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Original article

Impact of diabetes on muscle mass, muscle strength, and exercise tolerance in patients after coronary artery bypass grafting

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KEYWORDS
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Muscle mass

Summary
Background: The impact of diabetes mellitus (DM) on muscle mass, muscle strength, and exercise tolerance in patients who had undergone coronary artery bypass grafting (CABG) has not been fully elucidated.
Methods: We enrolled 329 consecutive patients who received cardiac rehabilitation (CR) after CABG (DM group, $n = 178$; non-DM group, $n = 151$) and measured lean body weight, mid-upper arm muscle area (MAMA), and handgrip power (HGP) at the beginning of CR. We also performed an isokinetic strength test of the knee extensor (Ext) and flexor (Flex) muscles and a cardiopulmonary exercise testing at the same time.
Results: No significant differences in risk factors, including age, gender, number of diseased vessels, or ejection fraction were observed between the 2 groups. The levels of Ext muscle strength, peak oxygen uptake, and anaerobic threshold were significantly lower in the DM group than in the non-DM group (all $p < 0.05$). Both peak oxygen uptake and MAMA correlated with Ext and Flex muscle strength as well as HGP (all $p < 0.005$). The MAMA, HGP, and Ext muscle strength were lower in patients who received insulin therapy than in those who did not. Interestingly, fasting glucose levels significantly and negatively correlated with Ext muscle strength.

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Conclusions: These data suggest that DM patients had a lower muscle strength and exercise tolerance than non-DM patients. Moreover, a high glucose level may affect these deteriorations in DM patients after CABG.

Introduction

Individuals with diabetes mellitus (DM) are at an increased risk of coronary artery disease (CAD) and DM patients with CAD have poor prognosis [1]. Indeed, DM patients have a 2—4 times higher risk of developing CAD and mortality due to CAD compared with non-DM patients [2]. DM patients benefit from revascularization techniques such as percutaneous coronary intervention and coronary artery bypass grafting (CABG). However, the benefit is less and the risks and complications are greater in DM patients than in non-DM patients. Previous studies have reported a high incidence of bypass graft dysfunction and mortality even in DM patients who underwent CABG [3].

It is clear that cardiac rehabilitation (CR) has numerous benefits such as modulation of risk factors and prevention of future cardiovascular events [4]. The improvement in peak $\dot{V}O_2$ after CR significantly reduces cardiovascular morbidity and mortality in patients with CAD [5]. However, Savage et al. demonstrated that in more than 20% of the patients who enrolled for CR, there was no improvement in peak $\dot{V}O_2$, and that the diagnosis for DM is negatively associated with the improvement in peak $\dot{V}O_2$ [6]. Vergès et al. reported a significant inverse relationship between fasting blood glucose levels and change in peak $\dot{V}O_2$ in CR participants with DM after acute coronary events [7].

However, the association between muscle mass, muscle strength, and exercise tolerance in patients with or without DM after CABG has not been fully elucidated. The aim of the present study was to investigate the impact of DM on muscle mass, muscle strength, and exercise tolerance in patients who had undergone CABG.

Methods

Subjects

We enrolled 329 consecutive patients who received CR after CABG at the Juntendo University Hospital from July 2002 to February 2005. The patients were divided into 2 groups: patients with DM (DM group, $n = 178$) and patients without DM (non-DM group, $n = 151$) according to the guideline of the Japan Diabetes Society (JDS), including a history of medical treatment, fasting plasma glucose $\geq$ 126 mg/dl or casual plasma glucose $\geq$ 200 mg/dl and hemoglobin (Hb) A1c (JDS) $\geq$ 6.1% [8]. All patients participated in CR after 6—8 days of undergoing CABG. All subjects gave written informed consent and the ethical committee of the institution approved this study.

