

学 位 論 文

A Randomized Controlled Trial of Short-term Toe  
Resistance Training to Improve Toe Pinch Force in  
Patients with Type 2 Diabetes

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## A Randomized Controlled Trial of Short-term Toe Resistance Training to Improve Toe Pinch Force in Patients with Type 2 Diabetes

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Resistance training is effective against type 2 diabetes (T2DM), but the effect of resistance training on toe pinch force (TPF) is unknown. Here we investigated the effect of short-term toe resistance training on TPF in patients with T2DM, in a prospective, parallel-group, single-blind, randomized controlled trial. Twelve patients with T2DM who were hospitalized to improve glycemic control were enrolled. The patients were randomly allocated to the intervention (n=6) and control (n=6) groups. The intervention group performed traditional aerobic exercise and 4 newly developed toe-resistance training exercises. The control group performed aerobic exercise only. After 2 weeks of the exercise intervention program, we evaluated anthropometric parameters, clinical parameters, motor function, and muscle parameters in each patient. After the exercise intervention program, the TPF and toe muscle quality, isometric knee extension force, and knee muscle quality were significantly higher in the intervention group compared to the control group. Two weeks of toe-resistance training significantly increased the TPF in the T2DM patients. Toe resistance training is thus recommended in clinical practice for patients with T2DM.

**Key words:** randomized controlled trial, type 2 diabetes mellitus, toe resistance training, toe pinch force, toe muscle quality

Type 2 diabetes mellitus (T2DM) is caused by impaired insulin secretion and/or insulin resistance, resulting in chronic high-glucose levels. Proper glycemic control is a critical therapeutic approach, and exercise (e.g., walking and jogging) is one of the major therapeutic approaches to T2DM treatment in clinical practice. Resistance training has also been effective for individuals with T2DM, and it was shown to improve glycemic control [1-3] by increasing muscle strength [4, 5]. However, several of these studies targeted major muscles, and to our knowledge there has been no

investigation focusing on toe pinch force (TPF).

TPF is essential for postural stability during standing and/or walking [6, 7] and in the propulsive force of gait [8]. Several studies have demonstrated that TPF decreases with aging [6, 9, 10], and decreasing TPF is closely linked to falls in elderly people [7, 11, 12]. Despite its importance, TPF has not been adequately addressed in clinical practice compared to other muscle parameters such as lower limb muscle strength. In patients with T2DM, a lower TPF value leads to a higher risk of falls and fractures, which in turn can result in decreased activities of daily living and/or

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reduced quality of life. Therefore, evaluations of the effect of toe resistance training on TPF in patients with T2DM could provide useful information.

We demonstrated higher internal reproducibility and the correlation between TPF and other muscle strength parameters (external reproducibility) by using a newly developed TPF measurement procedure [13, 14]. We also observed that the TPF in patients with T2DM was significantly lower than that in patients without diabetes [15]. In another study, we also explored a short-term toe resistance training program that consists of 4 sessions, and the results demonstrated that TPF was significantly improved after the training program [16].

We conducted the present prospective, parallel-group, single-blind, randomized controlled trial (RCT) to determine the effect of short-term toe resistance training on the TPF in patients with T2DM.

## Patients and Methods

**Study design.** This study was a prospective, parallel-group, single-blind, RCT of Japanese patients with T2DM, all of whom provided written informed consent to participate. We randomly assigned the patients into the intervention and control groups. The research ethics committee of KKR Takamatsu Hospital approved this study (Approval no. E112). The original study protocol was registered in the University Hospital Medical Information Network (UMIN000026488).

**Study subjects.** The study populations was 12 patients with T2DM (nine men and three women, age  $63.8 \pm 12.0$  years, and duration of T2DM  $9.4 \pm 8.2$  years) who were hospitalized for 2 weeks from January 23 to April 15, 2017 at KKR Takamatsu Hospital, Kagawa, Japan, for glycemic control (Tables 1, 2). The study was conducted at a rehabilitation center in KKR Takamatsu Hospital. The patients were randomly assigned into intervention and control groups (Fig. 1). The exclusion criteria included the following: severe cardiac or lung disease, acute or chronic musculoskeletal disorders, acute metabolic dysregulation, other neurological or endocrine disorders, a history of stroke, metal implants such as bolts and metallic prosthetic joints, placement of a stent and/or pacemaker, previous or current asymmetric proximal lower leg weakness, and toe deformity or atrophy of foot muscles, as described [16].

