Diabetic polyneuropathy is a risk factor for decline of lower extremity strength in patients with type 2 diabetes

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ABSTRACT

Aims/Introduction: The present study elucidated the effect of diabetic polyneuropathy (DPN) on lower extremity strength in a wide age range of type 2 diabetes patients.

Materials and Methods: Participants (n = 1,442) were divided into three age groups (30–49 years, 50–69 years and 70–87 years), and comparisons were made separately for each sex. Lower extremity strength was measured in terms of knee extension force (KEF) with a hand-held dynamometer. KEF was compared according to the presence or absence of DPN. Furthermore, the effect of DPN on KEF with other diabetic complications (diabetic retinopathy and diabetic nephropathy), diabetes status (diabetes duration and glycated hemoglobin) and habitual behavior (regular exercise, smoking and drinking behaviors) as explanatory variables was analyzed using multiple regression analysis in several models.

Results: The frequency of DPN differed among age groups, ranging from 14.3 to 49.6%, and increasing with age. There was no significant difference in KEF between patients aged 30–49 years with and without DPN. However, among both men and women aged 50–69 years and 70–87 years, patients with DPN showed significantly diminished KEF (11.0–12.9% and 11.9–16.6%, respectively) compared with those without DPN (P < 0.01–0.001). In women aged 50–69 years and 70–87 years, and in men aged 50–69 years, DPN was a significant explanatory variable for KEF in all multiple regression analysis models.

Conclusion: DPN might reinforce a KEF decline in middle-aged and elderly type 2 diabetes patients.

INTRODUCTION

In diabetic polyneuropathy (DPN), motor symptoms are not as noticeable compared with sensory symptoms. Recently, motor skills disorders for diabetes patients have been quantified1. The gradual loss of muscle strength in type 2 diabetes is related to the presence and severity of DPN2,3. Accordingly, consideration of DPN is crucial in investigations of diminished muscle strength in diabetes patients. However, no such population-based studies have been carried out, and the characteristics of diminished muscle strength have not been determined according to sex or broad age groups. Furthermore, investigating the degree of muscle strength loss resulting from DPN and the characteristics of high-risk patients who show diminished muscle strength is considered important for diabetes education and approaches to public health. In a cross-sectional investigation, the population-based Health ABC study showed that diabetes is associated with lower muscle strength in elderly patients4. A longitudinal investigation in the same study showed that diabetes accelerates loss of muscle strength with aging5; the loss of muscle strength was clarified using a measurement device, as well as from the results of several surveys. However, the effect of DPN on muscle strength was not investigated.

To address this, we carried out a multicenter study that investigated lower extremity strength and DPN in a wide age range of type 2 diabetes patients. The present study characterized lower extremity strength in type 2 diabetes patients by sex and age groups based on the presence of DPN.
METHODS
In the Multicenter Survey of the Isometric Lower-Extremity Strength in Type 2 Diabetes (MUSCLE-std) Study, we collected data from 30 hospitals in Japan between April 2010 and March 2015. The names of these 30 hospitals and the physical therapists that assisted in the data collection are listed in the supporting information Data S1. Inclusion criteria consisted of type 2 diabetes patients aged 30–89 years visiting a hospital on either an inpatient or outpatient basis. Exclusion criteria included the following: inability to adapt to exercise therapy, inability to walk independently, significant limitations in activities of daily living, severe heart and/or respiratory diseases, severe liver dysfunction and/or renal failure (serum creatinine >2.0 mg/dL), patients with acute or chronic orthopedic disease who were presently receiving medical treatment, non-symmetry of bilateral lower extremity muscular atrophy, impairment of the lower extremities, severe infectious disease, or patients requiring surgical treatment. The present study was carried out with the approval of the research ethics committee of Kansai University of Welfare Sciences (the principal researcher’s affiliated institution), as well as the research ethics committee or directors of all cooperating institutions. We registered the present study with UMIN-CTR (UMIN000002810). All patients provided written informed consent. Data were collected for 1,704 type 2 diabetes patients; after excluding 262 patients with incomplete data for body height, bodyweight, serum creatinine, diabetes duration, knee extension force (KEF), regular exercise habit, smoking habit and drinking habit, the analysis ultimately included 1,442 patients aged 30–87 years. Fasting plasma glucose values were not available for 77 men and 77 women, thus they were not included in the analysis. In contrast, glycated hemoglobin (HbA1c) values were not available for one man and one woman, each of whom was aged 50–69 years, but they were included in the analysis.