Measurements

We assessed body composition, muscle strength, and exercise tolerance at the beginning of CR. Anthropometric parameters were assessed using body mass index and waist circumference. Triceps skin-fold thickness of the dominant hand was measured in millimeters using a caliper, while the mid-upper arm circumference was measured in centimeters using a tape measure. The mid upper-arm muscle area (MAMA) was calculated according to the standard formula [9]. Moreover, we measured the handgrip power (HGP) of the dominant hand. The percentages of body fat and lean body weight were measured by a BOD POD® (Life Measurement, Inc., Concord, CA, USA), as we described previously [10,11]. In addition, thigh muscle power was measured using the Cybex770 system (Cybex Division of Lumex, Ronkonkoma, NY, USA), as reported earlier [10,11]. The isokinetic peak torques of the knee extensor (Ext) and flexor (Flex) muscles were measured at 60°/s; these were adjusted by body weight according to the following formula: strength (Nm) $\times$ 100/body weight (kg). 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) to measure peak oxygen consumption (peak $\dot{V}O_2$) and the anaerobic threshold (AT). After a rest period, a 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 ($\geq$2 mm), or sustained tachyarrhythmia. The AT point was determined by the ''V-slope'' method.

Statistical analyses

Results are expressed as the mean $\pm$ standard deviation and were analyzed using the StatView software (Version 5.0J for Windows, SAS Institute, Cary, NC, USA). Comparisons between the DM and non-DM groups were performed by a two-tailed Student's *t*-test. Correlation coefficients (*r*) were determined by linear regression analysis. Statistical significance of the 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 the study subjects

Clinical characteristics and anthropometric parameters of the subjects are presented in Tables 1 and 2. One hundred and seventy-eight patients (54%) were diagnosed as having DM. No significant differences in risk factors, including age, gender, number of diseased vessels, ejection fraction, and physiological variables were observed between the DM and non-DM groups. Three hundred and twenty-five patients (99%) received complete revascularization using the off-pump operation. Eight patients (4%) who had undergone re-CABG were in the DM group. No significant differences were observed between the 2 groups for the concomitant use of drugs such antiplatelet agents, calcium-channel blockers, β-blockers, angiotensin-converting enzyme inhibitors,

Table 1 Clinical characteristics of the study subjects.

	DM	Non-DM	*p* value
N	178	151	
Age (year)	64.7 ± 9.2	65.8 ± 9.2	NS
Male (%)	143 (80)	120 (79)	NS
Hypertension (%)	116 (66)	111 (74)	NS
Dyslipidemia (%)	109 (62)	108 (72)	NS
Current smoker (%)	91 (54)	72 (49)	NS
Familial history (%)	40 (24)	33 (23)	NS
Fasting blood glucose (mg/dl)	159 ± 63	108 ± 24	<0.01
HbA1c (%)	7.1 ± 1.3	5.1 ± 0.4	<0.01
LDL-C (mg/dl)	115 ± 34	110 ± 41	NS
HDL-C (mg/dl)	47 ± 13	48 ± 13	NS
Triglyceride (mg/dl)	140 ± 77	143 ± 76	NS
Creatinine (mg/dl)	1.3 ± 1.7	1.2 ± 1.9	NS
C-reactive protein (mg/dl)	0.5 ± 1.5	0.3 ± 0.3	NS
History of MI (%)	38 (28)	31 (25)	NS
History of PCI (%)	4 (2)	0 (0)	NS
History of previous CABG (%)	8 (4)	0 (0)	NS
Diseased vessels			
LMT (%)	36 (20)	21 (14)	NS
3VD (%)	103 (58)	89 (59)	NS
1—2VD (%)	39 (22)	41 (27)	NS
Ejection fraction (%)	57.3 ± 15.2	59.1 ± 16.3	NS
Off-pump CABG (%)	174 (98)	151 (100)	NS

Data are presented as the mean value ± SD. DM, diabetes mellitus; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary arterial bypass grafting; LMT, left main trunk; VD, vessel disease.

angiotensin II receptor blockers, and statins. In the DM group, 110 patients (61%) and 55 (31%) patients were treated with oral anti-diabetic agents and insulin, respectively.

