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Re-evaluation of exercise prescription for Japanese type 2 diabetic patients by ventilatory threshold

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Abstract

Prescription of aerobic exercise for Type 2 diabetes mellitus (Type 2 DM) in clinical practice is frequently based on exercise intensity at maximum heart rate ($60 < HR_{max} < 79\%$), heart rate reserve ($50 < HR_{reserve} < 74\%$), and rating of perceived exertion ($12 < RPE < 13$). We examined these parameters in Japanese males with Type 2 DM at ventilatory threshold (VT) to investigate the exercise capacity of Type 2 DM patients and re-evaluate the exercise prescription. Fifty-six Japanese Type 2 DM males without autonomic neuropathy [age, 53.5 ± 7.7 years; body mass index (BMI), 23.7 ± 3.6 kg/m^2] were enrolled and compared with 56 age- and BMI-matched healthy Japanese males. VT was determined breath by breath during exercise test using a ramp protocol and rates of oxygen consumption ($\dot{V}O_2$), work rate (WR), HR, ΔHR, $\%HR_{max}$, $\%HR_{reserve}$, and RPE were measured at VT. Type 2 DM patients had significantly lower $\dot{V}O_2$ (3.6 ± 0.4 metabolic equivalents (METs)) and WR (62 ± 14 W) than controls ($\dot{V}O_2$, 3.9 ± 0.6 METs; WR, 74 ± 13 W). $\%HR_{reserve}$, ($32.6 \pm 7.7\%$) was also significantly lower compared with controls ($37.6 \pm 8.3\%$), while $\%HR_{max}$, was not different. RPE was also similar in diabetics (12.4 ± 1.5) and controls (12.9 ± 1.2), however, it was significantly lower in diabetic patients aged 60–69 years (11.8 ± 2.0) and those with distal symmetric sensory neuropathy (12.2 ± 1.0). Our results indicate reduced exercise capacity in Japanese Type 2 DM males and the exercise intensity of $60\%HR_{max}$, $30\%HR_{reserve}$, and RPE 12 is recommended in elderly diabetics and those with diabetic sensory neuropathy.

Keywords: Ventilatory threshold; HR_{max}; $HR_{reserve}$; Rating of perceived exertion

1. Introduction

Exercise and calorie restriction are recommended as the initial therapeutic approach to non-insulin-dependent Type 2 diabetes mellitus (Type 2 DM) [1]. Exercise provides several

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benefits for the prevention of vascular complications in Type 2 DM patient since it frequently results in the improvement of obesity, body fat composition, insulin sensitivity, glycemic control, blood pressure, and atherogenic lipid profile, which are considered to be as risk factors for atherosclerosis [2]. The anaerobic threshold (AT) is defined as the upper limit of the aerobic exercise and is thought to serve as an accurate and reliable standard for exercise prescription. Since the exercise intensity at AT does not affect cardiovascular function, it can be applied for exercise prescription in patients with hypertension, obesity, and myocardial infarction [3,4]. Similarly, the exercise load at AT can be safely prescribed for Type 2 DM patients with macroangiopathy and microangiopathy, such as myocardial infarction and diabetic autonomic neuropathy. In this regard, aerobic exercise can be continued for long periods and it has been reported to result in improvement of glucose and lipid metabolism in diabetic patients [5,6].

Measurement of AT, however, requires the continuous monitoring of plasma lactate levels and is not practical for the management of Type 2 DM patients. The ventilatory threshold (VT) is another method for the measurement of aerobic exercise capacity and estimation of AT; however, it requires gas exchange analysis. Instead, the guidelines prescribing exercise reported by the American Diabetes Association (ADA) have been used and they recommend moderate intensity of exercise, which is estimated from individual's maximum heart rate ($60 < HR_{max} < 79\%$), heart rate reserve ($50 < HR_{reserve} < 74\%$), and rating of perceived exertion ($12 < RPE < 13$) [2,7].

Although exercise under the guideline of ADA can be safely performed in most Type 2 DM patients, several questions still need to be answered. For example, reduced aerobic exercise capacity was reported in Type 2 DM patients and those with diabetic vascular complications [8]. In addition, the formula of HR_{max} overestimates the maximum HR in Type 2 DM patients with autonomic neuropathy [6]. In such patients, we may prescribe heavy exercise by the application of HR_{max}, $HR_{reserve}$ and RPE, which are frequently used clinically. To address these issues, we measured VT and compared it with parameters of estimated exercise intensity; i.e. HR_{max}, $HR_{reserve}$ and RPE, in Japanese male Type 2 DM patients and control subjects.

