Impact of Lower-Extremity Muscle Strength on Exercise Capacity in Patients With Cardiovascular Disease and Diabetes Mellitus

Koya Takino, PhD, PT; Takuji Adachi, PhD, PT; Yoji Kuze, PT; Takashi Nagai, PT; Masaya Hori, PT MS; Masayasu Nakagawa, MD, PhD

Purpose: Although skeletal muscle abnormalities caused by diabetes mellitus (DM) suggest that peripheral muscle impairment may have a greater effect on exercise tolerance in patients with DM, the magnitude of this effect on reduced exercise capacity remains unclear. As such, this study aimed to compare the strength of the association between lower-extremity muscle strength and exercise capacity in patients diagnosed with cardiovascular disease (CVD) with and without DM.

Methods: This retrospective cross-sectional study included data from 262 patients divided into two groups: patients with DM (DM group; n = 106); and without DM (non-DM group; n = 156). Peak oxygen uptake (VO_{2peak}) and isometric knee extensor strength (IKES) were measured. Correlations between VO_{2peak} and IKES were analyzed using Pearson's correlation test in the DM and non-DM groups. Linear regression analyses were performed with VO_{2peak} as the dependent variable, and IKES, confounders, and the interaction term DM × IKES as the independent variables. Separate linear regression analyses were performed for the DM and non-DM groups.

Results: The correlation coefficient between VO_{2peak} and IKES was 0.58 in the DM group and 0.26 in the non-DM group. The interaction term DM × IKES had a significant effect on VO_{2peak}. The IKES was significantly associated with VO_{2peak} in the DM group (β = 0.83, P < .001), but not in the non-DM group (β = 0.01, P = .96).

Conclusion: A specific association between lower-extremity muscle strength and VO_{2peak} was observed in patients with both CVD and DM.

Key Words: cardiopulmonary exercise test • coronary artery disease • functional capacity • hyperglycemia • quadriceps muscle

KEY PERSPECTIVES

What is novel?

- This is the first study to demonstrate an interaction between diabetes mellitus and lower-extremity muscle strength on exercise capacity in patients with cardiovascular disease.
- The correlation coefficient between peak oxygen uptake (VO_{2peak}) and lower-extremity muscle strength was 0.58 in patients with diabetes mellitus and 0.26 in those without.
- In multiple regression analysis, the lower-extremity muscle strength was significantly associated with VO_{2peak} in patients with diabetes mellitus, but not in those without, with significant the interaction term diabetes mellitus × muscle strength on VO_{2peak}.

What are the clinical and/or research implications?

- The specific relationships between leg muscle strength and exercise capacity observed in patients with diabetes mellitus suggest that the comorbidity of diabetes mellitus may serve as a stratification indicator for specific interventions in patients with cardiovascular disease.
- Treatment and interventions targeting lower-extremity muscle strength, including resistance training and high-intensity interval training, may play a crucial role in enhancing exercise tolerance in patients diagnosed with both cardiovascular disease and diabetes mellitus.

Author Affiliations: *Department of Physical Therapy (Dr Takino), Department of Integrated Health Sciences (Dr Adachi), Toyohashi Sozo University School of Health Sciences, Toyohashi, Japan; and Department of Cardiac Rehabilitation (Dr Takino, Mr Kuze, Nagai and Hori), Department of Cardiology (Dr Nakagawa), Gifu Heart Center, Gifu, Japan.*

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Correspondence: *Koya Takino, PT, PhD, Toyohashi Sozo University, 20-1, Matsushita, Ushikawacyo, Toyohashi 440-8511, Aichicn (k-takino@sozo.ac.jp).*

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Exercise capacity is commonly assessed in clinical practice to evaluate prognosis, quality of life, and risk management in patients diagnosed with cardiac disease. Peak oxygen uptake (VO_{2peak}), the gold standard for measuring exercise capacity, is associated with physical disability, mortality, and quality of life.[1,2] The VO_{2peak} represents the cardiac response to oxygen demand during exercise, as demonstrated by the Fick equation. In addition to cardiac output as a central factor, muscle, and vascular dysfunctions as peripheral factors influence VO_{2peak} by affecting the maximal ability of skeletal muscles to use oxygen.[3] Exercise training has been attributed to improve peripheral factors, such as peripheral skeletal muscle function, leading to increased exercise tolerance in patients with cardiac disease.[4] The effects of skeletal muscle mass on exercise capacity vary widely among patients affected by different pathological conditions.[5-15]

