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Association between deterioration in muscle strength and peripheral neuropathy in people with diabetes

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ABSTRACT

Aims: Diabetic peripheral neuropathy (DPN) is a major risk factor for sarcopenia or frailty in older patients with diabetes. In this study, we investigated the association between DPN and muscle strength in type 2 diabetes.
Methods: DPN was assessed using the Michigan Neuropathy Screening Instrument Questionnaire (MNSI-Q) and Physical Examination (MNSI-PE) in 230 subjects with type 2 diabetes. Handgrip strength (HGS) was measured using an electronic grip strength dynamometer.
Results: The prevalence of DPN was 26.4% in men and 34.7% in women. HGS was significantly lower in men with DPN compared with men without DPN (27.0 ± 9.4 vs. 29.7 ± 8.4 kg, $p = 0.036$). This effect was not seen in women. In men, multivariate regression analysis showed that HGS was negatively associated with the MNSI-Q ($\beta = -1.200$, $p = 0.003$) and MNSI-PE scores ($\beta = -0.937$, $p = 0.046$) and resulted in an abnormal 10-gram monofilament test score ($\beta = -10.895$, $p < 0.001$). However, HGS was not significantly associated with neuropathy in women.
Conclusions: Muscle strength was lower in men with DPN than in those without DPN. Assessment of muscle function may have clinical implications in the prevention of sarcopenia and frailty in men with DPN.

1. Introduction

Diabetic peripheral neuropathy (DPN) is a major microvascular complication of diabetes.[1] This complication causes serious consequences such as neuropathic foot ulcers that may require amputation and it is related with prevalent cardiovascular events and mortality.[1,2] Previous reports have shown that the duration of diabetes and the age of the patients are key contributing factors in the development of DPN.[3] As the population ages, the number of people with diabetes and the burden of DPN will increase.

Sarcopenia is defined as an age-related, progressive decline in muscle mass and function, and is prevalent in people with diabetes.[4] In addition, DPN may contribute to the decrease of muscle quality in older people with diabetes.[5] The loss of skeletal muscle mass and function is a major component of frailty, and frail subjects with diabetes showed increased mortality.[6,7] Therefore, we need to pay attention to both muscle function and DPN.

Previous studies showed that lower muscle strength was decreased in both type 1[8] and type 2 diabetes patients with DPN.[9] To measure lower muscle strength, special equipment such as a leg extension machine and trained inspectors is needed. Therefore, we need more convenient tools to assess general muscle strength and/or muscle function and performance in people. Handgrip strength (HGS) can be an appropriate alternative measurement because it is easy to measure and has been validated for lower leg muscle function[10] and performance testing.[11] In this study, we investigated the association between DPN and muscle function using HGS in people with diabetes. We hypothesized that subjects with DPN had lower muscle power than those without DPN.

2. Materials and methods

2.1. Subjects

We recruited 260 people with type 2 diabetes from 10 primary care clinics and one tertiary care hospital. The primary care clinics and the

Abbreviations: AGE, Advanced glycation end-product; BMI, Body mass index; BUN, Blood urea nitrogen; HGS, Handgrip strength; DPN, Diabetic peripheral neuropathy; MNSI, Michigan Neuropathy Screening Instrument; MNSI-PE, Michigan Neuropathy Screening Instrument – Physical Examination; MNSI-Q, Michigan Neuropathy Screening Instrument – Questionnaire.

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tertiary care hospital used the same recruitment protocol for evaluating the participants. The inclusion criteria were: age >20 years and diagnosis of type 2 diabetes. The exclusion criteria were other causes of neuropathy such as heavy alcohol consumption, end-stage renal disease treated with dialysis, use of neurotoxic agents, neuromuscular disease, or cognitive impairment. However, we did not perform specific tests for autoimmune causes of neuropathy. Patients from the outpatient clinics were asked to participate in the study by their physicians, and we obtained informed consent from all participants. This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB Number: B-1807/478-102).

