Research Paper

Analysis of the Relationship between the Severities of Sarcopenia Complicated with Diabetes in Elderly

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To observe and analyze the relationship between the severities of sarcopenia complicated with diabetes in elderly men and bone density, pulmonary function, irisin and interleukin-6. 80 male patients aged 55 y or older with diabetes and 100 male patients aged 55 y or older with sarcopenia complicated with diabetes that was treated in our hospital from 2018 to 2020 were selected. All enrolled patients underwent bone density and pulmonary function tests, as well as plasma irisin levels and serum inflammatory factor detection, to analyze their relationship. Using sarcopenia, body mass index and glycated hemoglobin as independent variables and whether sarcopenia was complicated as the dependent variable, the results of multiple logistic regression analysis showed that sarcopenia in elderly male diabetic patients was an independent risk factor for osteoporosis ($p<0.05$); interleukin-2 of the study group was 160.1±32.4 ng/l, interleukin-4 was 13.5 (7.5-21.8) ng/l, interleukin-6 was 4.3 (1.8-8.1) ng/l, interleukin-8 was 14.5 (7.8-32.0) ng/l, forced expiratory volume 1/forced vital capacity was 65.44±14.68 % and forced expiratory volume 1 predicted value was 67.28±29.95 %. Through correlation analysis, it was found that the four-limb skeletal muscle index was correlated with pulmonary function indicators (forced expiratory volume 1/forced vital capacity and forced expiratory volume 1) and interleukin-6 ($p<0.05$); forced expiratory volume 1 was negatively correlated with interleukin-8 level ($t=-340$, $p<0.05$); the bone mineral content and irisin levels of the study group were lower than those of the reference group. Using bone mineral content and irisin as independent variables and whether sarcopenia was complicated as the dependent variable, the results of multiple logistic regression analysis showed that bone mineral content and irisin were independent protective factors for sarcopenia complicated with diabetes in elderly men (both $p<0.05$). The severity of sarcopenia complicated with diabetes in elderly men is closely related to bone density, pulmonary function, irisin, and interleukin-6 which have certain clinical value.

Key words: Sarcopenia, diabetes, bone density, pulmonary function, osteoporosis, interleukin-6

With increasing age, the physiological functions of human organs experience varying degrees of decline and the elderly become a high-risk group for various chronic diseases such as diabetes, sarcopenia and osteoporosis[1]. Studies have shown that early decline in muscle function is related to reduced activity and muscle consumption can further reduce physical activity, exercise endurance and quality of life is an important risk factor for declining lung function[2,3]. Sarcopenia, also known as skeletal muscle loss, is a type of progressive and widespread reduction in muscle mass and strength, which can lead to reduced physical function, decreased quality of life and even death[4,5]. Patients with sarcopenia have elevated levels of various inflammatory factors in their serum and high levels of inflammatory factors are negatively correlated with muscle strength and quality[6,7]. Literature has reported that compared to non-sarcopenia patients, sarcopenia patients have a 3-fold higher risk of falling or dying and sarcopenia itself can lead to increased disability rates and hospitalization risk[8]. Research has shown that the probability of sarcopenia occurring in elderly patients with Diabetes Mellitus (DM) is significantly increased, being 2-3 times that

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of healthy individuals[9]. Diabetes is a chronic metabolic disease clinically characterized by its high blood sugar levels. When diabetes occurs, there is an absolute or relative insufficiency of insulin in the body, which causes abnormalities in glucose metabolism, lipid metabolism and protein metabolism, which can damage many organs in the body[10]. Foreign reports have stated that the incidence of sarcopenia in elderly diabetic patients ranges from 7.0 % to 29.3 %, which may be related to insulin resistance, chronic inflammation and oxidative stress reactions in elderly diabetic patients, which alter muscle mass and function. Studies have indicated that the pathogenesis is also related to factors such as insulin resistance and blood glucose levels[11]. For elderly diabetic patients, especially those who are advanced in age, the more important indicator of evaluating their health status is their functional status. There are few reports on elderly diabetic patients with sarcopenia in China and there is a lack of clinical research. Therefore, this study observed and analyzed the relationship between the severity of sarcopenia in elderly men with diabetes and bone density, lung function, irisin and Interleukin (IL)-6.

MATERIALS AND METHODS

Study objects:

A total of 180 male patients aged 55 y or older who were admitted to our hospital from 2018 to 2020 were selected, including 80 patients with diabetes as the reference group and 100 male patients with sarcopenia and diabetes as the study group. The average age of the reference group was (65.84±6.85) y, with an average Body Mass Index (BMI) of (26.76±2.88) kg/m^2; the average age of the study group was (66.18±6.24) y, with an average BMI of (22.87±3.41) kg/m^2.