Diabetes mellitus (DM), a major risk factor for cardiovascular disease (CVD), causes skeletal muscle weakness,[16]

leading to sarcopenia[17] and increased risk of falls.[18] Insulin resistance and glucotoxicity cause skeletal muscle impairment, including reduced muscle strength, muscle atrophy, changes in muscle fiber composition with a relative decrease in type I fibers, and mitochondrial dysfunction.[19-21] In patients diagnosed with type 2 DM, exercise capacity is reduced,[22,23] with peripheral skeletal muscle dysfunction possibly one of the contributing factors.[22] A small-sample study demonstrated that limited exercise capacity was associated with insulin resistance, reduced type I muscle fiber content, and reduced muscle capillary density in individuals with DM.[24] Although skeletal muscle abnormalities due to DM suggest that peripheral muscle impairment may have a greater impact on exercise tolerance in patients with type 2 DM, the magnitude of this effect on reduced exercise capacity remains unclear. Clarifying this finding may help establish the comorbidity of DM as an indicator to stratify specific interventions on lower-extremity muscle strength within cardiac rehabilitation (CR) programs. Accordingly, this study aimed to compare the degree of association between lower-extremity muscle strength, a key indicator of peripheral skeletal muscle, and VO_{2peak} in patients diagnosed with CVD with and without DM. We hypothesized that the association between muscle strength and exercise capacity would be stronger in patients with DM than in those without DM.

METHODS

STUDY DESIGN AND PARTICIPANTS

The present investigation was a single-center, retrospective, cross-sectional study. It included 493 consecutive patients ≥18 years of age, who were diagnosed with acute coronary syndrome and underwent percutaneous coronary intervention between September 2015 and June 2021. Individuals with cognitive impairment (Mini-Mental State Examination score <23), those with orthopedic, neurological, and/or pulmonary comorbidities limiting functional capacity, those who terminated exercise testing before reaching a peak respiratory exchange ratio value of 1.0, and patients unable to undergo cardiopulmonary exercise testing (CPX) at discharge were excluded. All inpatients underwent CR for patients with acute myocardial infarction according to the *Japanese Circulation Society guidelines*.[25]

This study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Gifu Heart Center (Gifu, Japan; No. 2024001). Given the retrospective design of the study and the use of anonymized patient data, requirements for informed consent were waived. All patients were informed about participation in the study and each was offered an opportunity to opt out. Information regarding this study, such as the inclusion criteria and the opportunity to opt out, is provided on the hospital's website. The study protocol was approved by the local ethics committee. No patients had opted out of the study at the time of analysis.

CARDIOPULMONARY EXERCISE TESTING

Cardiopulmonary exercise testing was conducted at discharge using a cycle ergometer with a ramp protocol. Exhaled gases were analyzed using a gas analyzer (AE-310S, Minato Medical Science) to ensure accurate respiratory measurements. The CPX protocol included a 4-minute rest, a 3-minute warm-up at 10-20 W, followed by incremental workload increases of 10-20 W/min until voluntary exhaustion, with patients maintaining a cycling cadence of 50 revolutions per minute.[26] This protocol has been used in hospitalized patients with acute myocardial infarction.[27] Physiological parameters, including blood pressure, gas exchange, electrocardiogram, and oxygen saturation, were continuously monitored. Patients were rigorously instructed to exert maximum effort, and the test was continued until complete exhaustion or extremely high perceived exertion was reported. The test was terminated when the respiratory exchange ratio exceeded 1.15 and/or when a plateau in oxygen uptake was observed. If the respiratory exchange ratio was ≤1.15, the test was terminated based on clinical endpoints according to the criteria for stopping CPX as outlined in the *American College of Sports Medicine Guidelines for Exercise Testing and Prescription*.[28] Metabolic ventilatory variables, such as oxygen uptake, carbon dioxide output, and minute ventilation, were continuously monitored. Breath-by-breath data were post-processed to obtain 10 second averages. The anaerobic threshold was determined using the v-slope method.

