Endocrine Journal 2021, **68** (3), 291-298

ORIGINAL

Effects of resistance training using elastic bands on muscle strength with or without a leucine supplement for 48 weeks in elderly patients with type 2 diabetes

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Abstract. Type 2 diabetes is associated with sarcopenia. Resistance training and appropriate nutritional therapy are reported to be effective for muscle strength and mass. This study aimed to evaluate the effect of resistance training using elastic bands at home combined with a leucine-rich amino acid supplement on muscle strength, physical function, and muscle mass in elderly type 2 diabetes. We conducted a 48-week prospective single-center randomized controlled trial in 60 patients who were randomly allocated to one of three groups: control (C), resistance exercise (R), and resistance exercise plus supplement (RL). R and RL groups performed daily bodyweight resistance training with elastic bands exercises at home, and the RL group also took 6 g of a leucine-rich amino acid supplement daily. Knee extension strength (muscle strength), grip strength, usual gait speed (physical function), muscle mass, and cognitive function were assessed at 0 and 48 weeks. Although the change in knee extension strength from baseline was significantly increased by 6.4 Nm (95% CI 1.0, 11.7) in the RL group (p = 0.036), no significant difference was observed among the three groups (p = 0.090). Physical function, muscle mass, and cognitive function also had no changes during the study period among the three groups. No additive effect of a leucine-rich amino acid supplement on muscle strength or mass was observed. Although a *post hoc* analysis comparing with or without resistance training (C group *vs.* R + RL group) found that knee extension strength was significantly increased (p = 0.028), and cognitive decline was less (p = 0.046) than in the C group.

Key words: Type 2 diabetes, Elderly, Japanese, Resistance training, Amino acid

SARCOPENIA is defined as a combination of loss of muscle mass and strength with age [1, 2]. Sarcopenia is a known risk factor for falls, fractures, disability, institutionalization, poor quality of life, and increased mortality [3]. Type 2 diabetes is associated with an increased risk of sarcopenia [4], and skeletal muscle strength and mass are generally lower in older adults with diabetes compared to those without [5]. The underlying mechanisms of sarcopenia development in diabetes include insulin resistance [6], chronic inflammation [7], mitochondrial dysfunction [8], advanced glycation end products [9], and neuropathy [10].

Several interventional studies have been investigated for preventing sarcopenia, including resistance training and nutritional supplement [11]. Resistance training is reported to be effective in decreasing fat mass, alleviating insulin resistance, and improving glycemic control in patients with diabetes [12]. However, many exercise programs designed to increase muscle strength and mass often require gym attendance, personal trainers, expensive machines, and a specific time period [13, 14], creating potential barriers. Hence, there is a need to establish exercise therapy that can be performed at home in elderly patients with diabetes. In older healthy adults, resistance training using elastic bands or tubes as the resistive load has been shown to be as effective as conventional resistance training using own weight or weight machines [15]. Protein supplements, especially essential amino acids including leucine have also been shown to promote muscle synthesis and its effectiveness to prevent sarcopenia has been investigated [16], although with varying results [17]. In a previous study, a dietary supplement of essential amino acids and arginine improved

Submitted Aug. 31, 2020; Accepted Sep. 25, 2020 as EJ20-0550
Released online in J-STAGE as advance publication Oct. 17, 2020
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muscle strength, physical function, and lean body mass compared to baseline values in older adults [18]. Additionally, resistance training combined with taking 6 g/day of a leucine-rich essential amino acid supplement has been reported to be more effective in preventing sarcopenia in older healthy Japanese women [19].

However, no evidence has been established for the effect of resistance training combined with an essential amino acid supplement in elderly patients with diabetes.

Therefore, the purpose of this study was to clarify the effects of resistance training using elastic bands on muscle strength and mass in elderly Japanese patients with type 2 diabetes. We also investigated whether a dietary leucine-rich essential amino acid supplement had an additive effect on the resistance training for the prevention of sarcopenia.

