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Loss of lower extremity muscle strength based on diabetic polyneuropathy in older patients with type 2 diabetes: Multicenter Survey of the Isometric Lower Extremity Strength in Type 2 Diabetes: Phase 2 study

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ABSTRACT

Aims/Introduction: Diabetic polyneuropathy (DPN) is a factor that reduces lower extremity muscle strength (LEMS) in older type 2 diabetes patients. This relationship remains unclear in longitudinal studies. Therefore, we longitudinally investigated the apparent effects of DPN on changes in LEMS. Furthermore, we cross-sectionally examined relationships among DPN, LEMS, mobility and health-related quality of life.

Materials and Methods: Bodyweight-normalized (relative) knee extension force (KEF) was examined in 51 DPN and 54 non-DPN patients (68.9 ± 5.6 and 70.2 ± 5.9 years, respectively) at baseline and follow up at 3.6 ± 0.6 years. At follow up, mobility was measured using a 25-question geriatric locomotive function scale. Health-related quality of life was assessed using the five-dimensions of EuroQol for quality-adjusted life years calculation.

Results: Relative KEF in the DPN group was significantly lower at follow up (1.22 ± 0.47 Nm/kg) than at baseline (1.31 ± 0.47 Nm/kg; $P < 0.05$). DPN significantly affected changes in relative KEF. Mobility decreased by 41 and 65% in the non-DPN and DPN groups, respectively. Quality-adjusted life years were significantly lower in the DPN group (0.856 ± 0.131) than in the non-DPN group (0.920 ± 0.105; $P < 0.01$). Relative KEF was a significant independent variable that explained quality-adjusted life years.

Conclusions: DPN clearly reduced LEMS in older type 2 diabetes patients within 4 years. Furthermore, DPN resulted in a loss of LEMS and decrease in mobility. Therefore, DPN development should be monitored closely, with glycemic control and LEMS kept at a high level to maintain health-related quality of life in older patients with type 2 diabetes.

INTRODUCTION

Aging appears to result from an imbalance between muscle protein anabolic and catabolic pathways, leading to loss of skeletal muscle volume that causes a decline in muscle strength[1]. Older patients with type 2 diabetes might be more susceptible to developing a skeletal muscle disorder. Elevated blood glucose levels cause a decline in muscle mass through the action of two proteins: WW domain-containing E3 ubiquitin protein ligase 1 and Krüppel-like factor 15[2]. However, after adjusting for age, comparisons between type 2 diabetes patients and healthy controls have shown that muscle mass is not necessarily lower in the former[3,4]. The regulation of intracellular calcium ions, which is a prerequisite for optimal muscle

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contractile function, is impaired in affected individuals with elevated blood glucose levels[5]. The reduction in muscle volume and function then negatively affects skeletal muscle strength in these patients. Such decline in lower extremity muscle strength (LEMS) is seen in all diabetes patients regardless of age, with bodyweight-normalized (relative) knee extension force (KEF) being 10–20% lower in type 2 diabetes patients than in non-diabetes patients[6]. Furthermore, the presence and exacerbation of diabetic polyneuropathy (DPN) in this disorder further contributes to a weakening of muscle strength[7], and DPN-mediated reduction in KEF is particularly marked in middle-aged and older patients[8]. In healthy individuals, a 10–20% decrease in LEMS does not impair basic daily activities, such as standing and walking; however, the combination of diabetes- and age-related weaknesses might significantly affect mobility in older diabetes patients. Therefore, monitoring LEMS is crucial for preventing the requirement for long-term care[9].

A longitudinal study showed that the decline in LEMS over a 3-year period was greater in older type 2 diabetes patients than in age-matched non-diabetes controls[10], even though the presence of DPN was not considered. Physical exercise and frequent monitoring of glucose levels are associated with better health-related quality of life (HRQoL) in individuals with type 2 diabetes. Conversely, diabetic complications and reduced mobility are known to compromise HRQoL[11,12]. Even though the relationship between LEMS and HRQoL has not been studied, the fact that high LEMS levels ensure mobility maintenance raises the likelihood that they might also contribute to maintaining and improving HRQoL.

