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Original Article

The effect of blood glucose regulation on sarcopenia parameters in obese and diabetic patients

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ABSTRACT

Objectives: This study aims to evaluate the effect of blood glucose regulation on sarcopenia parameters in sarcopenic, obese, and poorly-regulated diabetic patients.

Patients and methods: Between June 2013 and December 2013, a total of 147 patients (64 males, 83 females; mean age 70.3±6.3 years; range, 60 to 90 years) who were diagnosed with sarcopenia according to the European Working Group on Sarcopenia in Older People (EWGSOP) criteria were included in the study. All patients were obese with a body mass index (BMI) of >30 kg/m^2 and their glycated hemoglobin (HbA1c) levels were above 8%. Sarcopenia parameters including the gait speed, muscle strength, muscle mass, and handgrip strength were assessed. After a six-month treatment period, the patients were divided into two groups according to their HbA1c levels as having <8% or >8%. Sarcopenia parameters were evaluated before and after receiving treatment.

Results: The mean disease duration was 16±6.2 years. Sixty patients were found to have a HbA1c level of <8% and 45 patients with a HbA1c level of ≥8% at sixth months of follow-up. In better regulated group, sarcopenia parameters such as gait speed, muscle mass, and handgrip strength improved; however, only the change in the muscle mass was found to be statistically significant (p=0.041). There was no significant change in the parameters of sarcopenia in the patient group with a HbA1c level ≥8%. A negative correlation was found between the muscle mass and HbA1c levels in good- and poorly-regulated groups (p=0.039 r:-0.327 and p=0.044 r:-0.183, respectively).

Conclusion: Our study demonstrates that lowering HbA1c levels may have positive effects on the muscle mass even in diabetic and sarcopenic obese elderly individuals.

Keywords: Diabetes mellitus; obesity; sarcopenia.

All over the world including developing countries, the life expectancy from birth has been increasing and, therefore, the number and rate of the elderly population has been increasing in recent years.[1]

Diabetes mellitus (DM) is a metabolic disorder which adversely affects the quality of life and life expectancy of elderly population.[2] According to the data from the World Health Organization (WHO), 2.1% of the world's population is diabetic, and the incidence and prevalence have been on the rise with advanced age.[3] In patients aged ≥65 years old, DM accounts for 40% of all DM cases.[4]

Sarcopenia is characterized by progressive, generalized loss of muscle mass and strength, which is derived from Latin words *sarx* (muscle) and *penia* (loss).[5] Although Rosenberg and Roubenoff[6] first described sarcopenia as a reduction of skeletal muscle mass and size with aging, clinical description was made by Baumgartner et al.[7] as muscle mass below two standard deviations of the mean of healthy young subjects muscle mass.

Obesity has reached to an epidemic proportion globally. It is no longer a problem solely affecting young individuals, but is also frequently seen among elderly. The prevalence of obesity in the United States was 22.9% between 60 and 69 years of age and 15.5% in age >70 years.[8] The term of sarcopenic obesity was contributed to the literature with the increased

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incidence of obesity.[9] Decreased lean body tissue and increased adipose tissue according to the body weight in elderly is defined as sarcopenic obesity of which the recognition has been more critical, recently.[10]

In recent years, sarcopenia has been accepted as one of the diabetic complications.[11] However, its underlying mechanism in type 2 diabetes mellitus (T_2DM) is still unclear. In this study, we aimed to evaluate the effect of blood glucose regulation on sarcopenia parameters in sarcopenic, obese, and poorly-regulated diabetic patients.

PATIENTS AND METHODS

Between June 2013 and December 2013, a total of 147 patients (64 males, 83 females; mean age 70.3±6.3 years; range, 60 to 90 years) who were admitted to geriatric and/or internal medicine outpatient clinics and diagnosed with sarcopenia according to the European Working Group on Sarcopenia in Older People (EWGSOP) criteria were prospectively included in the study. All patients were obese with a body mass index (BMI) of >30 kg/m^2 and their glycated hemoglobin (HbA1c) levels were above 8%. Patients aged under 60 years, those with a debilitating disease or deformities, terminal stage disease, chronic liver and kidney diseases, malignancy, diabetic polineuropathy, history of trauma, and infection in the past one month, and poor cognitive function leading to failure to complete the study tests were excluded.

The demographic characteristics and comorbidities of the patients were recorded and the Mini-Nutritional Assessment (MNA), Activities of Daily Living Test, Geriatric Depression Scale, Mini-Mental State Examination (MMSE), and Get-up and Go-test were performed. In addition, complete blood cell count, urea, creatinine, liver function tests, calcium, and phosphorus levels were recorded. According to the EWGSOP, sarcopenia was defined as having low muscle mass plus low grip strength or low gait speed.[12] Patients with sarcopenia according to the EWGSOP criteria and with a BMI of ≥30 kg/m^2 were considered sarcopenic obese.

