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A High Serum Cortisol/DHEA-S Ratio Is a Risk Factor for Sarcopenia in Elderly Diabetic Patients

Ikumi Yanagita,[1,2] Yuya Fujihara,[1] Yuichi Kitajima,[1] Misuzu Tajima,[1] Masanao Honda,[1] Tomoko Kawajiri,[1] Terumi Eda,[1] Kazue Yonemura,[1] Noriko Yamaguchi,[1] Hideko Asakawa,[1] Yukiko Nei,[1] Yumi Kayashima,[1] Mihoko Yoshimoto,[1] Mayumi Harada,[1] Yuhei Araki,[1] Shoji Yoshimoto,[1] Eiji Aida,[1] Toshihiko Yanase,[2] Hajime Nawata,[1] and Kazuo Muta[1]

[1]Muta Hospital, Fukuoka 814-0163, Japan; and [2]Department of Endocrinology and Diabetes Mellitus, Faculty of Medicine, Fukuoka University, Fukuoka 814-0180, Japan

ORCiD numbers: 0000-0001-5052-8821 (I. Yanagita).

Context: Elderly patients with type 2 diabetes mellitus (T2DM) have a high prevalence of frailty and/or sarcopenia. Sarcopenia is thought to be related to discordant secretions of the adrenal hormones cortisol and dehydroepiandrosterone (DHEA), as well as the sulfate ester of DHEA (DHEA-S). The current study sought to evaluate the risk factors for sarcopenia in elderly patients with T2DM.

Design and Patients: We enrolled 108 consecutive elderly patients aged ≥65 years with T2DM (mean age, 76.2 ± 7.3 years; 43.5% males). Sarcopenia was assessed and diagnosed based on the Asian version of the diagnostic criteria regarding muscular strength, physical function, and muscle mass. We assessed various physical parameters, blood tests, and atherosclerosis markers and statistically determined the risk factors for sarcopenia.

Results: Multiple regression analysis showed that the independent risk factors for sarcopenia were a serum cortisol/DHEA-S ratio ≥0.2, diastolic blood pressure <70 mm Hg, Hb concentration <13 g/dL, and an ankle brachial index <1.0. The strongest risk factor for sarcopenia was a serum cortisol/DHEA-S ratio ≥0.2. An increase in the serum cortisol/DHEA-S ratio reflected higher cortisol values and lower DHEA-S values in patients with sarcopenia compared with those in nonsarcopenic patients. The concentrations of cortisol and DHEA-S, as well as the cortisol/DHEA-S ratio, changed in accordance with the severity of sarcopenia.

Conclusions: A relative increase in cortisol may reflect the presence of stress and stimulate muscle catabolism, whereas a relative decrease in DHEA-S may cause a decrease in the anabolic action of DHEA on muscle; the combination of these factors may lead to sarcopenia.

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Freeform/Key Words: cortisol, DHEA-S, sarcopenia, type 2 diabetes

The number of patients with diabetes mellitus in Japan has reached 10 million, and 50% of these patients are elderly. The incidence of elderly patients with diabetes mellitus is likely to further increase due to the rapid expansion of an aging society. Furthermore, elderly subjects

Abbreviations: ABI, ankle-brachial index; ALT, alanine aminotransferase; AUC, area under the curve; BMI, body mass index; CFS, Clinical Frailty Scale; DBP, diastolic blood pressure; DHEA, dehydroepiandrosterone; DHEA-S, sulfate ester of DHEA; EWGSOP, European Working Group on Sarcopenia in Older People; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MMSE, Mini-Mental State Examination; OHA, oral hypoglycemic agent; ROC, receiver operating characteristics; SU, sulfonylurea; T2DM, type 2 diabetes mellitus.

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are often in a state of frailty, which comprises poor resolution of homeostasis after stress. Frailty is a consequence of a cumulative decline in multiple physiological systems, leading to falls, disability, hospitalization, and mortality [1–3]. Frailty is narrowly defined based on physical conditions [1], or broadly defined to include physical and psychosocial conditions [2]. Previous studies using the narrow definition of frailty show that the risk factors for frailty in patients with type 2 diabetes mellitus (T2DM) are high glycated Hb (HbA1c) concentrations [4, 5], or both appropriate and high (U-shaped curve) HbA1c concentrations [6]. However, it has recently been shown that only low HbA1c concentrations are associated with the broad definition of frailty [7]. Early detection and/or prevention of frailty in elderly patients with T2DM are essential for the prevention of associated complications.

Sarcopenia is defined as age-associated loss of muscle mass and is related to deterioration in physical disability, metabolic impairment, and increased mortality. Therefore, sarcopenia is well established as an important risk factor for frailty [3, 8–10]. The European Working Group on Sarcopenia in Older People (EWGSOP) introduced a diagnostic algorithm for sarcopenia based on walking speed, grip strength, and skeletal muscle mass in 2010 [9]. In 2014, the Asian Working Group for Sarcopenia introduced a new diagnostic algorithm for sarcopenia that considered the differences between European and Asian populations in ethnicity, physical characteristics, and culture [10]. Sarcopenia is affected by many factors, such as age-related alterations in various hormones, malnutrition, various chronic diseases, and inflammation [3, 8–11].