The primary aim of the present study was to explore the potential effect of DPN with hyperglycemia on LEMS among older type 2 diabetes patients using a longitudinal design. Our secondary aim was to clarify the relationship among DPN, LEMS, mobility and HRQoL in older type 2 diabetes patients using a cross-sectional design. To our knowledge, this is the first observational study to explore these relationships.

METHODS

Participants

This cohort study, termed Multicenter Survey of the Isometric Lower Extremity Strength in Type 2 Diabetes: Phase 2 (MUSCLE-std 2), used the baseline data of the MUSCLE-std study, which was a cross-sectional survey carried out among 30 hospitals from April 2010 to March 2015[8]. Follow-up data were collected in collaboration with nine of these hospitals from October 2015 to March 2019. All hospitals and medical staff involved in data collection are provided in Data S1. The inclusion criteria were type 2 diabetes patients aged 60–92 years who visited a hospital on an inpatient or outpatient basis. The period between baseline and follow-up measurements ranged between 2.5 and 6 years. The exclusion criteria were inability to adapt to exercise therapy, inability to walk independently, significant limitations in activities of daily life, severe heart and/or respiratory diseases, severe liver dysfunction and/or renal failure (serum creatinine level >2.0 mg/dL), patients with acute or chronic orthopedic disease who were receiving medical treatment at the time of enrollment, non-symmetry of bilateral lower extremity muscular atrophy, impairment of lower extremities, severe infectious disease and requirement of surgical treatment. The study protocol was approved by the ethics committee of Kansai University of Welfare Sciences, Japan, as well as by the ethics committees or directors of all participating institutions. It was registered in the UMIN Clinical Trials Registry as the MUSCLE-std 2 study (UMIN000029617). The study was carried out in accordance with the Declaration of Helsinki, and all participants provided consent before enrollment.

The sample size comprised 104 individuals (52 per group), as obtained using G*power version 3.1.9.7 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany)[13]. Based on the KEF values derived from the MUSCLE-std study[8], an effect size and a correlation among repeated measures were calculated as 0.21 and −0.125, respectively, to achieve an α error probability of 0.05 and a power ($1 - \beta$ error probability) of 0.8 within an *F*-test design. In the present study, data for 159 older patients with type 2 diabetes were registered. The analysis was carried out on 105 patients after excluding 36 patients for whom complete data could not be obtained and 18 patients whose diabetic neuropathy status changed (from present to absent, or absent to present).

Data regarding the following parameters were collected at baseline and during follow up: KEF, bodyweight, diabetes status, details of drug therapy, laboratory data, diabetic complications and habitual behavior. Data on locomotive syndrome (LS) and HRQoL were collected only during the follow-up period.

Diabetes status and drug therapy

Type 2 diabetes was diagnosed in accordance with the criteria established by the Japan Diabetes Association[14]. The median disease duration was 12 years (range 0.3–39 years). DPN was diagnosed in patients who fulfilled at least two of the following criteria: complaint of bilateral sensory symptoms in the toes and soles of the feet (specifically, at least two of the following: numbness, pain, and dysesthesia), bilateral diminished or absent Achilles tendon reflex, and bilateral decreased vibratory sensation in the medial malleoli[15]. Diabetic retinopathy was classified as none, simple, preproliferative or proliferative. Diabetic nephropathy was classified as prenephropathy (stage 1), incipient nephropathy (stage 2), overt nephropathy (stage 3) or renal failure (stage 4). Patients with stage ≥2 were classified as having diabetic nephropathy[16].

Sodium–glucose cotransporter 2 inhibitors might slightly decrease muscle volume[17,18], and insulin sensitizers and dipeptidyl peptidase-4 inhibitors might attenuate muscle volume loss[19,20]. These drugs were examined in detail, because a loss of muscle volume could be related to a decline in muscle strength. Regarding insulin sensitizers, thiazolidinediones and biguanide were assessed.

