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The Effect of Novel Antihyperglycemic Treatments on Sarcopenia in Type 2 Diabetic Patients

Busra CAN[1] ✉, Zehra KAYA[2], Bulent CAN[3]

[1]Marmara University, Faculty of Medicine, Department of Internal Medicine, Division of Geriatrics, Istanbul, Türkiye
[2]Istanbul Medeniyet University, Faculty of Medicine, Department of Family Medicine, Istanbul, Türkiye
[3]Istanbul Medeniyet University, Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology and Metabolism, Istanbul, Türkiye

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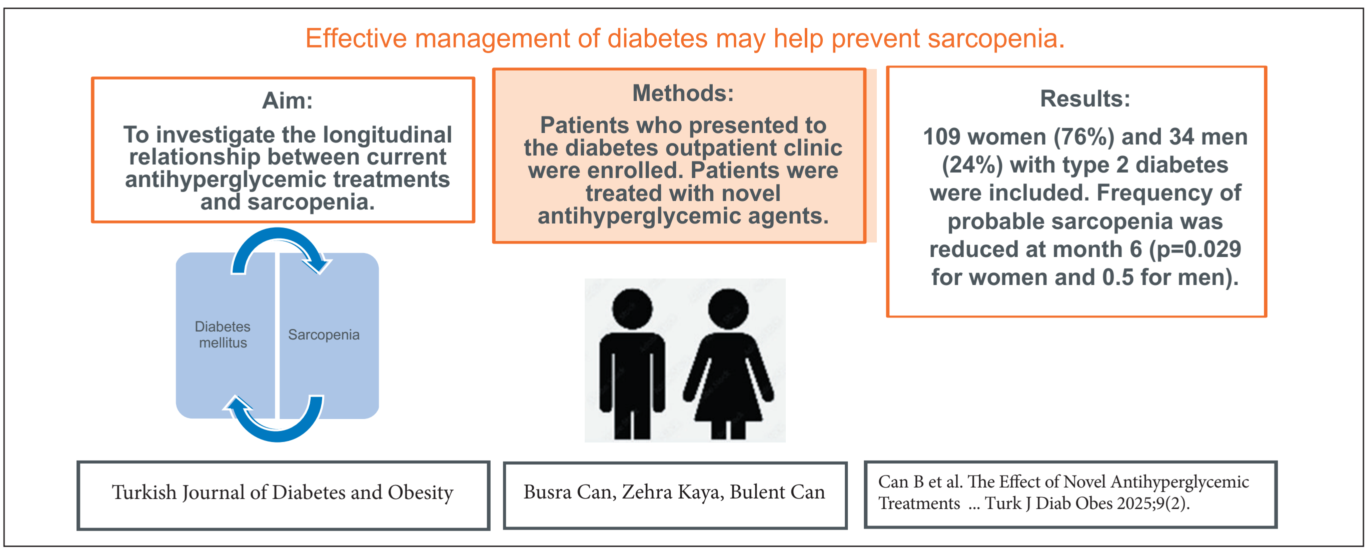
GRAPHICAL ABSTRACT



ABSTRACT

Aim: Previous studies indicate a possible association between weight losing interventions and reduced muscle function. There is scarce research on how novel glucose-lowering agents effect sarcopenia parameters. The present study aims to investigate the longitudinal relationship between current antihyperglycemic treatments and sarcopenia.

Material and Methods: Type 2 diabetic patients aged 18 and above were enrolled in this longitudinal observational study. Patient characteristics, list of medications, hours of physical activity per week, laboratory values, anthropometric measurements, handgrip strength and body composition analyzed with bioelectrical impedance analysis were recorded at the initial presentation and at 6 months.

Results: A total of 109 women (76%) and 34 men (24%) with type 2 diabetes mellitus (DM) were included. The mean age of study participants was 53.4±10.4 years, and the mean duration of DM was 10.2±8 years. At 6 months, weight, total fat mass, visceral fat mass, waist circumference, HbA1c, fasting glucose, serum insulin, LDL (low density lipoprotein) and vitamin B12 levels were significantly lower while muscle strength was significantly higher (p=0.012). There was a significant inverse association between age and muscle strength both initially and at 6 months (p=0.001 and 0.001 for women; p=0.005 and 0.001 for men, respectively). Duration of DM was inversely associated with muscle strength only for women (p=0.02 at initial presentation and p=0.001 at month 6). Frequency of probable sarcopenia was reduced at month 6 for both genders (p=0.029 for women and 0.5 for men).