**Sample size calculation.** In our earlier investiga-

tion [16], toe resistance training increased the TPF in patients with T2DM from  $2.92 \pm 1.19$  to  $3.65 \pm 1.58$  kg, indicating that the patients were able to improve their TPF by an average of 0.73 kg. We assumed a standard deviation of 0.37 of the response variable. Twelve patients were needed for 80% probability that the study would detect treatment differences at a two-sided 5% significance level.

**Exercise intervention program and toe-resistance training exercises.** The intervention group performed traditional aerobic exercise in the afternoon and four toe resistance training exercises [16] in the morning. The control group performed traditional aerobic exercise only, in the afternoon. The aerobic exercise was performed with a bicycle ergometer (AEROBIKE 2100R, Minato Medical Science Co. Osaka, Japan). The exercise intensity setting was calculated with the Karvonen method [16], and the exercise load was set at a moderate level. The exercise was performed 2 h after lunch for 30 min.

The 4 toe resistance training exercises were as follows [16]: (1) picking up a towel using toe fingers, (2) bending the toe fingers with a rubber tube, (3) bending the toe fingers with a rubber ball, and (4) grasping a small stick using the toe fingers. All procedures were performed 20 times by each foot with 3 sets every day for 2 weeks. Each of the 4 types of toe resistance training was performed at  $\geq 5$ -min intervals. During the weekends, the patients walked around the hospital, and the toe resistance training was performed in their hospital rooms.

**Measurement of muscle strength, skeletal muscle mass, and motor function.** The TPF measurements were performed using "Checker-kun," as described [13-16]. Each patient's handgrip strength, isometric knee extension force (KEF), skeletal muscle mass, knee muscle quality (KMQ), and toe muscle quality (TMQ), which are expressed as the ratio of the strength to the corresponding lower limb muscle mass in kilograms, were also measured as described [14, 16]. All of these parameters were measured twice, and the best records of the left and right arms and legs were averaged [14].

To evaluate motor function, we administered the single-leg standing test <[http://www.mext.go.jp/component/a\\_menu/sports/detail/\\_icsFiles/fieldfile/2010/07/30/1295079\\_04.pdf](http://www.mext.go.jp/component/a_menu/sports/detail/_icsFiles/fieldfile/2010/07/30/1295079_04.pdf)>, accessed 23 December 2016. (in Japanese), a functional reach test [17], and a walking speed test [18] as described.

Table 1 Clinical characteristics of the intervention and control groups

|                                     | Control       | Intervention  | <i>p</i> -value |
|-------------------------------------|---------------|---------------|-----------------|
| n (Male)                            | 6 (3)         | 6 (6)         |                 |
| Age (years)                         | 66.8 ± 9.8    | 60.8 ± 14.2   | 0.521           |
| Height (cm)                         | 159.9 ± 10.0  | 165.1 ± 0.1   | 0.336           |
| Body weight (kg)                    | 74.3 ± 20.6   | 69.8 ± 10.0   | 0.936           |
| BMI (kg/m <sup>2</sup> )            | 28.8 ± 5.9    | 25.5 ± 2.4    | 0.471           |
| SBP (mmHg)                          | 137.8 ± 9.2   | 125.2 ± 16.0  | 0.172           |
| DBP (mmHg)                          | 86.5 ± 6.9    | 74.5 ± 9.8    | 0.064           |
| HR (beat/min)                       | 80.2 ± 8.8    | 72.0 ± 10.5   | 0.108           |
| Duration of type 2 diabetes (years) | 9.8 ± 8.9     | 9.0 ± 8.4     | 0.935           |
| IPAQ (kcal/day)                     | 100.5 ± 120.8 | 182.6 ± 138.7 | 0.298           |
| HbA1c (%)                           | 9.7 ± 1.5     | 12.2 ± 2.5    | 0.128           |
| FBG (mg/dL)                         | 172.5 ± 43.3  | 211.0 ± 43.7  | 0.149           |
| Total cholesterol (mg/dL)           | 189.7 ± 33.4  | 199.8 ± 35.7  | 0.810           |
| Triglyceride (mg/dL)                | 145.5 ± 48.5  | 217.2 ± 171.3 | 1.000           |
| HDL-cholesterol (mg/dL)             | 51.2 ± 10.3   | 45.5 ± 10.6   | 0.377           |
| LDL-cholesterol (mg/dL)             | 115.7 ± 39.5  | 116.7 ± 30.9  | 1.000           |
| Serum creatinine (mg/dL)            | 0.76 ± 0.25   | 0.93 ± 0.48   | 0.575           |
| Albuminuria (mg/g·CRE)              | 12.3 ± 10.4   | 7.52 ± 6.5    | 0.379           |
| eGFR (mL/min/1.73m <sup>2</sup> )   | 72.9 ± 25.7   | 80.4 ± 29.6   | 0.575           |
| S-CPR (fasting) (ng/mL)             | 2.07 ± 0.90   | 1.38 ± 0.50   | 0.091           |
| S-CPR (postprandial) (ng/mL)        | 4.33 ± 1.88   | 2.25 ± 0.68   | 0.031           |
| ABI                                 | 1.13 ± 0.07   | 1.08 ± 0.01   | 0.172           |
| CAVI                                | 8.5 ± 1.6     | 8.4 ± 1.2     | 0.936           |
| Drinking habit (n)                  | 4             | 2             | 0.557           |
| Smoking habit                       |               |               |                 |
| Current smoker (n)                  | 0             | 1             |                 |
| Previous smoker (n)                 | 1             | 3             | 0.153           |
| Non smoker (n)                      | 5             | 2             |                 |
| Exercise habit (n)                  | 3             | 3             | —               |
| Neuropathy (n)                      | 1             | 1             | —               |
| Retinopathy                         |               |               |                 |
| None (n)                            | 5             | 6             |                 |
| Simple (n)                          | 1             | 0             | 0.224           |
| Nephropathy                         |               |               |                 |
| Stage 1 (n)                         | 6             | 6             | —               |
| Drug therapy                        |               |               |                 |
| none                                | 1             | 0             |                 |
| Insulin (n)                         | 0             | 3             |                 |
| OHA (n)                             | 5             | 2             | 0.041           |
| Insulin and OHA (n)                 | 0             | 1             |                 |