MEASUREMENT OF MUSCLE STRENGTH

Isometric knee extensor strength (IKES) was measured at discharge to assess lower-extremity muscle strength, as DM-related muscle impairments include both muscle weakness and functional decline.[19-21] Patients seated at the edge of a table while maintaining their hip and knee joints flexed at a 90° angle. A handheld dynamometer (μ-Tas F-1, Anima Corporation) was placed against the distal anterior surface of the distal shin and secured with a belt attached to the leg of the bed.[29] After one practice, patients performed two maximal knee extensions for 5 seconds on each side.[30] The rest time between trials was set at 30 seconds. The higher IKES per body weight value from the two measurements (IKES [kgf]/body weight [kg]) – whether on the right or left – was selected for analysis, as normalizing maximal isometric strength to body weight facilitates inter-patient comparisons.[21] Trained physical therapists measured IKES, and intraclass correlation coefficients were calculated for each examiner to assess the reliability across examiners and ensure data validity for between-patient comparisons, which ranged from .90 to 1.00.

CLINICAL DATA

Data collected at discharge included cardiac function, laboratory results, and coronary angiographic variables. Type 2 DM was diagnosed in accordance with the *2019 Japanese Clinical Practice Guidelines for Diabetes*.[31] The diagnosis of DM was based on comprehensive criteria including chronic hyperglycemia and additional factors such as symptoms, laboratory findings, family history, and body weight history. We divided the patients into two groups: those with DM (DM group) and those without DM (non-DM group). Cardiac function parameters were assessed using echocardiography. Left ventricular ejection fraction was evaluated using Simpson's biplane method. Diastolic function was thoroughly assessed by measuring the ratio of early transmitral flow velocity to early diastolic mitral annular velocity. Data on patient percutaneous coronary intervention, including the culprit lesion, demographics, medical history, prescribed medications, laboratory data, and echocardiographic parameters were obtained from their medical records before starting the inpatient CR program.

STATISTICAL ANALYSES

Normality of the distribution of continuous variables was assessed using the Shapiro–Wilk test. Patient background data are expressed as either mean ± SD or median (IQR) for continuous variables, with or without normal distribution, and frequency and percentage for categorical variables. Differences in patient characteristics between the DM and

non-DM groups were compared using Student's t-test or the Mann-Whitney U test for continuous variables and the χ^2 test for categorical variables, as appropriate. Correlations between VO_{2peak} and IKES were analyzed using the Pearson's correlation test for all patients and separately for the DM and non-DM groups. In addition, IKES was compared across glycemic control categories classified by hemoglobin A1c of ≥7.0%, 6.0-6.9%, and <6.0%, with reference to the *2019 Japanese Clinical Practice Guidelines for Diabetes*,[31] using the Jonckheere-Terpstra trend test.

Linear regression analyses were performed using VO_{2peak} as the dependent variable. The independent variables used in the linear regression models were defined as follows: Model 1 included a univariate analysis with IKES as the independent variable. Model 2 included IKES along with potential confounders, such as age (≥65 years vs. <65 years) and sex, which were associated with VO_{2peak}; body mass index, hemoglobin, left ventricular ejection fraction, and early diastolic mitral annular velocity, as contributors to exercise capacity in patients with cardiac disease;[3] estimated glomerular filtration rate, as a relevant factor for VO_{2peak} in patients with acute myocardial infarction;[27] and comorbidity of DM and

Table 1

Comparison of Patient Characteristics Between Patients With and Without Diabetes Mellitus[a]

