


# Isometric knee extension force in Japanese type 2 diabetic patients without apparent diabetic polyneuropathy: Data from the Multicenter Survey of the Isometric Lower Extremity Strength in Type 2 Diabetes study

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## Abstract

**Objectives:** To determine standard reference values for isometric knee extension force using a cohort of Japanese type 2 diabetic patients without diabetic polyneuropathy.

**Methods:** Patient data were collected from the Multicenter Survey of the Isometric Lower Extremity Strength in Type 2 Diabetes study and compared with previously published data of healthy control subjects. In total, we enrolled 898 patients with type 2 diabetes aged 30–87 years, who did not have diabetic polyneuropathy. The control group included 510 healthy subjects aged 30–88 years. Maximum isometric knee extension force (KEF) values were obtained by using a hand-held dynamometer with belt stabilization. In addition, KEF (kgf) was adjusted for bodyweight (kg) to calculate %KEF.

**Results:** KEF and %KEF decreased with age in both patients with diabetes and healthy control subjects. The mean values of KEF and %KEF in patients with diabetes were reduced by 9.7% and 20.8%, respectively, in males, and by 11.6% and 23.0%, respectively, in females compared to the values in healthy control subjects.

**Conclusion:** KEF and %KEF in patients with type 2 diabetes without diabetic polyneuropathy may reduce by approximately 10% and 20%, respectively, compared to these values in healthy control subjects. This study provides reference values for isometric KEF with respect to sex in a population covering a wide age range.

## Keywords

Knee extension force, reference value, type 2 diabetes

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## Introduction

Diabetes is associated with a significantly increased risk of physical disability in adults.<sup>1</sup> The Health, Aging, and Body Composition (Health ABC) study assessed the risk factors for reduced function in healthy older American adults aged 70–79 years at baseline, with a particular focus on body composition changes associated with age. This study reported that 273 elderly males and 212 elderly females with type 2 diabetes had a 7.2% and 7.0% reduction in leg muscle quality, respectively, (i.e. the ratio of knee extension force (KEF) to the entire corresponding leg muscle volume); these percentages were compared with those of non-diabetic older people (1004 males and 1129 females).<sup>2</sup> Similarly, the Invecchiare in Chianti, aging in the Chianti area (InCHIANTI)

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**Table 1.** Clinical characteristics and exercise habits in type 2 diabetic patients without diabetic polyneuropathy.

Males		30–39 years n = 43	40–49 years n = 115	50–59 years n = 125	60–69 years n = 162	70–79 years n = 107	80–87 years n = 7	p value
Duration	years	2.4 ± 3.2 <sup>†</sup>	3.8 ± 4.2 <sup>†</sup>	6.3 ± 6.6 <sup>‡,§</sup>	7.1 ± 7.0 <sup>§,e</sup>	11.5 ± 9.3 <sup>¶,e</sup>	13.2 ± 8.2 <sup>*</sup>	<0.001
HbA1c	%	11.3 ± 2.4 <sup>†</sup>	10.3 ± 2.3 <sup>†‡</sup>	10.0 ± 2.5 <sup>‡</sup>	8.6 ± 1.9 <sup>§,¶,*</sup>	8.1 ± 1.9 <sup>¶,*</sup>	7.2 ± 1.6 <sup>*</sup>	<0.001
DR	n (%)	0 (0) <sup>†</sup>	9 (7.8) <sup>†‡</sup>	22 (17.6) <sup>‡</sup>	23 (14.2) <sup>†‡</sup>	22 (20.6) <sup>‡</sup>	0 (0) <sup>†‡</sup>	<0.01
DN	n (%)	6 (14.0)	15 (13.0)	21 (16.8)	33 (20.4)	29 (27.1)	1 (14.3)	NS
Ex. habit	n (%)	2 (4.7) <sup>†</sup>	18 (15.7) <sup>†‡</sup>	23 (18.4) <sup>†‡,§</sup>	52 (32.1) <sup>§</sup>	58 (54.2) <sup>¶</sup>	4 (57.1) <sup>‡,§,¶</sup>	<0.001
Females		n = 19	n = 36	n = 69	n = 131	n = 72	n = 12	
Duration	years	3.0 ± 4.2 <sup>†</sup>	4.3 ± 4.0 <sup>†</sup>	6.2 ± 7.3 <sup>†‡</sup>	7.8 ± 7.1 <sup>†</sup>	9.2 ± 8.1 <sup>‡</sup>	8.9 ± 11.0 <sup>†‡</sup>	<0.001
HbA1c	%	9.0 ± 1.6 <sup>†‡</sup>	10.4 ± 2.5 <sup>‡</sup>	9.7 ± 2.4 <sup>†‡</sup>	8.5 ± 2.0 <sup>§</sup>	8.6 ± 2.1 <sup>§</sup>	8.7 ± 2.5 <sup>†‡,§</sup>	<0.001
DR	n (%)	1 (5.3)	6 (16.7)	10 (14.5)	28 (21.4)	20 (27.8)	2 (16.7)	NS
DN	n (%)	0 (0)	11 (30.6)	10 (14.5)	25 (19.1)	15 (20.8)	3 (25.0)	NS
Ex. habit	n (%)	2 (10.5) <sup>†‡</sup>	3 (8.3) <sup>‡</sup>	14 (20.3) <sup>†‡</sup>	52 (39.7) <sup>†</sup>	31 (43.1) <sup>†</sup>	4 (33.3) <sup>†‡</sup>	<0.001

