Title: Effect of cardiac rehabilitation on muscle mass, muscle strength, and exercise tolerance in diabetic patients after coronary artery bypass grafting

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Abstract:
Background: The effects of cardiac rehabilitation (CR) on muscle mass, muscle strength, and exercise tolerance in patients with diabetes mellitus (DM) who received CR after coronary artery bypass grafting (CABG) have not been fully elucidated.

Methods: We enrolled 78 consecutive patients who completed a supervised CR for 6 months after CABG (DM group, n=37; non-DM group, n=41). We measured mid-upper arm muscle area (MAMA), handgrip power (HGP), muscle strength of the knee extensor (Ext) and flexor (Flex), and exercise tolerance at the beginning and end of CR.

Results: No significant differences in confounding factors, including age, gender, ejection fraction, or number of CR sessions, were observed between the two groups. At the beginning of CR, the levels of Ext muscle strength and peak VO$_2$ were significantly lower in the DM group than in the non-DM group. At the end of CR, significant improvement in the levels of muscle strength, HGP, and exercise tolerance was observed in both groups. However, the levels of Ext muscle strength, HGP, peak VO$_2$, thigh circumference, and MAMA were significantly lower in the DM group than in the non-DM group. In addition, no significant improvement in thigh circumference and MAMA was observed in the DM group. At the end of CR, the levels of thigh circumference and MAMA correlated with Ext and Flex muscle strength as well as with HGP. Percent changes in the levels of Ext muscle strength were significantly correlated with those of MAMA and hemoglobin A1c.

Conclusions: These data suggest that improvement in muscle strength may be influenced by changes in muscle mass and high glucose levels in DM patients undergoing CR after CABG. A CR program, including muscle mass intervention and blood glucose control, may improve deterioration in exercise tolerance in DM patients after CABG.

Keywords: Cardiac rehabilitation, Coronary artery bypass grafting, Diabetes mellitus, Exercise tolerance, Muscle strength, Muscle mass

Introduction:
Patients with diabetes mellitus (DM) are at increased risk of coronary artery disease (CAD) [1]. Patients with DM are at 2–4 times higher risk of developing CAD and mortality due to CAD compared with non-DM patients [2]. Patients with CAD are treated by lifestyle modification, medical therapy, and coronary revascularization such as percutaneous coronary intervention and coronary artery bypass grafting (CABG). However, the benefits of revascularization are less and the risks and complications are greater than those in non-DM patients. Previous studies have also reported a high incidence of bypass graft dysfunction and a high mortality even in DM patients who underwent CABG [3].

Cardiac rehabilitation (CR) has numerous benefits such as modification of risk factors and prevention of future cardiovascular events [4]. Improvement in peak VO$_2$ after CR reduced cardiovascular morbidity and mortality in patients with CAD [5]. However, a previous study demonstrated that the presence of DM was a negative factor for improvement in peak VO$_2$ [6]. Another report showed a significant inverse relationship between fasting blood glucose...
levels and changes in peak VO₂ in CR participants with DM after coronary events [7]. Park et al. reported that a low level of muscle strength was a predictor of physical limitation, and diabetes was associated with a low level of skeletal muscle strength and deterioration in quality [8]. We recently reported that muscle strength and exercise tolerance were significantly lower in DM patients than non-DM patients at the beginning of CR after CABG [9]. However, the effects of CR on muscle mass, muscle strength, and exercise tolerance in DM patients undergoing CR after CABG has not been fully elucidated. The aim of this study was to investigate the effects of CR on muscle mass, muscle strength, and exercise tolerance in DM patients who received CR after CABG.

Methods

Subjects

We enrolled 78 consecutive patients who completed a supervised CR for 6 months after CABG at Juntendo University Hospital from July 2002 to February 2005. The patients were divided into 2 groups: those with DM (DM group, n = 37) and those without DM (non-DM group, n = 41), according to the guidelines of the Japan Diabetes Society (JDS), which includes history of medical treatment, fasting plasma glucose ≥ 126 mg/dl or casual plasma glucose ≥ 200 mg/dl, and hemoglobin (Hb) A1c ≥ 6.1% [10]. All patients participated in the CR program 6–8 days after CABG. All subjects gave written informed consent and the ethical committee of the institution approved this study.