KEF assessment

LEMS was evaluated based on KEF, which was equally measured both at baseline and follow up. Isometric KEF was measured using a handheld dynamometer with a fixation belt (μTas MT-1 or μTas F-1; Anima, Tokyo, Japan) in the sitting position with the hips and knees flexed to 90°[6]. After practicing, two measurements were carried out on both legs, and the maximum values were used to calculate the mean muscle strength values on the left and right. 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 KEF (Nm) was calculated by multiplying the absolute value of isometric KEF (N) by the length of the moment arm (m). Furthermore, the relative KEF (Nm/kg) was calculated by dividing the KEF (Nm) by the bodyweight (kg) and was used in the analyses.

Habitual behavior

Exercise behavior was defined as two sessions of exercise per week with a duration of at least 30 min. Stages of behavior change were assessed according to the transtheoretical model[21]; participants who continued exercise behavior for at least 6 months (maintenance stage or later) were defined as having engaged in regular exercise. Participants who had smoked for the past month or more (every day or occasionally) 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. Habitual behavior was recorded by recall among participants.

Locomotive syndrome and HRQoL

Mobility and HRQoL assessments were carried out in this study. LS was used as an index for evaluating mobility[22]. It is a condition in which deterioration in the locomotive organs (such as the bones, joints and muscles) results in impaired activities of daily living, such as walking, standing up and sitting down. If it progresses, LS increases the risk of long-term care requirement and, ultimately, can result in a patient becoming bedridden. Three tests are used to assess the risk of LS according to the Japanese Orthopedic Association: (i) two-step test; (ii) stand-up test; and (iii) the 25-question Geriatric Locomotive Function Scale (GLFS-25). In the present study, GLFS-25 was used for the detection of LS; this test consists of 25 items with a score of 0–4 for each item[22]. The GLFS-25 includes four questions on pain during the preceding month, 16 questions regarding activities of daily living during the preceding month, three questions regarding social activities and two questions regarding mental health status during the preceding month. The total score (ranging from 0 to 100) was used in the analysis; a higher score was indicative of the patient being in a worse condition. The validity and reliability of the GLFS-25 scores were psychometrically confirmed as sufficient[23]. A GLFS-25 score ≥7 was defined as "stage 1" LS (LS1); that is, the beginning of decline in mobility function. Furthermore, a GLFS-25 score ≥16 was defined as "stage 2" LS (LS2), and was associated with a progressive decline in mobility[24].

To evaluate HRQoL, we used the Japanese variant of the three-level version of the EuroQol five-dimensions descriptive system, which is composed of five questions[25]. Quality-adjusted life years (QALYs) were calculated using conversion tables created independently for each country, and health status scores were determined based on the responses, which are standardized from "complete health = 1" to "death = 0."

Statistical analysis

To examine the effects of DPN, we first compared the general baseline characteristics, diabetes indicators, and lifestyle factors between the DPN and non-DPN groups. To compare the groups, the Mann–Whitney *U*-test was used for continuous variables, and the χ^2-test was used for nominal variables. Next, intragroup comparisons between baseline and follow-up data were carried out using the Wilcoxon signed-rank test for continuous variables, and the χ^2-test for nominal variables.

To examine the effects of DPN on changes in KEF, we first used the Wilcoxon signed rank test for intragroup comparisons between before and after observations. Next, repeated measures analysis of covariance (ANCOVA) was carried out to test for interactions between group factors (DPN vs non-DPN groups) and time factors (before vs after observations), and covariance between baseline and follow-up glycated hemoglobin (HbA1c) levels.