ORCID: Busra Can / 0000-0002-7170-8044, Zehra Kaya / 0009-0003-9761-9060, Bulent Can / 0000-0001-6382-1306

Correspondence Address / Yazışma Adresi:
Busra CAN
Department of Internal Medicine, Division of Geriatrics, Faculty of Medicine, Marmara University, Istanbul, Türkiye
Phone: +90 (216) 625 45 45/9128 • E-mail: alpabusra@hotmail.com

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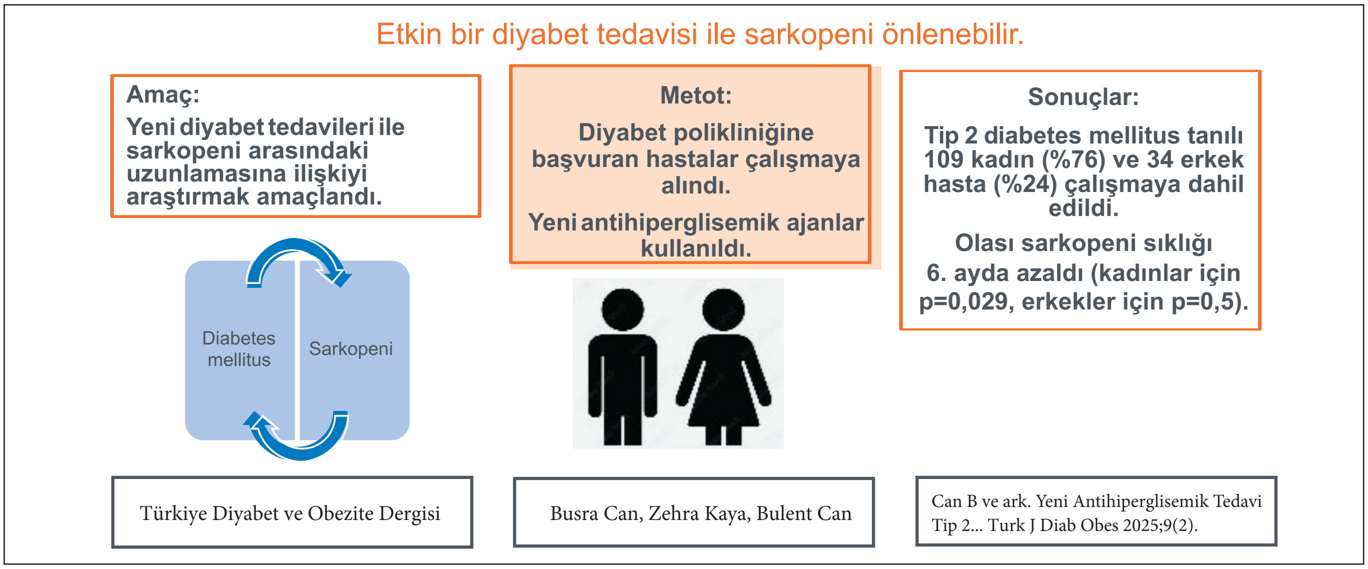
Conclusion: Glycemic control has a favorable effect on muscle function despite weight loss. Effective management of DM with novel antihyperglycemic agents may help prevent sarcopenia.

Keywords: *Antidiabetics, Diabetes mellitus, GLP-1 Receptor agonists, Muscle strength, Sarcopenia, SGLT-2 inhibitors*

Yeni Antihiperglisemik Tedavilerin Tip 2 Diyabetik Hastalarda Sarkopeni Üzerine Etkisi

GRAFİKSEL ÖZET



ÖZ

Amaç: Sarkopeni parametrelerinin glisemik kontrol ile ilişkisini inceleyen çok az sayıda araştırma bulunmaktadır. Bu çalışma, yeni diyabet tedavileri ile sarkopeni arasındaki uzunlamasına ilişkiyi araştırmayı amaçlamaktadır.