Rehabilitation protocol

The CR program consisting of warm-up stretching, aerobic exercise, resistance training, and cool-down, was scheduled once or twice a week for 6 months, as described previously [11,12]. Aerobic exercise consisted of a cycle ergometer, treadmill, and walking on an indoor track with a total duration of approximately 60 min exercise intensity was prescribed individually at the anaerobic threshold (AT) level, as measured by an ergometer test using expiratory gas analysis or a rating of 11–13 on a standard Borg’s perceived exertion scale. Resistance training, which was gradually added to the exercise program at least 6 weeks after participation, included sit-ups, back kicks and front raises, squats, and push-ups, using the patient’s own weight. This training consisted of 1–2 sets of 10–15 repetitions for each muscle group with 3–5 min rest between sets. Patients were encouraged to perform home-based aerobic exercise twice a week for more than 20 min at a rating of 11–13 of perceived exertion on Borg’s scale. All subjects were instructed to follow the phase II diet of the American Heart Association at the beginning of CR. An educational program regarding CAD and its risk factors at baseline was also provided for each subject by physicians, nurses, and dietitians.

Measurements

We assessed body composition, muscle strength, and exercise tolerance at the beginning and end of CR. Anthropometric parameters were assessed using body mass index (BMI), waist size, thigh circumference, triceps skin fold thickness measured on the dominant hand, and mid-upper arm circumference. Thigh circumference was measured directly below the gluteal fold of the right thigh according to WHO standards [13]. Mid-upper arm muscle area (MAMA) was calculated according to a standard method [14]. The percentages of body fat and lean body weight were measured by BOD POD® (Life Measurement, Inc., Concord, CA, USA), as described previously [11,12]. The power of the thigh muscles was measured using the Cybex770 system (Cybex Division of Lumex, Ronkonkoma, NY, USA), as also reported previously [11,12]. The isokinetic peak torques of the knee extensor (Ext) and flexor (Flex) muscles were measured at 60°/s, and those were adjusted by body weight according to the following formula: strength (Nm) × 100/kg body weight. Handgrip power (HGP) in the dominant hand was also measured. To measure peak oxygen consumption (peak VO₂) and oxygen uptake at the AT, patients underwent ergometer testing (Corival 400, Lobe B.V., Groningen, Netherlands) using an expiratory gas analysis machine (Vmax-295, SensorMedics Co., Yorba Linda, CA, USA). After a period of resting, warm-up was performed for a few minutes at 20 W, followed by ramp loading (15 W/min) until subjective exhaustion, progressive angina, ST-segment depression (≥2 mm), or sustained tachyarrhythmia. The point of AT was determined by the “V-slope” method.

Statistical analyses

The results are expressed as mean ± standard deviation and were analyzed using the StatView software (Version 5.0) for Windows, SAS Institute, Cary, NC, USA. Comparisons between the DM and non-DM groups were performed by Student’s t-test. Data at baseline and after 6 months of CR were compared for each patient by paired t-test to evaluate the singular effects of CR. Correlation coefficients were determined by linear regression analysis. Statistical significance of correlation coefficients was determined by the method of Fisher and Yates. A p-value of less than 0.05 was considered significant.

Results

Characteristics of CR subjects

The clinical characteristics of the subjects are presented in Table 1. Thirty-seven patients were diagnosed as having DM. No significant differences with regard to age, gender, coronary risk factors, number of diseased vessels, ejection fraction, or physiological variables, were observed between the DM and non-DM groups. Thirty-six patients received complete revascularization using the off-pump operation. One patient who had received re-CABG was in the DM group. No significant differences in the concomitant use of drugs, including antplatelets, calcium channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or statins, were observed between the two groups. In the DM group, 24 patients (65%) and 13 patients (35%)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics of the study subjects.</th>
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<tr>
<td></td>
<td>DM</td>
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<tr>
<td>N</td>
<td>37</td>
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<tr>
<td>Age (year)</td>
<td>63.5 ± 10</td>
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<tr>
<td>Male (%)</td>
<td>29 (78)</td>
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<tr>
<td>Hypertension (%)</td>
<td>22 (61)</td>
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<tr>
<td>Dyslipidemia (%)</td>
<td>28 (76)</td>
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<tr>
<td>Current smoker (%)</td>
<td>17 (49)</td>
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<tr>
<td>Familial history (%)</td>
<td>11 (26)</td>
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<tr>
<td>History of MI (%)</td>
<td>2 (5)</td>
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<tr>
<td>History of PCI (%)</td>
<td>2 (5)</td>
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<tr>
<td>History of previous CABG (%)</td>
<td>1 (3)</td>
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<tr>
<td>Diseased vessels</td>
<td></td>
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<tr>
<td>LMT (%)</td>
<td>9 (25)</td>
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<tr>
<td>3VD (%)</td>
<td>18 (48)</td>
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<tr>
<td>1–2VD (%)</td>
<td>10 (27)</td>
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<tr>
<td>Ejection fraction (%)</td>
<td>59.7 ± 16</td>
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<tr>
<td>Off-pump CABG (%)</td>
<td>36 (97)</td>
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<tr>
<td>Exercise in hospital (times)</td>
<td>16 ± 14</td>
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</table>