Diabetes assessment
Type 2 diabetes was diagnosed in accordance with criteria established by the American Diabetes Association. Newly diagnosed diabetes was considered as a diabetes duration of 0 years. Diabetes duration ranged from 0 to 45 years with a median duration of 7 years. Diabetic retinopathy was classified as none, simple, preproliferative or proliferative. Diabetic nephropathy was classified as prenephrinopathy (stage 1), incipient nephropathy (stage 2), overt nephropathy (stage 3) or renal failure (stage 4). Diabetic neuropathy was diagnosed in patients who fulfilled at least two of the following criteria: complaint of bilateral sensory symptoms in the toes and the soles of the feet (specifically, at least two of the following: numbness, pain and dyesthesia), bilateral diminished or absent Achilles tendon reflex, and bilateral decreased vibratory sensation in the medial malleoli.

Knee extension force assessment
Measurements of maximum isometric KEF values were obtained using a handheld dynamometer with belt stabilization (µTas MT-1 or µTas F-1; Anima Inc., Tokyo, Japan) with the participants in a sitting position at 90° hip joint flexion and 90° knee joint flexion. The non-dominant leg (the pivot leg, i.e., the leg with which an individual would not kick a ball) was designated as the leg from which the measurements were to be carried out. The length of the lower leg (moment arm) was measured from the knee joint space to the center of the sensor pad of the muscle strength-measuring instrument. The absolute value for isometric KEF (N) multiplied by the moment arm (m) was used to calculate the KEF (Nm). Furthermore, relative KEF (Nm/kg) was calculated by dividing KEF (Nm) by bodyweight (kg) and used in the analyses.

Habitual behavior assessment
Exercise behavior was defined as two sessions of exercise per week of at least 30-min duration. Stages of behavior change were assessed based on the transtheoretical model; participants who continued exercise behavior for at least 6 months (maintenance stage or later) were defined as engaging in regular exercise. Participants who had smoked for the past month or more and who had smoked every day or occasionally within the past month were defined as current smokers. Participants who consumed at least 20 g of pure alcohol in 1 day at least three times per week were defined as habitual alcohol drinkers.

Statistical analysis
Both men and women were divided into three groups based on age (30–49 years, 50–69 years and 70–87 years); data were compared among these three groups, with separate comparisons for men and women. Quantitative variables were compared between groups using the Kruskal–Wallis test; subsequent multiple comparisons were carried out using Tukey’s multiple comparison test. Qualitative variables were compared using the χ²-test; subsequent multiple comparisons were carried out using Z-tests. KEF, diabetes status (diabetes duration and HbA1c levels), other diabetic complications (diabetic retinopathy and diabetic nephropathy) and habitual behavior (regular exercise, smoking and drinking behaviors) were compared between the presence and absence of DPN by age group using the Mann–Whitney U-test or χ²-test, with separate comparisons for men and women.