The hormone dehydroepiandrosterone (DHEA) might be related to frailty or a decrease in physical activity [12–17]. DHEA and its sulfate ester, DHEA-S, are prominent adrenal steroid hormones in humans [18–21]. Serum DHEA concentrations in humans are similar to those of DHEA-S and are usually evaluated as DHEA-S [22]. DHEA affects peripheral tissues either indirectly via conversion to androgens, estrogens, or both, or directly as a steroid [19]. DHEA shows a characteristic secretion pattern, with serum concentrations declining with increasing age. Serum DHEA and DHEA-S concentrations peak in young adulthood and then gradually decline over time. Consequently, individuals aged 70 to 80 years have circulating DHEA concentrations that are 10% to 20% of their original young adult concentrations [18]. In contrast, there are no clear age-related changes in the concentrations of cortisol, which is also an adrenocortical hormone [18, 19]. Although little is known about the physiological role of DHEA, human epidemiological studies have suggested that its concentrations may represent a biomarker of longevity [19–21, 23–25] and successful aging [20]. Various *in vivo* and *in vitro* experiments have suggested that DHEA might be beneficial for cognitive function [22], obesity [26, 27], diabetes mellitus [28], atherosclerosis [29], and osteoporosis [30–32]. A relatively higher serum DHEA-S concentration was significantly correlated with an extended lifespan in calorie-restricted male rhesus monkeys and in a clinical study of males living in Baltimore [23]. A 27-year study in a community-based cohort in Japan also indicated that DHEA-S concentration may be a predictor of longevity in males, independent of age, blood pressure, and plasma glucose [24].

Cortisol is involved in various physiological systems, including metabolism, the immune response, and the body's response to stress. Production of cortisol is usually triggered by stress-induced activation of a hormonal system known as the hypothalamic–pituitary–adrenal axis. Cortisol also provides negative feedback to this axis to maintain a physiological concentration. However, the hypothalamic–pituitary–adrenal axis is dysregulated in pathological situations, such as the autonomous cortisol overproduction seen in Cushing syndrome or chronic physical or psychiatric stress. Continuous oversecretion of cortisol mediates muscle breakdown, thus possibly leading to sarcopenia. This extreme phenotype of muscle atrophy is typified in patients with Cushing syndrome.

These findings on sarcopenia prompted us to investigate the association between sarcopenia and various risk factors in elderly patients with T2DM, especially regarding the concentrations of adrenal hormones. Secretion of cortisol and DHEA-S in an appropriate balance is essential for the maintenance of biological function and homeostasis. A high cortisol/DHEA-S ratio is reportedly associated with mortality [33], dementia [34], metabolic

syndrome [35], and reduced immunity following physical stress [36]. Furthermore, discordant secretion of these two adrenal hormones is related to aging [18, 19]. Therefore, the current study sought to investigate the balance between cortisol and DHEA-S in elderly patients with T2DM and sarcopenia.

1. Materials and Methods

A. Subjects

In the current study, we retrospectively reviewed the data from 108 consecutive elderly patients aged ≥65 years with T2DM who were being treated as outpatients or were hospitalized in Muta Hospital from October 2016 to September 2017; all 108 patients (47 males, 61 females) were enrolled in the current study. Patients taking glucocorticoids by oral or inhalation administration were excluded, as glucocorticoid administration affects the serum concentrations of cortisol and DHEA-S. None of the included patients was taking psychiatric drugs because of mental illness, and none was affected by alcoholism. T2DM was diagnosed based on the criteria proposed by the Japan Diabetes Society [37] or was diagnosed when the patient had a history of taking medication comprising insulin or oral hypoglycemic agents (OHAs). Data regarding age, blood test results, general physical assessments, and administered drugs were obtained from the medical records. The duration of T2DM was estimated from the time of the initial detection of hyperglycemia.

B. Hematological Tests and Hormonal Measurements

Blood samples were obtained in the morning between 0900 and 1200 hours. We collected information on the concentrations of HbA1c, red blood cells, Hb, serum albumin, aspartate aminotransferase, alanine aminotransferase (ALT), creatinine, uric acid, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, and corrected calcium. The estimated glomerular filtration rate was calculated from the serum creatinine concentration. We collected information on height, body weight, and body mass index (BMI). BMI was calculated as the weight in kilograms divided by the squared height in meters. Systolic blood pressure and diastolic blood pressure (DBP) were measured using a mercury sphygmomanometer with the patient at rest in the sitting position.

Serum cortisol concentrations were measured using the chemiluminescence enzyme immunoassay method using an Abbott cortisol kit [38] (Abbott Japan, Tokyo, Japan). Serum DHEA-S concentrations were measured via chemiluminescence enzyme immunoassay using an Access DHEA-S kit [39] (Beckman Coulter, Tokyo, Japan). The detection limits for cortisol and DHEA-S were 0.8 μg/dL and 2.0 μg/dL, respectively. The respective intra-assay coefficient of variance values of cortisol and DHEA-S were both <10%. The cortisol (μg/dL)/DHEA-S (μg/dL) ratio was finally determined.