Exercise tolerance and muscle strength

The exercise tolerance and muscle strength of the 2 groups are presented in Table 3. The levels of peak $\dot{V}O_2$ ($12.5 \pm 3.7\,ml\,kg^{-1}\,min^{-1}$ vs. $13.7 \pm 4.0\,ml\,kg^{-1}\,min^{-1}$; $p = 0.01$) and AT ($8.3 \pm 1.6\,ml\,kg^{-1}\,min^{-1}$ vs. $8.8 \pm 2.1\,ml\,kg^{-1}\,min^{-1}$, $p = 0.02$) were significantly lower in the DM group than in the non-DM group. Ext muscle strength was significantly lower in the DM group than in the non-DM group ($131 \pm 40\,Nm\,kg^{-1} \times 100$ vs. $146 \pm 45\,Nm\,kg^{-1} \times 100$, $p < 0.01$). No significant differences in HGP (27.7 ± 9.0 kg vs. 29.5 ± 9.0 kg, NS) were observed between the 2 groups. Peak $\dot{V}O_2$ values were correlated with Ext muscle strength of thigh ($r = 0.49$, $p < 0.005$) (Fig. 1A) and HGP ($r = 0.44$, $p < 0.005$) (Fig. 1B); MAMA values were correlated with Ext muscle strength of thigh ($r = 0.42$, $p < 0.005$) (Fig. 2A) and HGP ($r = 0.64$, $p < 0.005$) (Fig. 2B). The same trends were observed in the DM and non-DM patients (Figs. 1C—F, 2C—F).

Diabetes mellitus and MAMA

To assess the effects of insulin treatment, we divided DM patients into the following 2 groups: DM patients undergoing insulin therapy (insulin-treated DM group) and DM patients

Table 2 Comparison of anthropometric parameters between the DM and non-DM groups.

	DM	Non-DM	*p* value
Body mass index (kg/m^2)	23.3 ± 2.7	23.2 ± 2.7	NS
Lean body weight (kg)	49.2 ± 8.6	48.0 ± 4.1	NS
Waist circumference (cm)	84.8 ± 8.0	84.0 ± 8.0	NS
Thigh circumference (cm)	47.0 ± 6.7	48.1 ± 4.1	NS
Arm forced circumference (cm)	28.3 ± 2.7	28.7 ± 2.5	NS
Triceps skinford thickness (mm)	10.9 ± 6.0	10.7 ± 4.0	NS
Mid-upper arm muscle circumference (cm)	24.9 ± 2.6	25.4 ± 2.5	NS
MAMA (cm^2)	50.0 ± 10.0	52.0 ± 10.0	NS

Data are presented as the mean ± SD. DM, diabetes mellitus; MAMA, mid-upper arm muscle area.

Table 3 Comparison of exercise tolerance and muscle strength between the DM and non-DM groups.

	DM	Non-DM	*p* value
Baseline			
SBP (mmHg)	134 ± 23	128 ± 19	<0.01
HR (min^{-1})	87 ± 13	90 ± 13	0.04
PRP ($mmHg\,min^{-1}$)	11673 ± 2333	11634 ± 2280	NS
Anaerobic threshold			
Anaerobic threshold ($ml\,kg^{-1}\,min^{-1}$)	8.3 ± 1.6	8.8 ± 2.1	0.02
Workload (W)	32 ± 12	34 ± 16	NS
HR (min^{-1})	101 ± 13	105 ± 13	0.01
Peak exercise			
Peak VO_2 ($ml\,kg^{-1}\,min^{-1}$)	12.5 ± 3.7	13.7 ± 4.0	0.01
Workload (W)	73 ± 22	71 ± 27	NS
RER	1.06 ± 0.14	1.07 ± 0.14	NS
SBP (mmHg)	180 ± 31	181 ± 30	NS
HR (min^{-1})	117 ± 17	121 ± 17	0.02
PRP ($mmHg\,min^{-1}$)	21177 ± 5097	22088 ± 5427	NS
Peak HR−resting HR (min^{-1})	30 ± 13	32 ± 15	NS
$\Delta VO_2/\Delta WR$ ($ml\,min^{-1}\,W^{-1}$)	8.4 ± 2.6	8.6 ± 2.2	NS
Muscle strength			
Knee extension ($Nm\,kg^{-1} \times 100$)	131 ± 40	146 ± 45	<0.01
Knee flexion ($Nm\,kg^{-1} \times 100$)	73 ± 23	79 ± 28	NS
Hand grip power (kg)	27.7 ± 9.0	29.5 ± 9.0	NS

Data are presented as the mean value ± SD. DM, diabetes mellitus; SBP, systolic blood pressure; HR, heart rate; PRP, pressure rate product; RER, respiratory exchange ratio; WR, work rate.