	DM (n = 106)	No-DM (n = 156)	*P* Value
Age, yr	63.8 ± 10.0	63.7 ± 11.0	.92
Male sex	95 (90%)	132 (85%)	.27
Body mass index, kg/m^2	25.9 ± 4.8	24.1 ± 3.9	<.001
Right coronary artery	28 (26%)	49 (31%)	.41
Left main coronary artery	1 (1%)	6 (4%)	.25
Left anterior descending coronary artery	55 (52%)	80 (51%)	1.00
Left circumflex coronary artery	21 (20%)	20 (13%)	.17
Atrial fibrillation	4 (4%)	8 (5%)	.77
Hypertension	81 (76%)	97 (62%)	.016
Dyslipidemia	70 (66%)	92 (59%)	.30
Chronic obstructive pulmonary disease	3 (3%)	0 (0%)	.065
Stroke	2 (2%)	1 (1%)	.57
Left ventricular ejection fraction, %	50.3 ± 11.8	53.2 ± 9.2	.027
E/e′	12.3 (10.3, 16.7)	12.5 (9.8, 17.5)	1.000
Aortic valve regurgitation	3 (3%)	8 (5%)	.53
Mitral valve regurgitation	2 (2%)	10 (6%)	.13
Tricuspid valve regurgitation	1 (1%)	7 (5%)	.15
Albumin, g/dL	3.8 (3.5, 4.0)	3.7 (3.4, 4.0)	.48
eGFR, mL/min/1.73 m^2	61.4 (51.5, 70.6)	63.7 (54.6, 72.5)	.37
Hemoglobin, g/dL	13.7 (12.6, 14.7)	13.3 (12.2, 14.3)	.038
Hemoglobin A1c, %	7.0 (6.6, 7.8)	5.7 (5.5, 5.9)	<.001
hs-CRP, mg/L	0.35 (0.14, 1.09)	0.44 (0.17, 1.12)	.33
Peak CK, U/L	1671 (739, 3245)	1644 (684, 3102)	.60
ACE-inhibitor/ARB	85 (80%)	119 (76%)	.68
Antiarrhythmic	2 (2%)	3 (2%)	1.00
Anticoagulant	32 (30%)	53 (34%)	.59
Antiplatelet	104 (98%)	153 (98%)	1.00
Beta blocker	85 (80%)	126 (81%)	1.00
Cardiotonic	1 (1%)	3 (2%)	.65
Diuretic	22 (21%)	26 (17%)	.42
Oral antihyperglycemic drug	66 (62%)	0 (0%)	<.001
Insulin therapy	1 (1%)	0 (0%)	.41
IKES, kgf/kg	0.54 ± 0.13	0.56 ± 0.14	.30

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CK, creatinine kinase; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; hs-CRP, high sensitive C-reactive protein; IKES, isometric knee extensor strength.
[a]Data are presented as mean ± SD, median (IQR), or n (%).

Table 2

Comparison of Cardiopulmonary Exercise Test Parameters Between Patients With and Without Diabetes Mellitus[a]

	DM (n = 106)	No-DM (n = 156)	*P* Value
$VO_{2peak,}$ mL/min/kg	15.7 ± 3.1	16.1 ± 3.4	.39
Peak MET	4.5 ± 0.9	4.6 ± 1.0	.39
AT-$VO_{2,}$ mL/min/kg	10.3 ± 1.7	10.7 ± 2.0	.12
VO_{2peak}/heart rate	9.2 ± 2.4	8.9 ± 2.6	.43
AT-VO_2/heart rate	7.7 ± 1.8	7.5 ± 2.1	.60
Minimum VE/VCO_2	37.5 ± 7.3	35.8 ± 5.5	.042
Minimum VD/VT	0.30 ± 0.04	0.30 ± 0.04	.89
Rest heart rate, beats/min	70.1 ± 10.3	70.4 ± 12.7	.82
Peak heart rate, beats/min	120.0 ± 17.4	120.3 ± 18.8	.91
Δ heart rate, beats/min	49.9 ± 15.7	49.9 ± 15.5	.97
% age-predicted maximal heart rate achieved during CPX, %	76.9 ± 10.1	77.0 ± 11.3	.91
Peak RER	1.2 ± 0.1	1.2 ± 0.1	.48
VE/VCO_2 slope	34.0 ± 8.7	31.7 ± 5.4	.010
Δ VO_2/Δ WR	8.9 ± 1.6	8.8 ± 1.3	.67
Reason for CPX termination			
Peak RER ≥ 1.15	53 (50%)	67 (43%)	.31
Leveling off	13 (8%)	8 (8%)	1.0
Leg fatigue	34 (32%)	58 (37%)	.43
ST change during exercise	1 (1%)	2 (1%)	1.0
Excessive rise in blood pressure[b]	6 (6%)	3 (2%)	.16
Achievement of the target exercise level[c]	1 (1%)	9 (6%)	.053
Dyspnea	3 (3%)	3 (2%)	.69
New onset of arrhythmia	0 (0%)	1 (1%)	1.0