The effect of DPN, in conjunction with diabetes status, other diabetic complications and habitual behavior, on KEF was analyzed by age and sex group using multiple regression analysis. The absence or presence of DPN (1 and 2, respectively) was used as an explanatory variable. Diabetic retinopathy and diabetic nephropathy were also considered as explanatory variables, and were defined as follows: for diabetic retinopathy, ‘none’ was defined as ‘1’, whereas ‘simple retinopathy or more severe retinopathy’ was defined as ‘2’; and for diabetic nephropathy, stage <3 was defined as ‘1’, whereas stage ≥3 was defined as ‘2’. These definitions of the explanatory variables were entered into all analysis models. The explanatory variables for model 1 were DPN, diabetic retinopathy and diabetic nephropathy. For model 2, explanatory variables included those...
RESULTS

Body mass index decreased with age in both men and women (Table 1). Diabetes duration increased as age increased; the mean diabetes duration in participants aged 70–87 years was 12.3 years and 13.3 years for men and women, respectively. Mean HbA1c ranged from 8.6 to 10.6%, and decreased as age increased; HbA1c was highest among participants aged 30–49 years for both men and women. DPN appeared more frequently as age increased in both men and women, and was most common among participants aged 70–87 years (49.6% of men and 47.5% of women). The prevalence of diabetic retinopathy also significantly increased with age in men, but not in women. There was no difference in the prevalence of diabetic nephropathy. The frequency of participants who exercised regularly was highest among patients aged 70–87 years (43.8% of men and 35.0% of women), and decreased as age decreased. The frequency of current smokers was highest among participants aged 30–49 years (45.2% of men and 27.8% of women). The percentage of alcohol drinkers among men was highest among patients aged 50–69 years (55.8%); women, however, showed no significant differences among age groups.

Figure 1 shows relative KEF (Nm/kg) by sex and the presence or absence of DPN. In comparisons of KEF by sex and age group, neither men nor women aged 30–49 years showed a significant difference in KEF based on DPN. However, among both men and women patients aged 50–69 years and 70–87 years, patients with DPN showed significantly diminished

Table 1 | Participant characteristics by sex and age

|                      | 30–49 years-of-age | 50–69 years-of-age | 70–87 years-of-age | P-value |
|----------------------|--------------------|--------------------|--------------------|---------|
| **Men**              |                    |                    |                    |         |
| Body height (cm)     | 170.8 ± 6.4†       | 167.4 ± 6.3‡       | 162.2 ± 6.1§       | <0.001  |
| Bodyweight (kg)      | 80.0 ± 16.2†       | 69.4 ± 12.7‡       | 61.8 ± 9.9§        | <0.001  |
| BMI (kg/m²)          | 27.3 ± 5.0†        | 24.7 ± 4.0‡        | 23.4 ± 3.2§        | <0.001  |
| Diabetes duration (years) | 4.4 ± 4.7†     | 9.0 ± 8.0‡         | 13.3 ± 10.3§       | <0.001  |
| HbA1c (%)            | 106.2 ± 24†        | 91.1 ± 2.1‡        | 86.2 ± 1.8§        | <0.001  |
| Fasting plasma glucose (mg/dL) | 172.9 ± 765 | 158.1 ± 65.2       | 1564 ± 512 NA      |         |
| Diabetic neuropathy  | 52 (24.8)†        | 170 (37.2)‡        | 112 (49.6)§        | <0.001  |
| Diabetic retinopathy | 30 (14.3)†        | 122 (26.7)‡        | 61 (27.0)‡         | <0.001  |
| Diabetic nephropathy | 16 (7.6)†         | 46 (10.1)‡         | 28 (12.4)NS        |         |
| Exercise regularly   | 26 (12.4)†        | 120 (26.3)‡        | 99 (43.8)§         | <0.001  |
| Current smoker       | 95 (45.2)†        | 149 (32.6)‡        | 31 (13.7)§         | <0.001  |
| Alcohol drinker      | 76 (36.2)†        | 255 (55.8)‡        | 91 (40.3)§         | <0.001  |
| **Women**            |                    |                    |                    |         |
| Body height (cm)     | 157.8 ± 6.6†       | 154.1 ± 5.7‡       | 150.3 ± 5.2§       | <0.001  |
| Bodyweight (kg)      | 73.1 ± 17.4†       | 59.5 ± 10.8‡       | 52.8 ± 10.2§       | <0.001  |
| BMI (kg/m²)          | 29.2 ± 6.5†        | 25.0 ± 4.1‡        | 23.3 ± 4.2§        | <0.001  |
| Diabetes duration (years) | 4.4 ± 4.3†     | 8.8 ± 8.1‡         | 12.3 ± 6.3§        | <0.001  |
| HbA1c (%)            | 100.0 ± 23.3†      | 92.2 ± 22.3‡       | 86.2 ± 20.0§       | <0.001  |
| Fasting plasma glucose (mg/dL) | 1655 ± 617 | 1568 ± 57.7       | 1602 ± 68.8 NA     |         |
| Diabetic neuropathy  | 17 (23.6)†        | 117 (36.9)‡†       | 76 (47.5)‡§        | <0.002  |
| Diabetic retinopathy | 16 (22.2)†        | 88 (27.8)‡         | 57 (35.6)NS        |         |
| Diabetic nephropathy | 10 (13.9)†        | 20 (6.3)‡          | 18 (11.3)NS        |         |
| Exercise regularly   | 7 (9.7)†          | 80 (25.2)‡         | 56 (35.0)§†        | <0.001  |
| Current smoker       | 20 (27.8)†        | 34 (10.7)‡         | 8 (5.0)§           | <0.001  |
| Alcohol drinker      | 13 (18.1)†        | 56 (17.7)‡         | 19 (11.9)NS        |         |