Duration: diabetes duration; HbA1c: glycated hemoglobin; DR: diabetic retinopathy; DN: diabetic nephropathy; Ex. Habit: presence of exercise habit; NS: not significant.

Data are expressed as mean ± standard deviation or n (%). The p value was derived from the one-way analysis of variance or  $\chi^2$  tests. Results by Tukey honestly significant difference test is shown by the superscripted symbols †, ‡, §, ¶, and \*. When there is the same symbol, there is no significant difference, and when there is a different symbol, there is a significant difference.

study reported that Italian elderly people with type 2 diabetes had significantly less lower extremity muscle strength (LEMS) than did elderly adults without diabetes.<sup>3</sup> Although all other previous studies have included only small samples, they have provided evidence supporting these findings.<sup>4–7</sup>

Abnormal mitochondrial function and free fatty acid metabolism, in addition to an inadequate increase in the microvascular blood supply during exercise, are likely to affect muscle function.<sup>8,9</sup> Moreover, diabetic polyneuropathy (DPN) is known to exacerbate the decline in physical ability in this patient population.<sup>10</sup> Andersen et al.<sup>11</sup> reported that a small group of patients with type 2 diabetes had a 7% (not statistically significant) reduction in KEF compared to that in healthy control subjects. In contrast, IJzerman et al.<sup>7</sup> revealed major differences in LEMS between diabetic patients with and without DPN. However, these small studies did not provide sufficient evidence to establish the relationship between DPN and LEMS. Unfortunately, the Health ABC and InCHIANTI studies did not consider DPN. Therefore, a large-scale study is needed to assess the role of DPN in reduced LEMS.

The Multicenter Survey of the Isometric Lower Extremity Strength in Type 2 Diabetes (MUSCLE-std) study aimed to identify groups of high-risk patients with the greatest reduction in LEMS.<sup>12</sup> In our first report, we reported that males and females aged 50–69 years and 70–87 years with DPN had significantly lower KEF values (10.9%–16.5%) than did patients without DPN.<sup>13</sup> Moreover, in our second report, we reported that maintaining KEF was also effective in maintaining exercise habits.<sup>14</sup> However, our previous reports did not assess the degree of reduction in KEF with respect to the levels in healthy control subjects. Furthermore, there have been no previous studies providing raw LEMS data. The aims and research questions of this study sought to establish

reference values for KEF in a cohort of patients with type 2 diabetes without DPN. Utilizing data from the MUSCLE-std study, we also aimed to answer the following research question: do patients with type 2 diabetes without DPN have lower KEF values than do healthy control subjects?