Abbreviations: AT, anaerobic threshold; CPX, cardiopulmonary exercise testing; DM, diabetes mellitus; MET, metabolic equivalent of task; RER, respiratory exchange ratio; VCO_2, carbon dioxide output; VD, volume of dead air space; VE, minute ventilation; VO_2, oxygen uptake; VT, tidal volume; WR, work rate.
[a]Data are presented as mean ± SD or n (%).
[b]Systolic pressure ≥230 mmHg or diastolic pressure ≥115 mmHg.
[c]As determined by a physician.

hemoglobin A1c level. Model 3 is a multivariable model that adds the interaction term DM × IKES to model 2. In addition, in the subgroup analysis for the DM and non-DM groups, linear regression analyses were performed with VO_{2peak} as the dependent variable and variables from model 2, except for comorbidity of DM. The number of variables included in the multiple regression analysis was determined based on 10 samples per variable.[32] Statistical analyses were performed using EZR version 1.66 (Saitama Medical Center, Jichi Medical University).[33]

RESULTS

Based on predefined criteria, 491 patients were eligible to participate in this study. However, 229 were excluded for the following reasons: cognitive impairment (Mini-Mental State Examination score <23, n = 28 [12%]); orthopedic, neurological, and/or pulmonary comorbidities limiting functional capacity (n = 92 [40%]); termination of exercise testing before reaching a peak respiratory exchange ratio value of 1.0 (n = 28 [12%]); and inability to undergo CPX at discharge (n = 81 [35%]). As such, the final sample consisted of 262 patients (mean age, 63.7 ± 10.6 years; 87% male), of whom 106 (41%) were diagnosed with DM. Characteristics and CPX data of the study participants are reported based on the presence of DM (Tables 1 and 2). The DM group had a higher body mass index and hemoglobin A1c levels and a higher prevalence of hypertension and use of oral antihyperglycemic drugs than the non-DM group (Table 1). The minimum ventilatory equivalent for carbon dioxide and ventilatory equivalent for carbon dioxide slopes were higher in the DM group than those in the non-DM group (Table 2). There were no differences between the groups in the reasons for stopping the exercise test.

Isometric knee extensor strength exhibited a significant correlation with VO_{2peak} among the entire cohort (r = 0.38: 95% CI, 0.27-0.48]; P < .001). As shown in Figure 1, the correlation coefficients between IKES and VO_{2peak}were 0.58: 95% CI, 0.44-0.69; P < .001 and 0.26: 95% CI, 0.11-0.40, P < .001 in the DM and non-DM groups, respectively. A comparison of IKES according to the glycemic control categories based on hemoglobin A1c is presented in Figure 2. The higher hemoglobin A1c group had a lower IKES score (P for trend = .021).

Results of multiple linear regression analysis for all participants are summarized in Table 3. The normality of the residuals from the linear regression models were ensured using quantile-quantile plots (Supplemental Digital Content Figure 1, available at: http://links.lww.com/JCRP/A607). Isometric knee extensor strength was significantly associated with VO_{2peak} after adjusting for several confounders (model 2, β = 0.32, P = .019). The interaction term DM × IKES had a significant effect on VO_{2peak} (model 3, P = .033). The results of multiple linear regression analysis of VO_{2peak} separately in the DM and non-DM groups are summarized in Table 4. In the DM group, the IKES score was significantly associated with VO_{2peak} after adjusting for potential confounders (β = 0.83, P < .001). In the non-DM group, IKES was not statistically associated with VO_{2peak} (β = 0.01, P = .96).

DISCUSSION

The results of this study support our hypothesis that the association between lower-extremity muscle strength and exercise capacity is stronger in patients with DM than in those without DM. To the best of our knowledge, this is the first study to demonstrate an interaction between DM and IKES on VO_{2peak} in patients with CVD. Our results suggest that the comorbidity of DM may serve as an indicator for stratifying interventions that focus on lower-extremity muscle strength within CR programs to enhance exercise capacity in patients with CVD.

The relationship between skeletal muscle indicators, including muscle strength,[5-11] skeletal muscle mass,[12,13] and muscular endurance,[14,15] and exercise tolerance in patients with cardiac diseases has been studied extensively. In this study, IKES was correlated with $VO_{2peak,}$ showing correlation coefficients of 0.38, in patients with CVD and a 40% DM comorbidity rate. Consistent with these findings, the correlation coefficients in simple linear models[6,7] between muscle strength and exercise capacity in patients with CVD, with a DM prevalence of 20-40%, ranged from 0.32 to 0.44.