2.2. Assessment of DPN

Trained health-care providers performed all neuropathic examinations and administered questionnaires using a standard operating procedure. We used the Michigan Neuropathy Screening Instrument (MNSI) protocol, which comprises two separate assessments: a 15-item self-administered questionnaire (MNSI-Q) and a physical examination of the lower extremity (MNSI-PE).[12] This MNSI has been validated in Korean patients with diabetes,[13–15] and the Neuropathy Study Group of the Korean Diabetes Association recommends the use of the Korean version of the MNSI to evaluate DPN.[16] We used a 10-gram monofilament test (5.07 Semmes–Weinstein) at 10 sites on each foot.[12] We diagnosed DPN according to following criteria: MNSI-Q ≥ 4, or MNSI-PE ≥ 2.5. For the MNSI-Q score, we modified the cut-off point and defined an abnormal MNSI-Q from ≥7 to ≥4, because using a cut-off point of MNSI-Q ≥ 7 could result in decreased sensitivity and missed diagnoses of many patients with clinically confirmed neuropathy.[17,18] We defined a 10-gram monofilament test as abnormal when the total correct responses on either foot were ≤7.0.

2.3. Assessment of muscle strength

Well-trained nurses measured muscle strength during daytime using a digital grip strength dynamometer (GRIP-D; Takei Scientific Instruments, Tokyo, Japan). The dynamometer was calibrated according to the manufacturer's protocol. HGS was measured for each hand twice by alternating between hands with a time gap of 1 min after more than a 10-min rest. We asked subjects not to perform vigorous exercise before measurement. Subjects were asked to place their arms naturally alongside the body. The dynamometer was placed away from the body at thigh level and there was no elbow support during HGS measurement. Patients were instructed to squeeze the dynamometer as strongly as possible without moving the rest of the body at a standing position.[19] The mean HGS of the dominant hand was used for analysis.

2.4. Statistical analysis

The data are presented as mean ± standard deviation or as number and percentage. We predicted a prevalence of DPN of 30% and calculated that the sample size in each gender group needed to detect a 10% difference in HGS was 100 patients. From a previous study, we assumed that around 10% of muscle strength might be decreased in patients with DPN compared with those without DPN.[9] We compared means using Student's *t*-test for parametric data, Mann–Whitney *U* test for nonparametric data, and chi-square test for frequencies. The associations between clinical or neuropathic parameters and HGS were evaluated using separate univariate and multivariate linear regression analysis for men and women, respectively. Statistical analysis was performed using IBM SPSS Statistics software (version 22.0; IBM Corp., Armonk, NY, USA). For all tests, $p < 0.05$ was considered significant.

3. Results

Thirty people were excluded because of incomplete data. The main reason for incomplete data was a missing physical examination. The patients excluded because of incomplete data were older than the included patients (56.7 ± 9.3 vs. 61.1 ± 11.0 years, $p = 0.021$). However, other clinical characteristics were not significantly different between the two groups. The mean age of the participants in the final analysis ($n = 230$) was 56.7 ± 9.3 years, and 56.1% were men. DPN was diagnosed in 26.4% of men and 34.7% of women. More patients were diagnosed with DPN in the cohort from the tertiary care hospital than from the primary clinics. Age and duration of diabetes did not differ significantly between participants with and without DPN. HbA1c levels tended to be higher in patients with DPN than without DPN, and more people in the DPN group were treated with insulin.

Systolic blood pressure and blood urea nitrogen levels were higher in women with DPN than without, and total cholesterol levels were lower in men with DPN than their counterparts without DPN. Body mass index (BMI), lipid profile, and estimated glomerular filtration rate did not differ significantly between those with or without DPN (Table 1). The coefficient of variance of HGS was 3.97% and 3.44% for dominant and nondominant hands, respectively. HGS was significantly lower in men with DPN than in those without DPN (27.0 ± 9.4 vs. 29.7 ± 8.4 kg, $p = 0.036$). By contrast, HGS did not differ between the DPN and non-DPN groups in women. Participants with DPN were more likely to have retinopathy and coronary artery disease.

The regression analysis is presented in Table 2. In men, multivariate regression analysis adjusted for age, BMI, insulin therapy, and the presence of comorbidities such as hypertension, dyslipidemia, coronary artery disease, and cerebrovascular disease showed that HGS was negatively associated with MNSI-Q ($\beta = -1.200$, $p = 0.003$), MNSI-PE scores ($\beta = -0.937$, $p = 0.046$), and the abnormal 10-gram monofilament test score ($\beta = -10.895$, $p < 0.001$). By contrast, in women, we found no significant correlations between HGS and neuropathic variables.

