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Original Research Article

Decreased Muscle Strength and Quality in Diabetes-Related Dementia

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Keywords

Dementia · Alzheimer disease · Diabetes mellitus · Muscle · Sarcopenia · Dynapenia

Abstract

Background/Aims: Diabetes-related dementia (DrD), a dementia subgroup associated with specific diabetes mellitus (DM)-related metabolic abnormalities, is clinically and pathophysiologically different from Alzheimer disease (AD) and vascular dementia. We determined whether skeletal muscle strength, quality, and mass decrease in individuals with DrD. ***Methods:*** We evaluated grip and knee extension strength, muscle mass, and gait speed in 106 patients with probable AD and without type 2 DM (AD[–DM] group), 74 patients with probable AD and with DM (AD[+DM] group), and 36 patients with DrD (DrD group). Muscle quality was defined as the ratio of muscle strength to muscle mass. ***Results:*** Both female and male subjects with DrD showed significantly decreased muscle strength and quality in the upper extremities compared with the subjects with AD[–DM] or AD[+DM]. Female subjects with DrD showed significantly decreased muscle quality in the lower extremities compared with the subjects with AD[–DM]. Both female and male subjects with DrD had a significantly lower gait speed compared with the subjects with AD[–DM]. However, there were no significant differences in muscle mass and the prevalence of sarcopenia between the groups. ***Conclusion:*** Subjects with DrD showed decreased muscle strength and quality, but not muscle mass, and had a low gait speed.

Introduction

Type 2 diabetes mellitus (DM) has been shown to increase the risk for cognitive decline and dementia, such as Alzheimer disease (AD) and vascular dementia [1, 2]. In addition to AD and vascular dementia, there may be a dementia subgroup associated with specific DM-related metabolic abnormalities rather than with AD pathology or cerebrovascular disease. This type

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of dementia, showing neither cerebrovascular disease on magnetic resonance imaging (MRI) nor hypoperfusion in the parietotemporal lobe on single-photon emission computed tomography (SPECT), was clinically characterized by a high hemoglobin A_{1c} level; a long duration of diabetes; a high frequency of insulin therapy; a low frequency of apolipoprotein E4 carrier; generalized (predominantly frontal) cortical atrophy, but less severe medial temporal lobe atrophy; more impaired attention and executive functions, but less impaired word recall; and slow progression of cognitive impairment. It might be referred to as "diabetes-related dementia" (DrD) [3, 4].

In our previous study, ^{11}C-Pittsburgh compound B positron emission tomography (PET) often showed negative or equivocal amyloid accumulation in the brains of subjects with DrD, indicating less amyloid pathology or none [5]. Our preliminary tau PET study demonstrated that most patients with DrD showed accumulation of ^{11}C-pyridinyl-butadienyl-benzothiazole 3 (PBB3) [6] in the brain, including the medial temporal lobe, suggesting tau deposition in the brain [unpubl. data]. Although we have no autopsy data, DrD may be associated with tauopathy, such as senile dementia of the neurofibrillary tangle type [7] or primary age-related tauopathy [8], and nonspecific neuronal damage due to glucose toxicity. In addition, cerebrospinal fluid (CSF) analysis demonstrated normal or slightly increased phosphorylated tau and normal amyloid β_{42} levels [9]. DrD is not suggestive of a particular underlying neuropathology, but merely describes a dementia state predominantly associated with DM-related metabolic abnormalities rather than AD or vascular pathology. This type of dementia accounted for about 10% of all patients with dementia associated with DM. Since glycemic controls can improve some domains of cognitive function, such as attention and executive functions, in subjects with DrD, the identification of DrD may be necessary for considering appropriate therapy and prevention in clinical practice.

Our previous study revealed that DrD is associated with a greater prevalence of frailty status, in particular low physical activity, weakness, and slowness, than is AD [10]. Some of the above components of frailty are associated with age-related loss of muscle mass or muscle strength. In the present study, we evaluated the muscle strength, quality, and mass of the upper and lower extremities, as well as gait speed, in subjects with DrD and those with AD with and without DM. Moreover, we compared the prevalence of sarcopenia between the subjects. The aim of the present study was to determine whether individuals with DrD show decreased skeletal muscle strength, quality, and mass compared with AD subjects with DM or without DM.