C. Evaluations of Frailty, Sarcopenia, Dementia, Arthrosclerosis, and Osteoporosis

A broad-definition frailty scale, the Clinical Frailty Scale (CFS) [2], was determined as previously described [7]. The CFS contains nine stages (1, very fit; 2, well; 3, managing well; 4, vulnerable; 5, mildly frail; 6, moderately frail; 7, severely frail; 8, very severely frail; and 9, terminally ill). Patients classified as CFS stages 1 to 4 were defined as having no frailty, as these patients could live independently; patients with CFS stages 5 to 9 were defined as having frailty, as these patients required assistance with the activities of daily life. The CFS stages of the 108 included patients ranged from 1 to 7.

Sarcopenia was assessed by handgrip strength as an indicator of muscular strength, walking speed as an indicator of physical function, and bioelectrical impedance analysis as an indicator of muscle mass. Handgrip strength was measured using a handgrip dynamometer (Takei Scientific Instruments, Tokyo, Japan) [40]. Bioelectrical impedance analysis has been

accepted as a method for detecting sarcopenia by the EWGSOP [9] and the Asian Working Group for Sarcopenia [10]. The actual diagnosis of sarcopenia was made in accordance with the Asian version of the diagnostic criteria for sarcopenia [10], based on the presence of low muscle mass plus low muscle strength and/or low physical performance. The cutoff values for sarcopenia regarding muscle mass were <7.0 kg/m^2 for males and <5.7 kg/m^2 for females; those regarding grip strength were <26 kg for males and <18 kg for females; those regarding walking speed were ≤ 0.8 m/s for both males and females [10].

The severity of sarcopenia was determined using the criteria of the EWGSOP [10]. Among the components of muscle mass, muscle strength, and physical activity, a decrease in muscle mass only was diagnosed as presarcopenia, a decrease in muscle mass plus a decrease in muscular strength or physical ability was diagnosed as sarcopenia, and a decrease in all three components was diagnosed as severe sarcopenia. Dementia was diagnosed using the Mini-Mental State Examination (MMSE) [41]. The maximum MMSE score is 30; a score of ≤ 23 indicates dementia, and a score of 24 to 27 indicates mild cognitive impairment. Brachial-ankle pulse wave velocity was used to evaluate arteriosclerosis, and the ankle-brachial index (ABI) [42] was measured as a screening marker for arteriosclerosis obliterans. Osteoporosis was diagnosed based on the bone mineral density evaluated by dual-energy X-ray absorptiometry [43].

D. Treatments for T2DM

At the time of sarcopenia evaluation, patients were divided into three groups in accordance with the T2DM treatment being received: (i) insulin therapy group, (ii) OHA using sulfonylurea (SU) or glinide group, and (iii) "others" group. The others group was treated with diet only and/or OHAs other than SU or glinide. Thus, the insulin therapy and the SU or glinide groups were considered to have a relatively higher risk of hypoglycemia than did the others group. Additionally, we investigated the administration of antihypertensive drugs and drugs for dyslipidemia, such as statins and fibrates.

E. Informed Consent

The Research Ethics Committee of Muta Hospital approved the current study (date of approval, 15 May 2017; approval no. 29-001), and the study conformed to the Helsinki Declaration, as revised in 2013. The current study was also registered in the UMIN Clinical Trials Registry (ID no. UMIN000031357). We obtained informed consent by publishing an opt-out option on the homepage of Muta Hospital.

F. Statistical Analysis

Data are expressed as mean ± SD, medians with quartile values (25% to 75%), or numbers with percentages. Differences in continuous variables between the two groups were compared using the unpaired t test for normally distributed data, or the Mann–Whitney U test for nonnormally distributed data. Differences in categorical variables between the two groups were examined using Fisher's exact test. Differences in continuous variables among four groups (nonsarcopenia, presarcopenia, sarcopenia, and severe sarcopenia) were compared by the multiple comparison method (Fisher's least significant difference method) after analysis of variance. An increased or decreased tendency of continuous variables (age, BMI, DBP, Hb concentration, cortisol concentration, DHEA-S concentration, MMSE score, ABI, frailty, and cortisol/DHEA-S ratio) in accordance with the severity of sarcopenia was tested by the Jonckheere–Terpstra test. Differences in categorical variables among the four groups were tested using the χ^2 test with a Bonferroni adjustment. Binary regression analysis was performed to identify the risk factors for sarcopenia in elderly patients with T2DM, and to calculate the ORs and 95% CIs. Univariate and multivariate binary regression analyses were performed with and without adjustment for other variables. As there were comparisons made between groups with and without medical endpoints, variables with $P < 0.05$ were selected

and used in the multiple binary regression model. When there were collinear characteristics between two variables, either of the two variables was excluded from the multiple regression model. Receiver operating characteristics (ROC) curve analysis was used to determine the cutoff values of continuous parameters as risk factors for sarcopenia, and their areas under the curve (AUCs) and 95% CIs were calculated. All statistical analyses were performed using SPSS version 18.0 (IBM). $P < 0.05$ was considered statistically significant.