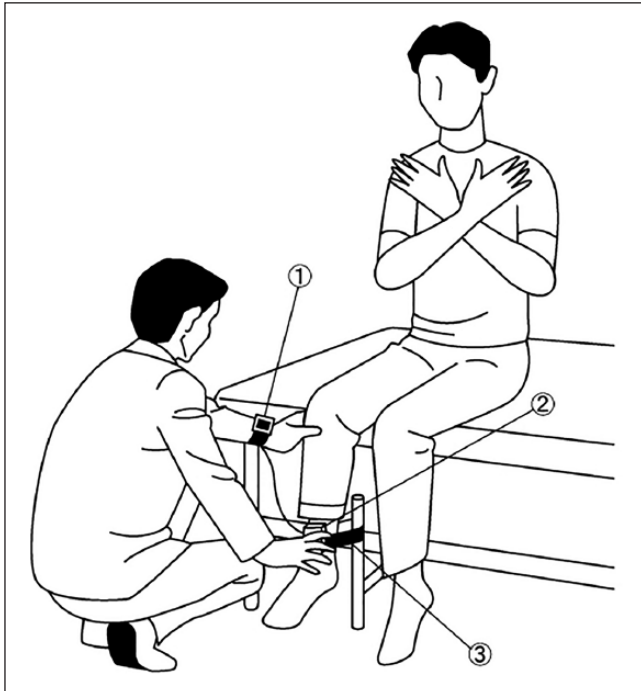
## Methods

### Study design and participants

In the MUSCLE-std study, data were collected for 1704 patients with type 2 diabetes, and the analysis ultimately included 1442 patients aged 30–87 years.<sup>13,14</sup> All patients provided written informed consent, and this study was registered with UMIN-CTR (UMIN000002810). In this study, medical data of Japanese patients with type 2 diabetes without severe complications such as the inability to adapt to the exercise therapy were utilized from the MUSCLE-std study.<sup>12</sup> The study population consisted of 898 patients with type 2 diabetes without DPN (Table 1). The raw data of patients are listed in the supporting information (Data S1). Because the MUSCLE-std study did not include a control group, we also acquired data for healthy Japanese people from a previous report, with the permission of the publisher, to act as control subjects.<sup>15</sup>

### Diabetes and exercise habit assessment

Patients with newly diagnosed diabetes were assigned a diabetes duration of 0 years, and diabetes duration ranged from 0 to 45 years, with a median duration of 7 years. Patients who fulfilled at least two of the following criteria were diagnosed with DPN: concerns about bilateral sensory symptoms in their toes and the soles of their feet, bilateral diminished or



**Figure 1.** Measurement of maximum isometric knee extension force using a muscle strength-measuring instrument with a fixed belt.

(1) Measurement monitor of the muscle strength-measuring instrument; (2) measurement sensor of the muscle strength-measuring instrument; and (3) fixed belt connecting the lower extremity to the muscle strength-measuring instrument.

absent Achilles tendon reflexes, and bilateral decreased vibratory sensations in the medial malleoli.<sup>16</sup> Diabetic retinopathy was classified as either none (absent) or as simple, pre-proliferative, or proliferative (present). Diabetic nephropathy was classified as stage <2 (absent) or stage  $\geq 2$  (present).<sup>17</sup>

Regular exercise behavior was defined as two sessions of exercise per week, of at least 30 min in duration. The stages of behavioral change were assessed based on the transtheoretical model;<sup>18</sup> participants who maintained this exercise behavior for at least 6 months (maintenance stage or later) were defined as engaging in regular exercise.

### Measurement of muscle strength in patients with type 2 diabetes

In the MUSCLE-std study, measurements that were obtained manually or by using an instrument were unified. KEF was measured by the same procedure in all participants. The maximum isometric KEF was measured by using a hand-held dynamometer (HHD;  $\mu$ Tas MT-1 or  $\mu$ Tas F-1; Anima Inc., Tokyo, Japan) with a fixed belt (Figure 1). The participants were instructed to maintain an upright posture with the hip and knee joints bent at 90° in the end-sitting position. Participants folded their arms in front of their chest during KEF measurement. The dynamometer sensor pad was placed

on the anterior face of the distal part of the lower leg, while the length of the stabilization belt was adjusted and tied to the posterior column supporting the testing board. During measurements, the tester supported the sensor pad lightly to prevent it from shifting. In each trial, participants applied isometric KEF at their maximum effort for about 5 s. This was performed with both legs twice, while the tester provided verbal encouragement. In all analyses, we employed the KEF value obtained from the non-dominant leg, in accordance with a previous report by Andersen et al.<sup>11</sup> The absolute value for isometric KEF (kgf) based on bodyweight (BW; kg) was used to calculate the relative KEF value (%KEF).

The intra-class correlation coefficients (ICCs) of this form of measurement in young adults (mean age = 21.9 years) has been reported to be  $\geq 0.9$ .<sup>19</sup> Similarly, the ICCs of the same measurements in older people (65–79 years) have been reported to be  $\geq 0.9$ .<sup>20</sup> Furthermore, the correlation coefficient between isometric KEF measured by using an HHD with a stabilization belt versus that measured with an isokinetic dynamometer has been reported to be 0.75.<sup>21</sup>

### Reference data of healthy subjects

The sample size, mean values, and standard deviations according to sex and age are shown in the tables included in a previous report.<sup>15</sup> The exclusion criteria for the control group were as follows: inability to walk unassisted, limitations in activities of daily living, and impairment of the lower extremities. In addition, any participants whose physical activity level was very low were not included.