without insulin therapy (non-insulin-treated DM group). No significant differences in risk factors, number of diseased vessels, prevalence of re-CABG, and ejection fraction were observed between the non-insulin-treated DM group and the insulin-treated DM group. The insulin-treated DM group had a significantly longer duration of DM history than the non-insulin-treated DM group (17.7 ± 9 years vs. 11.7 ± 10 years, $p < 0.01$). The prevalence of microvascular complications, including retinopathy, nephropathy, and neuropathy, tended to be higher in the insulin-treated DM group than in the non-insulin-treated DM group (86% vs. 67%, $p = 0.09$). MAMA levels were significantly lower in the insulin-treated DM group than in the non-insulin-treated DM group (45.9 ± 9.8 cm^2 vs. 51.9 ± 9.7 cm^2, $p < 0.01$). The insulin-treated DM group had a low thigh muscle strength (121.5 ± 29 $Nm\,kg^{-1} \times 100$ vs. 135.4 ± 42 $Nm\,kg^{-1} \times 100$, $p = 0.06$) and HGP (25.6 ± 8.0 kg vs. 28.9 ± 8.0 kg, $p = 0.05$). In addition, a significant inverse relationship was observed between fasting blood glucose and Ext muscle strength of thigh in the DM group ($r = -0.26$, $p < 0.005$) (Fig. 3). A weak but significant inverse relationship was also observed between HbA1c and Ext muscle strength of thigh ($r = -0.17$, $p < 0.05$).

Discussion

In the present study, we demonstrated that: (1) DM patients had a significantly lower exercise tolerance and muscle strength compared with non-DM patients; (2) exercise tolerance and muscle mass correlated with muscle strength; and (3) fasting glucose levels significantly and negatively correlated with muscle strength in patients who received CR after CABG. These data suggest that a high glucose level may affect these deteriorations in DM patients after CABG. A relationship between muscle strength and peak $\dot{V}O_2$ has already been reported [12,13]. However, to the best of our knowledge, this is the first report demonstrating the impact of DM on muscle mass, muscle strength, and exercise tolerance in patients at the beginning of CR after CABG.

The reason why DM patients have low levels of exercise tolerance and muscle strength should be discussed. Tesfamariam et al. showed that the dysfunction of endothelium-dependent relaxation associated with exposure to elevated glucose levels is due to the increased production of vasoconstrictor prostanoids by the endothelium as a consequence of protein kinase C activation [14]. Previous studies have demonstrated that metabolisms of both glucose and fatty acids by skeletal muscle as well as the bioenergetic capacity of skeletal muscle mitochondria are impaired in DM patients [15]. These proposed mechanisms may explain the data in the present study because a significant inverse relationship was observed between fasting blood glucose levels and thigh muscle strength in the DM group (Fig. 3). Recently, Womack et al. showed that DM patients with microvascular complications have impaired capillary recruitment to contractile exercise [16]. In the present study, the prevalence of microvascular complications tended to be higher in the insulin-treated DM group than in the non-insulin-treated DM group. This may also be one of the mechanisms by which thigh muscle strength and HGP were significantly lower in the insulin-treated DM group than in the non-insulin-treated DM group. Low exercise tolerance in DM patients may be caused by sensorineural and autonomic dysfunction. An impaired heart rate response to exercise has been regarded as chronotropic incompetence and is seen in DM patients with impaired