Inclusion and exclusion criteria:

Inclusion criteria: Meet the diagnostic criteria for diabetes of the American Diabetes Association (ADA) in 2013; patients who are aware of the study and voluntarily sign the informed consent form and the study has been approved by the hospital's ethics committee.

Exclusion criteria: Cognitive impairment that hinders normal communication; concurrent diseases affecting bone or calcium metabolism or recent use of drugs affecting bone metabolism and acute complications of diabetes, infections, other systemic diseases or tumors.

Diagnostic criteria:

The diagnostic criteria for male sarcopenia in this study were based on the diagnostic criteria of the European Working Group on Sarcopenia in Older People (EWGSOP)[12] and the research results of Verschueren *et al.* The cut-off point for the diagnosis of sarcopenia in men was Appendicular Skeletal Muscle Mass Index (ASMI) ≤7.26 kg/m^2, while meeting the criteria for low grip strength or low gait speed. Severe patients also met all three of the above criteria.

Study methods:

Height and body weight of all subjects were measured by a dedicated person. Subjects wore light clothing and were barefoot during measurements. BMI was calculated. The muscle mass, fat mass and bone density of various parts of the subjects were measured using dual-energy X-ray absorptiometry (Lunar iDXA, GE, United States of America (USA)).

Grip strength was evaluated using the Jamar grip strength dynamometer. The measurement unit was in kilograms (kg). The subject gripped the dynamometer three times with each hand, and the maximum value was recorded. Grip strength ≤29 kg when BMI ≤24 kg/m^2, grip strength ≤30 kg when 24 kg/m^2 <BMI ≤28 kg/m^2, and grip strength ≤32 kg when BMI >28 kg/m^2 were defined as low grip strength.

Gait speed was evaluated using the 6-meter walk test. A 12-meter straight line was drawn, with the starting point, 3-meter point, 9-meter point and endpoint marked. Each point was timed separately and the test was performed three times, with the fastest time recorded.

Appendicular Skeletal Muscle (ASM) mass was defined as the sum of the skeletal muscle mass in the upper and lower limbs, and the ASMI was calculated by dividing the ASM by the square of height (m^2).

Fasting venous blood samples (2 ml) were collected after an overnight fast of at least 8 h. Fasting Plasma Glucose (FPG), Triglycerides (TG), Total Cholesterol (TC), Low-Density Lipoprotein Cholesterol (LDL-C), High-Density Lipoprotein Cholesterol

(HDL-C), and Glycated Hemoglobin (HbA1c) were measured using an automated biochemical analyzer.

Lung function was assessed using the Master Screen PFT system (Jager, Germany). The measured parameters included Forced Expiratory Volume-1 (FEV1) and Forced Vital Capacity (FVC), and the percentages of predicted FEV1 (FEV1 % pred) and FEV1/FVC were calculated.

Fasting venous blood samples (5 ml) were collected in the morning, and plasma was separated by centrifugation at 3000 rpm for 15 min (centrifuge radius of 8 cm). The levels of IL-2, IL-4, IL-6, IL-8 and histone were measured using an Enzyme-Linked Immunosorbent Assay (ELISA).

Fasting venous blood samples (2 ml) were collected in the morning and anticoagulated with ethylenediaminetetraacetic acid. After centrifugation at 3000 rpm for 15 min (centrifuge radius of 8 cm), the plasma was separated and stored at -80°. Plasma levels of irisin were measured using a sandwich ELISA.

Statistical analysis:

The study used logistic regression analysis to examine the relationship between variables and Statistical Package for the Social Sciences (SPSS) 22.0 software was used to process the data. Count data [n (%)] and metric data ($\bar{x}\pm s$) were analyzed using Chi-square (χ^2) and t-tests, respectively, with $p<0.05$ indicating a statistically significant difference.

RESULTS AND DISCUSSION

In the study group, BMI, Hand Strength (HS), Gait Speed (GS), ratio of skeletal muscle weight to body weight (A/B), ratio of lower limb muscle mass to body weight (L/B), ratio of muscle mass to fat mass (M/F), ASM, and ASMI (22.87±3.41, 33.03±6.44, 1.19±0.95, 0.27±0.03, 0.21±0.03, 3.01±0.85, 19.14±2.08 and 6.45±0.68) were all lower than the reference group (26.76±2.88, 38.74±8.54, 1.21±0.33, 0.31±0.02, 0.23±0.02, 3.31±1.01, 23.35±2.28 and 8.17±0.74), while ratio of lower limb muscle mass to upper limb muscle mass (L/U) (3.11±0.34) was higher than the reference group (3.02±0.28). Comparison of the two groups showed that GS, L/U and M/F were not significant ($p>0.05$), while BMI, HS, A/B, L/B, ASM and ASMI were significant ($p<0.05$) as shown in Table 1.