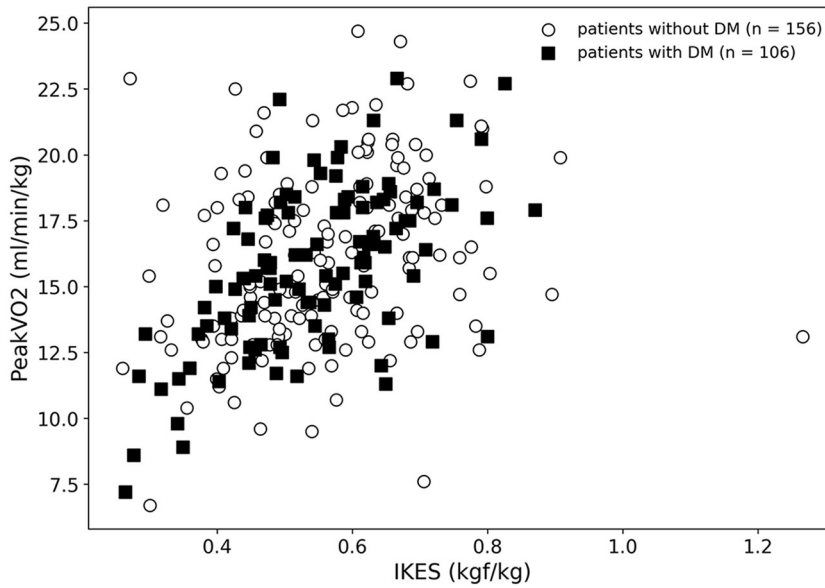

Figure 1. Correlation between the IKES and VO_{2peak} in patients with and without DM. Abbreviations: DM, diabetes mellitus; IKES, isometric knee extensor strength; $VO_{2,}$ oxygen uptake.

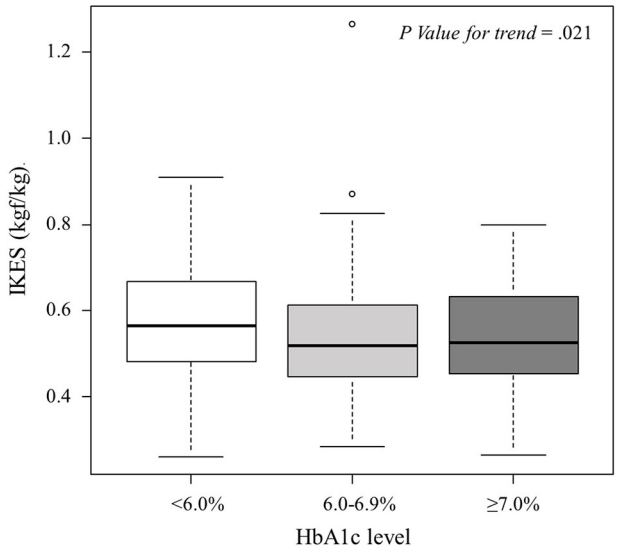

Figure 2. Comparison of IKES across glycemic control categories based on Hb A1c levels. Abbreviations: Hb, hemoglobin; IKES, isometric knee extensor strength.

Notably, the DM group showed a coefficient of 0.58, exceeding this range, whereas the non-DM group had a lower coefficient of 0.26. In patients with heart failure, the correlation coefficient ranges from 0.53 to 0.90,[8,9,11] suggesting a stronger association between these variables, possibly due to skeletal muscle dysfunction.[34,35] DM, a condition known to cause skeletal muscle impairment,[19-21] may have influenced the relationship between skeletal muscle strength and exercise tolerance in this study.