Locomotive syndrome was compared between the groups using the χ^2-test and *Z*-test (no LS = 0, LS1 = 1, LS2 = 2). The prevalence of LS as a parameter of statistical analysis was assessed using all questions of GLFS-25 and GLFS-25, except the four questions regarding pain (specific LS). Furthermore, using logistic regression analysis, the relationship between the prevalence of LS and KEF was analyzed for patients with and without DPN. The response variable was LS prevalence (none = 0, LS1 or LS2 = 1). Continuous explanatory variables included relative KEF, HbA1c and diabetes duration. Categorical explanatory variables included sex (men = 1, women = 2), exercise habits, DPN status and diabetic nephropathy status (0 = absence, 1 = presence).

The Mann–Whitney *U*-test was used to compare QALYs between groups. Multiple regression analysis was carried out to examine the effects of reduced LEMS and LS on HRQoL in the DPN and non-DPN groups using QALYs as the dependent variable. The explanatory variables were relative KEF (Nm/kg) at follow up, specific LS (no = 0, LS1 or LS2 = 1), and according to a previous study[10], diabetes duration at follow up, diabetic retinopathy (no = 0, yes = 1), diabetic nephropathy (no = 0, yes = 1), hypertension (no = 0, yes = 1) and exercise habits (no = 0, yes = 1).

Statistical analyses were carried out using SPSS Statistics 24.0 (IBM Corp., Chicago, IL, USA). Analysis items with *P*-values of <0.05 were considered statistically significant.

Table 1 | Clinical characteristics of older type 2 diabetes patients with or without diabetic polyneuropathy at baseline

Parameters	Units	Without DPN	With DPN	*P*-value
Sex (female/male)	*n*	21/30	29/25	0.242
Age	years	68.9 ± 5.6	70.2 ± 5.9	0.258
Body height	cm	158.4 ± 7.6	158.1 ± 8.7	0.835
Bodyweight	kg	59.9 ± 10.5	63.4 ± 12.7	0.233
Body mass index	kg/m^2	23.8 ± 3.5	25.3 ± 4.6	0.141
Diabetes duration	years	10.8 ± 9.0	17.3 ± 10.3	0.001
HbA1c	%	7.8 ± 1.9	8.4 ± 1.5	0.008
HbA1c	mmol/mol	62.5 ± 21.0	69.0 ± 17.2	0.008
Fasting plasma glucose	mg/dL	138.3 ± 39.9	154.8 ± 41.8	0.101
Diabetic retinopathy	*n* (%)	6 (12)	27 (50)	<0.001
Diabetic nephropathy	*n* (%)	11 (22)	22 (40)	0.038
Exercise regularly	*n* (%)	26 (51)	24 (44)	0.560
Current smoker	*n* (%)	10 (20)	4 (7)	0.087
Alcohol drinker	*n* (%)	19 (37)	15 (27)	0.404

Data are presented as the mean ± standard deviation or *n* (%). DPN, diabetic polyneuropathy; HbA1c, glycated hemoglobin.

RESULTS

The mean duration from baseline to follow up was 3.6 ± 0.6 years (range 2.6–5.8 years). The mean durations were 3.5 ± 0.5 years and 3.7 ± 0.7 years in the non-DPN and DPN groups, respectively, which were not significantly different.

Regarding baseline characteristics, disease duration was significantly longer in the DPN group than in the non-DPN group ($P = 0.001$; Table 1). The DPN group showed significantly higher HbA1c (%) levels ($P = 0.008$), and significantly higher prevalences of diabetic retinopathy ($P < 0.001$) and diabetic nephropathy ($P = 0.038$) than the non-DPN group. At follow up, the DPN group had significantly higher HbA1c levels ($P = 0.022$), and significantly higher prevalences of diabetic retinopathy ($P < 0.001$) and diabetic nephropathy ($P = 0.004$) than the non-DPN group, which are similar to those observed at the baseline (Table S1). In addition, the DPN group had a significantly higher frequency of current smokers than the non-DPN group ($P = 0.002$). At baseline, the DPN group received a significantly higher prescription rate of drug therapy and a significantly higher rate of insulin therapy than the non-DPN group; however, there was no significant difference at follow up (Table 2). At baseline and follow up, there were no significant differences in prescription rates of sodium–glucose cotransporter 2 inhibitors, insulin sensitizers and dipeptidyl peptidase-4 inhibitors between the groups.