Subjects and Methods

Subjects

We enrolled 106 patients with probable AD and without DM (63 women and 43 men; AD [–DM] group), 73 patients with probable AD and with DM (47 women and 26 men; AD[+DM] group), and 36 patients with DrD (18 women and 18 men; DrD group) from our Memory Clinic at Tokyo Medical University Hospital. The subjects with AD had to meet the DSM-5 criteria for a diagnosis of probable AD [11]. The diagnosis of DrD was based on our proposed guidelines for the clinical diagnosis of DrD [4]. We briefly describe its clinical diagnosis as follows:

1. Type 2 DM: long duration and less well-controlled glycemia
2. Dementia: impaired attention and executive function, but less impaired word recall; slow progression of cognitive impairment
3. Brain MRI: no evidence of vascular lesions; diffuse (predominantly frontal) cortical atrophy, but less severe medial temporal lobe atrophy
4. SPECT/PET: no significantly decreased hypoperfusion/hypometabolism in the posterior cerebral lobe; negative or equivocal amyloid accumulation

5. CSF analysis: normal or slightly increased phosphorylated tau and normal amyloid β_{42} levels
6. ApoE4 carrier: low frequency
7. Exclusion of other causes of dementia (e.g., hypothyroidism, vitamin B_1 or B_{12} deficiency, head trauma, chronic alcoholism, cerebrovascular disease, and other neurodegenerative diseases)

All patients underwent general physical examinations, clinical neurological examinations, laboratory tests, and brain imaging studies (MRI and SPECT) to exclude other potential causes of dementia. Amyloid PET and CSF analyses were performed on 28 and 14 of the 36 subjects with DrD, respectively.

DM was defined as the use of antidiabetic medication, a casual (nonfasting) plasma glucose level of 200 mg/dL, or a fasting plasma glucose level of 126 mg/dL, in accordance with the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [12]. The severity of cognitive impairment was assessed using the Mini-Mental State Examination (MMSE) [13]. Subjects showing an irregular periventricular signal extending into the deep white matter on MRI (grade 3 based on the scale of Fazekas) were excluded. We excluded subjects with severe disability, such as users of a cane or walker, those who could not walk without assistance, those with severe dementia (MMSE score <12 out of 30), and those with major depression. We also excluded subjects with malignancies, severe cardiac or pulmonary diseases, liver cirrhosis, and severe kidney diseases. We determined the prevalence of major chronic diseases of older adults using the Charlson comorbidity index [14].

Informed consent was obtained from all subjects or their relatives. This study was approved by the ethics committee of Tokyo Medical University.

Muscle Strength, Mass, and Quality

The upper and lower muscle functions were measured using a digital handgrip meter (MCZ-5041; Macros, Tokyo, Japan) for grip strength and a μTas F-1 handheld dynamometer (Anima, Tokyo, Japan) for knee extension strength. Isometric grip strength was assessed for each hand, and we analyzed the maximum grip strength of the right and the left hand. For knee extension, we analyzed the greater of two measurements for each leg. The interrater reliability of the isometric knee extension strength measurements was highly correlated with the data measured with the handheld dynamometers (correlation coefficient, both men and women: $r = 0.99$) [15].

The muscle masses of the upper and lower extremities were measured using bioelectrical impedance analysis (InBody S10; InBody Japan Inc., Tokyo, Japan). The skeletal muscle mass index (SMI) was calculated by dividing skeletal muscle mass by height (in meters) squared (kg/m^2). Similar to other reports in the literature, muscle quality was expressed as the ratio of muscle strength to muscle mass for the upper and lower extremities, such as grip strength/arm skeletal muscle mass (kg/kg) and knee extension strength/leg skeletal muscle mass (kg/kg). The lean body mass evaluated with this device was highly correlated with the data measured by dual-energy X-ray absorptiometry (correlation coefficients: men, $r = 0.96$; women, $r = 0.95$) [16].

Diagnosis of Sarcopenia

Sarcopenia was defined according to the consensus of the Asian Working Group for Sarcopenia (AWGS) criteria [17], which includes three components, namely, low handgrip strength (<26 kg for men and <18 kg for women), low gait speed (≤0.8 m/s on 6-m walking at the usual pace), and low muscle mass as assessed with the SMI (7.0 kg/m^2 for men and 5.7 kg/m^2 for women as measured by bioelectrical impedance analysis).