Data are presented as the mean value ± SD. DM, diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary arterial bypass grafting; LMT, left main trunk; VD, vessel disease.
were treated with oral anti-diabetic agents and insulin, respectively. No significant differences were observed between the two groups in exercise duration in the CR program (data not shown). No subject in either group showed any worsening of symptoms or had cardiovascular events during the 6 months of the study.

Serum lipid profiles and glucose parameters

Serum lipid profiles and glucose parameters at baseline and the end of CR are presented in Table 2. Fasting blood glucose and HbA1c levels before and after CR were significantly higher in the DM group than in the non-DM group (both p < 0.05). Lipid profiles were not significantly different between the two groups at both baseline and the end of CR.

Anthropometric parameters

The anthropometric parameters at baseline and after CR in both groups are presented in Table 3. The anthropometric parameters at baseline were not significantly different between the two groups. In the non-DM group, waist circumference (from 84.5 ± 7.8 to 82.2 ± 6.7 cm, p < 0.05) was significantly decreased, and thigh circumference (from 48.9 ± 4.1 to 50.7 ± 3.7 cm, p < 0.05), arm forced circumference (from 28.0 ± 2.6 to 30.0 ± 2.4 cm, p < 0.05), mid-upper arm muscle circumference (from 25.7 ± 2.5 to 26.5 ± 2.4 cm, p < 0.05), and MAMA (from 53.2 ± 10.3 to 56.5 ± 10.0 cm², p < 0.05) were significantly increased. In the DM group, waist circumference (from 83.4 ± 8.3 to 80.2 ± 5.7 cm, p < 0.05) was significantly decreased, however, thigh circumference, arm forced circumference, mid-upper arm muscle circumference, and MAMA were not significantly altered. At the end of CR, thigh circumference (47.3 ± 2.5 cm, 50.7 ± 3.7 cm, p < 0.05), arm forced circumference, (28.4 ± 1.6 cm vs. 30.0 ± 2.4 cm, p < 0.05), mid-upper arm muscle circumference (25.0 ± 1.8 cm vs. 26.5 ± 2.4 cm, p < 0.05), and MAMA (49.9 ± 7.1 cm² vs. 56.5 ± 10.0 cm², p < 0.05) were significantly lower in the DM group than in the non-DM group.

Exercise tolerance and muscle strength

Exercise tolerance and muscle strength at baseline and after CR in each group are presented in Table 4. At the beginning of CR, the levels of peak VO₂ (13.7 ± 4.0 ml kg⁻¹ min⁻¹ vs. 16.0 ± 4.7 ml kg⁻¹ min⁻¹, p < 0.05) and thigh muscle strength (136.3 ± 42.7 Nm kg⁻¹ × 100 vs. 162.7 ± 47.9 Nm kg⁻¹ × 100, p < 0.05) were significantly lower in the DM group than in the non-DM group. No significant differences in HGP (28 ± 9 kg vs. 31 ± 9 kg, NS) were observed between the two groups. At the end of CR, both groups showed significant improvements in exercise tolerance and muscle strength. Improvements in exercise tolerance and muscle strength were identical in the DM and non-DM groups. However, the levels of peak VO₂ (19.4 ± 3.8 ml kg⁻¹ min⁻¹ vs. 22.9 ± 5.4 ml kg⁻¹ min⁻¹, p < 0.05) and AT (11.3 ± 2.2 ml kg⁻¹ min⁻¹ vs. 13.3 ± 3.4 ml kg⁻¹ min⁻¹, p < 0.05) were still significantly lower in the DM group than in the non-DM group. The levels of thigh Ext muscle strength (164.1 ± 43.3 Nm kg⁻¹ × 100 vs. 193.3 ± 51.9 Nm kg⁻¹ × 100, p < 0.05) and HGP (30 ± 7 kg vs. 35 ± 8 kg, p < 0.05) were also significantly lower in the DM group than in the non-DM group.