Data are mean ± SD or n (%). P-values were derived from Kruskal–Wallis tests or χ²-tests. Results from Z-test or Tukey’s multiple test values showing †, ‡ or § are not different when the same symbol is present, and are significantly different when a different symbol is present (Z-test of Tukey’s multiple comparison test). BMI, body mass index; HbA1c, glycated hemoglobin; NA, not analyzed owing to some missing data; NS, not significant.
Men

Knee extension force (N m/kg)

0 30–49 years old 50–69 years old 70–87 years old

Without diabetic polyneuropathy With diabetic polyneuropathy

Women

Figure 1 | Isometric knee extension force in type 2 diabetes patients without neuropathy (□) and with neuropathy (■). Values are mean ± SD. **P < 0.001 and *P < 0.03 compared with patients without diabetic polyneuropathy (Mann–Whitney U-test).

Table 2 | Knee extension force and characteristics of type 2 diabetes patients with and without diabetic polyneuropathy

| Characteristics (units) | Men | | | | Women | | | |
|-------------------------|-----|--------|------------------|--------|------|--------|------------------|--------|------|
|                        |     | Without DPN | With DPN | P-value |     | Without DPN | With DPN | P-value |
| 30–49 years-of-age      | n = 158 | 159.2 ± 50.6 | 154.7 ± 48.1 | NS | n = 55 | 95.6 ± 36.9 | 95.0 ± 38.9 | NS |
| KEF (Nm)                | 1.99 ± 0.51 | 1.92 ± 0.48 | NS | 1.35 ± 0.52 | 1.29 ± 0.46 | NS |
| Diabetic retinopathy    | 9 (5.7) | 21 (40.4) | <0.001 | 7 (12.7) | 9 (52.9) | <0.001 |
| Diabetic nephropathy    | 7 (4.4) | 9 (17.3) | <0.01 | 5 (9.1) | 5 (29.4) | <0.05 |
| Diabetes duration (years) | 3.4 ± 4.0 | 69 ± 6.0 | <0.001 | 38 ± 4.1 | 58 ± 5.1 | NS |
| HbA1c (%)               | 10.6 ± 2.4 | 108 ± 2.6 | NS | 9.9 ± 2.3 | 10.3 ± 2.2 | NS |
| Exercise regularly      | 20 (12.7) | 6 (11.5) | NS | 5 (9.1) | 2 (11.8) | NS |
| Current smoker          | 76 (48.1) | 19 (36.5) | NS | 17 (30.9) | 3 (17.6) | NS |
| Alcohol drinker         | 59 (37.3) | 17 (32.7) | NS | 10 (18.2) | 3 (17.6) | NS |
| 50–69 years-of-age      | n = 287 | 118.7 ± 37.7 | 118 ± 2.6 | <0.001 | n = 200 | 70.3 ± 23.4 | 70.3 ± 23.4 | <0.001 |
| KEF (Nm)                | 1.95 ± 0.51 | 1.70 ± 0.45 | <0.001 | 1.39 ± 0.45 | 1.16 ± 0.35 | <0.001 |
| Diabetic retinopathy    | 45 (15.7) | 77 (45.3) | <0.001 | 38 (19.0) | 50 (42.7) | <0.001 |