2. Research design and methods

2.1. Subjects

A total of 56 Japanese males with Type 2 DM [age, 53.5 ± 7.7 years; body mass index (BMI), 23.7 ± 3.6 kg/m^2] who met the criteria defined below were enrolled in this study. We also examined 56 age- and BMI-matched healthy Japanese males (age, 53.7 ± 7.5 years; BMI, 23.8 ± 3.3 kg/m^2). The control subjects had normal levels of fasting plasma glucose (<110 mg/dl), were free of chronic diseases, not on any medications, and physical examination was normal. The levels of transaminases and serum creatinine were also normal in the control group. Control subjects were sedentary and they did not exercise on regular basis. Potential participants were excluded if they claimed they performed exercise at least 30 min, more than twice a week.

Diagnosis of Type 2 DM was established according to the 1985 criteria of the World Health Organisation [9]. The presence of diabetic complications, such as neuropathy, retinopathy and nephropathy, was also assessed in each subject. The presence of distal symmetrical neuropathy was evaluated by symptoms, such as loss of sensation, numbness and paresthesia. Diabetic neuropathy was diagnosed in 32 patients, but none of these patients showed autonomic dysfunction (defined as >20 mmHg fall in upright blood pressure), that might influence exercise performance. Diabetic retinopathy was noted in ten patients. Among these, three had proliferative retinopathy and had been treated by laser photocoagulation therapy, while seven patients had simple diabetic retinopathy. Patients with overt proteinuria (≥ 1 g per day) or renal dysfunction (creatinine ≥ 1.2 mg/dl) were excluded from the study. We also evaluated cardiovascular system to both the clinical and laboratory tests. The

Table 1
Clinical characteristics of control subjects and type 2 DM patients[a]

	Control	Type 2 DM
n	56	56
Age (years)	53.7 ± 7.5	53.5 ± 7.7
Height (m)	1.66 ± 0.06	1.67 ± 0.06
Body weight (kg)	65.3 ± 9.9	65.9 ± 10.5
Body mass index (kg/m^2)	23.8 ± 3.3	23.7 ± 3.6
HR at rest (bpm)	64 ± 6	66 ± 8
Disease duration (years)		4.1 ± 4.1
Glycated haemoglobin (%)		7.6 ± 1.9

[a] Values are mean ± S.D. No significant differences were found between control and diabetic patients.

presence of systolic blood pressure > 160 mmHg and/or diastolic pressure > 90 mmHg was set as an exclusion criterion. No Type 2 DM patients was being treated at the time of the study with antihypertensive drugs, such as β-blockers, Ca^{2+} antagonists or angiotensin converting enzyme inhibitors. Patients and healthy controls were also excluded from the study if they showed ischemic changes at rest or exercise ECG. All subjects gave written informed consent. Of the Type 2 DM patients, 18 were treated with diet therapy only, 24 with sulfonylureas, 10 with insulin therapy, and 4 patients with α-glucosidase inhibitor. The clinical characteristics of Type 2 DM patients and control subjects are summarised in Tables 1 and 2.

2.2. Exercise testing

A graded ergometer exercise protocol [10] was performed after an overnight fast. Diabetic patients were allowed to receive insulin injection or sulfonylureas in the morning of the exercise test. After breakfast (2 h), a resting ECG was recorded and blood pressure was measured. Then, all subjects were given graded exercise after a 3-min of pedalling on an unloaded bicycle ergometer (Road Corp., USA). The profile of incremental workloads was automatically defined by the method of Jones [10], in which the workloads reach the predicted $\dot{V}O_{2max}$ in 10-min. A pedalling 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 HR. Expired gas was collected and rates of oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were measured breath-by-breath using the MMC Horizon System 4400tc (Sensor Medics Corp., CA). VT was determined by the standard of Wasserman et al. [11], Davis et al. [12] and the V-slope method of Beaver [13] from $\dot{V}O_2$, $\dot{V}CO_2$, and minute ventilation (VE). At VT, $\dot{V}O_2$ (metabolic equivalents, METs), work rate (WR) (W), and HR (beats/min) were measured and recorded. In addition, ΔHR (HR at VT−HR at rest), $\%HR_{max}$ [(HR at VT/220-age)], $\%HR_{reserve}$ [(HR at VT−HR at rest)/

Table 2
Clinical characteristics of control subjects and type 2 DM patients in different age groups[a]