In accordance with the diagnosis, the gait speed, muscle strength, and muscle mass were calculated. The gait speed was measured over six-meter-distance. The isometric hand grip strength is strongly related with lower extremity muscle power, knee extension torque, and calf cross-sectional muscle area.[13] The muscle strength for hand grip strength was evaluated by an Tanita SA165 A-0950U-3 model electronic dynamometer device (Tanita Corp., Tokyo, Japan). The muscle mass was measured by bioelectrical impedance analysis (BIA) devices, which are useful tools to estimate the volume of fat and lean body mass, in our geriatric unit. In addition, anthropometric data were recorded such as weight, right, and left thigh and mid-upper arm circumference and waist circumference. Medical treatment was arranged and the patients were re-evaluated at sixth-month follow-up based on the same criteria. The patients were divided into two groups according to their HbA1c levels as having <8% or >8% and were analyzed based on changing parameters of sarcopenia.

The study protocol was approved by the local Ethics Committee. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

Statistical analysis was performed using the SPSS for Windows version 15.0 software package (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean ± standard deviation, median, and min-max. Paired sample t-test for binary comparisons of normally distributed numerical parameters, Mann-Whitney U test for abnormally distributed parameters, and the Pearson's chi-square test for categorical variables were used. Baseline and post-treatment normally distributed sarcopenia parameters were compared using the dependent Student's t-test. Since sarcopenia parameters and HbA1c showed normal distribution, the correlation coefficients (r) and statistical significance were calculated using the Pearson's test: r near ±1 indicates a perfect correlation; r between ±0.50 and ±1 indicates a strong relationship; r between ±0.30 and ±0.49 indicates a moderate correlation; and r below ±0.29 indicates a weak relationship.[14] A p value of <0.05 was considered statistically significant.

RESULTS

Of a total of 147 sarcopenic, diabetic, obese patients, the mean BMI was 33.2±3.1 kg/m^2, while the mean HbA1c level was 9.5±1.5%. The mean disease duration was 16±6.2 years. Of the patients, 61.2% were using insulin, 27.9% were taking oral antidiabetics, and 10.9% were taking insulin and oral antidiabetics concomitantly. Demographic characteristics, anthropometric measurements, comprehensive geriatric assessment test results, laboratory parameters, and related comorbidities are shown in Table 1.

Table 1. Baseline demographic characteristics, anthropometric measurements, comprehensive geriatric assessment test results, laboratory results, and comorbidities of sarcopenic, diabetic obese patients

	Diabetic patients with sarcopenic obesity (n=147)				
	n	%	Mean+SD	Median	Min-Max
Demographic features					
Age (year)			70.3±6.3		
Sex					
Male	64	43.5			
Female	83	56.5			
Anthropometric measurements					
Calf circumference (cm)			37.1±4.4		
Body mass index (kg/m^2)			33.2±3.1		
Waist circumference (cm)			104.3±11.0		
Hip circumference (cm)			112.8±14.6		
Mid-upper arm circumference (cm)			34.2±5.2		
Comprehensive geriatric assessment tests					
Activities of Daily Living test				2	0-20
Mini-Nutritional Assessment test-short form			12.6±1.4		
Mini-cog test			26.6±3.4		
Geriatric Depression scale			5.2±2.3		
Timed Up and Go test			7.4±2.2		
Laboratory parameters					
Hemoglobin (g/dL)			13.4±1.5		
White blood cell (/mm^3)			7,930±2,454		
Platelets (/mm^3)			274,040±61,820		
Erythrocyte sedimentation rate (mm/h)				31	4-110
C-reactive protein (mg/dL)				11	1-112
Blood urea nitrogen (mg/dL)			28.4±12.5		
Creatinine (mg/dL)			0.9±0.3		
Alanine aminotransferase (U/L)			24.1±16.3		
Aspartate aminotransferase (U/L)			32.4±20.0		
Vitamin B12 (pg/mL)			284.1±165.1		
Total cholesterol (mg/dL)			198.2±26.6		
Albumin (g/dL)			3.5±0.6		
HbA1c (%)			9.5±1.5		

SD: Standard deviation; Min: Minimum; Max: Maximum; HbA1c: Hemoglobin A1c.

