Sarcopenia in elderly patients with type 2 diabetes mellitus: prevalence and related clinical factors

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Received: 8 May 2017 / Accepted: 26 September 2017 / Published online: 20 October 2017
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Abstract

Aims Sarcopenia, which shortens healthy life expectancy, has recently been attracting attention because the Japanese population is rapidly aging. In this preliminary study, we estimated the prevalence of elderly diabetic patients who were complicated with sarcopenia and searched for any related clinical factors.

Methods Elderly (≥ 65 years of age) Japanese patients with type 2 diabetes mellitus were recruited by asking doctors to supply candidates for the study. The prevalence of sarcopenia was estimated based on the criteria proposed by the Asian Working Group for Sarcopenia in 2014.

Results Two hundred eighty-eight patients (151 males) were accepted for the study. The prevalence of sarcopenia was 15.2% in males and 15.3% in females. Multiple logistic regression analysis indicated that sarcopenia was significantly correlated with serum high-sensitivity C-reactive protein in females, in addition to age and body mass index. Female patients were then classified into four groups according to the presence or absence of impaired muscle mass and/or impaired strength. Serum high-sensitivity C-reactive protein was significantly higher in the sarcopenia group (those with impaired muscle mass and impaired strength) than in the other three groups.

Conclusions After clarifying the prevalence of sarcopenia in elderly Japanese patients with type 2 diabetes mellitus,

we found that serum high-sensitivity C-reactive protein was significantly higher in female patients with sarcopenia than in female patients without sarcopenia. Elevated serum high-sensitivity C-reactive protein requires impaired muscle mass and impaired strength.

Keywords Sarcopenia · Elderly patients · Type 2 diabetes mellitus · High-sensitivity C-reactive protein

Introduction

Japanese society is rapidly aging, meaning that the number of elderly people (≥ 65 years old) has been increasing markedly. Elderly diabetic patients are often complicated with diseases or syndromes associated with aging [1]. Sarcopenia is a condition characterized by significant decreases in skeletal muscle mass and function with age. The presence of sarcopenia is considered to indicate that the patient will be more likely to require care in the future, and it is also known to be a cause of falls and fractures that can shorten healthy life expectancy. In the present preliminary study, we estimated the prevalence of elderly diabetic patients who were complicated with sarcopenia, and looked for any related clinical factors.

Materials and methods

We asked doctors to select possible candidates for our study from among the outpatients at the Clinical Center for Diabetes in Fuchu Hospital. The number of outpatients with type 2 diabetes (≥ 65 years old) who were treated in our center in 2016 was 1041. Their mean age was 74.2 ± 6.5 years old. Only patients with type 2 diabetes mellitus who had been

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visiting our center at regular intervals for over a year, were ≥ 65 years old, and could work by themselves were included. Patients were excluded if they had a past history of cerebral arterial disease, were complicated with neuromuscular disease, or had been receiving hemodialysis. The study started on 1 April, 2015 and ended on 31 May, 2016.

Sarcopenia was defined using the criteria proposed by the Asian Working Group for Sarcopenia (AWGS) in 2014 [2]. Grasping power in the dominant hand was measured twice in the standing position and the stronger value was used. Impaired strength was defined as less than 26 kg in males and less than 18 kg in females. Walking speed (cm/s) was established using a 6-m walk at usual speed, and a speed of less than 80 cm/s was considered to indicate impairment in both males and females. Skeletal muscle mass was measured by an impedance method using a Tanita (Tokyo, Japan) MC780A body composition analyzer, and the skeletal muscle mass index (SMI, kg/m^2) for the extremities was calculated as the total skeletal muscle mass of the extremities divided by the square of the body height. A SMI of less than $7.0 \text{ kg}/\text{m}^2$ in males and less than $5.7 \text{ kg}/\text{m}^2$ in females was considered to indicate impairment. Sarcopenia was defined as the presentation of both impaired SMI and impaired muscle function (grasping power and/or walking speed). The estimated glomerular filtration ratio (eGFR) was calculated using both serum creatinine (eGFR_{cre}) and serum cystatin C (eGFR_{cys}) levels [3]. The serum high-sensitivity C-reactive protein (HS-CRP) concentration adopted was the average of the four most recent measurements obtained every 3 months, excluding values obtained when the patient had an infectious disease.