	40s		50s		60s	
	Control	Type 2 DM	Control	Type 2 DM	Control	Type 2 DM
n	19	19	21	21	16	16
Age (years)	45 ± 3	45 ± 3	54 ± 3	54 ± 3	63 ± 2	63 ± 2
Height (m)	1.68 ± 0.04	1.67 ± 0.06	1.67 ± 0.07	1.67 ± 0.06	1.64 ± 0.07	1.65 ± 0.06
Weight (kg)	66.8 ± 0.9	66.3 ± 10.8	67.8 ± 10	67.0 ± 11.8	62.8 ± 9	64.1 ± 8.6
BMI (kg/m^2)	23.7 ± 3.3	23.7 ± 3.4	24.3 ± 3.5	24.0 ± 4.3	23.5 ± 3.0	23.4 ± 2.8
HR at rest (bpm)	66 ± 5	67 ± 9	62 ± 6	66 ± 8	64 ± 6	65 ± 6
Disease duration (years)		3.3 ± 4.0		4.0 ± 3.5		5.3 ± 5.0
Glycated haemoglobin (%)		7.9 ± 1.7		7.8 ± 2.0		7.2 ± 1.8

[a] Values are mean ± S.D. No significant differences were found between control and diabetic patients.

Table 3
Absolute and relative exercise intensities at VT in control subjects and type 2 DM patients[a]

	Control	Type 2 DM
n	56	56
$\dot{V}O_2$ (METs)	3.9 ± 0.4	3.6 ± 0.6*
WR (W)	74 ± 13	62 ± 14*
HR (bpm)	102 ± 11	99 ± 11
ΔHR (bpm)	38 ± 8	33 ± 9*
$\%HR_{max}$ (%)	61.4 ± 6.2	59.4 ± 5.8
$\%HR_{reserve}$ (%)	37.6 ± 8.3	32.6 ± 7.7*
RPE	12.9 ± 1.2	12.4 ± 1.5
Exercise duration (min)	9.8 ± 1.2	9.3 ± 1.0

[a] Values are mean ± S.D.; *, $P < 0.05$ vs. control.

(220-age-HR at rest)] were also calculated. During exercise testing, subjects were asked to report the degree of exertion every min, based on the Borg scale [14], i.e. RPE.

2.3. Statistical analysis

All data are expressed as mean ± S.D. values. Differences between groups were examined for statistical significance using the Student's t-test (for paired or unpaired data). A P value less than 0.05 denoted the presence of a statistically significant difference.

3. Results

3.1. Exercise performance of Type 2 DM patients and controls at VT

All subjects reached VT. During graded ergometer exercise tests, Type 2 DM patients had a significantly lower $\dot{V}O_2$ (3.6 ± 0.6 metabolic equivalents (METs)) than controls (3.9 ± 0.4 METs) at VT. They also showed a significantly lower WR than controls (Table 3). The lower intensity of exercise at VT indicated that diabetic patients had significantly lower exercise performance at VT. The HR and $\%HR_{max}$ of Type 2 DM patients at VT were comparable with controls, but HR and $\%HR_{reserve}$ were significantly lower than controls. There was no difference in RPE at VT between the two groups (Table 3).

3.2. Age-related changes in exercise performance in Type 2 DM patients

We also compared exercise performance with VT between Type 2 DM patients and controls in different age groups (Table 4). In those aged 40–49 years $\dot{V}O_2$ and WR of Type 2 DM patients were significantly lower than controls, but there were no statistically significant differences in HR, ΔHR, $\%HR_{max}$, $\%HR_{reserve}$ and RPE. Similar re-

Table 4
Absolute and relative exercise intensities at VT in control subjects and type 2 DM patients in different age groups[a]

	40s		50s		60s	
	Control	Type 2 DM	Control	Type 2 DM	Control	Type 2 DM
n	19	19	21	21	16	16
$\dot{V}O_2$ (METs)	4.0 ± 0.5	3.6 ± 0.7*	4.0 ± 0.4	3.6 ± 0.7	3.8 ± 0.5	3.7 ± 0.4
WR (W)	76 ± 13	64 ± 15*	78 ± 13	60 ± 16*	66 ± 8	63 ± 10
HR (bpm)	106 ± 11	103 ± 12	100 ± 11	99 ± 9	99 ± 9	94 ± 9
ΔHR (bpm)	41 ± 9	36 ± 9	38 ± 8	33 ± 9	36 ± 6	29 ± 7*
$\%HR_{max}$ (%)	60.9 ± 5.8	58.7 ± 6.3	60.6 ± 6.9	59.7 ± 5.4	63.2 ± 5.6	59.7 ± 5.7
$\%HR_{reserve}$ (%)	37.3 ± 8.5	33.3 ± 8.0	37.3 ± 9.2	33.0 ± 7.7	38.3 ± 7.1	31.3 ± 7.5*
RPE	12.9 ± 1.3	12.7 ± 1.4	12.8 ± 1.3	12.6 ± 0.9	13.1 ± 1.0	11.8 ± 2.0*

[a] Values are mean ± S.D.; *, $P < 0.05$ vs. control.