Table 2. Post-treatment demographic characteristics, anthropometric measurements, comprehensive geriatric assessment test results, laboratory results, and comorbidities of sarcopenic, diabetic obese patients at six months

	HbA1c <8 sarcopenic obese patients (n=60)					HbA1c >8 sarcopenic obese patients (n=45)					
	n	%	Mean+SD	Median	Min-Max	n	%	Mean+SD	Median	Min-Max	*p*
Demographic features											
Age (year)			69.6±5.4					68.3±5.7			0.021*
Sex											0.062
Male	24	40				20	44.4				
Female	36	60				25	55.6				
Anthropometric measurements											
Calf circumference (cm)			36.7±5.8					38.5±6.1			<0.001*
Body mass index (kg/m^2)			32.7±3.3					33.8±3.9			0.026*
Waist circumference (cm)			102.3±15.8					104.2±16.1			0.009*
Hip circumference (cm)			109.4±14.3					111.7±12.4			0.036*
Mid-upper arm circumference (cm)			33.2±3.1					34.1±4.6			0.074
Comprehensive Geriatric Assessment tests											
Activities of Daily Living test				2	0-20				3	0-20	0.055
Mini-Nutritional Assessment test-short Form			12.3±2.2					12.8±2.2			0.284
Mini-cog test			26.3±4.9					26.0±4.4			0.342
Geriatric Depression scale			4.8±2.4					5.2±2.5			0.044*
Timed Up and Go test			7.0±1.4					7.3±1.9			0.035*
Laboratory parameters											
Hemoglobin (g/dL)			13.2±1.9					13.6±2.11			0.114
White blood cell (/mm^3)			7,910±2,325					7,360±2,145			0.662
Platelets (/mm^3)			284,120±64,505					257,445±70,280			0.084
Erythrocyte sedimentation rate (mm/h)				34	10-110				31	8-110	0.278
C-reactive protein (mg/dL)				7	0-32				6	0-66	0.284
Blood urea nitrogen (mg/dL)			36.4±14.3					29.3±11.5			0.728
Creatinine (mg/dL)			0.9±0.3					1.0±0.2			0.108
Alanine aminotransferase (U/L)			24.6±12.4					21.2±5.5			0.365
Aspartate aminotransferase (U/L)			28.2±16.1					32.4±14.2			0.478
Vitamin B12 (pg/mL)			346.0±108.1					363.2±147.3			0.912
Albumin (g/dL)			3.9±0.6					4.0±0.4			0.275
HbA1c (%)			7.6±2.1					8.9±2.8			0.029*

SD: Standard deviation; Min: Minimum; Max: Maximum; HbA1c: Hemoglobin A1c.

Table 3. Difference between baseline and post-treatment evaluation on sarcopenia parameters in patient with level of HbA1c <8%

Sarcopenia diagnostic criteria	First evaluation	Second evaluation	
	Mean	Mean	*p*
Gait speed (m/s)	0.76	0.78	0.143
Muscle mass (kg/m^2)	7.42	7.64	0.041*
Hand grip strength (kg)	24.51	25.08	0.184

Table 4. Difference between baseline and post-treatment evaluation on sarcopenia parameters in patient with level of HbA1c ≥8%

Sarcopenia diagnostic criteria	First evaluation	Second evaluation	
	Mean	Mean	*p*
Gait speed (m/s)	0.72	0.71	0.257
Muscle mass (kg/m^2)	7.37	7.36	0.197
Hand grip strength (kg)	25.74	24.85	0.351

The mean gait speed was measured as 0.73 m/s, the mean muscle mass as 7.32 kg/m^2, and the mean hand strength as 24.04 kg. Since 42 of the patients initially included in the study were unable to complete six-month follow-up, they were eventually excluded from the analysis. The remaining patients were divided into two groups based on their HbA1c levels as having <8% and ≥8% after six months of treatment. The demographic characteristics, anthropometric measurements, comprehensive geriatric assessment test results, and laboratory parameters of these two groups are shown in Table 2. For the HbA1c <8% group, values for calf circumference, BMI, waist and hip circumference were measured statistically significantly lower, compared to the other group (p<0.001, p=0.026, p=0.009, and p=0.036, respectively). However, daily activities, MNA-Short Form, and MMSE did not indicate a significant difference between the groups (p=0.055, p=0.284, and p=0.342, respectively). On the other hand, lower results were found using the Geriatric Depression Scale and Get-up and Go-test for the HbA1c >8% group (4.8±2.4 and 5.2±2.5, p=0.044; 7.0±1.4 and 7.3±1.9, p=0.035, respectively). The mean HbA1c level was found to be 7.62%±2.14% in the group with good blood glucose regulation and to be 8.9±2.8 in the group with poor blood glucose regulation (p=0.029). The changes in the sarcopenia parameters of both groups during the initial evaluations and at six-month follow-up are shown in Tables 3 and 4. Although an increase was observed in all three parameters (gait speed, muscle mass, and hand grip strength) in the HbA1c <8% group, only the increase in the muscle mass reached statistical significance in this group (p=0.041). In the poor blood glucose regulation group, all three parameters indicated a decline; however, none of these changes was statistically significant (p=0.257, p=0.197, and p=0.351, respectively). The correlation between the level of HbA1c and sarcopenia parameters are shown in Tables 5 and 6. For both good and poor blood regulation groups, a significant negative correlation was found between the muscle mass and HbA1c level (p=0.039, r:-0.327 and p=0.044, r:-0.183, respectively).

