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Comparison of ventilatory threshold between subjects with and without proteinuria in Japanese

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ABSTRACT

We compared the levels of ventilatory threshold (VT) between subjects with and without proteinuria. We used data of 402 men and 413 women who were not taking any medications, aged 20 - 77 years, in this cross-sectional investigation study. Aerobic parameters at VT *i.e.* oxygen uptake, work rate and heart rate, and exercise habits were evaluated, which are considered to be cardio respiratory fitness. Proteinuria was measured by using urine strip devices. Forty three men (10.7%) and 29 women (7.0%) were diagnosed as having the proteinuria (± ≦). There were no significant relationships between proteinuria and exercise habits in both sexes after adjusting for age. Oxygen uptake at VT in subjects with proteinuria was significantly lower than that in subjects without proteinuria after adjusting for age in men. However, such link was not noted in women after adjusting for age (p = 0.9964). Finally, associations were attenuated after adjusting for age and exercise habits in both sexes. Among Japanese not taking medications, proteinuria might be a modifiable factor of VT, especially in Japanese men.

Keywords: Proteinruia; Ventilatory Threshold (VT); Exercise Habits

1. INTRODUCTION

Chronic kidney disease (CKD) has become an important public health challenge in Japan and it is a major risk factor for the end stage renal disease, cardiovascular disease and premature death [1,2]. For example, about 20% of adults have CKD, which is defined as kidney damage or a glomerular filtration rate (GFR) < 60 ml/min /1.73 m^2 for at least three months regardless of cause [3]. We have also previously reported in a cross-sectional study that the estimated glomerular filtration rate (eGFR) [4] in men with abdominal obesity and in women with hypertension was significantly lower than that in subjects without these components of metabolic syndrome [5]. In addition, we have also showed that proteinuria was closely linked to lower eGFR and it might be useful marker for CKD in Japanese [6].

The ventilatory threshold (VT), which is one of parameters of the cardio respiratory fitness, is defined as the upper limit of the aerobic exercise and is thought to serve as an accurate and reliable standard for exercise prescription [7]. Since the exercise intensity at VT is not harmful to cardiovascular function, it can be safely applied to patients with myocardial infarction as exercise prescription [8]. However, the link between cardio respiratory fitness using VT and proteinuria remains to be investigated.

In this study, we investigated cardio respiratory fitness evaluated by VT in Japanese and evaluated the clinical impact of proteinuria on VT in subjects not taking medications.

2. METHODS

2.1. Subjects

We used all data on 815 Japanese (402 men and 413 women) aged 20 - 77 years in a cross-sectional study. All subjects met the following criteria: 1) they had wanted to change their lifestyle *i.e.* diet and exercise habits, and had received an annual health checkup at Okayama Southern Institute of Health; 2) they had received VT, urine examination and anthropometric measurements as part of their annual health checkups; 3) they had received no medications for diabetes, hypertension, and/or

dyslipidemia; and 4) they provided informed consent (**Table 1**).

The study was approved by the Ethics Committee of Okayama Health Foundation.

2.2. Anthropometric Measurements

The anthropometric parameters were evaluated by using the following respective parameters such as height, body weight, body mass index (BMI), abdominal circumference, and hip circumference. BMI was calculated by weight/[height]^2 (kg/m^2). The abdominal circumference was measured at the umbilical level and the hip was measured at the widest circumference over the trochanter in standing subjects after normal expiration [9].

