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Assessment of muscle mass and bone density in elderly patients with type 2 diabetes mellitus depending on the level of glycated hemoglobin

© Svetlana V. Bulgakova, Ekaterina V. Treneva, Dmitrii P. Kurmaev, Nikolai A. Pervyshin, Olga V. Kosareva, Lyudmila A. Sharonova, Yuliya A. Dolgikh

Samara State Medical University (Samara, Russia)

Abstract

Aim – to assess the prevalence of low muscle mass and low bone density in elderly patients with type 2 diabetes (T2DM), depending on the level of glycated hemoglobin (HbA1c).

Material and methods. The study included 187 patients (mean age 65.16 ± 4.31 years), who were tested for fasting blood glucose, HbA1c, osteocalcin (OC), procollagen type 1 N-terminal propeptide (P1NP), C-terminal type I collagen telopeptides (B-CTX), 25-hydroxyvitamin D, body composition and bone mineral density.

Results. The prevalence of low muscle mass, osteopenia, and osteoporosis in elderly patients with T2DM was 35.8%, 38.5%, and 30.5%, respectively. The prevalence of low muscle mass was significantly higher in women with HbA1c >9.0% (p=0.035). Osteopenia and osteoporosis prevailed in men with HbA1c >9.0% (p=0.007 and p=0.048, respectively). The appendicular skeletal muscle index (ASMI), bone mineral content (BMC) and bone mineral density (BMD) of the lumbar spine, BMC and BMD of the thigh were significantly reduced in the osteoporosis and osteopenia groups (p<0.05); while B-CTX, P1NP were significantly increased. In men, both ASMI (p=0.007) and P1NP levels (p=0.001) were important risk factors for osteopenia/osteoporosis, and in women such risk factor was ASMI (p=0.019).

Conclusion. In T2DM patients, the high HbA1c levels were associated with higher rates of low muscle mass in women and osteoporosis in men, and ASMI was a risk factor for osteoporosis in both sexes.

Keywords: gerontology, ageing, sarcopenia, osteoporosis, type 2 diabetes mellitus, glycated hemoglobin, body composition, dual-energy X-ray absorptiometry, bioimpedance analysis, metabolism.

Conflict of interest: nothing to disclose.

Citation

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Information about authors

Svetlana V. Bulgakova – PhD, Associate professor, Head of the Department of endocrinology and geriatrics. ORCID: 0000-0003-0027-1786
E-mail: s.v.bulgakova@samsmu.ru
Ekaterina V. Treneva – PhD, Associate professor, Department of endocrinology and geriatrics. ORCID: 0000-0003-0097-7252 E-mail: eka1006@yandex.ru
Dmitrii P. Kurmaev – assistant of the Department of endocrinology and geriatrics. ORCID: 0000-0003-4114-5233 E-mail: geriatry@mail.ru
Nikolai A. Pervyshin – assistant of the Department of endocrinology and geriatrics. ORCID: 0000-0002-9609-2725 E-mail: depoanalgin@yandex.ru
Olga V. Kosareva – PhD, Associate professor, Department of endocrinology and geriatrics. ORCID: 0000-0002-5754-1057 E-mail: o.v.kosareva@samsmu.ru
Lyudmila A. Sharonova – PhD, Associate professor, Department of endocrinology and geriatrics. ORCID: 0000-0001-8827-4919 E-mail: l.a.sharonova@samsmu.ru
Yuliya A. Dolgikh – PhD, assistant of the Department of endocrinology and geriatrics. ORCID: 0000-0001-6678-6411 E-mail: yu.a.dolgikh@samsmu.ru

Corresponding Author
Svetlana V. Bulgakova
Address: Samara State Medical University,
89 Chapaevskaya st., Samara, Russia, 443099.
E-mail: s.v.bulgakova@samsmu.ru

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Оценка мышечной массы и костной плотности у пожилых пациентов с сахарным диабетом 2 типа в зависимости от уровня гликированного гемоглобина

© С.В. Булгакова, Е.В. Тренева, Д.П. Курмаев, Н.А. Первышин, О.В. Косарева, Л.А. Шаронова, Ю.А. Долгих

ФГБОУ ВО «Самарский государственный медицинский университет» Минздрава России (Самара, Россия)

Аннотация

Цель – провести оценку распространенности низких мышечной массы, костной плотности у пожилых пациентов с сахарным диабетом 2 типа в зависимости от уровня гликированного гемоглобина (HbA1c).