Materials and Methods

Study Design

This prospective, single-center, randomized, 48-week, 3-group, open trial was conducted in Kawasaki, Japan. Participants were recruited between December 2017 and July 2019 at the outpatient clinic of the St. Marianna University Hospital (Kawasaki, Japan). The clinical research ethics committee of the St. Marianna University School of Medicine (No. 3752) approved this study protocol, which complies with the revised ethical guidelines of the Declaration of Helsinki. Written informed consent was obtained from all patients. This study was registered with the University hospital Medical Information Network Clinical Trials Registry (registration number: UMIN000030639).

Participants

The inclusion criteria were as follows: 1) type 2 diabetes, 2) age between 70 and 79 years, and 3) patients who had no dementia with a Mini-Mental State Examination (MMSE) score of 24 or higher [20]. The exclusion criteria were as follows: 1) diabetic ketosis, 2) proliferative diabetic retinopathy, 3) chronic kidney disease, 4) a history of ischemic heart disease, 5) musculoskeletal disease, 6) acute infection, 7) diabetic foot, 8) severe diabetic autonomic neuropathy, 9) malignancy, 10) current treatment for type 2 diabetes with a sodium-glucose cotransporter 2 inhibitor, pioglitazone, or glucagon-like peptide 1 receptor agonist due to the effects of these drugs on body weight, and 11) patients who were considered to be ineligible for other reasons at the discretion of the attending doctor.

Intervention design

A total of 60 patients were randomly allocated to one of three groups (1:1:1), using the minimization method and taking into account gender: control (C) group, resistance exercise (R) group, and resistance exercise plus dietary leucine-rich supplement (RL) group. Patients in the C group did not receive any lifestyle modifications but were instructed to maintain their daily activities. As described below, patients in the R and RL groups were instructed to perform resistance training using elastic bands for about 15 minutes every day for 48 weeks. In addition, patients in the RL group were provided with a leucine-rich supplement. After 12, 24, and 48 weeks of the study period, patients had their muscle strength, body composition assessed.

Exercise

The exercise intervention program included both bodyweight resisted and elastic band (THERABAND®, D&M corp., Tokyo, Japan) exercises. Five models (#TBB-1 (yellow), #TBB-2 (red), #TBB-3 (green), #TBB-4 (blue), and #TBB-5 (black)) of elastic band were used. Higher numbers indicate a larger resistance load, and the resistance of each band on 100% elongation was 1.3, 1.7, 2.1, 2.6, and 3.3 kg, respectively [21]. At the beginning of the exercise program, women who did not habitually perform exercise started with #TBB-1, women who normally exercised started with #TBB-2, and all men started with #TBB-3.

All upper limb exercises were performed using the elastic bands as follows: 1) Tube fly: Stretch arms forward, holding band straight at chest level. Open arms horizontally for 3 seconds and return arms for 3 seconds; 2) Front raise: Sit and step on the band with both hands at navel level. Raise the band to parallel to the floor, stop 3 seconds, and then return to the starting position; 3) Hammer curl: Sit and step on the band with both hands at navel level. Bend the elbow, stop 3 seconds, and then return to the starting position.

Lower limb exercises were performed using an elastic band and own bodyweight as follows: 1) Leg extension: Sit on a chair with knees and ankles at 90 degrees. Wrap the elastic band around ankles. Keeping one leg bent, extend the opposite knee, and then return to the starting position; 2) Calf raise: Stand with feet apart—about the width of shoulders. Lift heels off the ground, hold for 2 seconds, and then return to the starting position. If stagger, lightly support with hand on wall; 3) Squat: Stand with feet apart—about the width of shoulders or slightly wider. Sit back and down as though sitting on an imaginary chair. Then stand back to the starting position.

Participants were instructed to perform each exercise 20 times every day. Participants recorded daily whether they performed the instructed exercise program. When individuals felt they could easily complete the 20 repetitions, the color of the elastic band was changed to the next color.