2.3. Exercise Testing

A graded ergometer exercise protocol [10] was performed. Two hours after breakfast, a resting ECG was recorded and blood pressure was measured. Then, all participants were given graded exercise after 3 min of pedaling on an unloaded bicycle ergometer (Excalibur V2.0, Lode BV, Groningen, Netherlands). The profile of incremental workloads was automatically defined by the methods of Jones [10], in which the workloads reach the predicted VO_2 max in 10 min. A pedaling cycle of 60 rpm was maintained. Loading was terminated when the appearance of symptoms forced the subject to stop. During the test, ECG was monitored continuously together with the recording of heart rate (HR). Expired gas was collected and rates of oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were measured breath-by-breath using a cardiopulmonary gas exchange system (Oxycon Alpha, Mijnhrdt b.v., Netherlands). VT was determined by the standard of Wasserman *et al* [7], Davis *et al* [11], and the V-slope method of Beaver [12] from VO_2, VCO_2 and minute ventilation (VE). At VT, VO_2 (ml/kg/min), work rate (W), and heart rate (beats/min) were measured and recorded.

2.4. Urine Examination

Urine samples were collected from the second-morning urine (before 10 a.m.) and examined within 1 hour. The urine examination was performed using urine strip tests (BAYER, Tokyo, Japan). The reagent strip was dipped directly into the urine sample. Just after dipping, the sample is graded as −: negative, ±: trace positive, +: positive (30 mg/dl), 2+: positive (100 mg/dl), 3+: positive (300 mg/dl) or 4+: positive (1000 mg/dl) by comparison with a standard color chart found on the container's label [13].

2.5. Exercise Habits

The data on exercise habits was obtained at interviews by well-trained staff in a structured way. The subjects were asked if they currently exercise (over the level of 30 minutes per time, two times per week and prolong duration for 3 months). When the answer was "yes", they were classified as subjects with exercise habits. When the answer was "no", they were classified as subjects without exercise habits.

Table 1. Clinical profiles of enrolled subjects.

	Men			Women		
	Men ± SD	Minimum	Maximum	Men ± SD	Minimum	Maximum
Number of subjects	402			413		
Age	42.3 ± 11.5	20	77	45.1 ± 12.1	20	71
Height (cm)	169.7 ± 5.9	152.2	187.2	156.1 ± 5.5	141.7	176.1
Weight (kg)	78.8 ± 13.1	45.3	121.9	64.9 ± 12.0	39.9	116.9
Body mass index (kg/m^2)	27.3 ± 4.1	16.8	41.5	26.6 ± 4.8	15.4	48.7
Abdominal circumference (cm)	90.9 ± 10.8	62.5	130.0	81.5 ± 11.3	56.0	123.6
Hip circumference (cm)	98.5 ± 6.8	79.8	120.0	96.6 ± 8.5	72.5	132.0
Heart rate at rest (beat/min)	73.6 ± 12.4	43.0	117.0	73.2 ± 11.9	6.0	135.0
Systolic blood pressure (mm Hg)	137.3 ± 16.7	102.0	191.0	135.0 ± 20.9	82.0	188.0
Diastolic blood pressure (mm Hg)	86.1 ± 12.2	54.0	131.0	83.0 ± 12.8	50.0	122.0
Oxygen uptake at ventilatory threshold (ml/kg/min)	14.9 ± 3.9	8.7	33.9	12.6 ± 2.5	7.8	27.3
Work rate at ventilatory threshold (watt)	82.8 ± 24.5	35.0	190.0	51.2 ± 14.8	15.0	125.0
Heart rate at ventilatory threshold (beat/min)	105.9 ± 11.9	70.0	149.0	106.8 ± 11.7	71.0	147.0

2.6. Statistical Analysis

All data are expressed as mean ± standard deviation (SD) values. A statistical analysis was performed using an unpaired *t* test, χ^2 test, logistic regression analysis and covariance analysis, where $p < 0.05$ was considered to be statistically significant. We used the unpaired *t* test to compare parameters between subjects with and without proteinuria; the χ^2 test was used to evaluate the relationship between prevalence of proteinuria and exercise habits. Logistic regression analysis and covariance analysis were also used to adjust for parameters. ANOVA and Scheffe's F test were also used to compare among subjects with and without proteinuria and exercise habits.