The present study was approved by the institutional review board of Fuchu Hospital (approval number: D4, date: February 16, 2015). Informed consent based on the Helsinki Declaration revised in 2000 was obtained in writing from all participants when they visited the clinic for an evaluation of skeletal muscle mass. Data are shown below as mean $\pm$ SD values. Differences between two groups were assessed using

Student's *t* test for continuous normally distributed variables or Welch's *t* test for continuous non-normally distributed variables. The Omnibus test was employed to assess the normality of variable distributions using peakedness and the coefficient of skewness. Fisher's exact test was used for categorical variables. Differences in HS-CRP among the four groups were assessed using Scheffé's multiple comparisons test. These analyses and multiple logistic regression analyses were performed using Excel Statistics 2015, version 1.0 (Social Survey Research Information Co., Ltd., Tokyo, Japan), and a *P* value of less than 0.05 was considered to indicate statistical significance.

Results

Two hundred eighty-eight Japanese outpatients with type 2 diabetes mellitus (mean age: 73.3 ± 6.1 years; 151 males) were accepted for the study. They had received the standard education regarding diabetes and drug administration. There were no patients who were resident in a nursing home. The mean values for the duration of type 2 diabetes mellitus (years after diagnosis), body mass index (BMI), and HbA1c (average of the four most recent measurements obtained every 3 months) for the 288 patients were 17.0 ± 10.0 years, $23.9 \pm 3.5 \text{ kg}/\text{m}^2$, and $7.6 \pm 1.1\%$, respectively. Seventy percent of the patients (201 patients) were being treated with oral hypoglycemic agents: metformin, 120; dipeptidyl peptidase 4 (DPP4) inhibitor, 148; sulfonylureas or glinides, 144; pioglitazone, 2; α -glucosidase inhibitors, 0; sodium-glucose cotransporter inhibitor, 0. 20.3% were being treated with insulin. No patients were being treated with glucagon-like peptide-1 receptor agonists. The prevalence of sarcopenia in elderly type 2 diabetic patients was 15.2% in males and 15.3% in females. This prevalence increased with age in both groups, and approximately 40% of patients ≥ 80 years old were complicated with sarcopenia (Table 1).

Table 1 Prevalence of sarcopenia in elderly patients with type 2 diabetes mellitus

Gender	Age range (years)	Mean age (years)	Number of patients	Number of patients with sarcopenia	Prevalence of sarcopenia (%)
Male	65–69	67.0	52	3	5.8
	70–74	72.6	35	3	8.6
	75–79	76.7	36	5	13.9
	80–91	83.0	28	12	42.9
	65–91	73.5 ± 6.1	151	23	15.2
Female	65–69	67.2	51	4	7.8
	70–74	72.3	37	3	8.1
	75–79	76.7	25	4	16.0
	80–90	83.0	24	10	41.7
	65–90	73.1 ± 6.0	137	21	15.3

Comparisons of clinical data between patients complicated with and those without sarcopenia are shown in Table 2 for males and Table 3 for females. In both groups,

patients complicated with sarcopenia were significantly older and had a lower BMI and a higher serum level of HS-CRP than those not complicated with sarcopenia.