Table 1. Clinical characteristics of the female group

	AD[–DM]	AD[+DM]	DrD
Subjects, *n*	63	47	18
Age, years	82.1±5.2	82.2±5.7	84.1±4.8
Duration of dementia, years	3.2±1.0	3.4±0.8	3.3±1.3
Education, years	11.9±2.3	11.4±2.3	11.1±3.1
HbA_{1c}, %	5.7±0.3	6.9±1.1**	7.3±1.0**, #
Long duration of diabetes (≥15 years), *n* (%)	–	12 (25)	6 (33)
Insulin therapy, *n* (%)	–	6 (13)	7 (39)#
MMSE score	20.6±3.8	21.0±3.6	22.1±3.4
Charlson comorbidity index	1.3±0.5	2.3±0.4**	2.2±0.5**
Body mass index	22.0±3.3	22.5±4.0	24.6±3.0*, #

Values are presented as the mean ± SD unless specified otherwise. AD, Alzheimer disease; DM, diabetes mellitus; AD[–DM], probable AD without DM; AD[+DM], probable AD with DM; DrD, diabetes-related dementia; MMSE, Mini-Mental State Examination. * $p < 0.01$, ** $p < 0.0001$ compared with AD[–DM]; # $p < 0.05$ compared with AD[+DM].

Statistical Analysis

Values are expressed as the mean ± SD. Statistical analysis was performed using one-way analysis of variance with Fisher's post hoc partial least-squares difference test and the χ^2 test. We analyzed muscle strength, quality, and mass, SMI, and gait speed using analysis of covariance (ANCOVA). A p value <0.05 was considered to indicate a statistically significant difference.

Results

We analyzed the clinical characteristics and muscle functions in each female and male group, as muscle strength and physical performance are considerably different between men and women. In the female group, there were no significant differences in age, duration of dementia, education, and MMSE scores between the three subgroups. The HbA_{1c} levels and Charlson comorbidity indices were significantly higher in the AD[+DM] and DrD groups than in the AD[–DM] group. The HbA_{1c} levels were significantly higher in the DrD group than in the AD[+DM] group. The BMI was significantly higher in the DrD group than in the AD[–DM] and AD[+DM] groups. Although the frequencies of a long duration of DM (≥15 years) were comparable between the AD[+DM] group and the DrD group, the number of patients receiving insulin therapy was significantly higher in the DrD group than in the AD[+DM] group (Table 1). For the upper extremities, ANCOVA, taking into account HbA_{1c}, the Charlson comorbidity index, and the BMI as covariates, revealed that muscle strength, but not muscle mass, was significantly lower in the DrD group than in the AD[–DM] group, and muscle quality was significantly lower in the DrD group than in the AD[–DM] and AD[+DM] groups. For the lower extremities, muscle quality, but not muscle strength and mass, was significantly lower in the DrD group than in the AD[–DM] group (Table 2).

In the male group, there were no significant differences in age, duration of dementia, education, MMSE score, and BMI between the three subgroups. The HbA_{1c} levels and Charlson comorbidity indices were significantly higher in the AD[+DM] and DrD groups than in the AD[–DM] group. There were no significant differences in HbA_{1c} level, the frequency of a long duration of DM, and the number of patients receiving insulin therapy between the AD[+DM]

Table 2. Muscle function and frequency of sarcopenia in the female group

	AD[–DM]	AD[+DM]	DrD
Upper extremities			
Handgrip strength, kg	17.00±3.50	16.28±3.60	14.70±3.91*
Arm muscle mass, kg	1.37±0.26	1.37±0.25	1.44±0.30
Arm muscle quality, kg/kg	12.62±3.59	12.12±2.30	10.43±2.49**, #
Lower extremities			
Leg strength, kg	16.11±4.73	15.05±4.23	13.86±5.48
Leg muscle mass, kg	4.74±0.74	4.59±0.63	4.75±0.96
Leg muscle quality, kg/kg	3.43±1.11	3.30±0.89	2.82±0.80*
Skeletal muscle mass index	5.54±0.64	5.53±0.65	5.69±0.91
Gait speed, m/s	0.97±0.17	0.91±0.17	0.80±0.21**
Frequency of sarcopenia, *n* (%)	24 (38)	24 (51)	9 (50)

Values are presented as the mean ± SD unless specified otherwise. For explanations of the abbreviations, see footnote to Table 1. * $p < 0.05$, ** $p < 0.01$ compared with AD[–DM]; # $p < 0.05$ compared with AD[+DM].