Amino acid supplement

The leucine-rich amino acid supplement (Amino L40®, AJINOMOTO Co., Inc., Tokyo, Japan) contained 13.3 kcal of energy, 3.0 g of protein (1.2 g of leucine, and 1.8 g of other amino acids), 0.04 g of fat, 0.2 g of carbohydrate [22]. Patients in the RL group were instructed to take the supplement twice a day (6 g daily), three hours after breakfast, and lunch for 48 weeks.

Outcomes

The primary outcome of this study was the change in muscle strength as evaluated by knee extension strength in each of the three groups. Knee extension strength was measured twice using handheld dynamometry (μTas MF-01, ANIMA corp., Tokyo, Japan) by trained physical therapists. The averaged value from two consecutive measurements was recorded.

Secondary outcomes included changes in grip strength, gait speed, body mass index (BMI), and lean body mass. Grip strength was measured using a hand dynamometer (JAMAR® Hydraulic Hand Dynamometer, Sammons Preston Inc., Canada) with patients in a standing position with their arms straight at their sides. Gait speed was measured by the researcher over a 6-m distance in time units (0.01 s) using a stopwatch.

A *post hoc* analysis was performed to verify the effect of home-based resistance training using the elastic band. In this analysis, we compared the two elastic training groups (R + RL groups) with the C group.

Bodyweight, lean body mass, and fat mass were measured by dual-energy x-ray absorptiometry (DEXA) (Lunar PRODIGY Advance, GE Healthcare Japan Corp., Tokyo, Japan). BMI was calculated as body weight divided by height squared (kg/m^2).

Participants were tested for cognitive function with MMSE at the time of giving consent and at the end of the study. Any adverse events were recorded throughout the intervention period.

Statistical analysis

The normality of data was checked using the Shapiro-Wilk test. Results are reported as mean ± standard deviation or median [interquartile range] according to the data distribution. To determine the sample size to examine the significance of the mean at baseline and after 48 weeks of intervention ($\alpha = 0.05$, power = 0.80), a sample size of 16 patients per group with an effect size of 10 Nm was calculated based on a previous study [19]. We recruited 20 cases in each group to anticipate any dropout.

The change from baseline to the end of the intervention in each group, the between-group difference (48-week–0-week), and the 95% confidence interval (CI) of the difference were calculated. Paired *t*-tests were used to evaluate the changes before and after the intervention. For the primary outcome, a one-way analysis of variance (ANOVA) was performed to evaluate any differences among the three groups. A two-sided *t*-test was also conducted as an exploratory analysis comparing the control with resistance training (C *vs.* R + RL). All analyses were performed using BellCurve for Excel (SSRI Inc, Tokyo, Japan), and $p < 0.05$ was considered to indicate a significant difference.

Results

We screened 67 patients for eligibility, and 60 were allocated a place in the intervention or control groups. Fig. 1 shows the loss of participants during the study period. Seven patients (C = 3, R = 2, RL = 2) were unable to complete the intervention after randomization due to lack of motivation ($n = 3$), hospitalization for depression ($n = 1$), complete atrioventricular block ($n = 1$), operation for lumbar spine stenosis ($n = 1$), and acute myocardial infarction ($n = 1$).

Baseline physical characteristics for the 53 patients are listed in Table 1, with no differences identified among groups. The mean age of all participants was 72.9 ± 2.4 years, with an approximately equal proportion of men and women (47% women). The mean BMI was 23.7 ± 3.8 kg/m^2, and the mean MMSE score was 28.7 ± 1.5. The mean adherence rate to the exercise program, calculated from self-reports of whether the patients exercised daily, during the 48-week intervention was 87.8% in the R group and 87.5% in the RL group. The number of the participants who changed the color of the elastic band to the next color during the study period was 4 (22%) in the R group and 4 (22%) in the RL.