2. Results

Among the 108 elderly patients with T2DM with CFS stages 1 to 7, 38 had sarcopenia (13 males, 25 females), whereas 70 did not have sarcopenia (34 males, 36 females). Among the 108 patients, 7 were hospitalized, whereas the other 101 were outpatients. Among the seven hospitalized patients, six were categorized as having severe sarcopenia, whereas one was nonsarcopenic. Accordingly, the incidence of sarcopenia was 35.2%.

Table 1 shows the characteristics of elderly patients with T2DM stratified by the presence or absence of sarcopenia. Compared with patients without sarcopenia, patients with sarcopenia were significantly older and had a significantly lower bodyweight, BMI, DBP, red blood cell count, Hb concentration, and ALT concentration ($P = 0.016$ for ALT; $P < 0.001$ for the other variables). There were no differences between the groups with and without sarcopenia regarding sex, duration of T2DM, systolic blood pressure, serum concentrations of aspartate aminotransferase, creatinine, uric acid, triglycerides, LDL-C, HDL-C, and calcium, estimated glomerular filtration rate, and HbA1c concentration.

Compared with patients without sarcopenia, those with sarcopenia had a significantly lower serum DHEA-S concentration ($P < 0.001$) and a significantly higher serum cortisol concentration ($P = 0.005$). This resulted in a significantly higher cortisol/DHEA-S ratio in patients with sarcopenia than in those without sarcopenia ($P = 0.004$).

The ABI was significantly lower in patients with sarcopenia than in those without sarcopenia ($P = 0.027$). There were no significant differences between the groups with and without sarcopenia in the MMSE score, an arteriosclerotic marker (brachial-ankle pulse wave velocity), and an osteoporosis marker (vertebral young adult mean). However, the MMSE score tended to be lower in patients with sarcopenia than in those without sarcopenia ($P = 0.072$).

Regarding the diagnostic markers of sarcopenia, walking speed, grip strength, and the skeletal mass index were all significantly lower in patients with sarcopenia than in those without sarcopenia (all $P < 0.001$). In other physical ability tests, patients with sarcopenia had a significantly shorter ratio of two steps/height ($P < 0.001$) and a significantly longer standing time from a chair ($P = 0.024$) than did those without sarcopenia. These findings support the relative decrease in physical ability of patients with vs without sarcopenia.

The prevalence of frailty in accordance with the CFS criteria was significantly higher in patients with sarcopenia than in those without sarcopenia ($P = 0.048$). There was no difference between the groups with and without sarcopenia in the frequency of administration of antihypertensive or antidyslipidemia drugs. There were also no significant differences between the two groups in the type and number of T2DM medications.

Table 2 summarizes the results of single regression analysis or multivariate analysis by binary logistic regression analysis performed to clarify the risk factors for sarcopenia in elderly patients with T2DM. In single regression analysis without adjustment, all assessed variables showed significance for detecting sarcopenia, including age ≥75 years, BMI ≥25 kg/m^2, DBP <70 mm Hg, red blood cell count <420 × 10^4/mL, Hb concentration <13 g/dL, cortisol/DHEA-S ratio ≥0.2 (all $P < 0.001$), ALT <22 IU/L ($P = 0.05$), DHEA-S concentration <73 μg/dL ($P = 0.003$), ABI <1.0 ($P = 0.009$), and presence of frailty ($P = 0.039$) (Table 2). Variables with $P < 0.05$ were then selected for use in the multiple binary regression model. Among the three variables of DHEA-S concentration, cortisol concentration, and the cortisol/DHEA-S ratio, the most significant variable (cortisol/DHEA-S ratio) was chosen as the explanatory variable based on the collinear characteristics between two variables. Multiple

Table 1. Characteristics of the Elderly Patients With Diabetes Stratified by Sarcopenia