At baseline, KEF (Nm) was not significantly different between the groups, whereas relative KEF (Nm/kg) was significantly lower in the DPN group than in the non-DPN group ($P = 0.038$; Table 3). At follow up, both KEF and relative KEF were significantly lower in the DPN group than in the non-DPN group ($P = 0.047$, $P = 0.007$, respectively). In the comparison between before and after observations, KEF and relative KEF did not change significantly in the non-DPN group. In contrast, in the DPN group, both parameters were significantly lower at follow up than at baseline ($P = 0.001$, $P = 0.018$, respectively). We observed an interaction between DPN and KEF and relative KEF using repeated measures ANCOVA ($F = 3.877$, $P = 0.052$; $F = 4.234$, $P = 0.042$, respectively).

Table 2 | Details of drug therapy in older type 2 diabetes patients with or without diabetic polyneuropathy

	Without DPN	With DPN	*P*-value
Baseline			
Prescription of drug therapy	42 (82.4%)	53 (98.1%)	0.007
SGLT2-I	0	0	–
Insulin sensitizers	17 (33.3%)	19 (35.2%)	1.000
DPP4-I	14 (27.5%)	20 (37.0%)	0.307
Insulin therapy	16 (31.4%)	29 (53.7%)	0.030
Follow up			
Prescription of drug therapy	45 (88.2%)	53 (98.1%)	0.056
SGLT2-I	4 (7.8%)	4 (7.4%)	1.000
Insulin sensitizers	24 (47.1%)	25 (46.3%)	1.000
DPP4-I	16 (31.4%)	20 (37.0%)	0.681
Insulin therapy	15 (29.4%)	26 (48.1%)	0.071

Data are presented as *n* (%). DPN, diabetic polyneuropathy; DPP4-I, dipeptidyl peptidase 4 inhibitor; SGLT2-I, sodium–glucose cotransporter 2 inhibitor.

The prevalence rates of LS1 and LS2 were 16.3 and 27.5%, respectively, for men, and 25.8 and 36.4%, respectively, for women. For overall LS, the rates were 43.8% for men and 62.2% for women. The prevalence rates of LS were significantly different between the DPN and non-DPN groups ($P = 0.004$; Table 4). Similarly, the prevalence rates of specific LS were significantly different between the DPN and non-DPN groups ($P = 0.012$). Overall, 41% of the patients without DPN and 65% of the DPN patients had LS1 or LS2. Thus, the DPN group had a significantly smaller proportion of non-LS patients, and significantly more LS2 patients than the non-DPN group. Table S2 shows the relationship between the prevalence of LS

Table 3 | Changes in knee extension force after an average of 3 years in older type 2 diabetes patients with or without diabetic polyneuropathy

Parameters	Units	Group	*n*	Baseline	Follow-up	Interaction	
						F-value	*P*-value
KEF	Nm	Without DPN	51	92.5 ± 39.6	91.5 ± 42.2	3.877	0.052
		With DPN	54	81.7 ± 30.1	75.4 ± 30.6*,****		
Relative KEF	Nm/kg	Without DPN	51	1.51 ± 0.50	1.52 ± 0.57	4.234	0.042
		With DPN	54	1.31 ± 0.47*	1.22 ± 0.47**,***		

Data are presented as the mean ± standard deviation. Parameters of the repeated measures analysis of covariance (ANCOVA): between-subject factors with or without diabetic polyneuropathy (DPN); covariates were baseline and follow-up glycated hemoglobin levels. *$P < 0.05$ between patients without DPN and with DPN. **$P < 0.01$ between patients without DPN and with DPN. ***$P < 0.05$ among patients without DPN or with DPN. ****$P < 0.01$ among patients without DPN or with DPN.

and KEF for patients with and without DPN according to the logistic regression analysis. In the DPN group, KEF was a significant explanatory variable for the prevalence of LS in all models. In contrast, KEF was a significant explanatory variable for prevalence of LS in model 1 only in the non-DPN group.