Gereç ve Yöntemler: Tip 2 diyabetik 18 yaş ve üzeri hastalar bu çalışmaya dahil edildi. Hastaların demografik özellikleri, kullandıkları ilaçlar, haftalık fiziksel aktivite saati, laboratuvar değerleri, antropometrik ölçümleri, el kavrama kuvveti ve biyoelektrik empedans analizi ile analiz edilen vücut kompozisyonu başvuruda ve altıncı ayda kaydedildi.

Bulgular: Tip 2 diabetes mellitus tanılı toplam 109 kadın (%76) ve 34 erkek (%24) dahil edildi. Çalışmaya katılanların ortalama yaşı 53,4±10,4 yıl ve ortalama diyabet süresi 10,2±8 yıldı. 6. ayda, kilo, toplam yağ kütlesi, viseral yağ kütlesi, bel çevresi, HbA1c, açlık glikozu, serum insülin, LDL (düşük yoğunluklu lipoprotein) ve B12 vitamini düzeyleri azalırken kas gücü anlamlı düzeyde arttı (p=0,012). Yaş ve kas gücü arasında hem başlangıçta hem de 6. ayda önemli bir ters ilişki vardı (kadınlar için p=0,001 ve 0,001; erkekler için sırasıyla p=0,005 ve 0,001). Diyabet süresi yalnızca kadınlarda kas gücüyle ters ilişkiliydi (ilk başvuruda p=0,02 ve 6. ayda p=0,001). Olası sarkopeni sıklığı her iki cinsiyet için de 6. ayda azaldı (kadınlar için p=0,029 ve erkekler için 0,5).

Sonuç: Glisemik kontrolün kas fonksiyonu üzerinde olumlu bir etkisi vardır. Kilo verdirici özelliği olan yeni antidiyabetik tedaviler sarkopeniyi önlemektedir.

Anahtar Sözcükler: *Antidiyabetikler, Diabetes mellitus, GLP-1 Reseptör agonistleri, Kas kuvveti, Sarkopeni, SGLT-2 inhibitörleri*

INTRODUCTION

The European Working Group on Sarcopenia in Older People (EWGSOP) defines sarcopenia as a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength (1). Sarcopenia has numerous negative outcomes including impaired functionality, increased risk for falls, fractures, and mortality (1). Sarcopenia may be primary (age related) or secondary, a result of comorbid conditions. Insulin resistance and diabetes mellitus (DM) is an important cause of secondary sarcopenia. Loss of muscle quality due to increased intramuscular fat, dysfunction in the neuromuscular junction and reduced innervation are pathogenetic mechanisms linking DM to sarcopenia (2).

Diabetes mellitus represents a major public health problem worldwide, with an ever-increasing prevalence and incidence (3). Due to the global surge of DM, the burden of secondary sarcopenia is expected to continue rising. Although associated with an increased risk of adverse outcomes and mortality, there are no pharmacological agents approved for the treatment of sarcopenia; current evidence only recommends nutritional support and resistance training (4). It is against this background that glucose-lowering therapies are being investigated for added clinical benefit of improved muscle function (5).

Previous studies on the association between DM and sarcopenia are mostly observational (6-8). A very recent randomized placebo-controlled trial enrolled 72 participants to investigate the efficacy of metformin on physical performance (MET-PREVENT) and showed that metformin was ineffective (9). However, physical performance is the last parameter to change in the sarcopenia algorithm and the study was confined to older adults with prefrailty or frailty. There is scarce research on whether the primary parameters of sarcopenia improve with novel glucose-lowering interventions. The present study aims to investigate the longitudinal relationship between DM treatment and sarcopenia using the revised EWGSOP consensus.

MATERIAL and METHODS

Patients aged 18 and above who presented to the diabetes outpatient clinic of a university hospital between 01.07.2021 and 01.09.2021 were enrolled for this observational longitudinal study. The study was conducted at an obesity center that adheres to international standards and has been accredited by the European Association for the Study of Obesity (EASO). The ethical review board of the university hospital approved the study protocol (approval number: 2021/0314). The study was conducted in accordance with the Declaration of Helsinki.