Материал и методы. В исследовании приняли участие 187 пациентов (средний возраст 65,16 ± 4,31 года). Были определены уровни глюкозы крови натощак, HbA1c, остеокальцина (ОС), пропептида проколлагена 1 типа (P1NP), С-концевых телопептидов коллагена I типа (B-CTX), 25-гидроксивитамина D, а также композиционный состав тела и минеральная плотность костной ткани.

Результаты. Распространенность низкой мышечной массы, остеопении и остеопороза у пожилых пациентов с СД2 составила 35,8%, 38,5% и 30,5% соответственно. Распространенность низкой мышечной массы была значительно выше у женщин с уровнем HbA1c > 9,0% (p = 0,035), остеопении и остеопороза – у мужчин с уровнем HbA1c > 9,0% (p = 0,007) и 18,9% против 3,4% (p = 0,048) соответственно. Аппендикулярная скелетно-мышечная масса (АСММ), содержание костных минералов (BMC) и минеральная плотность костной ткани (МПКТ) поясничного отдела позвоночника, BMC и МПКТ бедра были значительно снижены в группах остеопороза и остеопении (p < 0,05); а B-CTX, P1NP значимо увеличены. У мужчин ИАСММ (p = 0,007) и

уровень P1NP (p = 0,001) являются важными факторами риска остеопении / остеопороза, у женщин – ИАСММ (p = 0,019).
Заключение. У пациентов с СД2 высокие уровни HbA1c ассоциировались с более высокими показателями распространенности низкой мышечной массы у женщин и остеопороза у мужчин, а ИАСММ является фактором риска развития остеопороза у лиц обоих полов.
Ключевые слова: геронтология, старение, саркопения, остеопороз, сахарный диабет 2 типа, гликированный гемоглобин, композиционный состав тела, двухэнергетическая рентгеновская абсорбциометрия, биоимпедансный анализ, метаболизм.
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Сведения об авторах
Булгакова С.В. – д-р мед. наук, доцент, заведующая кафедрой эндокринологии и гериатрии. ORCID: 0000-0003-0027-1786 E-mail: s.v.bulgakova@samsmu.ru
Тренева Е.В. – канд. мед. наук, доцент кафедры эндокринологии и гериатрии. ORCID: 0000-0003-0097-7252 E-mail: eka1006@yandex.ru
Курмаев Д.П. – ассистент кафедры эндокринологии и гериатрии. ORCID: 0000-0003-4114-5233 E-mail: geriatry@mail.ru
Первышин Н.А. – ассистент кафедры эндокринологии и гериатрии. ORCID: 0000-0002-9609-2725 E-mail: depoanalgin@yandex.ru
Косарева О.В. – канд. мед. наук, доцент кафедры эндокринологии и гериатрии. ORCID: 0000-0002-5754-1057 E-mail: o.v.kosareva@samsmu.ru
Шаронова Л.А. – канд. мед. наук, доцент кафедры эндокринологии и гериатрии. ORCID: 0000-0001-8827-4919 E-mail: l.a.sharonova@samsmu.ru
Долгих Ю.А. – канд. мед. наук, ассистент кафедры эндокринологии и гериатрии. ORCID: 0000-0001-6678-6411 E-mail: yu.a.dolgikh@samsmu.ru

Автор для переписки
Булгакова Светлана Викторовна
Адрес: Самарский государственный медицинский университет, ул. Чапаевская, 89, г. Самара, Россия, 443099.
E-mail: s.v.bulgakova@samsmu.ru

СД – сахарный диабет; АСММ – аппендикулярная скелетно-мышечная масса; МПКТ – минеральная плотность костной ткани; BMC – содержание минералов в кости; САД – систолическое артериальное давление; ДАД – диастолическое артериальное давление; ЖМ – жировая масса; ИАСММ – индекс аппендикулярной скелетно-мышечной массы; ОШ – отношение шансов; ДИ – доверительный интервал.

