Moderate-Intensity Single Exercise Session Does Not Induce Renal Damage

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Background: The aim of this study was to determine whether a single moderate-intensity exercise session induces renal injury based on various parameters that reflect kidney dysfunction, including urinary L-type fatty acid-binding protein (L-FABP). **Methods:** Adult outpatients ($n = 31$) with chronic kidney disease (CKD) not receiving renal replacement therapy participated in this study. Urine was collected before and after a single 20-min moderate-intensity exercise session. Urinary levels of L-FABP, albumin, *N*-acetyl- β -D-glucosaminidase (NAG), and α 1-microglobulin (α 1MG) were measured. In addition, 12 patients with estimated glomerular filtration fraction less than 30 ml/min/1.73 m² were selected from all patients

and evaluated using the same analysis. **Results:** Urinary values of L-FABP, albumin, NAG, and α 1MG did not increase significantly after exercise compared with before exercise (urinary L-FABP, from 8.3 to 9.4 μ g/g of creatinine; urinary albumin, from 293.1 to 333.7 mg/g of creatinine; urinary NAG, from 9.2 to 8.2 U/g of creatinine; urinary α 1MG, from 11.4 to 9.8 mg/g of creatinine, not significant). Similar findings were seen in all patients, regardless of degree of renal dysfunction. **Conclusions:** A single session of moderate-intensity exercise was not associated with an increase in renal parameters used to assess renal damage. *J. Clin. Lab. Anal.* 27:177–180, 2013. © 2013 Wiley Periodicals, Inc.

Key words: exercise; moderate-intensity; chronic kidney disease; urinary L-FABP; renal dysfunction

INTRODUCTION

The progression of chronic kidney disease (CKD) is known to be related to the degree of tubulointerstitial damage, rather than the degree of glomerular damage (1). Kidney hypoperfusion induces tubular hypoxia, which is an aggravating factor of tubulointerstitial damage and leads to the progression of CKD (2). Previous reports have shown that exercise increases blood flow and oxygen supply to muscles (3), decreases renal blood flow (RBF), induces kidney hypoperfusion, and decreases glomerular filtration rate (GFR; (4, 5). Therefore, it had been thought that exercise should be limited in patients with CKD.

However, recent clinical evidence has shown that exercise-induced decreases in RBF and GFR were tran-

sient (6) and that prolonged moderate-intensity exercise did not affect the progression of CKD (7, 8). Moreover, an experimental study showed that optimal exercise suppressed renal inflammation and renal fibrosis to improve CKD and emphasized the positive effect of exercise on CKD (9). Therefore, the Japanese guidelines for the treatment of CKD recommend moderate-intensity exercise for

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improvements in physical function and prevention of cardiovascular complications (10).

Urinary L-type fatty acid-binding protein (L-FABP) is a newly identified tubular biomarker of both CKD (11–15) and acute kidney injury (16, 17) and reflects not only the degree of tubulointerstitial damage, but also the decrease in RBF (2). Moreover, increases in urinary L-FABP have been shown to be a risk factor for progression of CKD (11, 13, 15). Therefore, we consider that urinary L-FABP may reflect renal hemodynamic changes and pathophysiological conditions due to exercise that cannot be detected by conventional markers, such as urinary albumin, urinary *N*-acetyl- β -D-glucosaminidase (NAG), and urinary α 1-microglobulin (α 1MG). However, the influence of exercise on urinary L-FABP levels has not been evaluated. This study assessed whether a single session of moderate-intensity exercise induces changes in variables used to assess renal damage, including urinary L-FABP levels as well as conventional parameters.

SUBJECTS AND METHODS

Subjects

Thirty-one adult patients with CKD were recruited from the outpatient clinics at the Division of Nephrology & Hypertension, Department of Medicine, St. Marianna University School of Medicine Hospital (Kanagawa, Japan). Inclusion criteria included no use of hemodialysis, no central nervous system or musculoskeletal disorders, no gait apraxia, and no contraindications to exercise (i.e., unstable angina, uncontrolled heart failure, or uncontrolled hypertension).

This research was carried out according to the principles of the Declaration of Helsinki, and informed consent was obtained from all patients. Our institutional review board approved the study protocol. Table 1 summarizes the clinical characteristics and laboratory findings of the study participants.