Table 2 presents the changes in muscle strength, physical function, and body composition with the 48-week intervention. Although the change in knee extension strength from baseline was significantly increased by 6.4 Nm (95% CI 1.0, 11.7) in the RL group ($p = 0.036$), no significant difference was observed among the three groups ($p = 0.090$). Changes in grip strength and gait speed also had no significant differences among the three groups ($p = 0.121$ and $p = 0.195$, respectively). In addition, bodyweight, including body composition evaluated by DEXA, and glycemic control showed no changes during the study period. We also did not find any additive effects of a leucine-rich amino acid supplement on muscle strength. As a *post hoc* exploratory analysis, we combined the R group and the RL group into an exercise group to clarify the effect of resistance exercise using elastic bands. When comparing the exercise group and control group, the change in muscle strength was

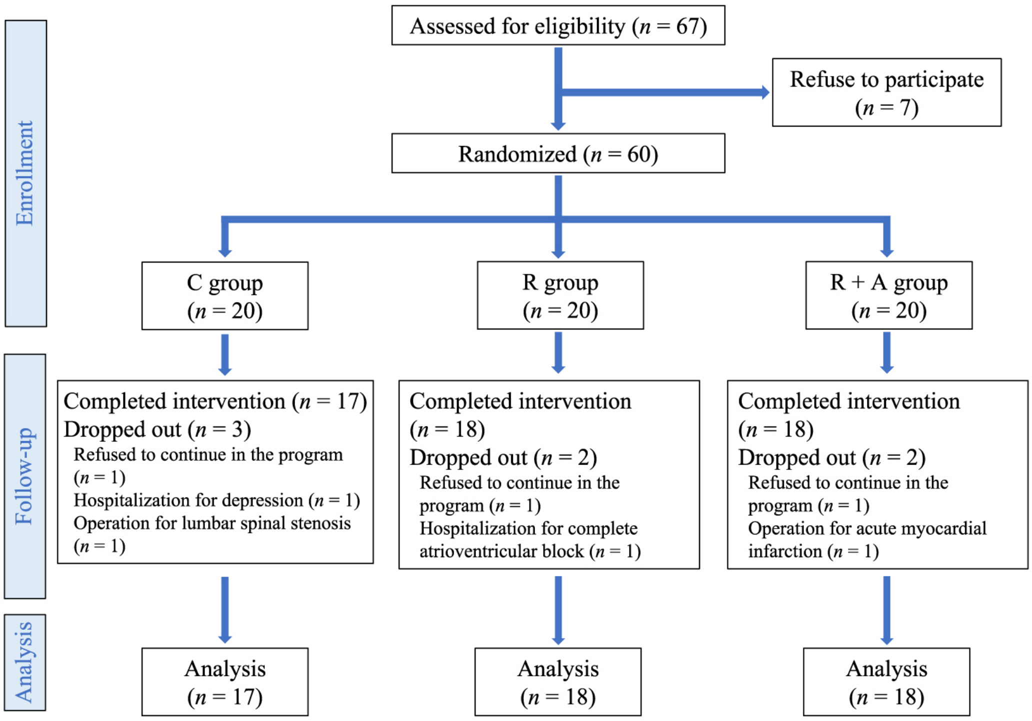

Fig. 1 Flow chart of study participants. Participants (n = 60) were randomly allocated to one of three groups: control group (c), resistance exercise group (R), resistance exercise plus leucine-rich essential amino acid supplement group (RL).

Table 1 Baseline clinical characteristics of participants

	C (n = 17)	R (n = 18)	RL (n = 18)	p value
Age	73.3 ± 2.5	73.2 ± 2.6	72.1 ± 2.1	0.281
Duration of diabetes (years)	17.3 ± 9.6	17.6 ± 10.0	16.0 ± 11.1	0.895
Sex (M/F)	10/7	9/9	9/9	0.834
Height (cm)	157.6 ± 7.8	158.9 ± 8.4	161.1 ± 8.4	0.478
Body weight (kg)	60.2 ± 10.4	60.4 ± 11.2	60.6 ± 10.8	0.995
BMI (kg/m^2)	24.4 ± 4.7	23.8 ± 3.0	23.3 ± 3.3	0.691
MMSE	28.5 ± 1.5	28.5 ± 1.7	29.1 ± 1.2	0.369
HbA1c (%)	7.0 ± 0.7	7.4 ± 0.9	7.3 ± 0.7	0.228
eGFR (mL/min)	59.0 ± 10.8	61.1 ± 8.7	63.4 ± 14.2	0.554
U-Alb (mg/gCr)	33.7 [7.7, 79.5]	12.3 [6.4, 61.3]	24.5 [8.5, 29.3]	0.679
Knee extension strength (Nm)	85.0 ± 27.5	82.8 ± 25.3	79.9 ± 15.0	0.821
Grip strength (kg)	26.0 ± 6.1	26.8 ± 7.4	28.6 ± 8.7	0.591
Gait speed (m/s)	1.20 ± 0.12	1.27 ± 0.19	1.22 ± 0.18	0.620
DEXA				
Lean body mass (kg)	42.5 ± 7.1	42.4 ± 7.5	44.7 ± 8.4	0.630
Fat mass (kg)	17.7 ± 6.7	18.0 ± 5.8	15.4 ± 6.6	0.445