Table 3. Clinical characteristics of the male group

	AD[–DM]	AD[+DM]	DrD
Subjects, *n*	43	27	18
Age, years	83.3±4.8	81.1±4.3	83.4±4.9
Duration of dementia, years	2.9±0.9	3.0±0.9	3.0±0.7
Education, years	14.4±2.2	13.9±2.5	13.8±2.4
HbA_{1c}, %	5.8±0.3	7.4±1.1*	7.3±1.0*
Long duration of diabetes (≥15 years), *n* (%)	–	10 (37)	8 (44)
Insulin therapy, *n* (%)	–	7 (26)	5 (28)
MMSE score	21.1±2.6	21.8±3.5	22.6±2.4
Charlson comorbidity index	1.5±0.6	2.3±0.6*	2.3±0.5*
Body mass index	22.7±2.6	23.9±3.4	24.3±3.4

Values are presented as the mean ± SD unless specified otherwise. For explanations of the abbreviations, see footnote to Table 1. * $p < 0.0001$ compared with AD[–DM].

group and the DrD group (Table 3). For the upper extremities, ANCOVA, taking into account HbA_{1c} and the Charlson comorbidity index as covariates, revealed that muscle strength, but not muscle mass, was significantly lower in the DrD group than in the AD[–DM] group. Muscle quality was significantly lower in the AD[+DM] and DrD groups than in the AD[–DM] group. For the lower extremities, there were no significant differences in muscle strength, mass, and quality (Table 4).

Both the female and the male subjects with DrD had a significantly lower gait speed than the subjects in the AD[–DM] group. However, there were no significant differences in SMI and the prevalence of sarcopenia between the groups (Tables 2, 4).

Discussion

Both female and male subjects with DrD showed decreased muscle strength and quality in the upper extremities, and female subjects with DrD showed decreased muscle quality in the lower extremities. Both female and male subjects with DrD had a low gait speed, but

Table 4. Muscle function and frequency of sarcopenia in the male group

	AD[–DM]	AD[+DM]	DrD
Upper extremities			
Handgrip strength, kg	26.29±5.72	23.83±4.57	21.93±4.70**
Arm muscle mass, kg	2.10±0.40	2.18±0.33	2.17±0.34
Arm muscle quality, kg/kg	12.63±1.85	11.17±2.48*	10.38±2.74**
Lower extremities			
Leg strength, kg	25.32±9.55	21.70±6.88	22.38±7.01
Leg muscle mass, kg	6.96±0.98	6.80±0.98	7.06±1.09
Leg muscle quality, kg/kg	3.62±1.20	3.21±0.94	3.21±1.06
Skeletal muscle mass index	6.98±0.74	6.95±0.82	6.91±0.93
Gait speed, m/s	0.99±0.16	0.92±0.19	0.86±0.27*
Frequency of sarcopenia, *n* (%)	16 (37)	15 (56)	9 (50)

Values are presented as the mean ± SD unless specified otherwise. For explanations of the abbreviations, see footnote to Table 1. * $p < 0.05$, ** $p < 0.001$ compared with AD[–DM].

showed no decreased muscle mass and SMI. Therefore, the prevalence of sarcopenia was comparable between the groups. Our results indicate that DrD is characterized by a decrease in muscle strength and quality, but not in muscle mass, and by an impairment of physical performance as assessed by a low gait speed.

Several studies have demonstrated that DM is associated with decreased skeletal muscle strength and quality [18–20]. A longitudinal study revealed an association of DM with accelerated loss of leg muscle strength and quality [21, 22]. Female individuals with DM showed especially rapid annual loss of skeletal muscle mass [22]. Kim et al. [20] found that DM was associated with an increased risk of sarcopenia. These findings suggest that DM is associated with a higher risk of physical disability. Multiple factors, such as hyperglycemia, diabetic complications, obesity, insulin resistance, inflammatory cytokines, and endocrine changes, have adverse effects on muscles [23, 24]. However, in spite of decreased muscle strength and quality in subjects with DrD, we found no significant differences in the prevalence of sarcopenia between the groups. This discrepancy may be due to differences in subject selection.