The QALYs were significantly lower in the DPN group (0.856 ± 0.131) than in the non-DPN group (0.920 ± 0.105; $P = 0.007$). In the DPN group, multiple regression analysis showed significant correlations between QALYs and relative KEF and LS at follow up ($P = 0.005$, $P < 0.001$, respectively; Table S3).

DISCUSSION

In the present study, we have, for the first time, elucidated the crucial relationships among DPN, KEF, LS and HRQoL in older type 2 diabetes patients. Specifically, our observations showed that after a mean observation period of 3.6 years, the decline in LEMS is more progressive in patients with DPN, and that DPN is an independent factor that accelerates the loss of muscle strength. The present findings further indicate that the prevalence of LS is strongly related to KEF, especially in patients with DPN; the HRQoL is more impaired among patients with DPN than among those without DPN, and KEF levels negatively correlated with HRQoL, emphasizing the importance of maintaining a high level of mobility.

Table 4 | Locomotive syndrome and health-related quality of life in older type 2 diabetes patients with or without diabetic polyneuropathy

Parameters	Units	Without DPN	With DPN	*P*-value
LS prevalence				
Non-LS	*n* (%)	30 (59)	19 (35)*	0.004
Stage 1 LS	*n* (%)	12 (23)	9 (17)	
Stage 2 LS	*n* (%)	9 (18)	26 (48)*	
Specific LS prevalence				
Non-LS	*n* (%)	34 (66)	24 (44)*	0.012
Stage 1 LS	*n* (%)	13 (26)	14 (26)	
Stage 2 LS	*n* (%)	4 (8)	16 (30)*	
EQ-5D	QALYs	0.920 ± 0.105	0.856 ± 0.131	0.007

Data are presented as the mean ± standard deviation or *n* (%). Specific locomotive syndrome (LS) prevalence evaluated using the 25-question Geriatric Locomotive Function Scale without four questions regarding pain. *$P < 0.05$ for comparison between patients without diabetic polyneuropathy (DPN) and with DPN. EQ-5D, EuroQol five-dimensions; QALY, quality-adjusted life year.

Neuropathy is a frequent complication of diabetes, and most commonly presents as a distal symmetrical sensorimotor polyneuropathy[26]; therefore, patients with DPN tend to more commonly present with a loss of distal LEMS rather than a loss of proximal LEMS[7]. Ankle joint movement consists of composite movements of multiple joints. However, knee joint motion consists of simple movements, such as flexion or extension. Therefore, it is easier to evaluate muscle strength in reference to the knee joint than in reference to the ankle joint. Furthermore, regarding LEMS, KEF is closely associated with basic activities of daily living, such as standing and walking. In addition, using a stabilization belt with a handheld dynamometer makes it possible to achieve levels of validity and reliability equivalent to measuring KEF with an isokinetic dynamometer[9]. Consequently, KEF is most suitable for monitoring LEMS among patients with diabetes.

At baseline, patients with and without DPN differed significantly with respect to bodyweight-normalized KEF and disease duration, with lower KEF and longer duration in the DPN group than in the non-DPN group. This is consistent with previous research that showed that the presence of DPN in older patients with type 2 diabetes leads to reduced strength[8]. A previous study on changes in LEMS in older individuals after a 3-year observation period did not consider the presence or absence of DPN[10], but the present study observed a significant decrease in KEF among patients with DPN. It has been reported that DPN causes muscle atrophy, which is associated with reduced strength[27]. Although the present study did not consider muscle mass, the change in bodyweight between the baseline and follow up, which was correlated with KEF at baseline, was not significant in either the non-DPN group or the DPN group. Although these have a two-way relationship, there is a positive correlation between KEF and exercise habits[28].