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BACKGROUND

Globally, the proportion of older people with senility is increasing. Type 2 diabetes mellitus (T2DM) is an age-associated disease characterized by insulin resistance and impaired carbohydrate metabolism, which affects the development of complications and decreases the quality and expectancy of life [1–3]. According to Hak (2019), patients with T2DM are characterized by sarcopenia, a high risk of falls, and fractures, which lead to disability, dependence on outside care, and death [4]. Osteoporosis is also a common age-associated disease, and its incidence increases with age. The Rotterdam study examined data on bone mineral density (BMD) and fractures in 792 and 5863 patients with and without T2DM, respectively. The results showed that patients with T2DM have a higher BMD of the hip and lumbar spine; however, the risk of fractures is 1.33 times higher [5]. According to Goldstein et al. (2018), the incidence of fractures of the hip, vertebral body, and distal radius in patients with T2DM and osteoporosis was significantly higher than that in patients with osteoporosis but without T2DM [6]. Musculoskeletal pathologies deteriorate the quality of life of patients in older age groups [7]. Patients with low muscle mass are at a high risk of falls and fractures [8]. Sarcopenia is an important risk factor for mortality, disability, and poor quality of life in patients aged >60 years [9]. Skeletal muscles and bones are the two main components of the musculoskeletal system [10]. Musculoskeletal interactions are caused by physical activity, changes in the balance of agonists and antagonists during muscle contraction, influence of vibration load, and biochemical signals that maintain muscle tone and bone density [11, 12]. The relationship between low muscle mass and osteoporosis in patients with T2DM, particularly those with poor carbohydrate metabolism control, remains unclear. Glycated hemoglobin (HbA1c) is an important indicator of diabetes control; its levels indicate the average glycemia over approximately 3 months and are directly related to DM complications [1].

AIM

This study aimed to estimate the prevalence of low muscle mass and bone density in older patients with T2DM according to glycated hemoglobin levels.

MATERIAL AND METHODS

The study involved 187 older patients with T2DM, including 82 men (mean age 65.23 ± 4.34 years) and 105 women (mean age 65.08 ± 4.28 years). Patients with T2DM aged 60 years who provided written informed consent were included. Patients who had dysfunction of the thyroid gland and/or taking thyroid hormones or antithyroid drugs; had diseases and conditions causing secondary osteoporosis; had received bone-sparing therapy; were taking sex hormones and glucocorticoids; had cognitive impairment and dementia that ruled out the possibility of communication; and had acute cardiovascular pathology and cancer were excluded.

Complaints and medical history were collected from all patients, and anthropometric parameters (height and weight) and blood pressure (BP; systolic BP and diastolic BP) were measured using standard methods. Dual-energy X-ray absorptiometry (DXA) on a Norland XR-46 was used to assess the bone mineral density (BMD) and bone mineral content (BMC, g) of the femur (femoral neck and total hip) and lumbar vertebral bodies L1–4. Normal bone mass was defined as a T-score of >–1.0 SD, osteopenia was defined as –1.0 SD > T-score > –2.49 SD, and osteoporosis was defined as a T-score of ≤–2.5 SD. Body composition was studied using

Indicator	Men (n=82)	Women (n=105)	P
Age (M ± SD), years	65,23 ± 4,34	65,08 ± 4,28	0,372
Duration of diabetes mellitus (Me [LQ; HQ]), years	13,0 [8,0; 19,0]	12,0 [6,0; 20,0]	0,521
Height (M ± SD), cm	178,0 ± 6,1	164,5 ± 5,2	**< 0,001**
Weight (M ± SD), kg	80,4 ± 10,9	68,0 ± 9,6	**< 0,001**
BMI (M ± SD), kg/m^2	24,97 ± 3,99	25,61 ± 3,62	0,259
SBP (M ± SD), mm Hg	136,2 ± 20,4	142,0 ± 21,9	0,068
DBP (M ± SD), mm Hg	77,3 ± 15,5	78,1 ± 10,3	0,695
Fasting glycemia (Me [LQ; HQ]), mmol/l	7,64 [6,16; 9,67]	7,68 [5,98; 10,10]	0,745
HbA1c (Me [LQ; HQ]), %	8,00 [6,70; 9,48]	8,60 [7,40; 9,50]	0,198
Serum creatinine (M ± SD), μmol/L	66,59 ± 13,02	55,57 ± 14,86	**< 0,001**
B-CTX (Me [LQ; HQ]), ng/mL	0,22 [0,16; 0,31]	0,28 [0,21; 0,40]	**0,015**
(Me [LQ; HQ]), ng/mL	9,0 [7,5; 11,5]	12,0 [9,0; 17,0]	**0,002**
P1NP (Me [LQ; HQ]), ng/mL	30,0 [24,0; 38,5]	38,0 [29,0; 58,5]	**0,003**
25-OH-D (M ± SD), ng/mL	22,62 ± 8,42	20,39 ± 7,67	0,064
Proportion of fat mass (M ± SD), %	27,20 ± 7,82	34,90 ± 5,24	**0,001**
ASMI (M ± SD), kg/m^2	7,03 ± 0,97	5,98 ± 0,76	**< 0,001**
BMC of the femur (M ± SD), g	36,63 ± 6,45	25,78 ± 7,03	**< 0,001**
BMC of the lumbar spine (M ± SD), g	71,10 ± 14,02	50,00 ± 11,23	**< 0,001**
BMD of the lumbar spine (M ± SD), g/cm^2	1,01 ± 0,17	0,86 ± 0,15	**0,002**
BMD of the femur (M ± SD), g/cm^2	0,90 ± 0,12	0,80 ± 0,12	**0,003**