Peripheral skeletal muscle impairment and reduced cardiac function due to DM may explain the stronger correlation observed between muscle strength and exercise capacity in patients with DM. First, skeletal muscle dysfunction caused by DM may reduce oxygen uptake during exercise, resulting in a lower exercise capacity. The DM pathophysiology contributes to muscle dysfunction,[19-21] decreasing skeletal muscle oxygen demand[36] and leading to lower VO_{2peak}.[22,23] In our study, glycemic control was associated with VO_{2peak} and IKES. Second, a reduced cardiac response to exercise due to DM may increase reliance on skeletal muscle function for oxygen uptake. In this study, the left ventricular ejection fraction was lower in the DM group than in the non-DM group, which is consistent with a previous report.[23] Since the peak creatinine kinase levels and culprit lesion location did not differ between the groups, preclinical ischemic cardiomyopathy, diabetic cardiomyopathy,[37,38] and coronary microvascular dysfunction[39] may have been present in the DM group.

In the non-DM group, IKES correlated with VO_{2peak}, but this correlation was no longer significant after adjustment for covariates. Age and sex were significant factors for the VO_{2peak} in the non-DM group, suggesting that these variables may act as confounders. Studies on outpatients with cardiac disease[5,9,10] have clarified the relationship between skeletal muscle factors and exercise capacity after adjusting for these variables. Differences in physical activity among outpatients may contribute to this relationship. In our study of hospitalized patients, prehospital physical activity likely had limited influence. Additionally, the non-DM group maintained preserved cardiac function, with a left ventricular ejection fraction of 53.2%, compared with 48.1% in previous studies for patients with CVD.[5] The limited effects of physical activity and cardiac function may have allowed age and sex to influence exercise tolerance significantly in the non-DM group.

DM is associated with reduced exercise capacity[22,23] and muscle strength.[16,21] In contrast to previous studies,[16,21-23] this study found no significant differences in the VO_{2peak} and IKES between the DM and non-DM groups. A possible explanation for our results is the small number of patients with severe DM. Insulin-treated patients with DM had greater muscle weakness[40] and lower exercise capacity.[41] Indeed, only one patient receiving insulin therapy was included in this study, whereas 12% of the patients in the DM group were receiving insulin therapy in the above-mentioned study.[23] However, regression analysis identified

Table 3

Multiple Regression Analysis for Peak Oxygen Uptake

	Model 1		Model 2			Model 3	
	β (95%CI)	*P* Value	*β* (95%CI)	*P* Value	VIF	*β* (95%CI)	*P* Value
IKES, increment by 0.1 kgf/kg	0.86 (0.59 to 1.13)	<.001	0.32 (0.05 to 0.59)	.019	1.31	−0.13 (−0.18 to 0.44)	.41
Age ≥ 65 yr, compared to age < 65 yr	–	–	−1.45 (−2.22 to −0.69)	<.001	1.43	−1.41 (−2.17 to −0.65)	<.001
Men, compared to women	–	–	2.47 (1.41 to 3.54)	<.001	1.27	2.46 (1.42 to 3.50)	<.001
Body mass index, increment by 1 kg/m^2	–	–	−0.11 (−0.19 to −0.02)	.012	1.33	−0.10 (−0.18 to −0.02)	.016
DM, compared to no-DM	–	–	0.62 (−0.29 to 1.52)	.18	1.91	−2.10 (−4.75 to 0.55)	.12
LVEF, increment by 1%	–	–	0.05 (0.01 to 0.08)	.0052	1.07	0.042 (0.01 to 0.07)	.0098
E/e', increment by 1	–	–	−0.07 (−0.12 to −0.02)	.0043	1.12	−0.07 (−0.11 to −0.03)	.0031
eGFR, increment by 1%	–	–	0.03 (0 to 0.05)	.035	1.18	0.03 (0.01 to 0.05)	.022
Hemoglobin, increment by 1 mg/dL	–	–	0.25 (0.01 to 0.49)	.043	1.37	0.23 (−0.01 to 0.47)	.058
Hemoglobin A1c, increment by 1.0%	–	–	−0.44 (−0.79 to −0.09)	.015	1.92	−0.41 (−0.76 to −0.06)	.024
Interaction term DM × IKES	–	–	–	–	–	0.53 (0.04 to 1.02)	.033
	Multiple R-squared: 0.13		Multiple R-squared: 0.37			Multiple R-squared: 0.38	

Abbreviations: DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; IKES, isometric knee extensor strength; LVEF, left ventricular ejection fraction; VIF, variance inflation factor.