In the study group, TG, TC, LDL-C and HDL-C (1.31, 4.07±1.06, 2.48±0.94 and 1.05±2.25) were all lower than the reference group (1.34, 4.23±1.11, 2.61±0.88 and 1.12±0.37), while FPG and HbA1c (9.66±3.51, 9.01±1.89) were higher than the reference group (9.11±3.47, 8.47±1.82). Comparison of TG, TC, LDL-C, HDL-C and FPG between the two groups was not significant ($p>0.05$), while HbA1c was significant ($p<0.05$) as shown in Table 2.

TABLE 1: COMPARISON OF CLINICAL DATA BETWEEN THE TWO GROUPS ($\bar{x}\pm s$)

Group	Reference group	Research group	t	p
Number of cases	80	100	-	-
BMI (kg/m^2)	26.76±2.88	22.87±3.41	8.141	<0.001
HS (kg)	38.74±8.54	33.03±6.44	5.113	<0.001
GS (m/s)	1.21±0.33	1.19±0.95	0.18	0.857
L/U	3.02±0.28	3.11±0.34	1.906	0.058
A/B	0.31±0.02	0.27±0.03	10.241	<0.001
L/B	0.23±0.02	0.21±0.03	5120	<0.0 01
M/F	3.31±1.01	3.01±0.85	2163	0.032
ASM (kg)	23.35±2.28	19.14±2.08	12928	<0.0 01
ASMI (kg/m^2)	8.17±0.74	6.45±0.68	16213	<0.0 01

TABLE 2: COMPARISON OF BLOOD GLUCOSE INDICATORS BETWEEN THE TWO GROUPS ($\bar{x}\pm s$)

Group	Reference group	Research group	t	P
Number of cases	80	100	-	-
FPG (mmol/l)	9.11±3.47	9.66±3.51	1.051	0.295
TG (mmol/l)	1.34 (0.93-2.50)	1.31 (0.95-2.01)	1.084	0.291
TC (mmol/l)	4.23±1.11	4.07±1.06	0.985	0.326
LDL-C (mmol/l)	2.61±0.88	2.48±0.94	0.948	0.344
HDL-C (mmol/l)	1.12±0.37	1.05±2.25	0.275	0.784
HbA1c (%)	8.47±1.82	9.01±1.89	1.936	0.045

The t-scores and bone density (-1.03±1.65, -1.42±1.33, -1.48±1.08, 1.15±0.18, 0.89±0.15 and 0.86±0.12) of the study group were all lower than those of the reference group (-0.44±1.69, -0.76±1.12, -0.91±1.04, 1.25±0.14, 1.01±0.23 and 0.98±0.09) and the comparison between the two groups was significant ($p<0.05$) as shown in Table 3.

The decline in bone density and muscle mass with age is significant, and there is a close relationship between sarcopenia and osteoporosis from the pathogenesis to the survival prognosis. Using sarcopenia, BMI and HbA1c as independent variables and the presence of sarcopenia as the dependent variable, a multiple logistic regression analysis showed that sarcopenia in elderly diabetic men was an independent risk factor for osteoporosis ($p<0.05$) as shown in Table 4.

The IL-2 level of the study group was 160.1±32.4 ng/l, IL-4 was 13.5 (7.5-21.8) ng/l, IL-6 was 4.3 (1.8-8.1) ng/l, IL-8 was 14.5 (7.8-32.0) ng/l, FEV1/FVC was 65.44±14.68 % and FEV1 was 67.28±29.95 % predicted as shown in Table 5.

Correlation analysis showed that the four-limb skeletal muscle index was correlated with lung function indicators (FEV1/FVC and FEV1) and IL-6 ($p<0.05$); FEV1 was negatively correlated with IL-8 levels ($t=-340$, $p<0.05$) as shown in Table 6.

The Bone Mineral Content (BMC) and irisin levels of the study group (2.41±0.22, 166.24±21.11) were lower than those of the reference group (3.03±0.31, 229.18±27.02), and the comparison between the two groups was significant ($p<0.05$) as shown in Table 7.

Using BMC and irisin as independent variables and the presence of sarcopenia with diabetes as the dependent variable, a multiple logistic regression analysis showed that both BMC and irisin were independent protective factors for sarcopenia with diabetes in elderly men (both $p<0.05$) as shown in Table 8.