The measurement procedure and instrumentation were the same as those used in the MUSCLE-std study. However, as in a previous study, the participants were permitted to hold the edge of the bed with both hands. However, in this study, the average of both legs was adopted as the KEF value in the analysis, in contrast to the MUSCLE-std study protocol.

### Statistical analysis

Males and females were divided into six groups based on age (30–39 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years, and 80–87 years); data were compared among the six groups separately for males and females. In addition, we conducted a sub-analysis for examining the influence of presence or absence of diabetic retinopathy or diabetic nephropathy on KEF. Quantitative variables were compared among the groups by using one-way analysis of variance (ANOVA). Subsequent multiple comparisons were performed by using Tukey's honest significance test. Qualitative variables were compared by using Pearson's chi-square ( $\chi^2$ ) test, and subsequent multiple comparisons were performed by using Z-tests. Body height (BH), BW, body mass index (BMI), KEF (kgf), and %KEF (%) were compared with regard to the presence or absence of diabetes, sex, and age among the six groups by using the same statistical methods.

**Table 2.** Comparison of knee extension force and body characteristics between type 2 diabetic patients without diabetic polyneuropathy and healthy control subjects.

Units	30–39 years	40–49 years	50–59 years	60–69 years	70–79 years	80 years	p value
<b>Males</b>							
T2DM	n=43	n=115	n=125	n=162	n=107	n=7	
KEF (kgf)	49.1 ± 15.1 <sup>†</sup>	44.6 ± 12.7 <sup>†,§</sup>	43.0 ± 11.6 <sup>†,§</sup>	38.0 ± 11.0 <sup>¶</sup>	31.5 ± 9.6 <sup>*,**</sup>	20.6 ± 6.5 <sup>***</sup>	<0.001
%KEF (%)	59.6 ± 14.6 <sup>†</sup>	57.0 ± 14.2 <sup>†</sup>	58.7 ± 14.8 <sup>†</sup>	58.3 ± 15.4 <sup>†</sup>	50.7 ± 14.5 <sup>†,§</sup>	34.9 ± 10.2 <sup>§</sup>	<0.001
BH (cm)	171.6 ± 6.5 <sup>†</sup>	170.2 ± 6.6 <sup>†</sup>	169.6 ± 5.6 <sup>†</sup>	165.5 ± 6.2 <sup>†,¶</sup>	162.4 ± 5.8 <sup>§</sup>	160.7 ± 4.2 <sup>¶</sup>	<0.001
BW (kg)	83.2 ± 18.4 <sup>†</sup>	78.7 ± 14.5 <sup>†</sup>	74.0 ± 13.5 <sup>§</sup>	65.4 ± 10.3 <sup>¶,*</sup>	62.3 ± 8.8 <sup>¶,*</sup>	58.8 ± 4.7 <sup>*</sup>	<0.001
BMI (kg/m <sup>2</sup> )	28.1 ± 5.6 <sup>†</sup>	27.1 ± 4.5 <sup>†,‡,*</sup>	25.7 ± 4.6 <sup>‡,*</sup>	23.8 ± 3.2 <sup>¶,*</sup>	23.5 ± 2.6 <sup>¶,*</sup>	22.8 ± 2.6 <sup>*</sup>	<0.001
Healthy	n=41	n=40	n=41	n=58	n=33	n=21	
KEF (kgf)	56.1 ± 12.7 <sup>†,§</sup>	49.4 ± 10.0 <sup>†,¶</sup>	50.8 ± 8.7 <sup>¶,¶</sup>	40.0 ± 8.5 <sup>*</sup>	31.3 ± 6.0 <sup>*,**,*</sup>	24.7 ± 4.7 <sup>***</sup>	<0.001