Table 2 Comparison of clinical data between sarcopenic and nonsarcopenic elderly male patients with type 2 diabetes mellitus

Clinical factor	Patients without sarcopenia (N)	Patients with sarcopenia (N)	P
Age (years)	72.6 ± 5.6 (128)	78.6 ± 6.6 (23)	< 0.001
BMI (kg/m ²)	24.2 ± 3.3 (128)	22.2 ± 2.7 (23)	0.007
Duration (years)	17.1 ± 10.5 (128)	19.4 ± 9.9 (23)	0.330
Insulin-treated patients (%)	18.0 (23/128)	13.0 (3/23)	0.767
Injected insulin (U/kg/day)	0.30 ± 0.17 (23)	0.32 ± 0.07 (3)	0.880
HbA1c (%)	7.51 ± 1.23 (128)	7.44 ± 0.96 (23)	0.789
Total protein (g/dl)	7.2 ± 0.4 (109)	7.4 ± 0.6 (18)	0.101
Serum albumin (g/dl)	4.2 ± 0.3 (109)	4.2 ± 0.4 (18)	0.568
LDL cholesterol (mg/dl)	113.9 ± 27.3 (123)	99.0 ± 30.8 (23)	0.019
HDL cholesterol (mg/dl)	138.5 ± 143.5 (123)	116.1 ± 80.6 (23)	0.468
eGFR _{cre} (ml/min/1.73 ²)	65.8 ± 16.3 (127)	62.5 ± 18.7 (23)	0.374
eGFR _{cys} (ml/min/1.73 ²)	72.2 ± 16.4 (121)	55.9 ± 18.3 (21)	< 0.001
HS-CRP (mg/l)	0.97 ± 0.95 (125)	1.95 ± 2.02 (22)	< 0.001
HOMA-IR	2.41 ± 1.58 (80)	1.98 ± 0.71 (11)	0.374
Retinopathy (%)	21.6 (21/97)	33.3 (4/12)	0.466
Macroangiopathy (%)	14.8 (19/128)	21.7 (5/23)	0.370

BMI body mass index, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *eGFR_{cre}* estimated glomerular filtration rate calculated via serum creatinine, *eGFR_{cys}* estimated glomerular filtration rate calculated via serum cystatin C, *HS-CRP* high-sensitivity C-reactive protein, *HOMA-IR* homeostasis model assessment for insulin resistance, *Retinopathy* preproliferative or proliferative diabetic retinopathy, *Macroangiopathy* ischemic heart disease or peripheral arterial disease

Table 3 Comparison of clinical data between sarcopenic and nonsarcopenic elderly female patients with type 2 diabetes mellitus

Clinical factor	Patients without sarcopenia (N)	Patients with sarcopenia (N)	P
Age (years)	72.2 ± 5.4 (116)	78.2 ± 7.6 (21)	< 0.001
BMI (kg/m ²)	24.5 ± 3.6 (116)	20.0 ± 1.9 (21)	< 0.001
Duration of diabetes (years)	15.7 ± 9.0 (116)	21.7 ± 11.2 (21)	0.008
Insulin-treated patients (%)	20.7 (24/116)	38.1 (8/21)	0.097
Injected insulin (U/kg/day)	0.37 ± 0.19 (24)	0.41 ± 0.23 (8)	0.584
HbA1c (%)	7.83 ± 1.76 (116)	7.79 ± 0.99 (21)	0.924
Total protein (g/dl)	7.3 ± 0.5 (103)	7.3 ± 0.4 (17)	0.973
Serum albumin (g/dl)	4.2 ± 0.4 (103)	4.1 ± 0.3 (17)	0.224
LDL cholesterol (mg/dl)	116.7 ± 28.7 (115)	121.0 ± 29.8 (21)	0.488
HDL cholesterol (mg/dl)	59.8 ± 17.2 (114)	63.1 ± 14.4 (21)	0.405
Triglyceride (mg/dl)	142.8 ± 75.0 (115)	111.4 ± 58.2 (21)	0.071
eGFR _{cre} (ml/min/1.73 ²)	67.3 ± 18.1 (116)	60.3 ± 13.0 (21)	0.096
eGFR _{cys} (ml/min/1.73 ²)	67.7 ± 19.6 (116)	57.7 ± 14.2 (21)	0.026
HS-CRP (mg/l)	1.17 ± 1.11 (116)	2.21 ± 2.33 (21)	0.002
HOMA-IR	3.03 ± 1.92 (65)	2.05 ± 1.34 (10)	0.125
Retinopathy (%)	22.5 (23/102)	42.1 (8/19)	0.089
Macroangiopathy (%)	10.3 (12/116)	19.0 (4/21)	0.190