| Diabetic nephropathy    | 13 (4.5) | 33 (19.4) | <0.001 | 8 (4.0) | 12 (10.3) | <0.05 |
| Diabetes duration (years) | 8.6 ± 6.8 | 125 ± 8.6 | <0.001 | 73 ± 7.2 | 113 ± 9.1 | <0.001 |
| HbA1c (%)               | 9.2 ± 2.3 | 90 ± 1.8 | NS | 8.9 ± 2.2 | 9.7 ± 2.1 | <0.01 |
| Exercise regularly      | 75 (26.1) | 45 (26.5) | NS | 66 (33.0) | 14 (120) | <0.001 |
| Current smoker          | 89 (31.0) | 60 (35.3) | NS | 19 (9.5) | 15 (12.8) | NS |
| Alcohol drinker         | 147 (51.2) | 108 (63.5) | <0.05 | 41 (20.5) | 15 (12.8) | NS |
| 70–87 years-of-age      | n = 114 | 118.7 ± 37.7 | <0.01 | 61.9 ± 21.7 | 549 ± 17.9 | <0.05 |
| KEF (Nm)                | 1.64 ± 0.52 | 1.46 ± 0.44 | <0.001 | 1.8 ± 0.39 | 1.04 ± 0.29 | <0.001 |
| Diabetic retinopathy    | 22 (19.3) | 39 (34.8) | <0.05 | 22 (26.2) | 35 (46.1) | <0.05 |
| Diabetic nephropathy    | 12 (10.5) | 16 (14.3) | NS | 5 (6.0) | 13 (17.1) | <0.05 |
| Diabetes duration (years) | 11.6 ± 9.2 | 150 ± 11.8 | <0.05 | 92 ± 8.0 | 15.6 ± 98 | <0.001 |
| HbA1c (%)               | 8.0 ± 1.9 | 9.1 ± 2.2 | <0.001 | 8.6 ± 2.1 | 8.7 ± 1.8 | NS |
| Exercise regularly      | 62 (54.4) | 37 (33.0) | <0.001 | 35 (41.7) | 21 (27.6) | NS |
| Current smoker          | 17 (14.9) | 14 (12.5) | NS | 3 (3.6) | 5 (6.6) | NS |
| Alcohol drinker         | 56 (49.1) | 35 (31.3) | <0.01 | 13 (15.5) | 6 (7.9) | NS |

Data are mean ± SD or n (%). DPN, diabetic polyneuropathy; HbA1c, glycated hemoglobin; KEF, knee extension force; KEF (Nm), knee extension force (N) multiplied by moment arm (m); KEF (Nm/kg), knee extension force (Nm) divided by bodyweight (kg); NS, not significant.
KEF (11.0–12.9%, 11.9–16.6%, respectively) compared with those without DPN ($P < 0.01$–$0.001$). Table 2 shows KEF (Nm), relative KEF (Nm/kg) and characteristics (diabetes status, other diabetic complications and habitual behavior) by sex and age group. The trend for a decline in relative KEF (Nm/kg) for patients with DPN was similar to that for KEF (Nm). Compared with patients without DPN, patients with DPN tended to have prolonged diabetes duration, and a high incidence rate of diabetic retinopathy and diabetic nephropathy. In contrast, HbA1c levels for patients with DPN were not always high in comparison with patients without DPN. DPN was not associated with habitual behavior.