mean ± SD or median [interquartile range]. DEXA, dual energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; MMSE, mini-mental state examination.

Table 2 Muscle strength, physical function, cognitive function, and body composition before and after 48 weeks of resistance training and supplement (mean [95% confidence interval]).

	group	Baseline (mean ± SD)	48 weeks (mean ± SD)	Δ48–0 weeks (mean)	95% Confidence Interval		*p*-value time points	*p*-value groups
					Lower	Upper		
Knee extension strength (Nm)	C	84.9 ± 27.5	81.6 ± 22.8	–3.4	–10.0	3.3	0.348	0.090
	R	82.8 ± 25.3	89.9 ± 32.3	7.1	–1.3	15.4	0.127	
	RL	79.9 ± 15.0	86.3 ± 20.0	6.4	1.0	11.7	0.036	
Grip strength (kg)	C	26.0 ± 6.1	25.4 ± 5.2	–0.6	–1.3	0.2	0.149	0.121
	R	26.8 ± 7.4	27.1 ± 8.2	0.3	–0.7	1.2	0.588	
	RL	28.6 ± 8.7	29.4 ± 8.9	0.8	–0.2	1.8	0.138	
Usual gait speed (m/s)	C	1.20 ± 0.21	1.17 ± 0.17	–0.03	–0.08	0.02	0.317	0.195
	R	1.27 ± 0.19	1.30 ± 0.14	0.03	–0.03	0.09	0.269	
	RL	1.22 ± 0.18	1.28 ± 0.19	0.06	–0.02	0.14	0.192	
MMSE	C	28.5 ± 1.5	27.5 ± 2.6	–1.0	–1.8	–0.2	0.030	0.075
	R	28.5 ± 1.7	28.7 ± 1.7	0.2	–0.4	0.8	0.592	
	RL	29.1 ± 1.2	28.7 ± 1.6	–0.4	–1.0	0.2	0.275	
HbA1c (%)	C	7.0 ± 0.7	6.8 ± 0.6	–0.2	–0.4	0.0	0.070	0.664
	R	7.4 ± 0.9	7.3 ± 0.8	–0.2	–0.6	0.2	0.409	
	RL	7.3 ± 0.7	7.3 ± 0.6	0.0	–0.2	0.2	0.752	
BMI (kg/m^2)	C	24.4 ± 4.7	24.1 ± 4.4	–0.2	–0.6	0.2	0.263	0.204
	R	23.7 ± 3.0	23.8 ± 3.0	0.1	–0.1	0.3	0.350	
	RL	23.3 ± 3.3	23.4 ± 3.4	0.1	–0.2	0.3	0.477	
Lean body mass (kg)	C	42.5 ± 7.1	42.6 ± 7.5	0.0	–0.5	0.6	0.896	0.742
	R	42.4 ± 7.5	42.6 ± 7.3	0.1	–0.4	0.6	0.595	
	RL	44.7 ± 8.4	44.6 ± 8.5	–0.2	–0.6	0.3	0.552	
Fat mass (kg)	C	17.7 ± 6.7	17.1 ± 6.6	–0.6	–1.4	0.2	0.195	0.159
	R	18.0 ± 5.8	18.1 ± 5.8	0.1	–0.3	0.5	0.771	
	RL	15.4 ± 6.6	15.7 ± 6.7	0.3	–0.3	0.8	0.347	