BMI body mass index, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *eGFR_{cre}* estimated glomerular filtration rate calculated via serum creatinine, *eGFR_{cys}* estimated glomerular filtration rate calculated via serum cystatin C, *HS-CRP* high-sensitivity C-reactive protein, *HOMA-IR* homeostasis model assessment for insulin resistance, *Retinopathy* preproliferative or proliferative diabetic retinopathy, *Macroangiopathy* ischemic heart disease or peripheral arterial disease

eGFR_{cys} was significantly lower in the group with sarcopenia. On the other hand, eGFR_{cre} did not significantly differ between these groups. HbA1c and serum lipids except for LDL cholesterol in males did not significantly differ between the groups. The prevalence of insulin-treated patients and the daily dose of injected insulin in insulin-treated patients did not significantly differ between the groups. Among the patients who were not receiving insulin therapy, the results of the homeostasis model assessment for insulin resistance (HOMA-IR) [4] did not significantly differ between the sarcopenic and nonsarcopenic groups. The *P* value for HOMA-IR was also not significant in either males or females when adjusted for the BMI. The other clinical factors, except for duration

of diabetes in males, did not significantly differ between the groups.

Multiple logistic regression analysis was performed using clinical factors that exhibited significant differences between the sarcopenic and nonsarcopenic patient groups (Tables 2 and 3) to detect factors that were independently related to sarcopenia. The results are shown in Table 4 for males and Table 5 for females. HS-CRP in females was found to be significantly correlated with sarcopenia, and age and BMI were extremely strongly correlated with sarcopenia.

Female patients were then classified into four groups according to the presence or absence of impaired muscle mass (SMI) and/or impaired muscle function (grasping power and/or walking speed), as shown in Table 6. Serum

Table 4 Multiple logistic regression analysis for sarcopenia in elderly male patients with type 2 diabetes mellitus (*N* = 134)

Explanatory variable	Standard partial regression coefficient	Odds ratio (95% CI)	<i>P</i>
Age (years)	0.114	1.121 (1.014–1.239)	0.026
BMI (kg/m ²)	– 0.199	0.820 (0.681–0.986)	0.035
LDL cholesterol (mg/dl)	– 0.017	0.983 (0.964–2.756)	0.097
eGFR _{cys} (ml/min/1.73 ²)	– 0.032	0.968 (0.933–1.005)	0.093
HS-CRP (mg/l)	0.357	1.428 (0.950–2.148)	0.087

BMI body mass index, *LDL* low-density lipoprotein, *eGFR_{cys}* estimated glomerular filtration rate calculated via serum cystatin C, *HS-CRP* high-sensitivity C-reactive protein

Table 5 Multiple logistic regression analysis for sarcopenia in elderly female patients with type 2 diabetes mellitus (*N* = 131)

Explanatory variable	Standard partial regression coefficient	Odds ratio (95% CI)	<i>P</i>
Age (years)	0.173	1.188 (1.050–1.345)	0.006
BMI (kg/m ²)	– 0.752	0.472 (0.328–0.678)	< 0.001
Duration of diabetes (years)	0.040	1.041 (0.975–1.111)	0.234
eGFR _{cys} (ml/min/1.73 ²)	– 0.017	0.983 (0.942–1.026)	0.444
HS-CRP (mg/l)	0.414	1.514 (1.021–2.244)	0.039

BMI body mass index, *LDL* low-density lipoprotein, *eGFR_{cys}* estimated glomerular filtration rate calculated via serum cystatin C, *HS-CRP* high-sensitivity C-reactive protein