Value are presented as mean ± SD. Bold values indicate *p* < 0.05.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; IPAQ, international physical activity questionnaire; FBG, fasting blood glucose; eGFR, estimated glomerular filtration rate; S-CPR, Serum C-peptide immunoreactivity; ABI, ankle-brachial index; CAVI, cardio-ankle vascular index; OHA, oral hypoglycemic agent.

**Clinical and laboratory measurements.** We collected data on each patient's age, height, body weight, body mass index (BMI), duration of T2DM, systolic blood pressure, diastolic blood pressure, heart rate (HR), ankle-brachial index (ABI), cardio-ankle vascular index (CAVI), medications, and laboratory test results. The patients' levels of fasting plasma glucose

(FBG), hemoglobin A1c (HbA1c), total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, serum creatinine, and albumin, the estimated glomerular filtration rate and the serum C-peptide immunoreactivity (S-CPR) were measured by standard laboratory methods. Well-trained medical staff interviewed each patient using the

Table 2 Motor function and muscle parameters of the intervention group and control groups

|   | Control (n = 6) | Intervention (n = 6) | p-value |
|---|-----------------|----------------------|---------|
| <b>Motor function</b>                   |                 |                      |         |
| Single-leg standing (open eyes) (sec)   | 22.4 ± 26.3     | 42.6 ± 30.2          | 0.230   |
| Single-leg standing (closed eyes) (sec) | 5.87 ± 5.82     | 5.71 ± 8.04          | 0.575   |
| Functional reach (cm)                   | 29.8 ± 3.3      | 35.8 ± 6.0           | 0.147   |
| Comfortable walking speed (m/sec)       | 1.10 ± 0.25     | 1.21 ± 0.24          | 0.379   |
| Walking rate (steps/sec)                | 1.93 ± 0.35     | 1.95 ± 0.18          | 1.000   |
| Maximum walking speed (m/sec)           | 1.57 ± 0.51     | 1.88 ± 0.67          | 0.337   |
| Walking rate (steps/sec)                | 2.54 ± 0.39     | 2.50 ± 0.41          | 1.000   |
| <b>Muscle strength</b>                  |                 |                      |         |
| Handgrip strength (kg)                  | 26.1 ± 5.1      | 33.3 ± 7.5           | 0.093   |
| Knee extension force (kgf)              | 26.1 ± 10.7     | 39.9 ± 6.9           | 0.066   |
| Knee muscle quality (kgf/kg)            | 6.7 ± 1.5       | 10.5 ± 1.9           | 0.013   |
| Toe pinch force (kg)                    | 3.50 ± 1.09     | 4.48 ± 0.90          | 0.174   |
| Toe muscle quality (kg/kg)              | 2.68 ± 0.72     | 3.35 ± 0.90          | 0.298   |
| <b>Skeletal muscle mass</b>             |                 |                      |         |
| Upper extremity (kg)                    | 1.13 ± 0.34     | 1.25 ± 0.20          | 0.689   |
| Brachial region (kg)                    | 0.68 ± 0.23     | 0.74 ± 0.18          | 0.689   |
| Antebrachial region (kg)                | 0.45 ± 0.11     | 0.50 ± 0.07          | 0.471   |
| Lower extremity (kg)                    | 5.26 ± 1.71     | 5.23 ± 0.73          | 0.689   |
| Femoral region (kg)                     | 3.83 ± 1.25     | 3.85 ± 0.46          | 0.936   |
| Leg region (kg)                         | 1.32 ± 0.28     | 1.38 ± 0.31          | 0.688   |