All patients provided written informed consent to participate. Patients who refused to participate; patients with hepatic/renal impairment, neuromuscular disease, thyroid disease and patients with pacemaker implantation were excluded. DM was defined as a fasting plasma glucose ≥126 mg/dl, or a post prandial or random plasma glucose ≥200 mg/dl with symptoms of DM, or HbA1c level ≥ %6.5. Urine albumin excretion between 30 and 300 mg/day was defined as moderately increased albuminuria (microalbuminuria).

Height was measured without shoes using a standard stadiometer (m), and weight (kg) was measured using an electronic scale to the nearest 0.1 kg with the patient wearing light clothes. Body mass index (BMI) was calculated as weight (kg)/height squared (m^2). Calf circumference (CC) was measured at the widest part of the calf using a non-stretching tape with the participant in a standing position. CC was evaluated using the national cut-off value (33 cm) (10). Waist circumference was measured using a flexible non-stretching tape at the minimal waist.

Handgrip strength was measured with Jamar® 5030J1 Hydraulic Hand Dynamometer (China). Three measurements were taken in which the individual was seated with the shoulder in adduction, the elbow at 90° flexion and the forearm in the neutral position, and was asked to hold the dynamometer with the dominant hand and squeeze as firmly as possible. Cut-off values defined by the revised EWGSOP consensus were used for handgrip measurements (<16 kg in females, <27 kg in males).

Muscle mass was measured using a bioelectrical impedance analysis (BIA). The BIA used for this study was Tanita® BC-601 Segmental Body Composition Analyzer. The skeletal muscle index (SMMI) was calculated as skeletal muscle mass (kg)/height squared (m^2). Based on the national cut-off values, an SMMI of <7.4 kg/m^2 for females and <9.2 kg/m^2 for males was considered significant for sarcopenia (10). A 4-meter walking test was performed for the physical performance evaluation. In the 4-meter walking test, a walking speed of ≤0.8 m/s was considered poor physical performance.

Low muscle strength indicated probable sarcopenia, while low muscle strength accompanied by low muscle mass indicated confirmed sarcopenia. Severe sarcopenia was defined as the combination of low muscle strength, low muscle mass and reduced physical performance.

Patient characteristics, list of medications, hours of physical activity per week, laboratory values, anthropometric measurements, handgrip strength and body composition analyzed with BIA were recorded at initial presentation. The blood samples were collected after a 12-hour fast, also at baseline. All measurements were repeated after 6 months, as weight losing treatments are most effective during the first 6 months after initiation.

Statistical Analysis

Normality of the variables was investigated using visual (histograms and probability plots) and Kolmogorov-Smirnov tests. Numerical variables were given as mean ± standard deviation (SD) for normally distributed variables and as median (minimum-maximum) for continuous variables. Paired sample t test was used to compare normally distributed variables while Wilcoxon test was used for non-normally distributed variables.

Chi-square test was run to compare categorical variables. McNemar test was used to compare categorical variables before and after follow-up. Inter-variable associations were evaluated using Spearman Rho Correlation Analysis. Groups were compared with independent sample T-test or Mann Whitney U test as appropriate. A *p*-value of less than 0.05 was considered significant. SPSS (SPSS Inc, Chicago, Ill, USA) for Windows 21.0 program was used for the analysis.

RESULTS

Enrolled in the study were 109 women (76%) and 34 men (24%) with type 2 DM. The mean age of study participants was 53.4±10.4 years, and the mean duration of DM was 10.2±8 years. Almost all patients were on metformin. A total of 90 patients (63%) were on Sodium Glucose Cotransporter-2 (SGLT-2) inhibitors and treatment was initiated to another 17 during follow up. Sixty-five patients (46%) were on Glucagon-Like Peptide-1 (GLP-1) receptor agonist therapy. GLP-1 receptor agonists were discontinued in 4 and initiated for 18 patients during follow up. Demographic characteristics are presented in Table 1.