Table 5
Absolute and relative exercise intensities at VT in type 2 DM patients with and without neuropathy[a]

	Type 2 DM without neuropathy	Type 2 DM with neuropathy
n	24	32
Age (years)	53.6 ± 7.1	53.4 ± 8.2
BMI (kg/m^2)	24.2 ± 3.7	23.4 ± 3.5
Disease duration (years)	3.4 ± 4.9	4.6 ± 3.5
Glycated haemoglobin (%)	7.1 ± 1.8	8.0 ± 1.9
$\dot{V}O_2$ (METs)	3.6 ± 0.7	3.6 ± 0.6
WR (W)	60 ± 15	64 ± 13
HR (bpm)	99 ± 9	99 ± 12
ΔHR (bpm)	32 ± 7	33 ± 10
%HR_{max} (%)	59.2 ± 5.0	59.4 ± 6.3
%$HR_{reserve}$ (%)	32.3 ± 7.4	32.9 ± 8.4
RPE	12.8 ± 1.9	12.2 ± 1.0

[a] Values are mean ± S.D. No significant differences were found between type 2 DM patients with neuropathy and without neuropathy.

sults were found in those aged 50–59 years. In contrast, exercise performance ($\dot{V}O_2$ and WR) in Type 2 DM patients in their 60s was comparable with the controls of similar age although these patients had a significantly lower HR and %$HR_{reserve}$ and RPE (Table 4).

3.3. Effect of distal symmetrical neuropathy on exercise performance

To examine the influence of diabetic neuropathy on exercise performance at VT, we divided Type 2 DM patients into two groups, i.e. diabetic patients with and without symptoms of distal symmetrical sensory neuropathy. The age and BMI matched in both group, and the presence of neuropathy did not affect the exercise performance, HR, ΔHR, %H_{max}, and %$HR_{reserve}$. In contrast, the relative intensity of exercises (RPE) of Type 2 DM patients with peripheral neuropathy was lower than the patients without neuropathy, although it was not statistically significant (Table 5). This suggested that the prediction of relative exercise intensity using formulas or RPE overestimate the actual exercise intensity at VT.

4. Conclusion

The main finding of our controlled study was that the absolute intensity of exercise at VT, i.e. $\dot{V}O_2$ and WR, was significantly lower in Type 2 DM patients ($n = 56$) than healthy subjects ($n = 56$). Only a few controlled studies have examined the exercise performance in Type 2 DM patients at AT or VT. Kawaji et al. [15] reported that WR of Type 2 DM subjects at AT was significantly lower than the healthy controls. The WR values reported in their study were 117 ± 6 W in healthy male ($n = 12$), 106 ± 8 W ($n = 8$) in healthy female, and 93 ± 6 W in Type 2 DM male ($n = 6$), 80 ± 10 W in Type 2 DM female ($n = 8$) [15]. Similarly, our data indicated that Type 2 DM patients reached the upper limit of aerobic exercise at lower workloads compared with healthy controls. However, the values of WR of both healthy controls and Type 2 DM subjects were lower than those of Kawaji's report. This difference may be due to following reasons, (1) the recruited subjects in our study were ~10 years older than those of KawaJi's; (2) the graded exercise test protocol and the criteria for the VT were different. We employed widely accepted protocol, in which the graded exercise reaches the predicted $\dot{V}O_{2max}$ in 10-min [16]. In turn, Kawaji et al. used the graded exercise, which slowly reaches the predicted $\dot{V}O_{2max}$ in 14–16 min. To ensure the accuracy of measurement, we determined the VT by three methods, i.e. methods of Wasserman et al. [11], Davis et al. [12] and the V-slope method of Beaver [13], while Kawaji et al. employed V-slope method [13]. The reduced exercise performance in Type 2 DM patients may be related with low cardiopulmonary function due to lower physical activity, impaired peripheral circulation [17–20], and/or reduced oxidative phosphorylation of the muscle due to insulin resistance [21].