Table 1. *The clinical data on patients with T2DM*
Таблица 1. *Клиническая характеристика больных СД2*

bioimpedance analysis with an ABC-02 apparatus (Medass, Russia). The proportion of fat mass (% FM) and appendicular skeletal muscle mass index (ASMI) were determined. The diagnostic criterion for low muscle mass was a decrease in ASMI of <7.0 kg/m2 in men and <5.5 kg/m2 in women [12]. Fasting blood glucose, HbA1c, and serum creatinine levels of all study participants were measured using a Beckman CX4CE automated analyzer. C-terminal type I collagen telopeptides (B-CTX), osteocalcin (OC), propeptide of type 1 procollagen (P1NP), and 25-hydroxyvitamin D (25-OH-D) levels were measured on a Roche-601 immunoluminescent analyzer using electrochemiluminescence.

Statistical analysis was performed using IBM SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as the mean and standard deviation (M ± SD). Variables that were not normally distributed were expressed as medians and quartiles (Me [LQ; HQ]). Univariate analysis of variance was used to compare normally distributed variables between the groups. The Kruskal–Wallis test was used for comparison if the data were not normally distributed. Categorical variables were presented as percentages and were analyzed using the chi-square test ($\chi 2$). Multivariate logistic regression analysis was performed to evaluate the factors associated with osteopenia/osteoporosis with stepwise inclusion of significant covariates. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using a logistic regression model. A p-value of < 0.05 was considered statistically significant.

RESULTS

The clinical characteristics of the participants are presented in **Table 1**. The average duration of T2DM in patients included in the study was 12.84 ± 7.83 years. HbA1c levels ranged from 4.7% to 15.6% (mean 8.56% ± 1.98%). Compared with men, women had significantly lower height and weight ($p < 0.001$) and higher serum levels of B-CTX ($p = 0.015$), OC ($p = 0.002$), and P1NP ($p = 0.003$). Women had a higher proportion of FM ($p = 0.001$) and lower ASMI ($p < 0.001$) than men. In addition, the BMC and BMD of the lumbar spine and femur were significantly lower in women ($p < 0.005$) than in men.

Moreover, 67 (35.8%) participants had low muscle mass, 72 (38.5%) had osteopenia, and 57 (30.5%) had osteoporosis. The prevalence of low muscle mass was significantly higher in women with HbA1c levels of >9.0% than in women with HbA1c levels <9.0% (35.0% vs. 16.9%, $p = 0.035$). The prevalence rates

	HbA1c	Normal muscle mass n (%)	Low muscle mass n (%)	P_1	Normal BMD n (%)	Osteopenia n (%)	Osteoporosis n (%)	P_2 P_3
Men	<9,0% (n = 53)	27 (50,9)	26 (49,1)	0,596	27 (50,9)	16 (30,1)	10 (18,9)	P_2 < 0,001 P_3 = 0,048
	≥ 9,0% (n = 29)	13 (44,8)	16 (55,2)		8 (27,6)	20 (69,0)	1 (3,4)	
	Итого (n = 82)	40 (48,8)	42 (51,2)		35 (42,7)	36 (43,9)	11 (13,4)	
Women	<9,0% (n = 65)	54 (83,1)	11 (16,9)	**0,035**	18 (27,7)	23 (35,4)	24 (36,9)	P_2 =0,762 P_3 = 0,007
	≥ 9,0% (n = 40)	26 (65,0)	14 (35,0)		5 (12,5)	13 (32,5)	22 (55,0)	
	Итого (n = 105)	80 (76,2)	25 (23,8)		23 (21,9)	36 (34,3)	46 (43,8)	

Note. P_1, significance of differences in the incidence of low muscle mass between groups for HbA1c of <9.0% and HbA1c of ≥9.0%; P_2, significance of differences in the incidence of osteopenia between groups for HbA1c of <9.0% and HbA1c of ≥9.0%; P_3, significance of differences in the incidence of osteoporosis between groups for HbA1c of <9.0% and HbA1c of ≥9.0%.