	All Cases (N = 108)	Nonsarcopenia (N = 70)	Sarcopenia (N = 38)	*P* Values
Age, y	76.2 ± 7.3	74.2 ± 7.0	79.8 ± 6.7	<0.001[a]
Male, n (%)	47 (43.5)	34 (48.6)	13 (34.2)	0.162[b]
Duration of T2DM, y	14.3 ± 12.1	12.5 ± 10.6	17.7 ± 14.1	0.054[a]
Body weight, kg	57.4 ± 11.1	61.8 ± 9.6	49.1 ± 8.5	<0.001[a]
BMI, kg/m^2	23.7 ± 3.6	24.9 ± 3.2	21.4 ± 3.0	<0.001[a]
SBP, mm Hg	135.8 ± 18.9	137.4 ± 18.3	133.0 ± 19.8	0.248[a]
DBP, mm Hg	72.9 ± 11.0	75.5 ± 10.5	68.3 ± 10.3	<0.001[a]
RBCs, $\times 10^4/\mu L$	422 ± 53	434 ± 52	400 ± 46	<0.001[a]
Hb, g/dL	12.9 ± 1.6	13.4 ± 1.6	12.1 ± 1.4	<0.001[a]
Albumin, g/dL	4.08 ± 0.36	4.11 ± 0.32	4.02 ± 0.41	0.197[a]
AST, IU/L	24.9 ± 9.9	25.7 ± 10.2	23.4 ± 9.3	0.253[a]
ALT, IU/L	17.0 [12.8–26.3]	18.0 [13.0–30.8]	14.0 [10.3–21.0]	0.016[c]
HbA1c, %	7.01 ± 0.83	7.06 ± 0.86	6.93 ± 0.78	0.432[a]
Serum creatinine, mg/dL	0.70 [0.60–0.91]	0.70 [0.60–0.90]	0.72 [0.53–0.91]	0.413[c]
eGFR, mL/min/1.73 m^2	61.4 ± 18.9	61.2 ± 17.2	61.7 ± 16.4	0.885[a]
Uric acid, mg/dL	5.19 ± 1.33	5.18 ± 1.24	5.19 ± 1.48	0.980[a]
Triglycerides, mg/dL	137 ± 67	144 ± 71	124 ± 57	0.140[a]
LDL-C, mg/dL	102 ± 31	106 ± 31	95 ± 32	0.093[a]
HDL-C, mg/dL	54.0 ± 13.8	52.7 ± 12.6	56.6 ± 15.6	0.162[a]
Calcium, mg/dL	9.28 ± 0.34	9.25 ± 0.33	9.33 ± 0.36	0.206[a]
DHEA-S, μg/dL	59.5 [40.5–90.8]	71.5 [48.3–106.0]	45.0 [32.0–60.8]	<0.001[c]
Cortisol, μg/dL	9.32 ± 2.78	8.76 ± 2.67	10.33 ± 2.74	0.005[a]
Ratio cortisol/DHEA-S	0.15 [0.09–0.24]	0.11 [0.09–0.18]	0.22 [0.16–0.30]	0.004[c]
MMSE	25.0 ± 5.2	25.7 ± 5.76	23.8 ± 4.5	0.072[a]
STFC, s	12.1 ± 5.3	11.3 ± 4.7	13.8 ± 6.1	0.024[a]
Ratio two steps/height	1.07 ± 0.25	1.17 ± 0.23	0.91 ± 0.20	<0.001[a]
ABI	1.08 ± 0.15	1.10 ± 0.12	1.04 ± 0.18	0.027[a]
baPWV, cm/s	2101 ± 431	2056 ± 405	2182 ± 468	0.149[a]
Vertebral YAM, %	83.9 ± 17.3	85.2 ± 18.2	81.6 ± 15.5	0.326[a]
Walking speed, m/s	0.94 ± 0.41	1.05 ± 0.42	0.72 ± 0.31	<0.001[a]
Grip, kg	21.4 ± 9.8	24.4 ± 10.1	15.8 ± 6.4	<0.001[a]
SMI, kg/m^2	6.27 ± 1.06	6.74 ± 0.88	5.39 ± 0.77	<0.001[a]
Frailty, n (%)	32 (29.6)	16 (22.9)	16 (42.1)	0.048[b]
Anti-HT drug use, n (%)	68 (63.0)	44 (62.9)	24 (63.2)	0.999[b]
Anti-DL drug use, n (%)	58 (53.7)	37 (52.9)	21 (55.3)	0.842[b]
Medications for T2DM				
Insulin, n (%)	24 (22.2)	13 (18.6)	11 (28.9)	0.234[b]
SU or glinide, n (%)	37 (34.4)	22 (31.4)	15 (39.5)	0.406[b]
Others, n (%)	47 (43.5)	35 (50.0)	12 (31.6)	0.072[b]

Data were expressed as means ± SD, medians [quartile 25% to 75% value], or numbers (%).
Abbreviations: AST, aspartate aminotransferase; baPWV, brachial-ankle pulse wave velocity; DL, dyslipidemia; eGFR, estimated glomerular filtration rate; HT, hypertension; RBC, red blood cell; SBP, systolic blood pressure; SMI, skeletal mass index; STFC, standing time from chair; YAM, young adult mean.
[a] *P* value determined by an unpaired *t* test.
[b] *P* value determined by a Fisher exact test or Mann–Whitney test.
[c] *P* value determined by a Fisher exact test.

binary regression analysis revealed that DBP <70 mm Hg ($P = 0.023$), Hb concentration <13 g/dL ($P = 0.040$), cortisol/DHEA-S ratio ≥0.2 ($P = 0.005$), and ABI <1.0 ($P = 0.015$) remained significant independent risk factors for sarcopenia (Table 2). Importantly, the presence of frailty was not an independent risk factor for sarcopenia.