Value are presented as mean ± SD. Bold values indicate  $p < 0.05$ .

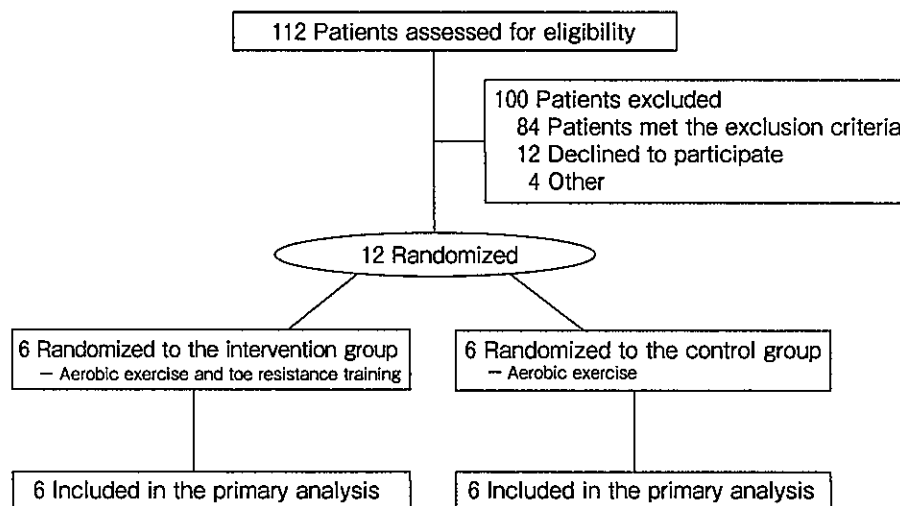


Fig. 1 Flow diagram of the T2DM patients enrolled in the study.

International Physical Activity Questionnaire (Short Version) [19] and to evaluate the patient's drinking, smoking, and exercise habits. Blood pressure (BP) and HR were measured with an HBR-2070 device (Omron Colin, Tokyo, Japan). The ABI and CAVI were measured with a VS-1500 device (Fukuda Denshi, Tokyo, Japan). Body weight, FBG, BMI, BP, HR, motor

function, and muscle parameters were also evaluated at the time of hospital discharge.

The diagnosis of T2DM was based on FBG and HbA1c levels as reported [16] and was performed according to the guidelines of the Japan Diabetes Society (JDS) [20]. Diabetic retinopathy, nephropathy, and neuropathy were also defined based on the diag-

nostic guidelines of the JDS [20].

**Outcome measures.** The primary outcome of this study was the effect of the short-term (2-week) toe resistance training on TPF. The secondary outcomes included TMQ, glycemic control, and motor function.

**Statistical analysis.** Data are expressed as the mean ± standard deviation. The Mann-Whitney U-test and  $\chi^2$  test were used to compare the clinical parameters between the control and intervention groups at baseline. The comparison of parameters between the 2 groups after the 2-week program was performed using the Mann-Whitney U-test, and *p*-values <0.05 were considered significant. All data were analyzed using JMP 12.2.0 software (SAS Institute, Cary, NC, USA).

### Results

Twelve Japanese patients with T2DM were recruited

and randomly assigned into the intervention group (*n*=6) and the control group (*n*=6). At baseline, the TPF in the intervention group was 4.48 ± 0.90 kg, and that in the control group was 3.50 ± 1.09 kg. Significant between-group differences in the baseline KMQ values (*p*=0.013) and postprandial S-CPR level (*p*=0.031) were noted. However, the other parameters showed no significant difference between the groups at baseline (Table 2).