Table 2. *The prevalence of low muscle mass, osteopenia, osteoporosis in patients with T2DM, stratified by sex and HbA1c level*
Таблица 2. *Распространенность низкой мышечной массы, остеопении, остеопороза у больных СД2, стратифицированная по полу, уровню HbA1c*

of osteopenia and osteoporosis differed significantly between men with HbA1c levels <9.0% and men with HbA1c levels of >9.0% (30.1% vs. 69.0% (p = 0.007) and 18.9% vs. 3.4% ($p = 0.048$)), respectively (**Table 2**).

According to the T-score value measured by DXA, patients with T2DM were divided into three groups (with normal BMD, osteopenia, and osteoporosis). Height and weight were significantly reduced ($p = 0.007$; $p < 0.001$ and $p = 0.005$; $p < 0.001$, respectively), and serum B-CTX and P1NP levels were increased in the osteoporosis and osteopenia groups compared with the normal BMD group ($p < 0.05$). The ASMI, BMC, and BMD of the lumbar spine, as well as the BMC and BMD of the hip, were significantly reduced in the osteoporosis and osteopenia groups ($p < 0.005$). Moreover, the BMC and BMD of the lumbar spine and hip were significantly lower in the osteoporosis group than in the osteopenia group. Compared with the normal BMD group, the osteoporosis group had higher serum OC levels ($p = 0.016$) (**Table 3**).

Indicator	Normal BMD (n = 58)	Osteopenia (n = 71)	Osteoporosis (n = 58)	P
Age (M ± SD), years	63,18 ± 7,71	65,14 ± 9,59	65,29 ± 8,66	P_1=0,210 P_2=0,168 P_3=0,926
Duration of diabetes [Me (LQ; HQ]), years	13,00 [7,75; 18,00]	12,00 [6,00; 20,00]	12,00 [7,50; 19,00]	P_1=0,860 P_2=0,772 P_3=0,963
Height (M ± SD), cm	174,05 ± 7,90	170,24 ± 7,86	165,60 ± 7,24	P_1=0,007 P_2<0,001 P_3=0,007
Weight (M ± SD), kg	81,64 ± 12,02	74,92 ± 9,44	70,77 ± 8,85	P_1=0,005 P_2<0,001 P_3=0,018
BMI (M ± SD), kg/m^2	26,33 ± 4,54	24,92 ± 3,03	24,63 ± 3,78	P_1=0,037 P_2=0,030 P_3=0,629
HbA1c (Me [LQ; HQ]), %	7,85 [7,18; 8,90]	8,70 [7,10; 10,20]	8,60 [7,20; 9,65]	P_1=0,122 P_2=0,098 P_3=0,103
Creatinine (M ± SD), μmol/L	56,01 ± 15,43	61,92 ± 14,34	64,56 ± 14,81	P_1=0,026 P_2=0,029 P_3=0,307
B-CTX (Me [LQ; HQ]), ng/mL	0,20 [0,15; 0,29]	0,25 [0,21; 0,34]	0,32 [0,21; 0,44]	P_1=0,011 P_2=0,006 P_3=0,029
(Me [LQ; HQ]), ng/mL	9,00 [7,00; 13,00]	11,00 [9,00; 13,00]	12,00 [9,00; 17,00]	P_1=0,058 P_2=0,016 P_3=0,129
P1NP (Me [LQ; HQ]), ng/mL	27,50 [22,75; 38,25]	34,00 [27,00; 46,50]	39,00 [32,00; 60,25]	P_1=0,014 P_2=0,005 P_3=0,019
25-OH-D (M ± SD), ng/mL	21,66 ± 6,89	22,23 ± 8,94	19,97 ± 7,93	P_1=0,691 P_2=0,223 P_3=0,135
Proportion of fat mass (M ± SD), %	31,64 ± 9,26	30,48 ± 6,75	32,67 ± 6,35	P_1=0,412 P_2=0,486 P_3=0,062
ASMI (M ± SD), kg/m^2	6,91 ± 1,16	6,35 ± 0,85	6,07 ± 0,84	P_1=0,002 P_2 < 0,001 P_3=0,065
BMC of the lumbar spine (M ± SD), g	72,67 ± 15,43	59,22 ± 11,99	45,88 ± 9,44	P_1<0,001 P_2<0,001 P_3<0,001
BMC of the femur (M ± SD), g	38,10 ± 7,60	29,12 ± 7,24	24,70 ± 5,18	P_1<0,001 P_2<0,001 P_3=0,002
BMD of the lumbar spine (M ± SD), g/cm^2	1,08 ± 0,12	0,92 ± 0,14	0,77 ± 0,09	P_1<0,001 P_2<0,001 P_3<0,001
BMD of the femur (M ± SD), g/cm^2	0,97 ± 0,09	0,82 ± 0,08	0,74 ± 0,10	P_1<0,001 P_2<0,001 P_3<0,001