DISCUSSION

In this prospective study, diabetic and sarcopenic obese elderly patients were followed for six months, and the patients with improved blood glucose regulation demonstrated improved values in sarcopenia parameters including the gait speed, muscle mass, and hand grip strength test, while no improvement was

Table 5. The correlation between sarcopenia parameters with HbA1c in patients with level of HbA1c <8%

Parameters	*p*	r
HbA1c-Gait speed	0.058	-0.156
HbA1c-Muscle mass	0.039	-0.327*
HbA1c-Hand grip strength	0.062	-0.161

Table 6. The correlation between sarcopenia parameters with HbA1c in patients with level of HbA1c ≥8%

Parameters	*p*	r
HbA1c-Gait speed	0.134	-0.233
HbA1c-Muscle mass	0.044	-0.183*
HbA1c-Hand grip strength	0.211	-0.247

observed in the poor blood glucose regulation group. Furthermore, the changes in the muscle mass within six months were found to be statistically significant in the group with HbA1c <8%. Based on the examination of the correlation between the Hb1Ac levels and sarcopenia parameters, we found a negative correlation between the Hb1Ac levels and the muscle mass in both groups. This negative correlation was moderate in good blood glucose regulation group and weak in the other group.

Although type 1 diabetes evidently affects protein metabolism by specifically increasing catabolism in the skeletal muscles due to lack of insulin,[15] T_2DM has a less evident effect on the protein metabolism, and the results of previous studies are controversial.[16-20] The muscle loss in T_2DM may be caused by insulin resistance, which leads to a decline in the protein synthesis and increase in the protein degradation.[21] Insulin as an anabolic hormone may induce muscle protein synthesis in young individuals; however, similar effects cannot be seen in older population. Supraphysiological insulin concentrations may bridge the gap between age-related insulin resistances of the muscle protein synthesis.[22] In addition, insulin resistance may contribute to the muscle loss in diabetes, by inactivating the mammalian target of rapamycin (mTOR) pathway and stimulating autophagy.[23,24] A recent experimental study by Nilsson et al.[25] showed that level of the domain-containing mTOR-interacting protein (DEPTOR), an endogenous mTOR inhibitor, was critical in the regulation of protein turnover in sarcopenic obese rats. Not only skeletal muscle size and mass reduced, bioenergy systems of the body including mitochondrial function may be also altered in these patients.[26-29] In the muscles of patients with T_2DM, peroxisome proliferator-activated receptor gamma coactivator, a transcriptional coactivator, can reduce gene expression and may contribute to prohibit muscle atrophy.[30,31] In addition, diabetes is characterized by decreased mitochondrial electron transport chain activity which leads to inefficient energy.[32,33] Nonetheless, insulin supplementation in non-diabetic population causes an increase of adenosine triphosphate (ATP) production in the skeletal muscles, while the same effect is not seen in diabetic population which may be related to impaired insulin response.[34] Patients with diabetes also show a lower *in vivo* mitochondrial function in muscles as measured with phophorus-31 magnetic resonance spectroscopy, than age-matched and BMI-matched controls.[35]