TABLE 3: COMPARISON OF T-SCORES AND BONE DENSITY VALUES BETWEEN THE TWO GROUPS (x̄±s)

Group	Example	t value			BMD (g/cm²)		
		Lumbar spine	Left femoral neck	Right femoral neck	Lumbar spine	Left femoral neck	Right femoral neck
Reference	80	-0.44±1.69	-0.76±1.12	-0.91±1.04	1.25±0.14	1.01±0.23	0.98±0.09
Research	100	-1.03±1.65	-1.42±1.33	-1.48±1.08	1.15±0.18	0.89±0.15	0.86±0.12
t		2.358	3.545	3.577	4.078	4.217	7.427
p		0.019	0.001	<0.0 01	<0.0 01	<0.0 01	<0.0 01

TABLE 4: REGRESSION ANALYSIS OF OSTEOPOROSIS IN ELDERLY DIABETIC MEN

	Regression coefficient (β)	Standard Error (SE)	χ^2 value	OR (95 % CI)	p value
Sarcopenia	1.013	0.425	6.697	2.77 (1.21-6.34)	0.016
BMI	-0.062	0.058	1.187	0.99 (0.85-1.04)	0.275
HbA1c	-0.041	0.098	0.168	0.96 (0.579-1.16)	0.681

TABLE 5: LUNG FUNCTION AND INFLAMMATORY FACTOR INDICATORS IN THE STUDY GROUP

	Number of patients	Research group
IL-2 (ng/l)	100	160.1±32.4
IL-4 (ng/l)	100	13.5 (7.5-21.8)
IL-6 (ng/l)	100	4.3 (1.8-8.1)
IL-8 (ng/l)	100	14.5 (7.8-32.0)
FEV1/FVC (%)	100	65.44±14.68
FEV1 accounted for estimated value (%)	100	67.28±29.95

TABLE 6: CORRELATION ANALYSIS OF FOUR-LIMB SKELETAL MUSCLE INDEX AND RELATED FACTORS

	SMI		IL-2		IL-6		IL-8		FEVI/FVC		FEVI	
	r	p	r	p	r	p	r	p	r	p	r	p
SMI			0.075	0.629	-0.63	0.000	0.022	0.894	0.76	0.000	0.696	0.000
IL-6	-0.63	0.000	0.136	0.38			0.225	0.162	-0.558	0.000	-0.524	0.000
FEV1	0.696	0.000	0.056	0.716	-0.524	0.000	-0.34	0.032	0.868	0.000		

TABLE 7: DETECTION INDICATORS AND HUMAN LEVELS (x̄±s)

Group	Example	ASMI	BMC (g/cm)	Irisin (μg/l)
Reference	80	8.17±0.74	3.03±0.31	229.18±27.02
Research	100	6.45±0.68	2.41±0.22	166.24±21.11
t	-	12.928	15.671	17.546
p	-	<0.0 01	<0.0 01	<0.0 01

TABLE 8: FACTORS AFFECTING SARCOPENIA WITH DIABETES IN ELDERLY

	Regression coefficient (β)	SE	χ^2 value	OR (95 % CI)	p value
BMC ≥2.79 g/cm	-3.267	1.027	10.118	0.038 (0.005-0.285)	0.001
Irisin ≥206.95 μg/l	-0.066	0.02	10.909	0.936 (0.901-0.974)	0.001