Table 3 summarizes the results of ROC analysis of various variables for the detection of sarcopenia. When the AUC was provided by ROC analysis based on single regression analysis, the AUC of the cortisol/DHEA-S ratio was the highest (0.769), followed by that of Hb concentration (0.734), DBP (0.711), and DHEA-S concentration (0.709) (Table 3).

Table 2. Risk Factors for Sarcopenia Determined by Binary Logistic Regression Analysis

	Before Adjustment		After Adjustment	
Variables	**OR (95% CI)**	***P* Values**	**OR (95% CI)**	***P* Values**
Age ≥75, y	7.05 (2.73–18.25)	<0.001	2.56 (0.74–8.84)	0.137
BMI ≥25, kg/m^2	0.10 (0.03–0.34)	<0.001	0.25 (0.05–1.17)	0.079
DBP <70, mm Hg	4.12 (1.78–9.51)	<0.001	5.18 (1.26–21.34)	0.023
Red blood cells <420, ×10^4/μL[a]	4.74 (1.99–11.31)	<0.001	0.67 (0.09–5.09)	0.701
Hb <13, g/dL[a]	7.97 (3.07–20.71)	<0.001	10.07 (1.11–91.48)	0.040
ALT <22, IU/L[a]	2.50 (1.00–6.24)	0.050	1.49 (0.38–5.84)	0.569
DHEA-S <73, μg/dL[a]	4.18 (1.63–10.76)	0.003	Not applicable	
Cortisol ≥9.3, μg/dL[a]	2.73 (1.21–6.17)	0.016	Not applicable	
Cortisol/DHEA-S ≥0.2	4.17 (1.78–9.74)	<0.001	7.85 (1.86–6.13)	0.005
ABI <1.0	4.02 (1.42–11.37)	0.009	6.51 (1.44–29.36)	0.015
Frailty	2.45 (1.05–5.75)	0.039	1.14 (0.33–3.95)	0.833

The χ^2 value was 1.772 for the Hosmer–Lemeshow test ($P = 0.987$).
[a]The mean value in all cases.

The patients were divided into four groups in accordance with the severity of sarcopenia: no sarcopenia (n = 54), presarcopenia (n = 16), sarcopenia (n = 18), and severe sarcopenia (n = 20). With an increase in the severity of sarcopenia, there were significant increases in age ($P < 0.001$), cortisol concentration ($P = 0.004$), and the cortisol/DHEA-S ratio ($P < 0.001$), whereas there were significant decreases in BMI ($P < 0.001$), DHEA-S concentration ($P < 0.001$), DBP ($P = 0.001$), Hb concentration ($P < 0.001$), and MMSE score ($P = 0.009$). Frailty was most common in the severe sarcopenia group, and the incidence of frailty significantly increased with the severity of sarcopenia ($P = 0.032$). The ABI did not show a significant trend of change in accordance with the severity of sarcopenia (Fig. 1).

3. Discussion

In the current study on 108 elderly patients with T2DM and CFS stages 1 to 7, the independent risk factors for sarcopenia were a serum cortisol/DHEA-S ratio ≥0.2, DBP <70 mm Hg, Hb concentration <13 g/dL, and an ABI <1.0. As frailty is closely associated with sarcopenia [3, 9, 10], it is reasonable to expect a significantly higher prevalence of frailty in the group with sarcopenia compared with the nonsarcopenic group. However, frailty did not remain a significant risk factor for sarcopenia in the multivariate analysis. These findings clearly indicate that sarcopenia is an important risk factor for frailty, but that these two conditions do not completely overlap and have certain pathological differences.

The serum cortisol/DHEA-S ratio was the strongest risk factor for sarcopenia in elderly patients with T2DM. An increase in the serum cortisol/DHEA-S ratio reflected the higher cortisol concentration and lower DHEA-S concentration in patients with sarcopenia compared with nonsarcopenic patients. Additionally, the concentrations of cortisol and DHEA-S and the cortisol/DHEA-S ratio changed in accordance with the severity of sarcopenia, further supporting a close association between these adrenal hormones and sarcopenia. The cutoff

Table 3. The Determination of Cutoff Values of Various Factors by ROC Analysis

Risk Factors	Cutoff Values	AUC (95% CI)	*P* Values
DBP, mm Hg	68	0.711 (0.610–0.813)	<0.001
Hb, g/dL	12.8	0.734 (0.634–0.833)	<0.001
ABI	1.09	0.612 (0.491–0.733)	0.058
DHEA-S, μg/dL	50	0.709 (0.611–0.808)	<0.001
Cortisol/DHEA-S	0.14	0.769 (0.682–0.857)	<0.001