Exercise Protocol

The moderate-intensity exercise consisted of 20 min of treadmill walking (Treadmill MAT-2500, Fukuda Denshi Co., Tokyo, Japan) after reaching the target heart rate. Target heart rate was calculated by the Karvonen formula using a range of 40–60% exercise intensity (18) in patients not receiving β -blockers. For patients receiving β -blockers, exercise intensity ranged from 11 to 13 on the Borg scale of rating of perceived exertion (19). Metabolic equivalents (METs), which represent the intensity of exercise, were expressed as the ratio of oxygen consumption between during exercise and at rest calculated by the following formula: oxygen consumption = $\{(0.1 \times \text{speed of}$

TABLE 1. Clinical Characteristics and Laboratory Findings of Patients

<i>N</i>	31
Sex (male/female)	23/8
Age (years)	60 (52–66)
Height (cm)	163 (158–170)
Weight (kg)	65 (54–72)
Serum creatinine (mg/dl)	1.42 (1.12–2.16)
eGFR (ml/min/1.73 m ²)	35.3 (20.2–49.1)
Hemoglobin (g/dl)	12.7 (11.3–14.9)
Degree of CKD (<i>n</i>)	
Mild (eGFR 60–89 ml/min/1.73 m ²)	5
Moderate (eGFR 30–59 ml/min/1.73 m ²)	14
Severe (eGFR 15–29 ml/min/1.73 m ²)	9
Kidney failure (eGFR <15 ml/min/1.73 m ²)	3
Cause of CKD, <i>n</i> (%)	
Chronic glomerulonephritis	11 (35)
Nephrosclerosis	8 (26)
Diabetic nephropathy	6 (20)
Unknown	4 (13)
Other	2 (6)
Medication, <i>n</i> (%)	
ARB	21 (68)
ACEI	7 (23)
β -blockers	7 (23)
Calcium antagonists	19 (61)

Values are medians (interquartile range).

eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; ARB, angiotensin-receptor blocker; ACEI, angiotensin-converting enzyme inhibitor.

treadmill) + $(1.8 \times \text{its speed} \times \text{slope of treadmill}) + 3.5$ (20). Heart rate and systolic blood pressure were measured during exercise and at rest (Medical telemeter WEP-4202, Nihon Kohden Co., Tokyo, Japan).

Measurements

Urinary variables

Spot urine samples were obtained before and within 60 min after exercise. Urinary levels of L-FABP in spot urine samples were measured by an enzyme linked immunosorbent assay (ELISA) using the Human L-FABP ELISA Kit (CMIC, Tokyo, Japan; (15)) and were expressed as a ratio to the level of urinary creatinine. Urinary creatinine, albumin, *N*-acetyl- β -D-glucosaminidase (NAG), and α 1-microglobulin (α 1MG) were also measured.

Levels of urinary parameters in spot urine samples were expressed as a ratio to urinary creatinine levels. GFR was estimated using the new equation proposed by the Japanese Society of Nephrology as follows:

estimated GFR (eGFR; ml/min¹/1.73 m²) = $194 \times \text{Cr}^{-1.094} \times \text{Age}^{-0.287} \times 0.739$ (if female) (21).

Blood variables

Blood samples were taken before exercise and serum creatinine and hemoglobin were measured.

Statistical Analysis

Levels of urinary parameters were given as medians (interquartile range, IQR). To compare two parameters before and after exercise, the Wilcoxon signed-rank test (nonparametric distributions) were used for the paired data. Statistical analyses were performed using SPSS (version 12.0, SPSS SAS, Inc., Chicago, IL). *P* values <0.05 were considered statistically significant.

RESULTS

Urinary Parameters Before and After Treadmill Walking

Urinary values of L-FABP, albumin, NAG, and α 1MG did not increase significantly after exercise compared with before exercise (Table 2). Similar findings were seen in all patients, regardless of degree of renal dysfunction.