As a high-risk group for multiple chronic diseases, elderly people are prone to develop diabetes, sarcopenia and osteoporosis. The latest international working group defines the syndrome of losing muscle mass and strength accompanied by functional impairment and adverse clinical outcomes as sarcopenia, which is a progressive and widespread decline in skeletal muscle mass and strength. Sarcopenia patients have a higher risk of falls or death, and sarcopenia itself can lead to increased disability and hospitalization risk[13,14]. Studies have shown that the probability of sarcopenia in elderly patients with DM is 2-3 times higher than that in healthy individuals. The prevalence of sarcopenia in elderly patients with DM is reported to be 7.0 %-29.3 % in foreign studies[15]. The reasons may be related to insulin resistance, chronic inflammation, oxidative stress response, and changes in muscle mass and function in elderly patients with DM. Studies have also pointed out that the pathogenesis is related to insulin resistance, blood glucose level and other factors. For elderly patients with DM, especially the elderly, the evaluation of functional status is a more important indicator of health status. The results of this study showed that BMI, HS, GS, A/B, L/B, M/F, ASM and ASMI (22.87±3.41, 33.03±6.44, 1.19±0.95, 0.27±0.03, 0.21±0.03, 3.01±0.85, 19.14±2.08 and 6.45±0.68) were lower than those in the reference group (26.76±2.88, 38.74±8.54, 1.21±0.33, 0.31±0.02, 0.23±0.02, 3.31±1.01, 23.35±2.28 and 8.17±0.74), and L/U (3.11±0.34) was higher than that in the reference group (3.02±0.28). The comparison of GS, L/U and M/F between the two groups was not significant ($p>0.05$), while the comparison of BMI, HS, A/B, L/B, ASM and ASMI was significant ($p<0.05$). The mutual influence between poorly controlled diabetes and sarcopenia indicates that elevated blood glucose levels can lead to a decrease in muscle mass and function, and the loss of muscle mass can further negatively affect glucose metabolism by reducing glucose handling capacity. The research results of Anbalagan and Sugimoto showed that the prevalence of pre-sarcopenia in the diabetic population was 39.5 %, and ASMI was related to BMI, age, fasting blood glucose and other factors. The prevalence of sarcopenia increased linearly with the concentration of HbA1c, which is consistent with the results of this study. The t-values and bone densities of the study group (-1.03±1.65, -1.42±1.33, -1.48±1.08, 1.15±0.18, 0.89±0.15 and 0.86±0.12) were all lower than those of the reference group (-0.44±1.69, -0.76±1.12, -0.91±1.04, 1.25±0.14, 1.01±0.23 and 0.98±0.09). The decline in bone density and muscle mass with increasing age was significant, and there is a close relationship between sarcopenia and osteoporosis in terms of pathogenesis and survival prognosis. Using sarcopenia, BMI, and glycosylated hemoglobin as independent variables, and sarcopenia as the dependent variable, a multivariate logistic regression analysis showed that sarcopenia in elderly male diabetes patients is an independent risk factor for osteoporosis ($p<0.05$). Bone Mineral Density (BMD) is closely related to muscle mass, possibly due to the decrease in muscle mass and function[16]. The decrease in physical activity in elderly people leads to a decrease in the mechanical stimulation of the skeletal muscles on the bone structure, which in turn causes a decline in bone formation and gradual atrophy of the bone-muscle unit[17]. The study group patients had IL-2 levels of 160.1±32.4 ng/l, IL-4 levels of 13.5 (7.5-21.8) ng/l, IL-6 levels of 4.3 (1.8-8.1) ng/l and IL-8 levels of 14.5 (7.8-32.0) ng/l, with a FEV1/FVC of 65.44±14.68 % and FEV1 predicted value of 67.28±29.95 %. Correlation analysis showed that the four-limb skeletal muscle index was correlated with lung function indicators (FEV1/FVC and FEV1) and IL-6 ($p<0.05$). FEV1 was negatively correlated with IL-8 levels ($t=-340$, $p<0.05$), and it is speculated that this is mainly due to the relationship between upper

limb muscle strength and maximal inspiratory and expiratory pressures. There are related reports both domestically and abroad indicating that respiratory muscle functional training can significantly increase peak expiratory flow rate and increase lung capacity. Due to the decline in respiratory muscle strength in patients with muscle wasting, the strength of lung inspiration and expiration decreases, resulting in a decrease in FVC and FEV1 values. In addition, the enhancement of systemic inflammatory response may also be involved in the mechanism of skeletal muscle decline, which affects lung elastic recoil and expansion, ultimately leading to a decrease in lung capacity and FEV1, which is consistent with the results of this study. The levels of BMC and irisin in the study group (2.41±0.22 and 166.24±21.11, respectively) were lower than those in the reference group (3.03±0.31 and 229.18±27.02, respectively). Using BMC and irisin as independent variables and sarcopenia as a dependent variable, a multiple logistic regression analysis showed that BMC and irisin were independent protective factors for sarcopenia with concomitant diabetes in elderly men (both $p<0.05$). Some studies have found that a slight increase in serum irisin levels can significantly increase energy expenditure[18]. Therefore, it is believed that irisin levels are related to energy expenditure, which is consistent with the results of this study. The decrease in plasma irisin levels can inhibit the activation of peroxisome proliferator-activated receptor alpha (α), leading to insulin resistance and the occurrence of diabetes. Irisin can also promote the growth and proliferation of muscle cells to maintain normal muscle mass and function. The reduction in muscle mass and activity can further decrease plasma irisin levels. Thus, plasma irisin levels are independent protective factors for sarcopenia with concomitant diabetes[19,20].

In summary, the severity of sarcopenia with concomitant diabetes in elderly men is closely related to bone density, lung function, irisin and IL-6 has certain clinical value.

Conflict of interests:

The authors declared no conflict of interests.

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