Similarly, in the present study, there was no significant difference in exercise habits at baseline and follow up between the two groups. KEF decreased significantly after approximately 4 years in older type 2 diabetes patients with DPN, which held true after normalizing the HbA1c level. The results of the present study show that when examined longitudinally, DPN has a large effect on changes in LEMS in older patients with type 2 diabetes, even if considered an effect of glycemic control and drug therapy. Therefore, when examining longitudinal changes in LEMS in these patients, it is essential to consider not only the presence of hyperglycemia, but also the presence of DPN.

Weakness in locomotive components causes difficulties in mobility. The prevalence rates of LS1 and LS2, as assessed using the 25-GLFS in a general older population aged ≥60 years, were 25.3 and 13.8% (39.1% overall), respectively, for men and 35.2 and 19.7% (54.9% overall), respectively, for women[23]. In the present study, the overall rates were 43.8% in men and 62.2% in women, which were comparable to those in the general older population, although in the present study, the rates of LS2 were higher (27.5% for men and 36.4% for women). Furthermore, the overall LS and LS2 prevalence was significantly higher in the DPN group than in the non-DPN group. Pain limited to the little fingers and feet is a clinical symptom of DPN among diabetes patients. Nevertheless, the proportion of patients with specific LS was significantly different between the DPN and non-DPN groups. Furthermore, the prevalence of LS was strongly related to KEF, especially among patients with DPN. Therefore, the presence of DPN in older patients with type 2 diabetes is considered to be a factor influencing the presence and progression of LS.

The EuroQol five-dimensions index score in patients with type 2 diabetes is an independent factor predicting mortality, cardiovascular events and diabetic complications[29]. LS prevalence also appears to be associated with reduced HRQoL in type 2 diabetes patients[12]. Unlike previous studies, in the present study, multiple regression analysis with HRQoL as the objective variable identified KEF to be an independent explanatory variable in the DPN group. Although there is insufficient evidence supporting an effect of exercise therapy on patients with DPN, the present findings and those of others suggest that it is likely to improve LEMS in older patients with type 2 diabetes[30,31]. The present results also indicate that a high level of LEMS appears to be important for maintaining HRQoL in older patients with type 2 diabetes, and exercise therapy might be the chief strategy to achieve this goal.

The number of type 2 diabetes patients is ever increasing around the world, with the Western Pacific region having the highest incidence[32]. It is estimated that one in five individuals aged ≥65 years has diabetes, and because the older population is rapidly increasing in Japan, Korea and China, it is particularly important to take measures toward addressing the development of this disease in these Western Pacific nations[33]. Furthermore, it is key to focus on DPN in older diabetes patients, because its presence can reduce LEMS, cause patients to require long-term care and reduce HRQoL.

The present study had several limitations. First, the evaluation of DPN was limited to clear cases of this disorder, so the effect of latent DPN remains to be elucidated. We did not carry out body composition analyses, electromyography or other such examinations; thus, it is unclear whether the observed declines in KEF resulted from a reduction in muscle mass or physiological changes to the muscles. Second, we did not comprehensively evaluate physical activity, such as the type, duration or intensity of the exercise carried out in daily activities. Hence, we cannot comment on how much total amount of physical activity contributed to maintaining muscle strength. Third, as one question regarding pain was included in the EuroQol five-dimensions, DPN could have affected HRQoL, which might in turn have affected the present results. Fourth, as LS and HRQoL were assessed as single data in the follow up, we could not confirm a longitudinal change. Further studies are required to clarify some of these issues, and to make further contributions for preventing the need for long-term care and maintaining HRQoL in older patients with type 2 diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1 | Listing of the Multicenter Survey of Isometric Lower Extremity Strength in Type 2 Diabetes: Phase 2 (MUSCLE-std 2) study group.

Table S1 | Clinical characteristics of older type 2 diabetes patients with or without diabetic polyneuropathy at follow up.

Table S2 | Influence of knee extension force in combination with other parameters on the prevalence of locomotive syndrome as the response variable in logistic regression analysis.

Table S3 | Multiple regression analysis comparing health-related quality of life with observed parameters.