Table 3 shows the results of multiple regression analysis for relative KEF (Nm/kg) as the response variable. Participants aged 30–49 years did not show an association between KEF and all explanatory variables. However, in women aged 50–69 years and 70–87 years, and in mean aged 50–69 years, DPN was a significant explanatory variable for KEF. Furthermore, in both men and women aged 50–69 years and 70–87 years, regular exercise behavior was a significant explanatory variable for KEF.

### DISCUSSION

Patients with type 2 diabetes have reduced lower extremity muscle strength compared with age-matched control subjects. 

In the present study, both men and women participants aged 50–69 years and 70–87 years with DPN showed significantly reduced KEF. The trend for a decline in KEF (Nm/kg, relative KEF) for patients with DPN compared with patients without DPN and compared with age-matched control subjects was observed.

| Explanatory variables                  | 30–49 years-of-age | 50–69 years-of-age | 70–87 years-of-age |
|----------------------------------------|--------------------|--------------------|--------------------|
| **Men**                                |                    |                    |                    |
| Model 1 Diabetic polyneuropathy        | 0.001              | 0.001              |                    |
| Model 1 Diabetic retinopathy           | −0.117             | −1.397             |                    |
| Model 1 Diabetic nephropathy           | −0.039             | −0.502             |                    |
| Model 2 Diabetic polyneuropathy        | 0.003              | 0.034              |                    |
| Model 2 Diabetic retinopathy           | −0.125             | −1.431             |                    |
| Model 2 Diabetic nephropathy           | −0.038             | −0.484             |                    |
| Model 2 Diabetes duration              | −0.028             | −0.395             |                    |
| Model 2 HbA1c                          | 0.007              | 0.086              |                    |
| Model 3 Diabetic polyneuropathy        | 0.003              | 0.043              |                    |
| Model 3 Diabetic retinopathy           | −0.131             | −1.500             |                    |
| Model 3 Diabetic nephropathy           | −0.019             | −0.239             |                    |
| Model 3 Diabetes duration              | 0.013              | 0.172              |                    |
| Model 3 HbA1c                          | −0.007             | −0.100             |                    |
| Model 3 Exercise behavior              | 0.121              | 1.715              |                    |
| Model 3 Smoking behavior               | 0.015              | 0.221              |                    |
| Model 3 Drinking behavior              | 0.044              | 0.623              |                    |
| **Women**                              |                    |                    |                    |
| Model 1 Diabetic polyneuropathy        | 0.021              | 0.256              |                    |
| Model 1 Diabetic retinopathy           | −0.125             | −0.910             |                    |
| Model 1 Diabetic nephropathy           | −0.075             | −0.577             |                    |
| Model 2 Diabetic polyneuropathy        | 0.040              | 0.298              |                    |
| Model 2 Diabetic retinopathy           | −0.113             | −0.807             |                    |
| Model 2 Diabetic nephropathy           | −0.082             | −0.599             |                    |
| Model 2 Diabetes duration              | −0.057             | −0.439             |                    |
| Model 2 HbA1c                          | −0.098             | −0.766             |                    |
| Model 3 Diabetic polyneuropathy        | 0.035              | 0.258              |                    |
| Model 3 Diabetic retinopathy           | −0.129             | −0.901             |                    |
| Model 3 Diabetic nephropathy           | −0.104             | −0.747             |                    |
| Model 3 Diabetes duration              | −0.109             | −0.813             |                    |
| Model 3 HbA1c                          | −0.097             | −0.723             |                    |
| Model 3 Exercise behavior              | −0.036             | −0.284             |                    |
| Model 3 Smoking behavior               | −0.185             | −1.446             |                    |
| Model 3 Drinking behavior              | −0.043             | −0.323             |                    |