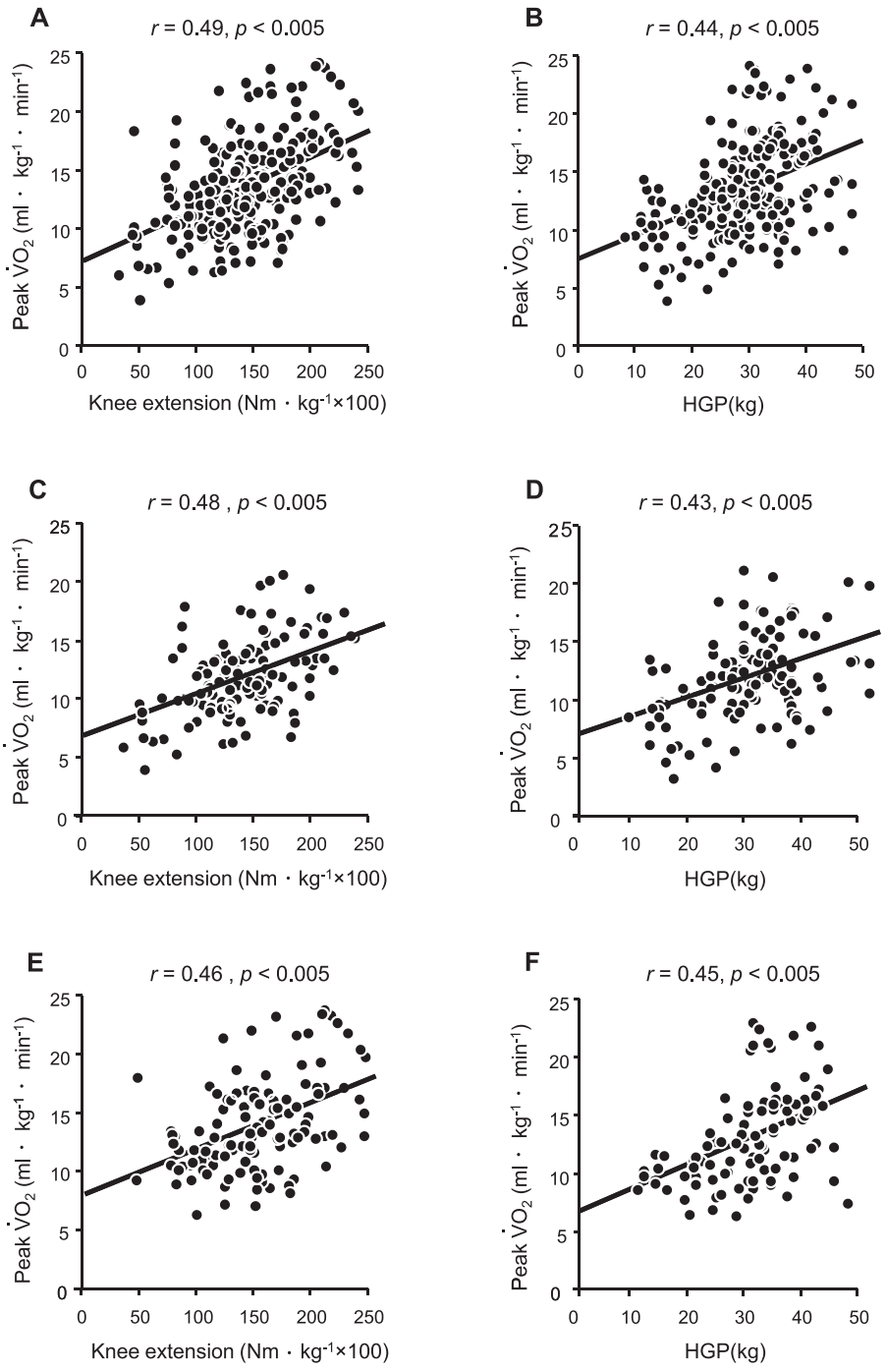

Figure 1 Correlations between exercise tolerance and muscle strength. Peak $\dot{V}O_2$ correlated with extensor muscle strength of thigh ($r = 0.49$, $p < 0.005$) (A), and HGP ($r = 0.44$, $p < 0.005$) in all patients (B) ($n = 259$). Peak $\dot{V}O_2$ correlated with extensor muscle strength of thigh ($r = 0.48$, $p < 0.005$) (C), and HGP ($r = 0.43$, $p < 0.005$) in the DM group (D) ($n = 128$). Peak $\dot{V}O_2$ correlated with extensor muscle strength of thigh ($r = 0.46$, $p < 0.005$) (E), and HGP ($r = 0.45$, $p < 0.005$) in the non-DM group (F) ($n = 131$). HGP, hand grip power; DM, diabetes mellitus.

exercise capacity. A previous study showed that low exercise capacity may be an impaired chronotropic response to exercise in DM patients with acute myocardial infarction [17]. In the present study, the heart rate values at peak $\dot{V}O_2$ and AT were significant lower in the DM group than in the non-DM group; however, the increased changes in heart rate were identical for the two groups (Table 3). Therefore, sensorineural and autonomic dysfunction may not have affected exercise intolerance in the DM group. The changes in sympathetic nervous activity (e.g. plasma catecholamine levels and R—R interval variability on an electrocardiogram) would be assessed in the subsequent step. Besides, a delta-$\dot{V}O_2$/delta-WR ($\Delta\dot{V}O_2/\Delta$WR) is determined by the rate of increase in cardiac output and the rate of