Table 6 Comparison of HS-CRP among the four female patient groups defined according to SMI and muscle power (grasping power and/or walking speed)

Patient group (<i>N</i>)	SMI	Grasping power or walking speed	HS-CRP (mg/l)	Significance of difference from group S
NS (69)	Normal	Normal	1.11 ± 0.83	*
PS (13)	Impaired	Normal	1.16 ± 1.15	#
D (32)	Normal	Impaired	1.30 ± 1.57	\$
S (19)	Impaired	Impaired	2.21 ± 2.33	

SMI: skeletal muscle mass index of the extremities; impaired values are <7.0 kg/m² for males and <5.7 kg/m² for females

Grasping power: impaired values are <26 kg for males and <18 kg for females

Walking speed: impaired values are <80 cm/s

NS nonsarcopenic, PS presarcopenia, D dynapenic, S sarcopenic

Multiple comparisons test : *P = 0.002, #*P* = 0.032, \$*P* = 0.021

HS-CRP was compared among those four groups. The HS-CRP of group S (sarcopenic group; impaired muscle mass and impaired muscle function) was significantly higher than it was for the other three groups.

Discussion

The concept of sarcopenia was first proposed by Rosenberg [5], and the definition of sarcopenia and the criteria for diagnosing it were proposed by the European Working Group on Sarcopenia (EWGSOP) [6] in 2010, and more recently by the Asian Working Group for Sarcopenia (AWGS) [2] in 2014 for Asian people. A recent review [7] found that diabetes is associated with a strong increase in the risk of physical disability in older adults, as well as decreases in skeletal muscle mass and strength. Physical performance was also reported to be decreased, especially in elderly diabetic patients [8–11]. However, studies of sarcopenia in elderly diabetic patients are scarce. When Chinese citizens aged 60 years and older were investigated, the prevalence of sarcopenia based on the AGWS criteria in diabetic patients was observed to be 14.8%, which was significantly higher than in nondiabetic subjects (11.2%, $P = 0.035$) [12]. In Korean patients with type 2 diabetes, the prevalence of sarcopenia was reported to be 15.7% [13], although sarcopenia was not diagnosed based on the AWGS criteria in that study. This prevalence was also significantly higher than the prevalence of sarcopenia in nondiabetic subjects (6.9%).

This is the first report of the prevalence of sarcopenia in Japanese type 2 diabetic patients (prevalence: 15.2% in males and 15.3% in females) where sarcopenia diagnosis was based on the AWGS criteria. The prevalence observed here is consistent with the abovementioned reports [12, 13], although the condition of the subjects and the criteria for diagnosing sarcopenia varied slightly between the studies. There are some reports in which the prevalence of sarcopenia in Japanese nondiabetic subjects was determined with the aid of the EWGSOP algorithm [14, 15]. Tanimoto et al. [14] reported the prevalence of sarcopenia in community-dwelling elderly subjects. The ages of the subjects were almost the same as those in the present work. When our patients were diagnosed with sarcopenia according to the algorithm in [14], the prevalence of sarcopenia in type 2 diabetic patients was found to be 21.9% in males and 23.4% in females; both of these values were significantly higher (male: $P = 0.0242$, female: $P = 0.0166$) than those for community-dwelling elderly patients. Our data were also compared with the results reported by Yamada et al. [15] in the same way; the prevalence of sarcopenia in our type 2 diabetic patients was found to be low, especially in females. As the average age of the subjects differed between the studies, we compared the prevalence while stratifying by age. The

prevalence of sarcopenia in our diabetic patients was slightly (nonsignificantly) higher in males under the age of 75 years and in females aged between 80 and 84 years. Only one other study that used the AWGS criteria to diagnose sarcopenia has been reported, and that study found that the prevalence of sarcopenia in Japanese elderly people living in a community setting was 9.6% in males and 7.7% in females [16]. The sarcopenia prevalence in our type 2 diabetic patients was clearly high compared to that prevalence, although the condition of our subjects differed slightly from the subjects reported in [16]. The differences in prevalence between these studies may be due to differences in the reference value used for low SMI or the use of small samples. Further investigations, such as a multicenter study comparing type 2 diabetic patients with nondiabetic subjects, should be carried out.