%KEF (%)	84.0 ± 14.2 <sup>†</sup>	77.9 ± 11.9 <sup>†</sup>	76.3 ± 15.8 <sup>†</sup>	63.6 ± 11.6 <sup>‡</sup>	56.3 ± 9.4 <sup>‡,§</sup>	48.5 ± 6.6 <sup>§</sup>	<0.001
BH (cm)	168.7 ± 6.8 <sup>†</sup>	166.5 ± 5.5 <sup>†</sup>	167.8 ± 5.5 <sup>†</sup>	165.5 ± 5.3 <sup>†</sup>	156.0 ± 7.4 <sup>†,§</sup>	155.7 ± 6.7 <sup>§</sup>	<0.001
BW (kg)	68.2 ± 7.7 <sup>†</sup>	64.1 ± 8.8 <sup>†,‡</sup>	67.3 ± 8.2 <sup>†</sup>	62.0 ± 5.5 <sup>‡</sup>	54.1 ± 8.0 <sup>¶,¶</sup>	51.0 ± 7.9 <sup>¶</sup>	<0.001
BMI (kg/m <sup>2</sup> )	24.0 ± 2.3 <sup>†</sup>	23.1 ± 2.8 <sup>†,‡</sup>	24.2 ± 1.1 <sup>†</sup>	22.9 ± 2.1 <sup>†,‡</sup>	22.4 ± 3.1 <sup>‡,§</sup>	20.9 ± 2.3 <sup>§</sup>	<0.001
<b>Females</b>							
T2DM	n=19	n=36	n=69	n=131	n=72	n=12	
KEF (kgf)	31.3 ± 10.0 <sup>†</sup>	28.6 ± 11.1 <sup>†,‡</sup>	27.1 ± 8.2 <sup>†,‡</sup>	25.3 ± 7.8 <sup>‡</sup>	21.2 ± 6.9 <sup>§</sup>	13.7 ± 2.4 <sup>¶</sup>	<0.001
%KEF (%)	43.4 ± 14.6 <sup>†,‡</sup>	41.3 ± 16.9 <sup>†,‡</sup>	44.0 ± 12.9 <sup>†</sup>	45.7 ± 15.1 <sup>†</sup>	40.3 ± 12.8 <sup>†,‡</sup>	29.4 ± 4.4 <sup>‡</sup>	<0.002
BH (cm)	158.0 ± 7.2 <sup>†</sup>	158.6 ± 6.5 <sup>†</sup>	155.3 ± 5.5 <sup>†,‡</sup>	153.3 ± 5.5 <sup>‡,§</sup>	151.0 ± 5.3 <sup>¶,¶</sup>	147.5 ± 4.2 <sup>¶</sup>	<0.001
BW (kg)	75.0 ± 16.2 <sup>†</sup>	71.5 ± 17.2 <sup>†</sup>	62.9 ± 11.5 <sup>‡</sup>	56.3 ± 9.4 <sup>§</sup>	53.4 ± 9.9 <sup>§</sup>	47.4 ± 9.3 <sup>§,*</sup>	<0.001
BMI (kg/m <sup>2</sup> )	30.0 ± 6.4 <sup>†</sup>	28.3 ± 6.4 <sup>†,‡</sup>	26.0 ± 4.3 <sup>‡</sup>	23.9 ± 3.4 <sup>§</sup>	23.4 ± 4.1 <sup>§</sup>	21.7 ± 4.0 <sup>§</sup>	<0.001
Healthy	n=44	n=42	n=44	n=56	n=54	n=36	
KEF (kgf)	33.4 ± 6.8 <sup>†</sup>	33.3 ± 5.7 <sup>†</sup>	30.2 ± 5.6 <sup>†</sup>	26.2 ± 5.6 <sup>‡,§</sup>	23.2 ± 6.1 <sup>§</sup>	18.8 ± 3.2 <sup>¶</sup>	<0.001
%KEF (%)	65.3 ± 12.1 <sup>†</sup>	63.0 ± 12.4 <sup>†</sup>	59.0 ± 12.1 <sup>†</sup>	50.2 ± 9.6 <sup>‡,§</sup>	45.9 ± 10.1 <sup>§</sup>	38.6 ± 4.9 <sup>¶</sup>	<0.001
BH (cm)	160.1 ± 3.9 <sup>†</sup>	156.2 ± 4.0 <sup>‡,§</sup>	154.4 ± 4.3 <sup>¶,¶</sup>	152.1 ± 6.6 <sup>¶</sup>	149.8 ± 5.7 <sup>¶</sup>	149.2 ± 5.2 <sup>¶</sup>	<0.001
BW (kg)	50.9 ± 5.2 <sup>†,‡</sup>	53.7 ± 8.0 <sup>†</sup>	51.7 ± 5.5 <sup>†,‡</sup>	52.7 ± 6.9 <sup>†,‡</sup>	50.8 ± 7.8 <sup>†,‡</sup>	48.6 ± 6.5 <sup>‡</sup>	<0.02
BMI (kg/m <sup>2</sup> )	19.9 ± 2.2 <sup>†</sup>	22.1 ± 3.5 <sup>‡</sup>	21.9 ± 2.6 <sup>‡</sup>	22.8 ± 2.8 <sup>‡</sup>	22.6 ± 3.0 <sup>‡</sup>	21.8 ± 2.6 <sup>‡</sup>	<0.001

T2DM: type 2 diabetes mellitus without diabetic polyneuropathy; healthy: healthy controls; BH: body height; BW: bodyweight; BMI: body mass index; KEF: knee extension force; %KEF: KEF/bodyweight × 100.