Most previous studies have included well-functioning older adults, contrary to our study, which enrolled only individuals with dementia, including AD and DrD. Low muscle mass and muscle strength have been linked to higher levels of cognitive impairment, dementia, and brain atrophy [25, 26], although their relationship with cognitive impairment is less clear. Body weight loss was accelerated before the development of clinical symptoms of AD [27]. A study by Burns et al. [26] showed that loss of lean mass is accelerated in AD and is associated with brain atrophy and cognitive impairment. Therefore, individuals with AD, who were enrolled as control subjects in the present study, are likely to have had a higher prevalence of sarcopenia than those without cognitive impairment or dementia. Actually, the prevalence of sarcopenia in AD found in this study (38% among women and 37% among men) is apparently higher than that in community-dwelling elderly Japanese based on the consensus of the AWGS (about 15–20% at 75–84 years) [28]. A weak statistical power because of the small sample size may also be another reason that we found no significant difference in prevalence of sarcopenia between the groups. Since muscle mass is correlated with body weight or BMI, a substantial muscle reduction may not be expected in subjects with DrD who had a high BMI. Decreased muscle mass and quality without obvious loss of muscle mass may be termed as dynapenia (age-related loss of muscle strength and power) [29]. There may be a different pathophysiology between sarcopenia and dynapenia. Muscle strength is lost at a substantially

faster rate than muscle mass [30]. In addition, loss of muscle strength is a more consistent risk for physical disability than is loss of muscle mass [31]. Therefore, potential therapy and rehabilitation strategies for dynapenia may be different from those for sarcopenia.

There have been several studies investigating muscle quality in older adults with DM [19, 21, 32]. Park et al. [19] demonstrated that muscle quality was consistently lower in older adults with DM. In this study, we also found decreased muscle quality in the upper extremities of both female and male subjects with DrD. In particular, female subjects with DrD showed decreased muscle quality without any reduction of muscle strength in the lower extremities, associated with a low gait speed. Although the pathophysiological mechanisms of poor muscle quality remain unclear, muscle quality rather than muscle strength and mass may be a more sensitive measure for detecting physical disability.

Previous studies have demonstrated that a longer duration of DM and poor glycemic control are associated with poorer muscle quality or with functional disability [19, 32]. In this study, we also found that female subjects with DrD had significantly higher HbA_{1c} levels and a higher frequency of insulin therapy than those with AD[+DM]. Although we failed to investigate differences in diabetic complications, including retinopathy, neuropathy, and nephropathy, between the groups, medical comorbidities not evaluated by the Charlson comorbidity index may be associated with muscle strength and mass, as well as with physical impairment. In addition, our previous study revealed that inflammatory markers [33], oxidative stress [34], and advanced glycation end products [35] are more strongly associated with development of dementia and progression of cognitive decline in the DrD group than in the AD[+DM] or AD[–DM] group. Even though it remains uncertain whether decreased muscle quality and strength without loss of muscle mass are specific features of DrD, DM-related metabolic abnormalities may also be contributing factors for poor muscle function. Further studies are required to determine whether there may be some differences in muscle function between DrD and other types of dementia, such as vascular dementia and dementia with Lewy bodies.

Our study has some limitations. It has a cross-sectional design with a relatively small sample size. A longitudinal study with a larger sample size will be needed to confirm our results. Since the aim of this study was to determine whether muscle function in DrD could differ from that in AD with or without DM, enrolment of subjects was limited to outpatients with dementia. Community-dwelling healthy individuals were not included in this study. To determine an association of DM with muscle function, it is necessary to investigate cognitively normal subjects with and without DM.

Considering these limitations, we conclude that muscle strength and quality, but not muscle mass, decreased in subjects with DrD. These characteristics may be associated with physical disability, as subjects with DrD had a low gait speed. Therefore, geriatric interventions, including nutritional, hormonal, pharmacological, and exercise therapies, are necessary to improve clinical outcomes for patients with DrD.

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