The values of the parameters in the control and intervention groups at the end of the exercise intervention program are summarized in Table 3. After the exercise intervention program, the TPF of the intervention group was significantly higher than that of the control group (5.18 ± 0.74 vs. 3.44 ± 0.65 kg, *p*=0.008). The TMQ, KEF, and KMQ values of the intervention group were also significantly higher than those of the control group.

**Table 3** Clinical characteristics, motor function, and muscle parameter after exercise intervention program

|   | Mean ± SD (95% CI)            |                               | <i>p</i> -value |
|---|-------------------------------|-------------------------------|-----------------|
|   | Control ( <i>n</i> = 6)       | Intervention ( <i>n</i> = 6)  |                 |
| Body weight (kg)                        | 72.0 ± 19.2 (51.9 to 92.2)    | 69.2 ± 10.5 (58.3 to 80.3)    | 1.000           |
| BMI (kg/m <sup>2</sup> )                | 28.1 ± 5.5 (22.4 to 33.9)     | 25.3 ± 2.5 (22.7 to 28.0)     | 0.336           |
| FBG (mg/dL)                             | 126.2 ± 10.2 (115.5 to 136.9) | 125.3 ± 30.5 (93.3 to 157.4)  | 0.873           |
| SBP (mmHg)                              | 129.2 ± 12.1 (116.5 to 141.9) | 116.7 ± 15.0 (100.9 to 132.4) | 0.119           |
| DBP (mmHg)                              | 76.8 ± 6.8 (69.7 to 84.0)     | 69.3 ± 16.8 (51.7 to 87.0)    | 0.422           |
| HR (beat/min)                           | 79.0 ± 9.6 (68.9 to 89.1)     | 66.5 ± 9.9 (56.1 to 76.9)     | 0.093           |
| <b>Motor function</b>                   |                               |                               |                 |
| Single-leg standing (open eyes) (sec)   | 17.4 ± 19.9 (-3.50 to 38.3)   | 39.5 ± 30.0 (8.06 to 71.0)    | 0.575           |
| Single-leg standing (closed eyes) (sec) | 3.69 ± 2.62 (0.93 to 6.44)    | 5.89 ± 6.34 (-0.76 to 12.54)  | 0.810           |
| Functional reach (cm)                   | 31.0 ± 3.9 (26.9 to 35.1)     | 33.9 ± 7.0 (26.6 to 41.3)     | 0.336           |
| Comfortable walking speed (m/sec)       | 1.26 ± 0.20 (1.05 to 1.47)    | 1.34 ± 0.22 (1.11 to 1.56)    | 0.936           |
| Walking rate (steps/sec)                | 1.93 ± 0.62 (1.65 to 2.20)    | 1.97 ± 0.12 (1.84 to 2.09)    | 0.689           |
| Maximum walking speed (m/sec)           | 1.72 ± 0.31 (1.39 to 2.05)    | 2.24 ± 0.54 (1.67 to 2.80)    | 0.128           |
| Walking rate (steps/sec)                | 2.39 ± 0.35 (2.02 to 2.76)    | 2.67 ± 0.73 (1.90 to 3.44)    | 0.630           |
| <b>Muscle strength</b>                  |                               |                               |                 |
| Handgrip strength (kg)                  | 27.1 ± 4.7 (22.1 to 32.0)     | 36.0 ± 7.0 (28.7 to 43.3)     | 0.065           |
| Knee extension force (kgf)              | 27.4 ± 11.5 (15.3 to 39.5)    | 45.0 ± 10.4 (34.0 to 55.9)    | 0.031           |
| Knee muscle quality (kgf/kg)            | 7.2 ± 1.5 (5.6 to 8.8)        | 11.8 ± 2.1 (9.5 to 14.1)      | 0.031           |
| Toe pinch force (kg)                    | 3.44 ± 0.65 (2.76 to 4.12)    | 5.18 ± 0.74 (4.40 to 5.95)    | 0.008           |
| Toe muscle quality (kg/kg)              | 2.76 ± 0.45 (2.30 to 3.23)    | 3.88 ± 0.91 (2.92 to 4.83)    | 0.020           |
| <b>Skeletal muscle mass</b>             |                               |                               |                 |
| Upper extremity (kg)                    | 1.09 ± 0.37 (0.70 to 1.48)    | 1.25 ± 0.21 (1.03 to 1.48)    | 0.471           |
| Brachial region (kg)                    | 0.64 ± 0.21 (0.42 to 0.87)    | 0.77 ± 0.17 (0.59 to 0.95)    | 0.336           |
| Antebrachial region (kg)                | 0.47 ± 0.13 (0.34 to 0.61)    | 0.48 ± 0.06 (0.42 to 0.54)    | 0.575           |
| lower extremity (kg)                    | 5.06 ± 1.54 (3.44 to 6.68)    | 5.19 ± 0.75 (4.40 to 5.97)    | 0.689           |
| Femoral region (kg)                     | 3.79 ± 1.26 (2.47 to 5.10)    | 3.79 ± 0.50 (3.27 to 4.32)    | 0.575           |
| Leg region (kg)                         | 1.27 ± 0.31 (0.94 to 1.60)    | 1.39 ± 0.35 (1.02 to 1.76)    | 0.748           |

BMI, body mass index; FBG, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. Bold values indicate *p* < 0.05.