Data from healthy control subjects were extracted from Hirasawa et al.<sup>15</sup> Data are expressed as means ± standard deviations. The p values were derived by using one-way analysis of variance. Results determined by using Tukey's honestly significant difference test is shown by the superscripted symbols †, ‡, §, ¶, \*, \*\*, and \*\*\*. When there is the same symbol, there is no significant difference, and when there is a different symbol, there is a significant difference.

Statistical analyses for patients with diabetes were performed by using IBM SPSS 24 software (Chicago, IL, USA). Based on the methods reported by Larson,<sup>22</sup> statistical analyses for healthy participants were performed by using JMP Pro 13 software (SAS Institute Japan Ltd., Tokyo, Japan).

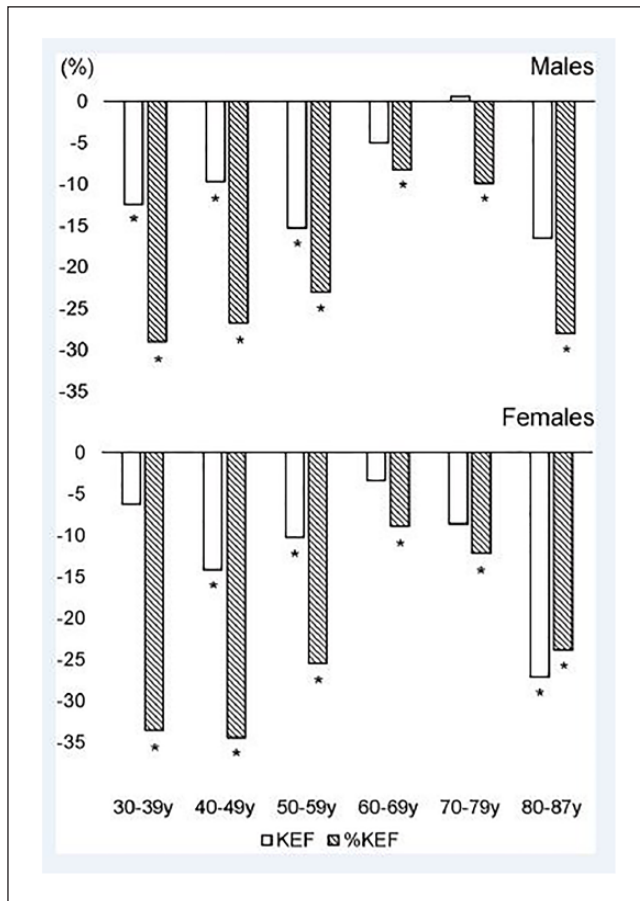
The values of KEF and %KEF in type 2 diabetic patients without DPN with respect to sex and age were compared with the corresponding data from healthy control subjects. Comparisons between this study data and previous study data (mean values, standard deviations, and N) were performed using t-tests. Moreover, an effect size was calculated when a significant difference by t-test was found between the patients with diabetes group and the healthy subjects group. We calculated the Cohen's d to determine effect size, and determined statistical values are as follows: small,  $0.2 \leq d < 0.5$ ; medium,  $0.5 \leq d < 0.8$ ; and large,  $0.8 \leq d$ .<sup>23</sup> These statistical analyses were performed using Microsoft Excel (2016) software. These results showed the percentage values of KEF and %KEF in patients with type 2 diabetes

without DPN with respect to the same values in healthy control subjects. This percentage was calculated according to the following formula: ("mean value in healthy controls" – "mean value in patients with diabetes")/values in healthy controls × 100. In all statistical analyses, a p value <0.05 was considered statistically significant.

## Results

### Change in muscle strength by age

In patients with type 2 diabetes without DPN, the values for KEF, %KEF, BH, BW, and BMI decreased with age (Table 2). In males, the rate of decline in KEF and %KEF from 30 to 39 years and from 80 to 87 years was 58.0% and 41.4%, respectively. In females, these rates were 56.2% and 32.2%, respectively. In healthy control subjects, KEF, %KEF, BH, BW, and BMI decreased with age. In males, the rate of decline in KEF and %KEF from 30 to 39 years and from 80 to 88 years



**Figure 2.** Percentage of muscle strength in type 2 diabetic patients without diabetic polyneuropathy relative to muscle strength in healthy control subjects.