Note. P_1, comparison of the osteopenia group with normal BMD; P_2, comparison of the osteoporosis group with normal BMD; P_3, comparison of the osteoporosis and osteopenia groups.

***Table 3.** A comparison of anthropometric data, markers of bone metabolism and body composition in patients with T2DM with osteopenia, osteoporosis, normal BMD*

***Таблица 3.** Сравнение антропометрических показателей, маркеров костного метаболизма, состава тела у больных СД2 с остеопенией, остеопорозом, нормальной МПКТ*

The multivariate logistic regression analysis of osteopenia/osteoporosis in patients with T2DM is presented in **Table 4**. The adjusted factors included age, height, weight, fasting blood glucose, HbA1c, fat mass proportion, ASMI, B-CTX, OC, P1NP, and 25-OH-D. In male patients, the ASMI ($p = 0.007$) and P1NP levels ($p = 0.001$) were important risk factors for osteopenia/osteoporosis, whereas in women, ASMI was a significant risk factor ($p = 0.019$).

DISCUSSION

The results of this study showed that in patients with T2DM, the incidence rates of low muscle mass, osteopenia, and osteoporosis were 35.8%, 38.5%, and 30.5%, respectively. In men with T2DM and HbA1c levels of >9.0%, osteopenia ($p = 0.007$) and osteoporosis ($p = 0.048$) were more common than in men with T2DM and HbA1c levels <9.0%. The rates of low muscle mass in women with T2DM and HbA1c levels of >9.0% were higher ($p = 0.035$) than those in women with T2DM and HbA1c levels <9.0%. Compared with patients with T2DM who had normal BMD, the ASMI was significantly reduced in patients with T2DM having osteopenia and osteoporosis ($p < 0.005$). The serum levels of B-CTX, OC, and P1NP were significantly higher in patients with T2DM and osteoporosis ($p < 0.05$), whereas the serum levels of B-CTX and P1NP were significantly higher in patients with osteopenia ($p < 0.05$). Multivariate logistic regression analysis showed that the ASMI is a risk factor for the development of osteoporosis/osteopenia in men and women with T2DM.

Both T2DM and osteoporosis are metabolic diseases with a complex relationship. In a meta-analysis, Si et al. (2019) showed that the rates of osteoporosis in patients with T2DM were 44.8% in women and 37.0% in men [13]. According to the literature, in patients with T2DM, changes in BMD are contradictory (normal, decreased, and increased values of bone density), which does not have a clear explanation [14, 15]. Moreover, the risk of fractures is higher in patients with T2DM than in those without T2DM. According to Wang

Gender	Adjusted factors	Osteopenia or osteoporosis		
		OR (odds ratio)	(95% CI)	p
Men	ASMI	0,422	(0,226–0,787)	**0,007**
	Age	1,013	(0,952–1,078)	0,675
	HbA1c	1,279	(0,946–1,728)	0,110
	P1NP	1,127	(1,055–1,202)	**0,001**
Women	ASMI	0,441	(0,223–0,872)	**0,019**
	Age	1,053	(0,988–1,121)	0,112
	HbA1c	1,192	(0,904–1,570)	0,213
	P1NP	1,009	(0,986–1,033)	0,447

Таблица 4. *Многофакторный логистический регрессионный анализ остеопении / остеопороза у пациентов с СД2*

Table 4. *A multivariate logistic regression analysis of osteopenia / osteoporosis in patients with T2DM*

et al. (2019), the relative risk of hip fracture, vertebral body fracture, and all fractures in patients with T2DM is increased by 1.27, 1.74, and 1.22 times, respectively [16].