3. RESULTS

Clinical profiles are summarized in **Table 1**. Oxygen uptake at VT was 14.9 ± 3.9 ml/kg/min in men and 12.6 ± 2.5 ml/kg/min in women. Prevalence of proteinuria in enrolled subjects is also summarized in **Table 2**. A total of 43 men (10.7%) and 29 women (7.0%) was diagnosed as having the proteinuria (± ≦).

We further evaluated the relationship between proteinuria and exercise habits (**Table 3**). Significant relationships between proteinuria and exercise habits were not noted in both sexes after adjusting for age.

We compared the parameters at VT between subjects with and without proteinuria (**Table 4**). In men, oxygen uptake at VT in subjects with proteinuria was significantly lower than that in subjects without proteinuria even after adjusting for age by using covariance analysis ($p = 0.0114$). It is well known that exercise habits are closely associated with ventilatory threshold [14], and significant difference of oxygen uptake at VT was attenuated after adjusting for age and exercise habits ($p = 0.4628$). The significant differences of work rate and heart rate at VT were not noted in men. In women, parameters at VT in subjects with proteinuria were not significant different compared to those in subjects without proteinuria.

We finally compared parameters at VT between subjects with and without proteinuria and exercise habits [A: proteinuria (−) exercise habits (+), B: proteinuria (−) exercise habits (−), C: proteinuria (+) exercise habits (+), D: proteinuria (+) exercise habits (−)] (**Table 5**). In men, oxygen uptake at VT in Group B and D was significantly lower than that in Group A. Heart rate at VT in Group D was significantly higher than that in Group A. In women, oxygen uptake at VT in Group B was significantly lower than that in Group A. Heart rate at VT in Group D was significantly higher than that in Group A.

4. DISCUSSION

In this study, we firstly evaluated the link between proteinuria and cardiorespilatory fitness using VT in Japanese without any medications. Proteinuria might be a modifiable factor of VT, especially in Japanese men.

It is well known that proteinuria and/or reduced renal function were closely associated with cardio vascular disease (CVD) [15,16]. Irie *et al* reported that they evaluated 30,764 men and 60,668 women aged 40 - 79 years for 10 years, and proteinuria and hypercreatinemia or reduced GFR and their combination were significant predictors of CVD and all-cause mortality [15]. Anavekar *et al* also showed that even mild renal disease

Table 2. Prevalence of proteinuria in enrolled subject.

	−		±		1+		2+		3+		Total
		%		%		%		%		%	
Men	359	89.3	21	5.2	14	3.5	5	1.2	3	0.7	402
Women	384	93.0	17	4.1	9	2.2	3	0.7	0	0.0	413

Table 3. Relationship between proteinuria and exercise habits.

	Proteinuria (−)	Proteinuria (± ≦)	*p*	*p* (After adjusting for age)
Men				
Exercise habits (+)	152	12	0.0688	0.0921
Exercise habits (−)	207	31		
Women				
Exercise habits (+)	105	4	0.1104	0.1667
Exercise habits (−)	279	25		

Table 4. Comparison of parameters at ventilatory threshold between subjects with and without proteinuria.

	Proteinuria (−)	Proteinuria (± ≦)	*p*	*P* (After adjusting for age)	*p* (After adjusting for age age and exercise habits)
	Men ± SD	Men ± SD			
Men					
Number of subjects	359	43			
Age	42.7 ± 11.5	39.2 ± 11.5	0.0564		
Oxygen uptake at ventilatory threshold (ml/kg/min)	15.1 ± 4.0	13.7 ± 2.8	**0.0275**	**0.0114**	0.4628
Work rate at ventilatory threshold (watt)	83.3 ± 25.3	78.7 ± 15.9	0.2440	0.3603	0.2947
Heart rate at ventilatory threshold (beat/min)	105.5 ± 12.0	109.1 ± 11.2	0.0591	0.4155	0.1050
Women					
Number of subjects	384	29			
Age	45.2 ± 12.2	42.6 ±11.0	0.2571		
Oxygen uptake at ventilatory threshold (ml/kg/min)	12.6 ± 2.5	12.3 ± 1.7	0.5751	0.9964	0.2939
Work rate at ventilatory threshold (watt)	51.2 ± 15.1	51.4 ± 10.0	0.9477	0.3446	0.2382
Heart rate at ventilatory threshold (beat/min)	106.4 ± 11.6	112.2 ± 12.5	**0.0102**	0.4685	0.2028

Table 5. Comparison of parameters of ventilatory threshold between subjects with and without proteinuria and exercise habits.