Abbreviations: y, years; KEF, knee extension force; %KEF, KEF/body-weight  $\times$  100. This percentage was calculated by using the following formula (“mean value in healthy controls” – “mean value in patients with diabetes”)/data in healthy controls  $\times$  100.

was 55.9% and 42.2%, respectively. In females, the corresponding rates were 43.7% and 40.8%, respectively.

On performing sub-analysis to examine the influence of diabetic complications, we did not recognize any significant differences in KEF in the presence or absence of diabetic retinopathy. However, KEF was significantly lower in the presence of diabetic nephropathy than that in its absence among females aged 50–59 years ( $37.1 \pm 9.1$  kgf vs  $45.2 \pm 13.2$  kgf). We did not recognize significant differences in KEF in any other age group or in males.

### *Difference in muscle strength between patients with diabetes and healthy subjects*

Figure 2 shows the percentage values of KEF and %KEF in type 2 diabetic patients without DPN with respect to the same values in healthy control subjects. After excluding males aged 70–79 years, the percentages of KEF and %KEF

fell within the following ranges: –5.0% to –16.5% and –8.3% to –29.0%, respectively, in males and –3.4% to –27.1% and –8.9% to –34.4%, respectively, in females. The mean percentage of KEF and %KEF was –9.7% and –20.8% in males and –11.6% and –23.0% in females, respectively.

Based on a t-test, KEF was significantly lower in the 30–39, 40–49, and 50–59 year age groups in males and in the 40–49, 50–59, and 80–87 year age groups in females than were the corresponding values in healthy control subjects. Cohen’s d with t-test for KEF between the two groups gave the following results: large effect size for females aged 80–87 years; medium effect size for 30–39 and 50–59 years for males and 40–49 years for females; and small effect size for 40–49 years for males and 50–59 years for females. Furthermore, %KEF was significantly lower in all age groups in both male and female patients as compared to that in healthy control subjects. Cohen’s d with t-test for %KEF between the two groups was as follows: large effect size for 30–39, 40–49, 50–59, and 80–87 years for males and females and small effect size for 60–69 and 70–79 years for male and females.

## **Discussion**

To the best of our knowledge, this is the first study to provide standard reference values for LEMS based on data from a population of patients with type 2 diabetes with respect to sex, across a wide age range.

This study was performed by using data on patients with type 2 diabetes without DPN, severe diabetic retinopathy, or diabetic nephropathy patients of the inability to adapt to the exercise therapy. The Japan Diabetes Clinical Data Management (JDDM) study group reported that the mean HbA1c of patients with type 2 diabetes is 7.01%.<sup>24</sup> In this study, the mean HbA1c was 9.25% in males and 9.15% in females. Many patients were recruited because it had been recommended that they begin blood glucose control measures. We believe that this explains why our mean HbA1c was higher than that reported by the JDDM study group. Furthermore, the JDDM study group reported a mean BMI of 24.7 kg/m<sup>2</sup> in patients with type 2 diabetes (mean age, 65.8 years) in 2015.<sup>25</sup> In this study, the mean BMI was 25.2 kg/m<sup>2</sup> (mean age, 57.8 years) in males and 24.9 kg/m<sup>2</sup> (mean age, 61.1 years) in females. While the BMI of patients in this study was higher than that found in the JDDM study, we do not believe that this difference is significant, because BMI decreases with age. The mean BMI of Japanese adults in 2012 was 23.6 kg/m<sup>2</sup> in males (20–69 years) and 22.5 kg/m<sup>2</sup> in females (40–69 years).<sup>26</sup> We believe that the healthy control subjects in a previous study represent the average Japanese physique, because the mean BMI was 25.2 kg/m<sup>2</sup> in males and 24.9 kg/m<sup>2</sup> in females. These facts suggest that the results of this study represent the general Japanese type 2 diabetic population as well as healthy people.