Impairment of microarchitectonics decreases bone tissue strength and increases the risk of fractures in patients with T2DM. Nilsson et al. (2017) assessed the bone microstructure using high-resolution peripheral quantitative computed tomography, and the bone material strength index (BMSI) was calculated using a bone indentation probe. They found that porosity and low BMSI in the radial cortex bones were typical for female patients with T2DM [17]. Our study showed that men with HbA1c levels of >9.0% had a significantly higher prevalence of osteopenia ($p = 0.0007$) and osteoporosis ($p = 0.05$) than those with HbA1c levels <9.0%. According to Majima et al. (2005), the mean HbA1c level negatively correlated with the BMD of the distal radius in both sexes and the femoral neck in women [18]. A negative correlation between HbA1c levels and calcaneal BMD was also noted in Chinese postmenopausal women [19]. Thus, the prevalence of osteoporosis increases with high blood glucose levels.

However, some studies have reported contradictory results. According to Oei et al. (2013), patients with T2DM and an HbA1c level of >7.5% had higher BMD and BMI than participants without T2DM [20]. Patients with T2DM tend to be heavier than those without T2DM, which may lead to the overestimation of BMD values. In our study, participants with osteopenia and osteoporosis had significantly lower weights than those with normal BMD, which explains why our results are inconsistent with those of the Rotterdam study. Poor glycemic control increases the risk of fractures in patients with T2DM. Thus, in a cohort study by Li et al. (2015), among patients with T2DM, the risk levels of hip fractures in patients with HbA1c of 9%–10% and >10% were significantly higher than those in patients with HbA1c of 6%–7% [21].

Markers of bone metabolism indicate resorption and bone formation and are important for the selection and monitoring of anti-osteoporotic therapy. P1NP is a marker of bone formation, whereas B-CTX is a marker of bone resorption. OC represents the levels of bone metabolism (both bone formation and resorption). We revealed that those with T2DM and osteoporosis had higher levels of B-CTX, P1NP, and OC than patients without T2DM without osteoporosis. According to Klimontov et al. (2016), a high level of bone metabolism in patients with T2DM and osteoporosis indicates a decrease in bone mass and an increased risk of fractures [22]. A cross-sectional study including 1499 participants showed that serum levels of bone metabolism markers negatively correlated with the BMD in patients with T2DM [23].

Hyperglycemia, microvascular complications, and glucose-lowering therapy affect the bone tissue in patients with T2DM. The accumulation of advanced glycation end products (AGEs) in the bones causes nonenzymatic cross-linking of type 1 collagen, which affects the strength properties of bone tissue. Type 1 collagen modified by AGEs inhibits osteoblast differentiation and activity. AGEs also increase the expression of the receptor-activating transcription factor kappa-B ligand by activating nuclear transcription factor-κB (NF-κB) and stimulating the production of interleukin-6 (IL-6), which increases osteoclast activity [24].

The European Working Group on Sarcopenia Consensus Revision 2 (EWGSOP2) defined three stages of sarcopenia: probable sarcopenia (low muscle strength), confirmed sarcopenia (low muscle strength and mass), and severe sarcopenia (low muscle mass, low muscle strength, and low physical performance). Based on the threshold values defined by EWGSOP2, low muscle mass is diagnosed as ASMI <7.0 kg/m2 in men and <5.5 kg/m2 in women [12]. Low muscle mass is typical in patients with T2DM. In our study, patients with T2DM had poor glycemic control (mean HbA1c 8.56% ± 1.98%) and a longer DM duration (mean 12.84 ± 7.83 years), with a prevalence of low muscle mass of 35.8%.

Sugimoto et al. (2019) revealed a negative association between low muscle mass and both T2DM duration and high HbA1c levels [25]. The incidence of low muscle mass in female patients with T2DM who had an HbA1c level of >9.0% was significantly higher ($p = 0.035$) than that in patients with an HbA1c level <9.0%. A longitudinal cohort study performed in Baltimore revealed that high HbA1c levels may predict decreased muscle mass and strength [26].