Some factors that may be associated with the pathogenesis of sarcopenia in diabetic patients have been reported in review articles [8, 9, 17, 18]. Among them, it is likely that low skeletal muscle mass in patients with sarcopenia results in a reduced glucose disposal capacity, leading to insulin resistance. Possible mechanisms for amino acid metabolism in skeletal muscle in relation to insulin resistance in vitro have also been reported [19, 20]. In the present study, HOMA-IR and the amount of insulin injected daily were not associated with sarcopenia. Although these markers do not always accurately indicate peripheral insulin sensitivity, the present study was not able to demonstrate an association between insulin resistance and sarcopenia in elderly type 2 diabetic patients.

Recently, renal function, eGFRcre [21], and albuminuria [22] were reported to be associated with sarcopenia in type 2 diabetic patients. In the present study, we utilized the serum cystatin C concentration to calculate eGFR, because serum creatinine cannot be used to calculate eGFR in patients with sarcopenia who have low skeletal muscle mass, given that creatinine originates in muscle. Although eGFRcys was significantly lower in sarcopenic patients according to a stratified analysis of both males and females (Tables 2 and 3), eGFRcys was not found to be statistically significantly associated with sarcopenia based on multivariate analysis of both groups adjusted for age and BMI (Tables 4 and 5). Furthermore, there was no significant difference in albuminuria between the sarcopenic and nonsarcopenic groups.

It was reported that DPP-4 inhibitors [23], β -cell function [24], and HbA1c [18] are associated with sarcopenia. In the present study, no significant association of sarcopenia with DPP-4 inhibitor, insulin therapy, or HbA1c level was observed in either males or females according to multiple logistic regression analysis adjusted for age and BMI. We also evaluated the prevalence of sarcopenia in patients stratified according to HbA1c level (<7.0, 7.0–8.0, and >8.0%). No significant difference in sarcopenia prevalence between patients with different HbA1c levels was found in either

males or females. Other factors that may influence the sarcopenic state, such as dietary protein and exercise, were not examined in this study.

This is the first report, to our knowledge, in which serum HS-CPR was shown to be associated with sarcopenia in diabetic patients, especially females. C-reactive protein (CRP) is secreted from the liver in response to inflammatory cytokines. It has been reported that inflammatory cytokines such as interleukin 6 and tumor necrosis factor alpha are associated with sarcopenia [25, 26]. Our results may reflect the presence of elevated cytokine levels due to chronic inflammation [27] at the muscle tissue. Why this phenomenon was only observed in females is unclear at present. The small sample size used in this study or gender differences in adipose tissue or sexual hormones [28, 29] may have influenced the results. Although the underlying mechanism for the association between sarcopenia and type 2 diabetes is still uncertain, our finding that the serum level of HS-CPR was elevated only in female diabetic patients with sarcopenia (exhibiting low muscle mass and low muscle strength; group S), not in those with presarcopenia (low muscle mass only; group PS) or dynapenia (low muscle strength only; group D; see Table 6), may provide further insight into the mechanisms of sarcopenia in type 2 diabetic patients. This finding is also in line with the notion that proinflammatory cytokines play a key role in the development of sarcopenic obesity [30]. Given the results obtained here, further study of sarcopenia, including measurements of cytokines, adipokines, or myokines, should be carried out in type 2 diabetic patients.

Acknowledgements No specific grant from funding agencies in the public, commercial, or not-for-profit sectors was received for this research.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Human rights statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions of it.

Informed consent Informed consent was obtained from all patients before they were included in the study.

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