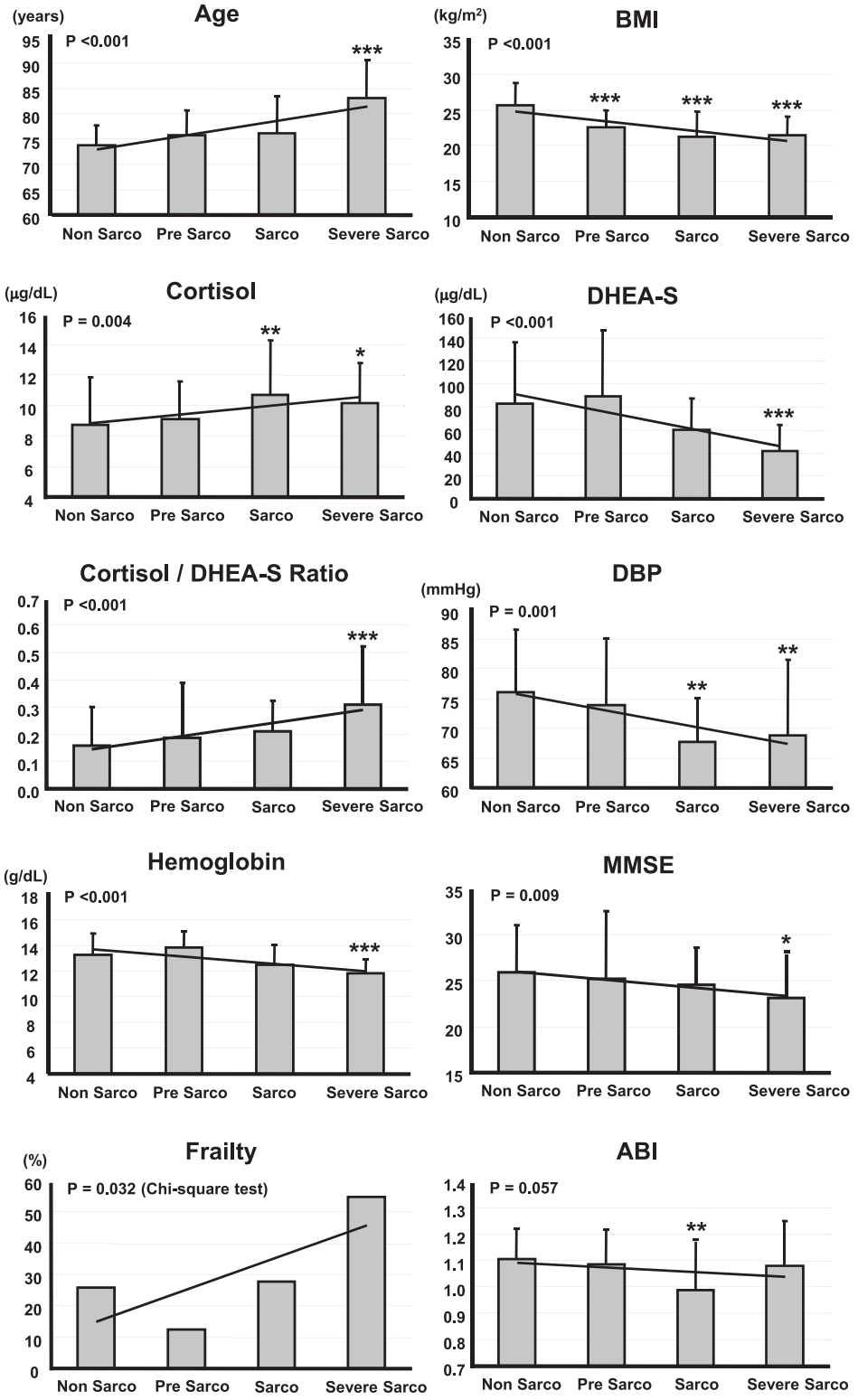

Figure 1. Important variables for sarcopenia stratified by the severity of sarcopenia.The graphs are plotted as mean ± SD. *P* values were determined by the Jonckheere–Terpstra test for increased or decreased tendency of continuous variables. Differences in percentages of frailty were investigated by the χ^2 test. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs nonsarcopenia as determined by a multiple comparison method (Fisher least significant difference test) after ANOVA.

values of the cortisol/DHEA-S ratio and the DHEA-S concentration for detecting sarcopenia in our study were 0.14 and 50 μg/dL, respectively. The usefulness of these cutoff values requires further investigation in a larger-scale clinical study.

The relatively higher cortisol concentration in patients with T2DM with sarcopenia suggests that they may be exposed to a greater degree of stress than those without sarcopenia. Chronic stress often results in increased cortisol secretion with decreased secretion of DHEA-S [18], thus resulting in an increased cortisol/DHEA-S ratio. Elderly individuals show dissociated secretions of cortisol and DHEA-S, even at basal concentrations [18]. This dissociation is much more enhanced by gradual adrenocorticotropic hormone infusion, which mimics the condition of subacute stress [46]. Interestingly, hyperglycemia itself in T2DM causes similar discordant secretions of cortisol and DHEA-S because of decreased activity of 17,20-lyase (the enzyme responsible for DHEA production) relative to 17α-hydroxylase (the enzyme responsible for cortisol production) [47]. Therefore, exposure to stress due to sarcopenia plus T2DM may lead to more enhanced discordant secretion of cortisol and DHEA in elderly patients. Furthermore, the state of dementia in elderly people may also promote cortisol secretion, as elderly people with dementia secrete relatively higher amounts of cortisol in the evening and late at night than do young people [46]. The exact mechanism for the relative decrease in the secretion of DHEA-S relative to cortisol in the stress condition remains unclear. One explanation is based on the phenomenon known as "pregnenolone steal," in which pregnenolone serves predominantly as a precursor for the production of cortisol, thus decreasing the supply for the formation of DHEA in times of stress [47]. Although DHEA production is decreased by lipid peroxidation of cytochrome P450c17 and decreased expression of the electron transport system (cytochrome b5 or P450 oxidoreductase) to P450c17 [18], no evidence has been demonstrated for the effect of these processes on the stress response.