4. Discussion

In this study, 69 of 230 participants with type 2 diabetes recruited from primary clinics and a tertiary care hospital were diagnosed with DPN according to MNSI scores. HGS was lower in men with DPN than in those without DPN. The multivariate regression analysis showed that HGS correlated significantly with neuropathy examination results in men but not in women. These findings suggest that DPN is associated with deterioration in muscle function but that this association seems to occur only in men.

Patients with diabetes are associated with faster age-related decline in muscle function than those without diabetes.[20] Skeletal muscle is connected to nerves through the neuromuscular junction. Therefore, it is possible that nerve and muscle function are connected when pathologic conditions develop. Even though the pathophysiology of both DPN and sarcopenia remains largely unknown, these conditions share some mechanisms. Epidemiological studies have shown that poor glycemic control is associated with the prevalence of DPN[21] and decreased muscle quality.[22] Elevated advanced glycation end-products (AGEs) resulting from hyperglycemia can contribute to microvascular damage that is associated with impaired muscle function[23] and DPN.[24] Receptors for AGEs are expressed in both muscle and neurons and may be involved in the pathogenesis in both tissues.[25] In addition, oxidative stress and inflammation adversely affect both muscle and nerve tissues.[26] Our data provide objective evidence of an association between DPN and decreased muscle function, at least in men with diabetes.

Interestingly, in our study, women with DPN did not show a decrease in muscle function. Several factors might lead to this gender discrepancy. First, in women, DPN was diagnosed more frequently according to the MNSI-Q score than the MNSI-PE results. By contrast, the frequencies of DPN diagnosed according to each test were similar in men. Women may be more likely to be diagnosed with DPN using a subjective tool

Table 1
Clinical and biochemical characteristics according to the presence of diabetic peripheral neuropathy and gender.