Table 4

Subgroup Analysis of Multiple Regression Analysis on Peak Oxygen Uptake in Patients With and Without Diabetes Mellitus

	DM (n = 106)			No-DM (n = 156)		
	β (95%CI)	*P* Value	VIF	β (95%CI)	*P* Value	VIF
Age ≥65 yr, compared to age <65 yr	−0.97 (−2.1 to 0.15)	.088	1.64	−1.77 (−2.83 to −0.72)	.0011	1.44
Men compared to women	1.07 (−0.72 to 2.85)	.24	1.55	3.26 (1.9 to 4.62)	<.001	1.25
Body mass index, increment by 1 kg/m^2	−0.02 (−0.13 to 0.09)	.68	1.43	−0.20 (−0.33 to −0.07)	.0026	1.25
LVEF, increment by 1%	0.06 (0.03 to 0.1)	.0014	1.10	0.02 (−0.02 to 0.07)	.33	1.06
E/e′, increment by 1	−0.07 (−0.15 to 0.02)	.11	1.31	−0.07 (−0.13 to −0.01)	.027	1.12
eGFR, increment by 1%	0.02 (−0.02 to 0.05)	.33	1.18	0.04 (0 to 0.07)	.026	1.23
Hemoglobin, increment by 1 mg/dL	0.24 (−0.14 to 0.61)	.21	1.73	0.28 (−0.05 to 0.6)	.093	1.28
Hemoglobin A1c, increment by 1.0%	−0.46 (−0.79 to −0.12)	.0085	1.18	0.70 (−0.73-2.14)	.34	1.09
IKES, increment by 0.1 kgf/kg	0.83 (0.44-1.22)	<.001	1.38	0.01 (−0.35 to 0.37)	.96	1.28
	Multiple R-squared: 0.50			Multiple R-squared: 0.36		

Abbreviations: DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; IKES, isometric knee extensor strength; LVEF, left ventricular ejection fraction; VIF, variance inflation factor.

hemoglobin A1c as an independent factor associated with VO_{2peak}, which is consistent with previous findings.[23] Furthermore, glycemic control was associated with IKES through trend analysis. These findings suggest that CR interventions targeting the lower-extremity muscles may be particularly beneficial for patients with DM, especially those with poor glycemic control.

Exercise-based CR improves exercise tolerance in patients with acute myocardial infarction; however, DM attenuates the effects of exercise training.[42] This study identified a specific association between lower-extremity muscle strength and exercise tolerance in patients with DM. Better glycemic control is associated with enhanced cardiorespiratory fitness in patients with DM.[42,43] Considering these findings, CR programs to improve exercise tolerance in patients with CVD and DM may be more individualized from the perspectives of skeletal muscle training and glycemic control. Resistance training combined with aerobic exercise improves exercise capacity and glycemic control in patients with DM.[44] High-intensity interval training is another promising approach, as a meta-analysis[45] showed its benefits for glycemic control, exercise capacity, and lower-limb strength in patients with DM. In older adults, high-intensity interval training[46] may be an effective strategy for improving muscle strength and sarcopenia. Therefore, the comorbidity of DM may serve as a stratification indicator for implementing increased resistance training and/or high-intensity interval training within CR programs to improve exercise capacity and potentially mitigate sarcopenia and physical disabilities.

The present study had several limitations. First, its retrospective, single-center design may have introduced bias. However, we utilized multivariable analysis to examine the association between lower-extremity muscle strength and exercise capacity, adjusting for covariates. Second, skeletal muscle functions, such as mitochondrial function and microcirculation were not directly assessed, but muscle strength may reflect both the power and muscle function, because sarcopenia, a condition involving reduced muscle strength, is linked to impaired muscle function.[47] Third, a selection bias may have occurred because patients unable to undergo CPX at discharge were excluded from the study. Fourth, a causal relationship between muscle strength and exercise capacity could not be determined because of the cross-sectional study. Nevertheless, the findings of this study suggest that lower-extremity muscle strength has a greater impact on exercise intolerance in patients diagnosed with both CVD and DM.

CONCLUSIONS

This cross-sectional study revealed that lower-extremity muscle strength was associated with VO_{2peak} in the DM, but not the non-DM, group after adjusting for several confounders. In addition, a significant interaction between DM status and IKES score on exercise intolerance was observed in patients with CVD. These findings suggest that the comorbidity of DM may serve as a stratification indicator for including lower-extremity strength training in CR programs to improve exercise capacity in patients with CVD.

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