Correlations between muscle mass, muscle strength, and HbA1c

At the end of CR, the values for thigh muscle strength were correlated with thigh circumference (r = 0.44, p < 0.01) and MAMA (r = 0.37, p < 0.05) (Fig. 1). The values of HGP were correlated with thigh circumference (r = 0.52, p < 0.01), and MAMA (r = 0.48, p < 0.05) (Fig. 1). The same trends were observed at the beginning of CR [9]. Moreover, the percent change in Ex muscle strength was...
Comparison of exercise tolerance and muscle strength between the DM and non-DM groups.

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<th>DM group (n = 37)</th>
<th>Non-DM group (n = 41)</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>After</td>
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<tr>
<td>Anaerobic threshold (ml kg⁻¹ min⁻¹)</td>
<td>8.3 ± 1.6</td>
<td>11.3 ± 2.2</td>
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<tr>
<td>Peak VO₂ (ml kg⁻¹ min⁻¹)</td>
<td>13.7 ± 4.0</td>
<td>19.4 ± 3.8</td>
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<tr>
<td>Anaerobic threshold workload (W)</td>
<td>34 ± 15</td>
<td>52 ± 21</td>
</tr>
<tr>
<td>Peak workload (W)</td>
<td>73 ± 23</td>
<td>107 ± 21</td>
</tr>
<tr>
<td>Knee extension (Nm kg⁻¹ x 100)</td>
<td>136.3 ± 42.7</td>
<td>164.1 ± 43.3</td>
</tr>
<tr>
<td>Knee flexion (Nm kg⁻¹ x 100)</td>
<td>80.0 ± 26.7</td>
<td>102.4 ± 30.3</td>
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<tr>
<td>Power of hand grip (kg)</td>
<td>28 ± 9</td>
<td>30 ± 7</td>
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Data are presented as the mean value ± SD. DM, diabetes mellitus.

* p < 0.05 compared with the DM group at baseline.

** p < 0.05 compared with the DM group after 6 months.

Correlated with MAMA (r = 0.47, p < 0.005) and HbA1c (r = −0.41, p < 0.05) (Fig. 2).

Discussion

In the present study, we demonstrated that: (1) the levels of muscle strength and exercise tolerance at the beginning and end of CR were significantly lower in the DM group than in the non-DM group; (2) exercise tolerance and muscle strength after CR were significantly improved in both groups; (3) muscle mass was significantly increased after CR in the non-DM group, but not in the DM group; and (4) percent change in muscle strength was correlated with that of HbA1c in patients undergoing CR after CABG. Our group and others previously reported a relationship between muscle strength and peak VO₂ in patients with cardiovascular disease [15,16]. However, to the best of our knowledge, this is the first report to simultaneously demonstrate the effects of CR on muscle mass, muscle strength, and exercise tolerance, and to compare DM and non-DM patients undergoing CR after CABG.

CR is described as a class I recommendation in most contemporary cardiovascular clinical practice guidelines. Following CR, patients show increased exercise tolerance and muscle strength, which have proven to be the strongest predictors of the risk of death among subjects both with and without known cardiovascular disease [17,18]. Boulé et al. reported in a meta-analysis that
structured exercise training in DM patients achieved an 11.8% increase in peak VO₂ [19]. This is particularly important, because an improvement in peak VO₂ of 1.44 ml·kg⁻¹·min⁻¹ was equivalent to a 7.9% reduction in overall mortality [20]. Moreover, exercise has many potential benefits, including not only improving exercise tolerance, but also improving glucose metabolism, insulin signaling, lipid profile, endothelial function, and blood pressure, reducing vascular inflammation and facilitating weight maintenance [7]. Either aerobic or resistance training alone improves glycemic control in DM patients, however, a combination of both may be more beneficial for improving risk factors than each alone [18]. Williams et al. have reported a combination of aerobic and resistance training exercise improved through neuromuscular adaptation, muscle fiber hypertrophy, and increased muscle oxidative capacity [21]. A previous study demonstrated the beneficial effects of resistance training on muscle mass and strength in chronic heart failure [18]. We also reported that CR with aerobic and resistance training had beneficial effects not only on the modification of metabolic risk factors, but also on improvement in exercise tolerance and muscular strength in patients with metabolic syndrome following CABG [12].