	Male			Female		
	DPN (−) (n = 95)	DPN (+) (n = 34)	p	DPN (−) (n = 66)	DPN (+) (n = 35)	p
Tertiary hospital, n (%)	17 (17.9%)	22 (64.7%)	<0.001	10 (15.2%)	15 (42.9%)	0.002
Age (years)	56.3 ± 8.6	57.6 ± 10.9	0.327	56.7 ± 8.2	59.1 ± 10.1	0.194
Height (cm)	164.9 ± 8.5	164.1 ± 8.6	0.520	156.6 ± 3.8	157.9 ± 5.1	0.159
BMI (kg/m^2)	25.1 ± 3.3	25.9 ± 3.6	0.126	24.2 ± 3.4	25.3 ± 3.2	0.096
SBP (mmHg)	126.3 ± 12.6	131.1 ± 13.8	0.159	122.9 ± 13.6	129.1 ± 12.5	0.007
DBP (mmHg)	78.2 ± 9.1	77.9 ± 10.0	0.615	74.8 ± 8.5	76.0 ± 9.7	0.655
Diabetes duration (years)	9.6 ± 6.8	12.1 ± 9.3	0.274	9.2 ± 6.5	10.0 ± 7.0	0.556
Glucose (mg/dL)	139.2 ± 36.9	142.9 ± 45.9	0.747	134.5 ± 35.4	143.7 ± 45.5	0.277
HbA1c (%)	7.5 ± 1.2	8.0 ± 1.9	0.096	7.4 ± 1.1	7.8 ± 1.5	0.092
Cholesterol (mg/dL)	173.1 ± 36.5	168.7 ± 49.2	0.006	171.4 ± 35.6	179.4 ± 41.7	0.329
Triglyceride (mg/dL)	165.8 ± 91.4	189.9 ± 186.3	0.611	156.0 ± 89.4	168.3 ± 118.3	0.726
HDL cholesterol (mg/dL)	47.4 ± 11.8	47.4 ± 14.6	0.393	49.3 ± 12.1	49.8 ± 13.1	0.835
LDL cholesterol (mg/dL)	98.1 ± 32.9	84.9 ± 34.9	0.057	95.5 ± 36.4	95.7 ± 31.1	0.982
BUN (mg/dL)	15.3 ± 4.2	15.9 ± 5.9	0.062	14.5 ± 3.9	17.8 ± 6.6	0.028
Creatinine (mg/dL)	0.9 ± 0.2	0.9 ± 0.3	0.121	0.7 ± 0.2	0.8 ± 0.3	0.564
eGFR (mL/min/1.73 m^2)	77.5 ± 24.8	82.0 ± 26.0	0.244	72.8 ± 26.5	76.6 ± 27.5	0.543
MNSI-Q (score)	1.3 ± 0.9	4.4 ± 1.8	<0.001	1.4 ± 1.0	5.0 ± 1.5	<0.001
MNSI-PE (score)	0.4 ± 0.7	2.3 ± 1.8	<0.001	0.5 ± 0.8	1.8 ± 1.9	<0.001
10-gram monofilament (score)	9.9 ± 0.2	9.3 ± 1.4	<0.001	9.9 ± 0.3	9.7 ± 0.7	0.024
HGS, dominant hand (kg)	29.7 ± 8.4	27.0 ± 9.4	0.036	21.3 ± 2.8	21.0 ± 4.1	0.656
HGS, nondominant hand (kg)	27.1 ± 8.0	24.3 ± 9.2	0.033	19.5 ± 3.3	19.1 ± 4.2	0.618
Antidiabetic medication, n (%)						
Metformin	78 (83.9%)	26 (76.5%)	0.338	50 (75.8%)	30 (88.2%)	0.139
Sulfonylurea	41 (44.1%)	11 (32.4%)	0.234	23 (34.8%)	14 (41.2%)	0.535
DPP-4 inhibitor	51 (54.8%)	14 (41.2%)	0.173	32 (48.5%)	18 (52.9%)	0.673
SGLT-2 inhibitor	8 (8.6%)	2 (5.9%)	0.999	1 (1.5%)	1 (2.9%)	0.999
Thiazolidinedione	7 (7.5%)	2 (5.9%)	0.999	4 (6.1%)	1 (2.9%)	0.659
Insulin	3 (3.2%)	8 (23.5%)	0.001	4 (6.1%)	6 (17.6%)	0.085
Comorbidities, n (%)						
Hypertension	45 (48.4%)	14 (41.2%)	0.471	25 (37.9%)	22 (62.9%)	0.017
Dyslipidemia	51 (54.8%)	20 (58.8%)	0.689	32 (48.5%)	20 (57.1%)	0.407
Microvascular complications, n (%)						
Retinopathy	3 (3.2%)	8 (23.5%)	0.001	4 (6.1%)	6 (17.1%)	0.091
Nephropathy	21 (22.1%)	9 (26.5%)	0.605	21 (31.8%)	15 (42.9%)	0.270
Macrovascular complications, n (%)						
Coronary artery disease	2 (2.2%)	7 (20.6%)	0.001	1 (1.5%)	4 (11.4%)	0.048
Cerebrovascular disease	1 (1.1%)	3 (8.8%)	0.058	2 (3.0%)	3 (8.6%)	0.338
Peripheral artery disease	5 (5.4%)	1 (2.9%)	0.999	3 (4.5%)	3 (8.6%)	0.415

Data are reported as mean ± SD or number (%). DPN, diabetic peripheral neuropathy; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration ratio; MNSI-Q, Michigan Neuropathy Screening Instrument Questionnaire; MNSI-PE, MNSI Physical Examination; HGS, hand grip strength; DPP-4, dipeptidyl peptidase-4; SGLT2, sodium-glucose cotransporter-2. p-Values are given for the t test or chi-square test.

such as a questionnaire than men. Women might score higher in the MNSI-Q and have an increased chance of being diagnosed with DPN. Therefore, the impact of DPN on muscle strength might have been diluted in women. Second, there might be a sexual dimorphism in the susceptibility to muscle dysfunction associated with DPN. A previous observational study showed that muscle function declined acutely above the age of 55 years in women, a finding that was different from men whose muscle function decreased gradually.[27] In addition, hormone replacement therapy also influences muscle function of postmenopausal women.[28,29] Therefore, HGS might be influenced by other vital factors except DPN in women.