The main risk factors for a decrease in muscle mass due to decompensation of carbohydrate metabolism (high blood glucose or HbA1c) in patients with T2DM

are insulin resistance and AGEs. Insulin resistance is a key link in the pathogenesis of T2DM [1]. Various inflammatory markers, including IL-6, tumor necrosis factor alpha, and C-reactive protein, correlate with insulin resistance. Muscle protein metabolism includes its synthesis and breakdown. Muscle protein breakdown is regulated by inflammatory signaling through four major proteolytic pathways: the ATP-dependent ubiquitin-proteasome pathway, calpains, macrophage autophagy, and cell apoptosis [27]. AGEs, which are formed by the nonenzymatic binding of glucose, proteins, and lipids, cause oxidative stress and chronic inflammation, leading to tissue damage.

Skin autofluorescence (AF) is a marker of AGE accumulation in the skin. In a cross-sectional study, Mori et al. (2019) showed that AF in patients with T2DM negatively correlated with muscle mass and strength [28]. In addition, diabetic microangiopathy, peripheral neuropathy, and protein, testosterone, and vitamin D deficiencies are involved in the reduction of muscle mass in patients with T2DM [29]. Decompensation of carbohydrate metabolism (high HbA1c levels) contributes to the development of DM complications. Therefore, patients with T2DM are at increased risk of muscle loss.

The skeletal muscles and bones are anatomically interdependent and interact mechanically and physically [10, 11]. In addition, they can secrete cytokines such as ILs, prostaglandin (PGE), OC, osteoprotegerin, and NF-κB receptor activator. PGE2 and OC secreted by bone cells can promote the development of muscle mass; however, adult skeletal muscles express myostatin, which has a regulatory effect on bone density. Thus, in myostatin-deficient mice, the cortical mineral density in the distal femur increased. In addition, decreased muscle mass increases insulin resistance and contributes to T2DM development, thereby affecting bone mass and structure [30].

Low muscle mass is a risk factor for osteoporosis. In this study, the ASMI was significantly reduced in patients with T2DM and osteopenia ($p = 0.002$) and osteoporosis ($p < 0.001$) compared with patients with T2DM and normal BMD. Logistic regression analysis showed that the ASMI was a risk factor for the development of osteopenia and osteoporosis in both men ($p = 0.007$) and women ($p = 0.019$). According to the 2009–2011 Korean National Health and Nutrition Examination Survey, low muscle mass in men and women is associated with osteoporosis, particularly of the femoral neck [31]. A cross-sectional study conducted in Finland demonstrated that the ASMI and femoral neck BMD decreased linearly with a decline in menstrual function. Thus, the ASMI decreased significantly in women in late perimenopause, and the BMD decreased in postmenopausal women. Moreover, a decrease in muscle mass precedes a decrease in bone mass [32]. However, patients with osteoporosis are at risk of decreased muscle strength [33].

Thus, the pathogenesis of low muscle mass and osteoporosis are interrelated and often create a vicious circle. This process in patients with T2DM may be exacerbated by insulin resistance and chronic inflammation; low muscle mass increases the risk of osteoporosis and fractures in patients with T2DM. However, due to conflicting results, further research is required to confirm the association between low muscle mass and osteoporosis in patients with T2DM, particularly in patients with poor blood glucose control.

CONCLUSION

1. The rates of low muscle mass, osteopenia, and osteoporosis in older patients with T2DM are 35.8%, 38.5%, and 30.5%, respectively.
2. The prevalence of low muscle mass was significantly higher in women with HbA1c of >9.0% than in women with HbA1c <9.0% (35.0% vs. 16.9%, $p = 0.035$).
3. The rates of osteopenia and osteoporosis are significantly higher in men with HbA1c < .0% than in men with HbA1c of >9.0% (30.1% vs. 69.0% ($p = 0.007$) and 18.9% vs. 3.4% ($p = 0.048$)), respectively.
4. In patients with T2DM and osteoporosis, the levels of B-CTX, P1NP, and OC are significantly increased, whereas in patients with osteopenia and T2DM, B-CTX and P1NP levels are increased, which indicates a high level of bone metabolism.
5. The ASMI, BMC, and BMD of the lumbar spine, as well as the BMC and BMD of the femur, were significantly reduced in the osteoporosis and osteopenia groups ($p < 0.05$).
6. In men, the ASMI ($p = 0.007$) and P1NP level ($p = 0.001$) are significant risk factors for osteopenia/osteoporosis, whereas the ASMI is a risk factor in women ($p = 0.019$).

***Conflict of** interest. The authors declare no conflict of interest.*

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