*P < 0.05. HbA1c, glycated hemoglobin.
diminished KEF by 11.0–16.6% compared with those without DPN. Furthermore, in women aged 50–69 years and 70–87 years, and in men aged 50–69 years, DPN was a significant explanatory variable for KEF in all multiple regression analysis models. However, no such significant loss of muscle strength was observed in either men or women participants aged 30–49 years. In addition, there was no significant relationship between KEF and the presence of DPN in multiple regression analysis. Andersen et al. found in electrophysiological studies that the presence and increased severity of DPN were associated with reduced muscle strength in both type 1 and type 2 diabetes patients. Almurdhi et al. reported the loss of KEF with DPN, and that this is related to muscle atrophy. Muscle mass is a major determinant of muscle strength, the age-related decline in muscle mass begins at approximately 40 years-of-age. In addition to diabetic neuropathy, the effects of age might have led to a significant loss of muscle strength between middle-aged and elderly patients with and without DPN.

In previous studies, comparisons of muscle strength were often carried out using strength normalized to bodyweight, and this normalization muddles interpretation of the results when study populations involve both sexes and wide ranges of age groups. In the present study, using KEF normalized to bodyweight (Nm/kg), we showed that the presence of DPN resulted in significant loss of muscle strength. We obtained strikingly similar results using the absolute value of KEF (Nm). In the present population-based study, we investigated the effect of DPN on KEF in different sex and age groups of type 2 diabetes patients. Consequently, we confirmed that, in addition to aging, the presence of DPN was a significant risk factor for reduced KEF, which might result in a decline in activities of daily living, novel findings not observed in any previous study. The evaluation of KEF is clinically important, as it can estimate the degree of muscle strength of the lower extremities. When KEF was below a certain level, activities of daily living, such as independence of gait, stair climbing and rising from a chair, became impossible. Evaluation of KEF might also help predict activities of daily living. However, because there are various measurement devices and methods by which to measure muscle strength, it is difficult to directly compare the current results with those of previous studies. Accordingly, we believe it is important to have a discussion regarding international measurement methods and the establishment of standard values of key muscle strength, and that it is necessary to study this in the future.

Almost all participants with type 2 diabetes in the current study were inpatients who required better glucose control. This might explain why average HbA1c levels in the present study were high in comparison with typical Japanese patients with type 2 diabetes. We evaluated HbA1c as an explanatory variable for KEF using multiple regression analysis in several models. However, the current HbA1c level was not a significant factor. In contrast, in both men and women aged 50–69 years and 70–87 years, regular exercise behavior was a significant explanatory variable for KEF. Exercise and physical activity effectively prevent the onset of complications in patients with diabetes mellitus. Although exercise and physical activity are important therapies for type 2 diabetes, exercise and physical activity adaptation are also important from the perspective of maintaining motor function. The results of the present study also might provide guidance for middle-aged and elderly diabetes patients who require regular exercise to maintain lower extremity strength. However, we did not collect data regarding activities of daily living or other aspects of overall physical activity, nor did we collect data regarding past physical activity, despite the potential effects of these data on KEF. Owing to limitations regarding the definition of regular exercise behavior, we are currently unable to determine how a lack of exercise contributes to the loss of lower extremity muscle strength.

The present study had several limitations. It was a cross-sectional study that examined only KEF as a measure of muscle strength in relation to sex, age and DPN, as well as the association between KEF and regular exercise behavior. The degree of seriousness and symptoms of DPN were not considered, thus it is not clear whether the degree of seriousness of DPN will further influence KEF. Because the duration of DPN could also have an effect, there might be less influence of DPN on KEF in a younger patient than that in an older patient. Furthermore, the present study did not include healthy subjects as a control group. Therefore, we were unable to assess the influence of diabetes per se on KEF, such as might be shown by altered cytokine levels and insulin resistance. Regardless of these limitations, the present study characterized the loss of lower extremity strength by sex and age group based on the presence of DPN. Furthermore, prospective studies are required to clarify the contribution of DPN to the loss of muscle strength in diabetes patients.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION
Additional Supporting Information may be found in the online version of this article:

Data S1| Multicenter Survey of Isometric Lower-Extremity Strength in Type 2 Diabetes (MUSCLE-std) Study Group.