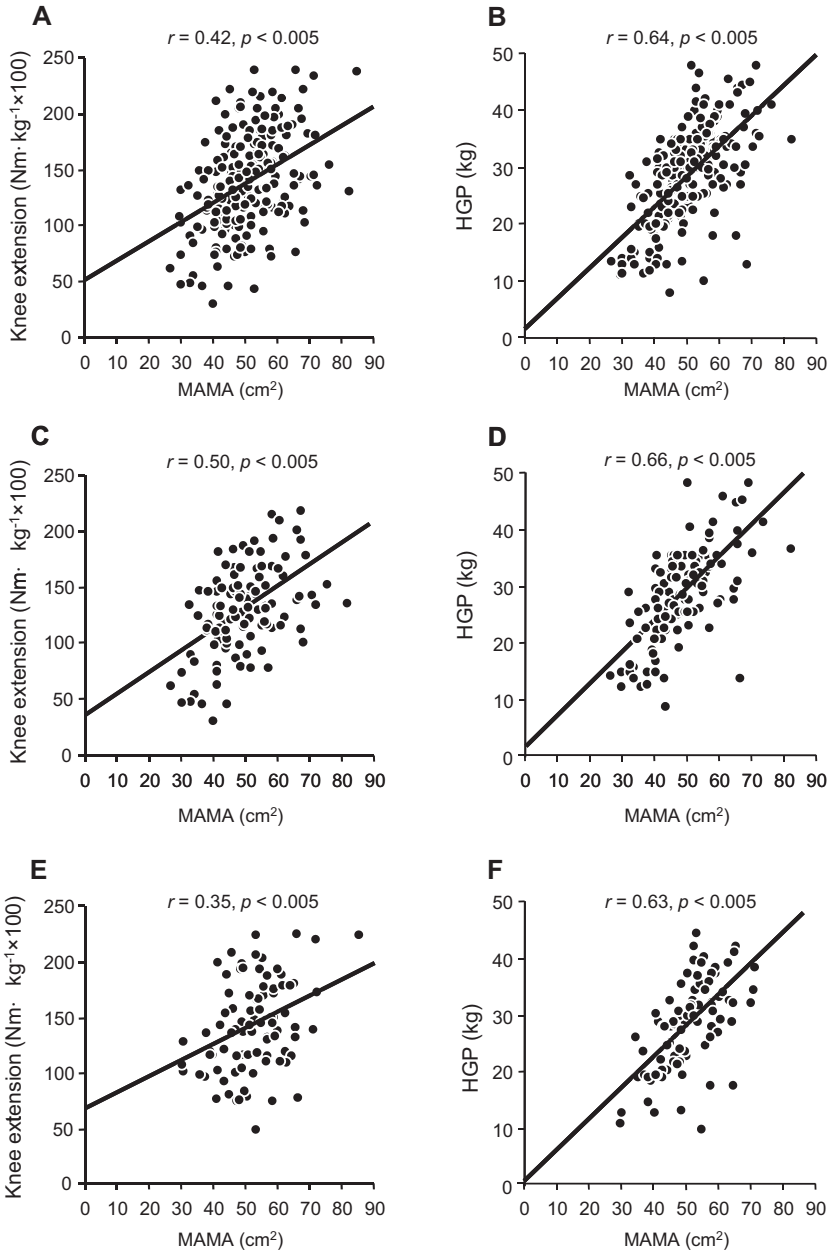

Figure 2 Correlations between muscle strength and muscle mass. MAMA correlated with extensor muscle strength of thigh ($r = 0.42$, $p < 0.005$) (A), and HGP ($r = 0.64$, $p < 0.005$) (B) in all patients ($n = 201$). MAMA correlated with extensor muscle strength of thigh ($r = 0.50$, $p < 0.005$) (C), and HGP ($r = 0.66$, $p < 0.005$) (D) in DM patients ($n = 108$). MAMA correlated with extensor muscle strength of thigh ($r = 0.35$, $p < 0.005$) (E), and HGP ($r = 0.63$, $p < 0.005$) (F) in non-DM patients ($n = 93$). MAMA, mid-upper arm muscle area; HGP, hand grip power; DM, diabetes mellitus.

difference in arterial mixed venous oxygen during incremental exercise [18]. Comparing with the non-DM group, $\Delta\dot{V}O_2/\Delta WR$ values were low but not significant in the DM group (Table 3).