	Proteinuria (−)	Proteinuria (−)		Proteinuria (+)	Proteinuria (+)	
	Exercise habits (+)	Exercise habits (−)		Exercise habits (+)	Exercise habits (−)	
Men						
Number of subjects	152	207		12	31	
Oxygen uptake at ventilatory threshold (ml/kg/min)	16.7 ± 5.0	13.9 ±2.6	a	14.8 ± 4.1	13.2 ± 2.0	a
Work rate at ventilatory threshold (watt)	90.9 ± 31.0	77.7 ± 18.4	a	74.5 ± 16.3	80.3 ± 15.6	
Heart rate at ventilatory threshold (beat/min)	104.5 ± 13.1	106.1 ± 11.1		103.1 ± 12.4	111.4 ± 10.0	a
Women						
Number of subjects	105	279		4	25	
Oxygen uptake at ventilatory threshold (ml/kg/min)	13.4 ± 3.4	12.3 ± 2.1	a	10.6 ± 1.6	12.6 ± 1.6	
Work rate at ventilatory threshold (watt)	54.3 ± 18.9	50.0 ± 13.2		41.2 ± 9.5	53.0 ± 9.2	
Heart rate at ventilatory threshold (beat/min)	104.1 ± 12.0	107.3 ± 11.3		101.8 ± 11.6	113.8 ± 12.0	a

a: $p < 0.05$ vs Proteinuria (−), Exercise habits (+)

was considered a major risk factor for CVD after myocardial infarction in 14527 patients with acute myocardial infarction [16]. However, according to the link between reduced renal function and cardiorespiratory fitness, there were few studies especially in Japan. Okuno *et al* reported that they evaluated 109 community-dwelling frail elderly, aged 65 years and over, and they found that functional reach and tandem stance were significantly affected by eGFR [17]. Takhreen reviewed that relationship between exercise intervention and quality of life (QOL) in CKD patients. Exercising patients have shown improvements in physical fitness, psychological function, reaction times and lower extremity muscle strength, and these factors help improve QOL [18]. In this study, we solely evaluated the relationship between proteinuria and aerobic exercise level defined by VT in the Japanese without any medications. Exercise habits were not significantly linked to proteinuria in both sexes and the differences of parameters at VT between subjects with and without proteinuria were attenuated

after adjusting for age and exercise habits in men. However, oxygen uptake at VT in women with proteinuria was not significantly lower than that in women without. In addition, we compared oxygen uptake at VT among subjects with and without proteinuria and exercise habits, and found that oxygen uptake at VT in Group D was the lowest among 4 groups in men. Oxygen uptake at VT in Group A was the highest among 4 groups in both sexes. Taken together, promoting exercise habits might be considered for improving aerobic exercise level, and proteinuria might be a modifiable factor of VT, especially in Japanese men.

Potential limitations still remain in this study. First, our study was a cross sectional and not a longitudinal study. Second, 402 men and 413 women in our study voluntarily underwent measurements: they were therefore more likely to be health-conscious compared with the average person. Third, we could not show clear mechanism between proteinuria and oxygen uptake at VT. We have previously reported that brachial-ankle pulse wave velocity (baPWV) in subjects with reduced eGFR was significantly higher than that in subjects without [19]. Arterial stiffness might affect the results. In addition, low prevalence of proteinuria also affected the results, especially in women. To show this, further prospective studies are needed in the Japanese.

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