significantly increased in the exercise group compared with the C group (Table 3, $p = 0.028$). After 48 weeks, the mean change in the MMSE score was –1.00 ± 1.73 in the C group and –0.11 ± 1.35 in the exercise group, with a significant difference between the two groups ($p = 0.046$). No other differences were observed between the two groups. Whereas comparing with or without amino acid supplement (C + RL group *vs.* R group) showed no significant changes between the two groups (data not shown). No adverse effects were reported throughout the study period regarding exercise or the nutritional supplement.

Discussion

The present study assessed the effects of resistance training using elastic bands on muscle strength and mass in elderly Japanese patients with type 2 diabetes. The primary outcome—change in muscle strength as evaluated by knee extension strength—did not reach statistical significance among the three groups. Neither was an effect observed for a leucine-rich amino acid supplement on muscle mass or strength in older patients with type 2 diabetes. Although a *post hoc* analysis, muscle strength was significantly increased, while cognitive function was significantly preserved in the exercise group compared with the control group.

Change in muscle strength did not reach the statistical significance; likely because the change of 6.4 ± 11.6 Nm in the RL group was smaller than the 10 Nm originally anticipated. Resistance training using elastic bands might be insufficient for finding significant results in the present study. However, resistance training using elastic tubing was shown to be as effective as conventional

Table 3 Comparison of muscle strength, physical function, cognitive function, and body composition in control and resistance exercise group at 48 weeks.

	Control (*n* = 17)			Resistance exercise (*n* = 36)			Interaction *p*-value
	0 w	48 w	Δ48-0	0 w	48 w	Δ48-0	
Knee extension strength (Nm)	85.0 ± 27.5	81.6 ± 22.8	–3.4	81.4 ± 20.8	88.1 ± 26.9	6.7	0.028
Grip strength (kg)	26.0 ± 6.1	25.4 ± 5.2	–0.6	27.7 ± 8.1	28.3 ± 8.7	0.5	0.059
Usual gait speed (m/s)	1.20 ± 0.21	1.17 ± 0.17	–0.03	1.24 ± 0.19	1.29 ± 0.17	0.04	0.079
MMSE	28.5 ± 1.5	27.5 ± 2.6	–1.0	28.8 ± 1.5	28.7 ± 1.7	–0.1	0.046
HbA1c (%)	7.0 ± 0.7	6.8 ± 0.6	–0.2	7.4 ± 0.8	7.3 ± 0.7	–0.1	0.549
BMI (kg/m^2)	24.4 ± 4.7	24.1 ± 4.4	–0.2	23.5 ± 3.1	23.6 ± 3.2	0.1	0.073
DEXA							
Lean body mass (kg)	42.5 ± 7.1	42.6 ± 7.5	0.0	43.5 ± 8.0	43.5 ± 7.9	0.0	0.898
Fat mass (kg)	17.7 ± 6.7	17.1 ± 6.6	–0.6	16.7 ± 6.3	16.9 ± 6.4	0.2	0.062

mean ± SD

weight machines training in middle-aged to older healthy adults [15]. Additionally, the patients assigned to the exercise group showed high compliance with over 85% of their daily performance. Therefore, our result is unlikely to be due to insufficient exercise intensity or adherence. One possible reason for the small magnitude of change for the primary outcome could be that resistance training is less effective for diabetes. A previous study assessed lower muscle strength gains after resistance training in older men with type 2 diabetes [23]. According to an animal model for the analysis of diabetes-related sarcopenia [24], disruption to insulin/insulin-like growth factor-1 (IGF-1)-Akt signaling due to insulin resistance and low serum IGF-1 levels reduced muscle protein synthesis and provoked abnormalities in muscle strength and mass. In addition, phosphorylation of adenosine monophosphate-activated protein kinase due to reduced cellular uptake of glucose leads to suppression of muscle protein synthesis [25]. The results of these studies suggest that elderly patients with diabetes would be less trainable for muscle strength compared with their healthy counterparts.