Table 2 shows the change in baseline clinical and laboratory parameters. At 6 months, weight, BMI, total fat mass, visceral fat mass, waist circumference, HbA1c, fasting glucose, serum insulin, LDL (low density lipoprotein) and vitamin B12 levels were significantly lower while muscle strength was significantly higher (p=0.012) compared to the baseline measurements. Level of physical activity and gait speed did not show a significant change (p=0.24 and 0.99, respectively). Initially there were 30 patients with moderately increased albuminuria. At 6 months, this number decreased to 23 (p=0.09). Intergroup analysis between women and men showed similar results. As shown in Table 2, There was a significant inverse association between age and muscle strength both initially and at 6 months (p=0.001 and 0.001 for women; p=0.005 and 0.001 for men, respectively). Duration of DM was inversely associated with muscle strength only for women (p=0.02 at initial presentation and p=0.001 at month 6). The frequency of probable sarcopenia was reduced at month 6 for both genders (p=0.029 for females and p=0.50 for males).

DISCUSSION

The present study showed that in patients with DM, glucose-lowering intervention for 6 months resulted in reduced weight, fat mass, waist circumference and HbA1c but increased muscle strength for both genders.

Table 1: Characteristics of study participants

Characteristics *		Findings (n=143)	
Gender	Female	109	(76.2)
	Male	34	(23.7)
Smoking	Smoker	21	(14.6)
	Non-smoker	122	(85.3)
Metformin	Using	134	(93.7)
	Discontinued	2	(1.3)
	Initiated	7	(4.8)
SGLT-2 inhibitor	Using	90	(62.9)
	Not using	36	(25.1)
	Initiated	17	(11.8)
GLP-1 agonist	Using	65	(45.4)
	Not using	56	(39.1)
	Discontinued	4	(2.8)
	Initiated	18	(12.6)
DPP-4 inhibitor	Using	29	(20.3)
	Not using	107	(74.8)
	Discontinued	7	(4.8)
Sulfonylurea	Using	3	(2.1)
	Not using	138	(96.5)
	Discontinued	2	(1.4)
Insulin injection	Using	35	(24.5)
	Not using	105	(73.4)
	Discontinued	1	(0.7)
	Initiated	2	(1.4)
Pioglitazone	Using	3	(2.1)
	Not using	138	(96.5)
	Discontinued	1	(0.7)
	Initiated	1	(0.7)
Acarbose	Using	1	(0.7)
	Not using	142	(99.3)

*Data are presented as number and percentages, n(%).
DPP-4: Dipeptidyl peptidase-4, **GLP-1:** Glucagon-like peptide-1, **SGLT-2:** Sodium Glucose Cotransporter-2.

The inverse association between age and muscle strength comes as no surprise, as aging is the primary cause of sarcopenia. However, secondary reasons for sarcopenia may also be evident, as is the case in diabetic individuals. Oxidative stress is considered to have a role in the pathogenesis of both DM and sarcopenia. Insulin resistance, increased advanced glycation end-products, mitochondrial dysfunction and altered lipid metabolism associated with DM may cause increased oxidative stress, which hampers muscle repair (11-14). Hyperglycemia has been shown to have negative effects on the muscle through the Insulin-like Growth Factor-1-Akt-Forkhead box O pathway (15). Microvascular and macrovascular complications of DM limiting the capillarization of the muscle, along with diabetic neuropathy, may also be related to poor muscle health observed in diabetic individuals (12). In addition to hyperglycemia management, some glucose-lowering treatments also have a direct impact on muscle metabolism. Insulin has anabolic effects on the muscle by stimulating muscle protein synthesis and reducing protein degradation (16). Metformin inhibits the mechanistic target of rapamycin (mTOR), leading to muscle growth (17). Research has even suggested that metformin, GLP-1 receptor agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors and SGLT-2 inhibitors may have a potential role in the treatment of sarcopenia (5, 18, 19).