Glucocorticoids, including cortisol, have catabolic actions in many tissues, including muscle [48, 49]. Glucocorticoids induce atrogin-1 and MuRF-1 in the ubiquitin-proteasome system, thus causing protein degradation of skeletal muscle [48, 49]. Cortisol also inhibits the production of IGF-1, which is an anabolic hormone. Furthermore, cortisol increases the production of myostatin from myocytes, which acts on the autocrine function of muscle cells to inhibit myogenesis (muscle cell growth and differentiation) [48]. Therefore, there appears to be a positive feedback loop between the relative increase in cortisol secretion and sarcopenia. In contrast, DHEA-S has an anabolic action on muscle as a weak androgen and precursor for sex steroids [50–53]. In rats, DHEA-S decreases the MuRF-1 mRNA of myoblasts at physiological concentrations, increases the number of myosin heavy chains, uniquely increases the concentration of chaperone heat shock protein 70, and maintains skeletal muscle mass [50]. In rats, exercise and administration of DHEA increase the concentrations of *de novo* steroid biosynthetic enzymes, as well as concentrations of testosterone, DHT, and estradiol, resulting in an increase in skeletal muscle mass [52]. This beneficial role of DHEA-S could be related to several actions of DHEA, such as a direct effect of DHEA, an indirect effect via its transformation to the sexual hormones testosterone, DHT, and estradiol, and its antagonistic action on cortisol [19]. Therefore, an increase in cortisol concentration and a decrease in DHEA-S concentration may lead to the aggravation of sarcopenia.

In humans, serum DHEA-S concentrations are positively correlated with muscle strength and skeletal muscle mass [53]. DHEA-S administration in patients with myotonic dystrophy increases muscle strength and skeletal muscle mass and improves the ability to perform activities of daily living [54]. In elderly people, administration of DHEA and exercise increase muscle mass and muscle strength [55] or muscle strength of the lower limbs [56]. However, a randomized, controlled trial showed that the administration of 50 mg of DHEA daily to elderly males resulted in no changes in upper and lower extremity strength or physical performance [57]. Although the effect of DHEA or DHEA-S on muscle in elderly patients may still be controversial, the possibility of their clinical use should be considered because of the various beneficial effects of DHEA on age-related disorders [19].

In our study, the independent risk factors for sarcopenia in elderly patients with T2DM were an ABI <1.0, DBP <70 mm Hg, and Hb concentration <13 g/dL. In agreement with our findings, sarcopenia reportedly develops in those with peripheral arterial disease [58]. Furthermore, low blood pressure appears to be beneficial in nonfrail elderly adults. However, emerging evidence has shown that low blood pressure is associated with poor outcomes in elderly frail adults or those with poor functional status [59]. Low blood pressure has been hypothesized to lead to inadequate perfusion of various organs, including muscle. Therefore, low DBP may be associated with sarcopenia; however, this remains debatable. Anemia is a risk factor for sarcopenia [60].

The current study had a potential limitation. As the blood sampling was conducted between 0900 and 1200 hours, the cortisol concentration may have been affected by the circadian rhythm of cortisol secretion. However, this circadian effect seems unlikely, as the circadian profile of serum cortisol in elderly subjects is clearly flattened compared with that of young subjects, and especially disappears in the morning (from 0800 to 1200 hours) [61].

In summary, the current study shows that the independent risk factors for sarcopenia in elderly patients with T2DM are a serum cortisol/DHEA-S ratio ≥0.2, DBP <70 mm Hg, Hb concentration <13 g/dL, and an ABI <1.0. Among these risk factors, the serum cortisol/DHEA-S ratio has the strongest effect on sarcopenia. This finding may reflect the condition of increased stress in patients with sarcopenia and is also pathologically related to the increased catabolic effect of cortisol on muscle, as well as the decreased protective action of DHEA-S on muscle mass.

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Correspondence: Toshihiko Yanase, MD, PhD, Department of Endocrinology and Diabetes Mellitus, Faculty of Medicine, Fukuoka University, 45-1, Nanakuma, Jonan-Ku, Fukuoka 814-0180, Japan. E-mail: tyanase@fukuoka-u.ac.jp; or Hajime Nawata, MD, PhD, Muta Hospital, 3-9-1 Hoshikuma, Sawara-ku, Fukuoka 814-0163, Japan. E-mail: h-nawata@seiwakai-muta-hp.or.jp.

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