The first epidemiological study showing the effect of T_2DM on the muscle strength and mass was conducted by Park et al.[36] The arm and leg muscle strength and mass of a total of 1,840 elderly individuals were examined during three years, and the final results showed a 13.5% decrease in the knee extensor muscle strength in patients with T_2DM and a 9% decrease in individuals without diabetes. The authors also demonstrated a more rapid decline in the muscle quality in older diabetic patients, and diabetes was associated with functional impairment of the lower extremity muscles without losing any muscle mass. According to the results, the authors found no correlation between the changes in the muscle strengths of the upper and lower extremities. On the other hand, some other studies indicated better maintenance of the muscle strength in the upper extremities with aging.[37,38] Our study did not demonstrate any significant changes in the muscle strengths of the upper extremities in either groups during a six-month follow-up period. In another study, Park et al.[39] reported a rapid loss of skeletal muscle mass in elderly patients with T_2DM. Intriguingly, decreased muscle mass was higher in undiagnosed diabetic individuals, indicating that T_2DM begins to affect the muscle mass from early stages of the disease. There is also a negative linear relationship between the muscle quality and duration of diabetes and poor glycemic control.[40] Insufficient energy use and muscle protein degradation occur depending on the severity of catabolism caused by uncontrolled hyperglycemia. This progression leads to sarcopenia and fatty infiltration of muscle tissue, resulting in limited functional capacity of the muscle. In diabetic individuals with poor glycemic control, increased tumor necrosis factor-alpha and inflammatory cytokines such as interleukin-6 in the muscle tissue induce apoptosis, leading to the destruction of the muscular structure.[41,42]

The Korea Sarcopenic Obesity Study showed that sarcopenia was more common in elderly individuals with T_2DM (6.9 to 15.7%).[43] Sarcopenic obese adults also had higher cardiovascular disease risk than non-sarcopenic obese adults.[44] The Third National Health and Nutrition Survey Study found a negative correlation between the skeletal muscle index and insulin resistance, HbA1c, and diabetes-prediabetes prevalence.[45] Tanaka et al.[46] concluded that the levels of endogenous insulin were positively associated with indices of the muscle mass independently of serum IGF-I in patients with T_2DM and they suggested that reduction in endogenous insulin was an independent

risk factor for diabetes-related sarcopenia, and maintaining endogenous insulin was critical to prevent it.

In another study, there was evident overexpression of messenger ribonucleic acid (mRNA) for myostatin, a peptide in the muscle of patients with T_2DM which negatively regulates the skeletal muscle mass.[47] Physiological responses to exercise and nutrition were impaired and anti-proteolytic effects of insulin decreased. As a potent growth factor, insulin increases collagen synthesis, and stimulates arterial smooth muscle proliferation.[48,49] Insulin resistance leads to impaired vasodilation, increased oxidative stress, and chronic inflammation by released high concentration of non-esterified fatty acids, vasoconstrictors, cellular adhesion molecules, and the other mediators.[50] While sarcopenia negatively affects insulin sensitivity and increases insulin resistance, this resistance aggravates to sarcopenia by increasing the loss of skeletal muscle.

Although overweight and obesity are more common in older diabetic individuals, higher BMI values are proportional to increased fat infiltration in the muscle tissue. As increased intramuscular fat infiltration is associated with oxidative activity and a reduction of maximum aerobic capacity, epidemiological studies have indicated muscle fat infiltration as a predictor of developing mobility limitations in older individuals.[51] Mogi et al.[52] demonstrated that diabetic mice had increased intramuscular fat deposition due to unusual cell differentiation.

Walking performance in older individuals provides information about the general health status and functional capacity and is helpful to predict disability, life expectancy, and other important health parameters.[53,54] A study by Volpato et al.,[55] although the calf circumference of diabetic elderly patients was wider than the non-diabetic individuals, the muscle strength, muscle quality, and gait speed values were lower. Our results indicating lower gait speed in the patients with poor blood glucose regulation also support this finding. Moreover, the muscle strength, gait speed, and muscle quality in diabetic and non-diabetic elderly patients were evaluated independently from motor neuropathy and peripheral arterial disease, suggesting a direct effect of diabetes on the muscle structure and performance.

Nonetheless, there are some limitations to this study. First, we were unable to evaluate the effect of different medications on sarcopenic obesity due to small sample size in each treatment group in which we allowed cross-over from one to another during follow-up. Second, we were unable to examine insulin resistance. Although we are aware of that there is a correspondent interaction between sarcopenia and insulin resistance, this relationship has been, so far, evaluated only in cross-sectional studies, but not in prospective studies. Our third limitation is that neurophysiological studies were unable to be conducted to evaluate the initial and post-treatment nerve conduction velocity.

In conclusion, our study is considerably significant, as it is the first study to evaluate the changes in the parameters of sarcopenia and the decline in the HbA1c levels during a six-month follow-up period in older patients with obesity, sarcopenia, and diabetes mellitus. Even in a six-month period, we observed significant increases in the muscle mass by regulating blood glucose. In addition, we found a negative correlation between the HbA1c levels and muscle mass. Based on our study results, we suggest that patients should be followed for longer periods of time to obtain more detailed information about the muscle quality and functionality in elderly.

Declaration of conflicting interests

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