Although DM and sarcopenia share common pathological pathways, there are contradictory findings in the literature regarding the association between glycemic control and sarcopenia. In line with our study, an inverse association has been observed between higher HbA1c quartiles and lower knee extensor strength (20). In a meta-analysis by Anagnostis et al., diabetic patients were found to have a higher

Table 2: Change in baseline clinical and laboratory parameters

Clinical and laboratory parameters*	Baseline	6-month Follow-up	*p*
BMI (kg/m²)	36.6±6.9 (20.2-64.4)	36.4±6.5 (24.2-65.2)	**0.001****
Weight (kg)	95.9±18.3 (63.1-165.1)	94.7±17.1 (62.4-158.5)	**0.001****
Sarcopenia			
Muscle Mass (kg)	55.7±8.7 (40.4-92)	55.6±8.5 (36.9-90.7)	0.162**
SMM (kg)	23.7±4.8 (16.6-47.9)	23.8±4.6 (17.4-46.8)	0.551***
SMMI (kg/m²)	9.0±1.3 (6.6-14.1)	9.1±1.3 (6.8-13.8)	0.730***
Fat Mass (kg)	37.1±12.2 (12.7-79.7)	36.1±11 (13-77.5)	**0.001****
Visceral Fat Mass (kg)	16.1±5.5 (5.7-41.7)	15.2±5 (5.6-39.5)	**0.001*****
Muscle Strength (kg)	29.1±9.9 (12-70)	30.1±9.9 (12-72)	**0.012****
Waist C. (cm)	109.4±11.8 (80-137)	106.9±11.9 (78-144)	**0.001*****
Calf C. (cm)	40.2±4.4 (30-53)	40.4±4.5 (31-57)	0.268**
Plasma Markers			
HbA1c (%)	7.3±1.8 (4.8-14.7)	7.0±1.3 (5.1-13.1)	**0.001****
Fasting Glucose (mg/dl)	141.5±50 (74-335)	122.6±30.2 (69-254)	**0.001****
Insulin (mIU/l)	14.5±12.4 (2.2-93.4)	12.4±13 (2-128)	**0.001****
C-peptide (mg/l)	3±1.3 (0.4-8.9)	2.9±1.5 (0.18-9.9)	0.052**
LDL (mg/dl)	101.5±36.1 (34-213)	93.2±32.4 (14-170)	**0.001****
Triglyceride (mg/dl)	166.7±87.1 (38-615)	169±91.6 (36-764)	0.385**
Creatinine (mg/dl)	0.7±0.2 (0.4-1.8)	0.7±0.2 (0.4-1.6)	0.699**
TSH (mIU/l)	3.2±12.3 (0.01-148)	2.2±2.2 (0.01-23.1)	0.118**
Free T4 (ng/dl)	1.3±0.2 (0.3-3)	1.2±0.2 (0.7-2.8)	0.593**
Albumin (g/l)	45.8±2.8 (35.9-54.2)	45.4±2.6 (39.3-53.6)	0.118***
Hemoglobin (g/dl)	13.5±1.7 (6.3-18)	13.4±1.5 (10.6-17.8)	0.121***
Vitamin B12 (ng/l)	385.5±213 (100-1996)	341.9±131.7 (100-1893)	**0.001****
Ferritin (mg/l)	79.5±94.3 (10-301)	47.4±58 (7-213)	0.349***

*Data are shown as mean±SD (minimum - maximum).**Wilcoxon test ***Paired sample t test **Paired sample t test ***Wilcoxon tes**t.**
BMI: Body Mass Index, **C:** Circumference, **fT4:** free thyroxine, **HbA1c:** Hemoglobin A1c, **LDL:** Low Density Lipoprotein, **TSH:** Thyroid Stimulating Hormone, **SMM:** Skeletal Muscle Mass, **SMMI:** Skeletal Muscle Mass Index.

risk of sarcopenia compared with non-diabetic peers (7). Muscle strength and performance of diabetic patients were lower, with no significant difference in muscle mass. Contrary to these results, Volpato et al. have shown that diabetic patients have lower muscle mass compared to non-diabetic controls (8). Similarly, Sugimoto et al. have reported an association between DM and low muscle mass in non-obese individuals (21). It is worth noting that all of the aforementioned studies had a cross-sectional design.

In a multi-center observational longitudinal study (the MUSCLES-DM) investigating the effect of DM treatment on sarcopenia in 588 Japanese patients with type 2 DM (22), a ≥1% decrease in HbA1c has been found to improve gait speed, but not hand grip strength. Contrary to our findings, the MUSCLES-DM study has failed to demonstrate a favorable effect of glycemic control on probable sarcopenia. Study participants had a mean baseline BMI of 24.7 kg/m^2 as opposed to 36.6 kg/m^2 in our study. Moreover, participants of the MUSCLES-DM study were weight neutral at the end of the follow-up period, whereas our patients experienced weight loss. It is possible that reduced fat mass underlies the relationship between DM management and improved sarcopenia demonstrated in our study.