## Discussion

We evaluated the effect of short-term toe resistance training on the TPF in patients with T2DM in a randomized controlled trial. Our analyses demonstrated that the TPF as a main outcome in the intervention group was significantly higher than that in the control group after the intervention. Moreover, significantly higher levels of the secondary outcomes TMQ, KEF, and KMQ were also noted in the intervention group. Thus, the force parameters of toe pinch force and isometric knee extension force were higher in the intervention group than in the control group after the intervention.

During the initial stage of resistance training, muscle hypertrophy is not generally observed, but only muscle strength increases, as suggested by Kraemer *et al.* [21], who hypothesized that neural factor, which increases and synchronizes the motor units of muscle fibers, is closely associated with the initial increased muscle strength. Moritani *et al.* [22] reported that neural factor is associated with increasing muscle strength within approx. 3 weeks and muscle hypertrophy is observed after around 4 weeks. In addition, increasing muscle strength without muscle hypertrophy was reported in other studies [23, 24]. In our present investigation, no skeletal muscle mass changes in the femoral region (pre:  $3.85 \pm 0.46$ , post:  $3.79 \pm 0.50$  kg) and leg region (pre:  $1.38 \pm 0.31$ , post:  $1.39 \pm 0.35$  kg) were identified (Tables 2, 3). In addition, the muscle quality (muscle strength/skeletal muscle mass) of the toe and knee was significantly higher in the intervention group than in the control group, which was consistent with the previous hypothesis. Moreover, the higher KEF in the intervention group compared to the control group after the 4 toe-resistance training exercises suggested that toe-resistance training could improve KEF without targeting it. The four toe-resistance training exercises were easily performed and could be a useful exercise strategy in clinical practice.

Allet *et al.* [25] showed that balance function and walking ability are significantly increased by a combination of resistance training, balance training, and walking for 12 weeks. Richardson *et al.* [26] reported that the results of single-leg standing test and functional reach test were significantly improved for 3 weeks by resistance training and balance training in patients with T2DM with diabetic neuropathy. These results suggest

that physical therapy could improve motor function in patients with T2DM. In the present study, however, no differences in motor function based on the results of the single-leg standing test, functional reach test, and walking speed test were found. Our training program was only 2 weeks long, and was comprise of only toe resistance training (not other resistance and/or balance training) and walking exercise. This may be why we did not observe an increase in motor function in this study. In patients with T2DM, falls and fractures are common [27], and a long-term program targeting improved motor function is vital.

The performance rate of exercise therapy is only 52.3%, as previously reported [28]. The effect of exercise therapy requires a certain minimum period of time and continuous motivation. Nevertheless, our 2-week program increased the patients' TPF, TMQ, KEF, and KMQ, and these improvements could help increase and maintain patients' motivation for performing exercise therapy. In addition, the 4 toe-resistance training exercises can be performed in a sitting position and can be done by patients with lower activity levels, such as elderly people, patients with lower limb pain and/or disability, patients who cannot walk, patients at high risk for falls, and those with a diabetic foot. Therefore, TPF training might be a useful therapeutic approach for patients with T2DM.

This study has potential limitations. First, patients with diabetic neuropathy were included. The TPF and KEF in T2DM patients with diabetic neuropathy were reported to be significantly lower than those in T2DM patients without diabetic neuropathy [15, 29], but an association between TPF and diabetic neuropathy was not been identified in this study. Second, we evaluated only the short-term effects of toe resistance training.

In conclusion, the short-term toe resistance training improved our T2DM patients' toe pinch force as well as their toe muscle quality, isometric knee extension force, and knee muscle quality, which indicates that the program could be a useful exercise strategy for individuals with T2DM. Hence, toe resistance training is recommended in clinical practice for patients with T2DM. The long-term effect of the training program and the association between TPF and complications such as diabetic neuropathy must be evaluated in future studies.

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