl Physiol* 103: 376–377, 2007
 42. Li H, Forstermann U: Nitric oxide in the pathogenesis of vascular disease. *J Pathol* 190: 244–254, 2000
 43. Kojda G, Hambrecht R: Molecular mechanisms of vascular adaptations to exercise. Physical activity as an effective anti-oxidant therapy? *Cardiovasc Res* 67: 187–197, 2005
 44. Kingwell BA: Nitric oxide-mediated metabolic regulation during exercise: Effects of training in health and cardiovascular disease. *FASEB J* 14: 1685–1696, 2000
 45. van den Ham EC, Kooman JP, Christiaans MH, van Hooff JP: Relation between steroid dose, body composition and physi-

- cal activity in renal transplant patients. *Transplantation* 69: 1591–1598, 2000
46. Nielens H, Lejeune TM, Lalaoui A, Squifflet JP, Pirson Y, Goffin E: Increase of physical activity level after successful renal transplantation: A 5 year follow-up study. *Nephrol Dial Transplant* 16: 134–140, 2001
47. van den Ham EC, Kooman JP, Schols AM, Nieman FH, Does JD, Akkermans MA, Janssen PP, Gosker HR, Ward KA, MacDonald JH, Christiaans MH, Leunissen KM, van Hooff JP: The functional, metabolic, and anabolic responses to exercise training in renal transplant and hemodialysis patients. *Transplantation* 83: 1059–1068, 2007
48. Mitch WE: Insights into the abnormalities of chronic renal disease attributed to malnutrition. *J Am Soc Nephrol* 13[Suppl 1]: S22–S27, 2002
49. Shephard RJ: Limits to the measurement of habitual physical activity by questionnaires. *Br J Sports Med* 37: 197–206, 2003

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