The cumulative negative effect of DM on the muscle may be more pronounced over time. However, we failed to show a relationship between the duration of DM and muscle strength in men. The fact that men had higher baseline muscle strength to begin with may have attenuated the contribution of DM chronicity. Another reason may be that women constituted the majority of the study population.

The present study differed from previous studies in the literature with its accessibility of new treatment options for DM. Namely, about three fourths of the participants were on a SGLT-2 inhibitor and more than one half was on a GLP-1 receptor agonist. Weight reducing antidiabetics were actively adopted, as obese patients constituted the majority of the study population. Loss of lean mass may compromise the metabolic benefits of weight loss and place some patients at a high risk for adverse outcomes associated with sarcopenia (23). This risk becomes more worrisome with advancing age. In light of the findings that weight loss in older adults may lead to significant loss of lean mass and therefore aggravate the development of sarcopenia (24), the European Society for Clinical Nutrition and Metabolism (ESPEN) guideline for older adults advised caution about weight reducing interventions even for obese individuals (25). The aforementioned study recruited adults over the age of 70. However, we recruited relatively younger individuals (mean age: 53±10 years) and showed that weight loss has a beneficial effect on muscle function.

Of note, almost all patients were on metformin, which could explain the observed vitamin B12 deficiency.

The present study contributes to the existing literature (6-8, 26) by providing follow-up information to assess the effectiveness of glycemic control interventions. In addition to presenting real world data regarding novel glucose-lowering agents, it has valuable clinical implications for sarcopenia treatment. Our findings demonstrate the beneficial effect of novel antihyperglycemic drugs on muscle function, representing a promising therapeutic approach against sarcopenia. Another strength of the study is that the most current and widely accepted EWGSOP criteria for sarcopenia have been used, as opposed to previous studies on the association of sarcopenia and DM that have used either the muscle mass or muscle strength as a proxy of sarcopenia.

This study has several limitations. First, since the study was not designed as a randomized control trial, study findings should be interpreted with caution. Second, HbA1c levels provide a crude estimation of blood glucose profile and do not provide information regarding hypoglycemic episodes; an established risk factor for sarcopenia. However this limitation was mostly overcome, since our clinic avoids hypoglycemic agents whenever possible (Only 1 patient continued to use sulfonylurea and patients on insulin therapy received basal insulin). Lack of nutritional assessment is another shortcoming of the study. We do not have information regarding the patients' energy and protein intake during the follow-up period. Nevertheless, all patients have been evaluated by the same clinical dietitian. Therefore, all patients received age and disease appropriate dietary advice. Finally, a separate analysis has not been performed for sarcopenic obesity, as it would lead to reduced statistical power.

In conclusion, glycemic control with novel antihyperglycemic treatments plays a valuable role in the prevention of sarcopenia. Still, larger prospective studies with long-term follow-up are warranted to substantiate the study findings. Understanding the change in skeletal muscle may pave the path for developing appropriate interventions that are urgently needed in the field of sarcopenia.

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Authorship Contributions

Conception and Design: **Busra Can, Zehra Kaya, Bulent Can,** Materials, Data Collection or Processing: **Zehra Kaya, Bulent Can,** Analysis or Interpretation: **Busra Can, Zehra Kaya, Bulent Can,** Literature Search: **Busra Can, Zehra Kaya,**Writing: **Busra Can, Zehra Kaya , Bulent Can,** Critical Review: **Busra Can, Zehra Kaya, Bulent Can,** Supervision: **Busra Can.**

Conflict of Interest

No conflict of interest was declared by the authors.

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The authors declare that this study received no financial support.

Ethical Approval
Istanbul Medeniyet University Ethical Review Board approved the study protocol (approval number: 2021/0314).

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

All participants provided informed consent in the format required by the ethical review board.

Peer Review Process
Extremely and externally peer-reviewed.

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