Levels of exercise tolerance and muscle strength were lower in DM than in non-DM patients in the present study. A previous report showed that endothelial dysfunction associated with high glucose levels is caused by the increased production of vascular constriction prostanoids as a consequence of protein kinase C activation [22]. Other studies have demonstrated that DM patients have impaired metabolism of both glucose and fatty acids in skeletal muscles. In addition, the bioenergetic capacity of skeletal muscle mitochondria was found to be impaired in DM patients [23]. We previously observed a significant inverse relationship between fasting glucose levels and thigh muscle strength at the beginning of CR in DM patients after CABG [9].

The DM group showed no increase in muscle mass such as MAMA and thigh circumference (Table 3), both of which correlated with thigh muscle strength and HGP (Fig. 1). Vergès et al. reported that the effects of CR on exercise capacity were significantly lower in DM than in non-DM patients, and the response to CR was influenced by blood glucose levels [7]. Moreover, we showed a significant inverse relationship between percent change for HbA1c and that for thigh muscle strength in the DM group (Fig. 2). Park et al. demonstrated that functional muscle quality was relatively low in DM patients. Furthermore, long duration of diabetes and poor glycemic control were associated with deterioration in muscle quality. Diabetes with poor glycemic control is related to the presence and severity of peripheral neuropathy and inflammatory cytokines, which have detrimental effects on muscle function [8]. Chronic hyperglycemia induces a condition of oxidative stress that is causally involved in the development of skeletal muscle depletion [24]. The increased production of reactive oxygen species induced by hyperglycemia has also been suggested to be involved in the redox regulation of glucose transport in skeletal muscle [25]. Hyperglycemia leads to the production of Amadori products between glucose and reactive amino groups of serum proteins [26]. These products undergo further irreversible reactions to form advanced glycation end products that promote insulin resistance and trigger inflammation, which leads to diabetic vascular complications [26]. The DM group had 11.0 ± 6.7 years’ duration of DM history in the present study, and the prevalence of microvascular complications, including retinopathy, nephropathy, and neuropathy was 38%. These data may explain the mechanisms by which improvements in muscle mass and strength, and exercise tolerance, were impaired in the DM group. Thus, not only exercise but also glycemic control may be important in improving muscle structure.

Several studies have shown a U-shaped association between BMI and mortality. Increased risk was independent of abdominal and general obesity, and lifestyle and cardiovascular risk factors such as blood pressure and lipid levels were related to early cardiovascular morbidity and mortality. Additionally, Heitmann et al. reported that this risk was related more to thigh than waist circumference [13]. A study in a cohort of community-dwelling Japanese elderly demonstrated that low arm muscle area was an independent risk factor for 2-year mortality [27]. We would like to clarify whether arm muscle area after CR can predict morbidity and mortality in DM patients after CABG.

There are some limitations to the present study. First, because this was a single-center study with a small sample size, studies of larger sample size are required to confirm these findings. Second, the exercise session at the outpatient clinic was encouraged once a week with at least 2 exercise sessions at home. However, while the mean number of CR sessions in hospital was 16–18 times, we have no data regarding home-based exercise frequency and intensity for either group, and we need to assess the effects of exercise frequency and intensity in a future study. The program used in this study may not have been sufficiently rigorous to alter parameters such as glucose control and lipid profiles. Third, we enrolled patients undergoing CR after CABG. Therefore, the results may not necessarily be representative of all DM patients with CAD. In a future study,
we need to investigate DM patients undergoing percutaneous intervention and/or those with acute coronary syndrome. Finally, we need to investigate whether different treatments, including intensive glucose control and a combination of aerobic and resistance training, can enhance muscle mass and ameliorate future cardiovascular events and long-term mortality in DM patients after CABG.

Conclusions

Patients with DM had lower muscle strength and lower exercise tolerance than non-DM patients at the beginning of CR after CABG. Both groups showed improved exercise tolerance and muscle strength after undergoing CR. However, DM patients had lower muscle mass, lower muscle strength, and lower exercise tolerance than non-DM patients at the end of CR. Moreover, improvement in muscle strength may be influenced by changes in muscle mass and high glucose levels in DM patients. Further studies are needed to assess whether a CR program including muscle mass intervention and aggressive glucose control would improve muscle mass and ameliorate future cardiovascular events in DM patients after CABG.

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References