TABLE 2. Clinical Urinary Parameters Before and After Exercise

	Before exercise	After exercise	<i>P</i> -value
All patients (<i>n</i> = 31)			
Urinary L-FABP (μ g/g of creatinine)	8.3 (4.6–29.5)	9.4 (4.6–21.5)	0.81
Urinary albumin(mg/g of creatinine)	293.1 (112.7–1167.6)	337.7 (153.6–1462.9)	0.92
Urinary NAG (U/g of creatinine)	9.2 (5.8–12.9)	8.2 (5.5–12.3)	0.88
Urinary α 1MG (mg/g of creatinine)	11.4 (7.2–20.8)	9.8 (5.2–21.8)	0.51
Patients with eGFR $\leq$ 30 ml/min/1.73 m ² (<i>n</i> = 12)			
Urinary L-FABP (μ g/g of creatinine)	23.0 (7.7–54.2)	20.2 (4.8–52.2)	0.53
Urinary albumin (mg/g of creatinine)	748.5 (110.3–1446.7)	705.7 (106.7–1494.1)	0.94
Urinary NAG (U/g of creatinine)	10.5 (4.9–13.8)	9.3 (5.6–13.3)	0.88
Urinary α 1MG (mg/g of creatinine)	27.7 (11.0–35.2)	22.0 (8.5–47.6)	0.27

Values are medians (interquartile range).

L-FABP, liver-type fatty acid-binding protein; NAG, N-acetyl- β -D-glucosaminidase; α 1MG, α 1-microglobulin; eGFR, estimated glomerular filtration rate.

TABLE 3. Treadmill Indicators and Physical Findings of Patients During Treadmill Walking

Speed (km/h)	5.0 (4.2–5.0)
Slope (%)	2 (2–3)
Exercise intensity (METs)	4.11 (3.27–4.61)
Heart rate at rest (bpm/min)	73 (68–81)
Maximum heart rate (bpm/min)	115 (105–123)*
Systolic blood pressure at rest (mmHg)	133 (121–140)
Maximum systolic blood pressure (mmHg)	154 (140–170)*
Diastolic blood pressure at rest (mmHg)	80 (71–90)
Maximum diastolic blood pressure (mmHg)	80 (70–90)

Values are medians (interquartile range).

**P* < 0.01 versus at rest.

METs, metabolic equivalents.

Treadmill Indicators

Table 3 shows the speed and the slope of treadmill and METs performed in this study. Patients' maximum heart rate and systolic blood pressure for exercise were significantly higher than those at rest (*P* < 0.01).

DISCUSSION

The exercise-intensity performed in this study was considered to be moderate based on METS values that ranged from 3 to 5 (22). Because urinary levels of L-FABP, albumin, NAG, and α 1MG did not differ significantly between before and after a single session of moderate-intensity exercise, this type of exercise is not thought to influence renal function. This finding was maintained even in patients with severe CKD.

Moderate-intensity exercise has beneficial effects on obesity (23), hypertension (24), and glycemic control (25). With regard to CKD, although moderate-intensity exercise is recommended (10, 26), no study to date has suggested a detailed exercise program or has shown a direct positive effect of such an exercise on progression of CKD with sufficient power to be definitive. However, increases in urinary excretion of total protein or albumin were shown to be significantly correlated with exercise intensity in healthy men (27). Therefore, the valuable effect of exercise may depend not only on the optimal type, frequency, and duration of exercise, but also the intensity of exercise.

Urinary L-FABP is a newly identified tubular biomarker that reflects the degree of tubulointerstitial damage (12). In a clinical study of patients receiving living-related kidney transplants, urinary L-FABP levels in virgin urine obtained after anastomosis of the renal artery and vein of the transplanted kidney was established and was significantly correlated with ischemic time, defined as the period between the time point of clamping the donor's renal artery and the time point of the appearance of

virgin urine from the recipient's ureter (2). Moreover, only the decrease in urinary L-FABP, and not urinary NAG and α 1MG, correlated with the gradual increase in peritubular capillary blood flow after initiation of reperfusion (2). From these results, urinary L-FABP was considered to be a biomarker that represents renal hemodynamic changes such as tubular hypoxia. Because significant increases in urinary L-FABP levels were not observed in virgin urine obtained after the exercise performed in this study, moderate-intensity exercise was considered not to induce tubular hypoxia.

The primary limitation of the present study is that only a single session of moderate-intensity exercise was assessed. It is unknown whether prolonged moderate-intensity exercise or high-intensity exercise will increase urinary L-FABP levels or promote or inhibit the progression of CKD. We are planning an interventional study to determine the effects of prolonged moderate-intensity exercise on CKD progression.

In conclusion, a single session of moderate-intensity exercise in patients with CKD was not associated with an increase in any renal parameter measured, regardless of the level of kidney dysfunction.

CONFLICT OF INTEREST

None of the other authors have conflicts of interest or financial disclosures of any relevance to the present study.

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