The values of KEF and %KEF decreased with age in both patients with diabetes and healthy control subjects. A decline of muscle strength is part of the natural aging process. However, we found that the mean values for KEF and %KEF tended to be lower in patients with diabetes than those in healthy control subjects. Moreover, KEF was significantly lower in the 30–39, 40–49, and 50–59 year age groups in males, as well as in the 40–49, 50–59, and 80–87 year age groups in females than in corresponding healthy control subjects. Contrastingly, the trend of these results was not observed in males aged 60–69 years. A difference in participant's characteristics (e.g. BW and physical activity) may affect KEF; however, we could not identify the cause for bimodal distribution, and therefore, this contributed to the study limitations. Furthermore, %KEF was significantly lower in patients with diabetes than in healthy control subjects for all age groups and both sexes. The values of KEF and %KEF in patients with diabetes were –9.7% and –20.8% in males and –11.6% and –23.0% in females as compared to the values in healthy control subjects. We did not calculate the sample size in this study. Therefore, we calculated the effect size (Cohen's *d*) of *t*-tests in the comparison between patients with type 2 diabetes and healthy subjects. Nine parameters showed a “large” effect size, and we did not accept the effect size to be less than “Small.” We think that these results approve significant differences by *t*-test. Therefore, we propose that KEF and %KEF in patients with type 2 diabetes without DPN may be reduced by approximately 10% and 20%, respectively. It has been reported that the continuation of regular exercise maintains muscle strength, and higher LEMS may be important for the continuation of exercise regimens.<sup>27</sup> We believe that physical activity influences muscle strength;<sup>28</sup> however, a previous study did not include physical activity in the analysis.<sup>15</sup> In patients with diabetes, 28.1% of males and 31.3% of females performed regular exercise. As reported by the Ministry of Health, Labor and Welfare in 2012, of Japanese people aged  $\geq 20$  years who performed regular exercise, 36.1% were males and 28.2% were females.<sup>26</sup> If the healthy control subjects in this study maintained exercise habits similar to those of the general Japanese population, we propose that there should be no difference in the levels of physical activity observed in the diabetes group.

The importance of medical professionals paying attention to muscle strength in elderly patients, especially those with diabetes, has been reported.<sup>27</sup> Muscle strength grade is usually 4 (Good) or 5 (Normal) as measured by using a manual muscle test for the majority of patients with diabetes without severe diabetic nephropathy. However, it is difficult to determine an accurate assessment of muscle strength reduction of greater than grade 4 by using a manual muscle test.<sup>29,30</sup> Therefore, we propose that muscle strength must be measured with an appropriately calibrated instrument. Moreover, performance of the simple and easy procedure we have outlined, which uses small and portable equipment with the

same reliability as that of expensive, large instruments, is important to accurately measure muscle strength and raise awareness in clinical practice. Use of an HHD with a fixed belt meets these criteria.<sup>20</sup>

Our report will contribute to the appropriate prescription of exercise therapy by providing criteria for identifying the need for interventions aimed at muscle strengthening, designing protocols for gradual muscle strengthening, and estimating the muscle strengthening effects of various physical activities in patients with diabetes. Moreover, we have provided reference values for KEF and %KEF that can be used in clinical practice when an HHD is employed to measure muscle strength. The HHD device we employed was calibrated using a Japanese mass traceability system traceable to the international standard kilogram prototype. When muscle strength is measured by using equipment with equivalent performance, HHD readings can be compared with our reference values, assuming that the measuring method is the same. Thus, the reference values reported in this study should be valuable regardless of location or available measurement devices. Finally, because the world's elderly population is rapidly increasing along with the need for long-term care, preventing a general decline in the physical function of older adults is crucial. Therefore, we believe our results will assist medical professionals in determining whether long-term care is required for an older individual.

This study has several limitations. First, the nerve conduction velocity test was not used in this study did not evaluate diabetic neuropathy. Therefore, patients with non-apparent diabetic neuropathy presenting with mild diabetic polyneuropathy may have been included in the study population. Second, physical activity may influence KEF; however, differences in physical activity between patients with diabetes and healthy control subjects were not clarified in this study. Third, we used *t*-tests to compare muscle strength between the groups. Fourth, there is a lack of raw data on healthy control subjects published in the literature; therefore, the statistical methods used in our study were not optimal. Fifth, the average value for KEF was calculated for both legs in previous study and for the non-dominant leg in the MUSCLE-std study. The adoption of different KEF values in both studies may have affected the analysis. Finally, because the data of patients with type 2 diabetes in this study were compared with previous data of healthy subjects released in 2004, there is a time gap of 10 years. Future studies should, therefore, be performed to compensate for these limitations.

## Conclusion

In patients with type 2 diabetes without DPN, KEF and %KEF may be reduced by approximately 10% and 20%, respectively. An HHD with a fixed belt is useful in detecting this form of muscular functional impairment. Employment of our simple protocol along with the use of the reference values provided in this report will aid in the assignment of

effective exercise/treatment regimens for improving the quality of life in this population of patients.

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### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Ethical approval

The MUSCLE-std study was conducted with the approval of the institutional review board of Kansai University of Welfare Sciences (the principal researcher's affiliated institution), as well as the institutional review boards or directors of all cooperating institutions. This study conforms to the tenets of the Declaration of Helsinki.

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### Informed consent

Verbal and written informed consent was obtained from patients with type 2 diabetes.

### Supplemental material

Supplemental material for this article is available online.

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