The present study demonstrated that MAMA correlated with thigh muscle strength and HGP and MAMA levels were significantly lower in the insulin-treated DM group than the non-insulin-treated DM group. Chronic hyperglycemia leads to the production of amadori products through nonenzymatic glycation reactions between glucose and reactive amino groups of serum proteins [19]. These products undergo further irreversible reactions to form advanced glycation end products that promote insulin resistance as well as trigger inflammation and secretion of cytokines and growth factors, which leads to amplification or progression of various diseases including diabetic vascular complications (metabolic memory) [20]. In the present study, the insulin-treated DM group had a significantly longer duration of DM history than the non-insulin-treated DM group. The loss of muscle mass may be caused by chronic hyperglycemia, the so-called negative legacy effect, particularly in the insulin-treated DM group. A recent study demonstrated that a low

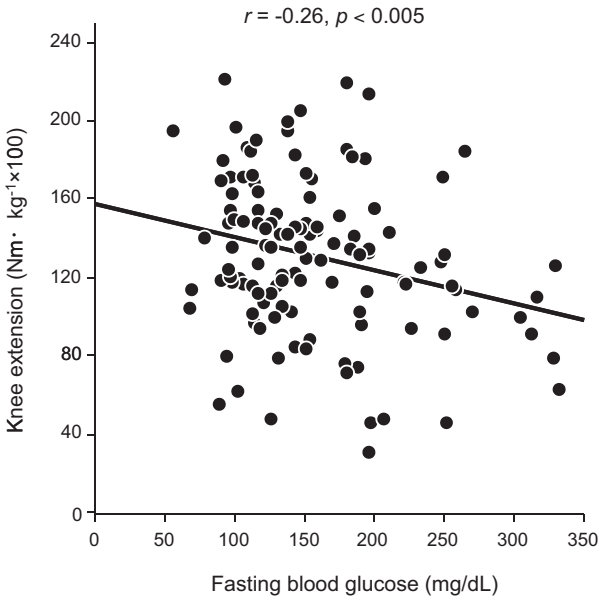

Figure 3 Correlation between fasting glucose levels and extensor muscle strength of thigh. A significant inverse relationship was observed between fasting blood glucose levels and extensor muscle strength of thigh in the diabetes mellitus group ($r = -0.26$, $p < 0.005$) ($n = 120$).

level of arm muscle area was an independent risk factor for the 2-year mortality in a cohort of community dwelling Japanese elderly [21]. We would like to further clarify whether the levels of arm muscle area before and after CR can predict morbidity and mortality in DM patients after CABG.

CR is class I recommendation in most contemporary cardiovascular clinical practice guidelines. Exercise tolerance has proven to be the strongest predictor of the risk of death among subjects with and without known cardiovascular disease [22]. Vergès et al. reported that the benefit of CR on exercise capacity is significantly lower in DM patients than non-DM patients and the response to CR was influenced by blood glucose levels [7]. A previous study demonstrated that exercise increases the activity of AMP-activated protein kinase in muscle, which in turn, promotes translocation of the glucose transporter-4 from the cytosol to the plasma membrane, increases insulin-independent glucose uptake by muscle, and improves muscle insulin resistance by a reduction of intramyocellular lipids [23]. Therefore, it is necessary to investigate the effects of CR on muscle mass, muscle strength, exercise capacity, and long-term outcome.

The present study has some limitations. First, this was a single-center study with a small sample size. Studies with larger sample sizes can confirm these results. Secondly, we performed a cardiopulmonary exercise test at the beginning of phase I CR (6—8 days after CABG). Therefore exercise tolerance and muscle strength might be attenuated by confounding factors. However, no significant differences in the clinical characteristics were observed between the DM group and the non-DM group. Thirdly, we enrolled patients who received CR after CABG. Therefore, the results of the present study may not be representative of all DM patients with CAD. Finally, this was a cross-sectional study. As discussed above, the clinical importance of muscle parameters and exercise tolerance prospectively as well as the effects of CR on muscle mass, muscle strength, exercise capacity, and future cardiovascular events in DM patients after CABG must be investigated.

Conclusions

DM patients had a lower muscle strength and exercise tolerance than non-DM patients at the beginning of CR after CABG. Moreover, a high glucose level may affect these deteriorations in DM patients after CABG. Further studies are required to assess whether CR would ameliorate these deteriorations and improve the clinical prognosis in DM patients after CABG.

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