In the present study, the effect of a leucine-rich amino acid supplement on muscle strength or mass was not obvious. Leucine promotes protein synthesis in human skeletal muscle through activation of the mammalian target of the rapamycin complex 1 signaling pathway *via* its metabolite acetyl-coenzyme A [26, 27]. However, our data showed no additive effect of a leucine-rich amino acid supplement on muscle mass. Regarding muscle strength, although a significant difference was only observed before and after the intervention in the RL group, the changes among groups did not reach the statistical significance. Older people appear to require 1.0 to 1.3 g/kg/day (60 to 78 g/day for the present study) of dietary protein to optimize physical function, particularly while undertaking resistance exercise [28]. Thus, the 6 g of daily amino acid supplement might have been insufficient to obtain an additive effect with resistance exercise in older patients with type 2 diabetes. In the present study, no adverse effect, including renal dysfunction, of a leucine-rich amino acid supplement was observed (data not shown). Thus, future studies are needed to determine whether a higher amount of a leucine-rich amino acid supplement in combination with resistance exercise will increase muscle strength or mass in older patients with type 2 diabetes.

Based on a *post hoc* analysis, it was suggested that the resistance exercise using elastic bands increased muscle strength in the combined R and RL group. This is the first study in which resistance training using low-cost elastic bands was shown to increase muscle strength in older patients with type 2 diabetes. In comparison, a previous study found that a home-based training program using resistance exercise bands for 16 weeks did not improve functional capacity, anthropometric measures, or glycemic control in obese patients with type 2 diabetes [29]. Similarly, in the present study, no significant difference was observed in the muscle strength at 24-week (data not shown). Therefore, a more extended intervention of 48-weeks was required to achieve a significant effect on muscle strength. However, no improvement in muscle mass was observed even after the longer intervention, which is consistent with a previous meta-analysis indicating that type 2 diabetes may have negative effects on the alterations of muscle mass [30].

The exercise group showed a significantly better MMSE score following the intervention compared with the control group. This finding is consistent with previous studies in which physical activity interventions resulted in better cognitive function in patients with diabetes [31, 32]. Although robust randomized controlled trials are needed, our result could help physicians recommend resistance training to their patients.

This study has several limitations. First, the sample size was relatively small, although we performed a sample size calculation before commencing the study. Also, the participants were only Japanese with a BMI of about 24 kg/m^2, and therefore the results may be difficult to generalize to other patient populations. Second, despite being randomly allocated, the patients who were allocated to the exercise group, especially to the RL group, might be highly motivated. Third, the instructions for resistance training using elastic bands were provided at the beginning of the study period. Thus, it was left to the initiative and judgment of each participant to change the band to a larger resistance one. Fourth, we did not evaluate dietary intake and physical activity. While the random allocation of groups should minimize any resulting bias and preserve comparability between groups, the possibility cannot be excluded that leucine-rich supplement of the RL group might have some effect even on this result.

In addition, the global pandemic of the new coronavirus infection (COVID-19) commenced toward the end of the study period. In the present study, 27 participants had not completed the study as of January 2020. Fortunately, however, no participants dropped out since then. However, this would not affect the obtained results because our study aimed to clarify the effect of resistance training performed at home. Rather, this has become one of the major strengths of the present study in the COVID-19 era. Another strength is the randomized design with a longer study period of 48-week compared with previous studies.

In conclusion, change in muscle strength as evaluated by knee extension strength in older patients with type 2 diabetes did not reach the statistical significance among the three groups: control, resistance exercise, and resistance exercise plus supplement. However, a *post hoc* analysis comparing with or without resistance training found that a 48-week home-based training using elastic bands might be effective in increasing muscle strength and maintaining cognitive function. Further study is warranted to confirm the effects of training using elastic bands on muscle strength and cognitive function.

Acknowledgements

The authors are indebted to Yuko Yasuda and the staff at the department of rehabilitation for their expert assistance with this study.

Disclosure

The authors declare no conflicts of interest.

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