Without measurement of actual HR_{max} in diabetic individuals, we calculate HR_{max} using a formula to prescribe the exercise intensity, i.e. 60–79%HR_{max} or 50–74%$HR_{reserve}$ according to the guideline of ADA [2]. For Japanese diabetic patients, the Japanese Medical Association recommends the prescription of 40–60%$HR_{reserve}$ as relative intensity of exercise. In healthy Japanese males enrolled in this study, the upper limit of aerobic exercise examined by VT corresponded to exercise intensity of 40%$HR_{reserve}$. In contrast, ΔHR and %$HR_{reserve}$ at VT was significantly lower in Type 2 DM males (32.6 ± 7.7%) than in controls (37.6 ± 8.3%), suggesting the reduced cardiopulmonary function or diabetic autonomic neuropathy in Type 2 DM males. Thus, we might prescribe anaerobic exercise by using $HR_{reserve}$ criteria of ADA as well as Japanese Medical Association. Another criteria of the relative exercise intensity is Borg's RPE [14]. The exercise intensity at RPE 13 (fairly hard) has been considered to correspond to workload VT in all generations and used for the prescription of exercise intensity in Type 2 DM patients. In the present study, RPE at VT were 12.9 ± 1.2 in controls and 12.4 ± 1.5 in Type 2 DM patients, which were not statistically different.

Comparison to exercise performance between Type 2 DM patients and controls in various age groups indicated that the absolute exercise intensity at VT was significantly reduced in 40s and 50s. In 60s, the exercise performance was comparable with age-matched healthy controls, however, the relative-exercise intensity at VT, such as %$HR_{reserve}$ (31.3 ± 7.5) and RPE (11.8 ± 2.0), was significantly lower than controls. Thus, in elderly Type 2 DM patients, we may prescribe the heavy exercise by the ADA guideline, 50–74%$HR_{reserve}$ or 12–13 RPE [2], and it is possible that these individuals continue the anaerobic exercise that is hazardous to cardiovascular systems.

Autonomic dysfunction occurs in aging [22] as well as DM, and is closely correlated to impaired cardiac output response at exercise [23]. In Type 2 DM patients with symptoms of distal symmetrical sensory neuropathy, RPE (12.2 ± 1.0) was lower than Type 2 DM patients without symptoms related to neuropathy (12.8 ± 1.9), although it was not statistically significant. CV_{R-R} and ^{123}I-MIBG scintigram are sensitive tests for autonomic neuropathy, but they are not practical and cannot be performed in all diabetic patients on outpatient basis. Our results suggest that the prescription of a low exercise intensity, i.e. 30%$HR_{reserve}$ and RPE 12, is recommended in Type 2 DM patients with symptoms of peripheral sensory neuropathy.

Several reports have recently described the short- and long-term effects of low intensity exercise (< 50% $\dot{V}O_{2max}$) on glucose metabolism in Type 2 DM patients. Maehium and Pruett [24] reported that low intensity exercise (< 30–40% $\dot{V}O_{2max}$) did not have a beneficial effect on blood glucose levels by single load of acute exercise. However, studies in Japanese diabetics conducted by Fujii [25] indicated that low–moderate intensity exercise (40–60% $\dot{V}O_{2max}$) resulted in the improvement of insulin sensitivity and lipid metabolism particularly when performed at 30–60 min daily for 1 year. In another recent study of Japanese patients, Ishii et al. [26] demonstrated that a 6-week resistance training program was associated with a significant improvement of insulin sensitivity in Type 2 DM patients. These studies suggest that long-term low intensity exercise have a favourable effect on glycemic control in Type 2 DM.

In conclusion, exercise prescription of 30%$HR_{reserve}$ and 12 RPE is considered to be as the upper limit of aerobic exercise and could be safely applied to Japanese males with Type 2 DM. This prescription of relative exercise intensity is lower than that recommended by the ADA and Japanese Medical Association. This is mainly due to reduced exercise capacity of Type 2 DM patients demonstrated by comparison to age- and BMI-matched healthy controls. In addition, aging and the presence of diabetic neuropathy further reduce exercise performance in diabetics. It is important to evaluate the exercise capacity of individual Type 2 DM patients by measuring VT or AT, and it is unsafe to prescribe the recommended exercise limits uniformly to all patients. However, since it is not practical to measure VT in the clinic, we suggest that it is safe to prescribe a low-exercise intensity especially in elderly Type 2 DM patients and those with diabetic neuropathy. The effectiveness of low intensity exercise on glucose metabolism and prevention of vascular complications remain to be investigated in future studies.

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