There are several limitations to this study. First, because of its cross-sectional nature, we could not identify any causal relationship between muscle function and DPN, and we could not examine the effects of glycemic control, specific treatments, and comorbidities on DPN and muscle function. Longitudinal observational studies are needed to determine whether neuropathy precedes the decline in muscle function. Furthermore, it would be necessary to test the day-to-day variability of

Table 2
Univariate and multivariate linear regression analysis of handgrip strength and neuropathy examination results.

	Model 1			Model 2			Model 3		
	β (SE)	95% CI	p	β (SE)	95% CI	p	β (SE)	95% CI	p
Men									
MNSI-Q	−1.156 (0.345)	−1.838, −0.473	0.001	−1.033 (0.359)	−1.744, −0.322	0.005	−1.200 (0.393)	−1.979, −0.421	0.003
MNSI-PE	−0.837 (0.398)	−1.626, −0.048	0.038	−0.745 (0.422)	−1.580, 0.089	0.080	−0.937 (0.465)	−1.857, −0.017	0.046
Abnormal monofilament	−11.125 (2.577)	−16.228, −6.023	<0.001	−10.474 (2.585)	−15.595, −5.354	<0.001	−10.895 (2.695)	−16.235, −5.556	<0.001
Women									
MNSI-Q	−0.122 (0.157)	−0.433, 0.190	0.441	0.035 (0.162)	−0.287, 0.357	0.830	0.034 (0.166)	−0.296, 0.364	0.837
MNSI-PE	−0.207 (0.231)	−0.665, 0.251	0.373	−0.014 (0.243)	−0.497, 0.468	0.953	0.011 (0.259)	−0.503, 0.524	0.968
Abnormal monofilament	−4.195 (3.358)	−10.861, 2.472	0.215	−4.609 (3.233)	−11.032, 1.814	0.157	−4.968 (3.308)	−11.543, 1.606	0.137

MNSI-Q, Michigan Neuropathy Screening Instrument Questionnaire; MNSI-PE, MNSI Physical Examination; monofilament, 10-gram monofilament test. Model 1 was unadjusted. Model 2 was adjusted for age, body mass index, and insulin therapy. Model 3 was adjusted for the same variables as Model 2 plus the presence of hypertension, dyslipidemia, coronary artery disease, and cerebrovascular disease.

HGS measurements for future longitudinal studies. Second, we enrolled a relatively small number of subjects; therefore, we cannot conclude that there was no significant association between DPN and HGS in women. The small study population might have as well contributed to the fact that we saw no significant difference in age and diabetes duration between subjects with and without DPN. Third, we did not perform electrophysiology studies that can detect subclinical neuropathy. Fourth, we included mainly middle-aged adults; therefore, we cannot generalize our findings to the older population. A future study including a population with a broad age range is needed to provide a concrete conclusion as to whether DPN accelerates muscle dysfunction or vice versa.

The current study is clinically important for an aging population with increasing diabetes prevalence. As life expectancy is increasing, the quality of life (QOL) and being independent will become important. DPN with pain is associated with a poor health-related QOL[30] and depression.[31] In addition, sarcopenia and frailty are thought to be highly related with disability.[32] Therefore, identification of high-risk subjects for sarcopenia is necessary to prevent functional decline among older diabetic subjects. This study demonstrates that DPN is related with decreased muscle power in men. In this population, we need to emphasize to use MNSI-PE for screening DPN, and HGS might be a reliable tool to distinguish high-risk subjects who will progress to sarcopenia and frailty.

In conclusion, muscle function assessed by HGS was significantly lower in men with DPN than in those without DPN, and the association between HGS and DPN was significant. Although a causal relationship between muscle function and DPN remains to be established, the current study suggests that assessment of muscle function using HGS may be helpful in men with DPN to predict poor health outcomes.[33–35]

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Contribution statement

All authors were involved in revising the manuscript and gave final approval. TJO, SK, and HCJ contributed to the study design and performed the primary analysis. TJO, SK, and JL collected the data. TJO and SK wrote the manuscript. JHM, SHC, and SL critically reviewed the manuscript.

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