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ORIGINAL RESEARCH

Semaglutide Therapy and Accelerated Sarcopenia in Older Adults with Type 2 Diabetes: A 24-Month Retrospective Cohort Study

Qingjuan Ren, Lei Zhi, Hongfang Liu

Department of Geriatrics, Shijiazhuang People's Hospital, Shijiazhuang, Hebei, People's Republic of China

Correspondence: Qingjuan Ren, Department of Geriatrics, Shijiazhuang People's Hospital, Shijiazhuang, Hebei, People's Republic of China, Email 15930170635@163.com

Purpose: This study aimed to investigate changes in muscle mass and strength among older adults with type 2 diabetes who were treated with Semaglutide.

Methods: This was a retrospective cohort study comparing elderly patients with type 2 diabetes receiving Semaglutide to a matched control group. Changes in muscle mass and function over 24 months were assessed. Muscle mass was measured using the appendicular skeletal muscle mass index (ASMI), while muscle function was evaluated through grip strength and gait speed measurements. Differences between the two groups and changes before and after treatment were analyzed using the *t*-test. Additionally, multivariable linear regression models were constructed to identify clinical predictors of accelerated muscle loss during Semaglutide treatment.

Results: The study involved 220 patients treated with Semaglutide and 212 control subjects. The prevalence of sarcopenia among participants was 27.7%. Semaglutide treatment significantly reduced both body mass index and muscle mass compared to controls. Notably, divergent patterns emerged in functional measures. Grip strength initially improved but then declined in men, while it continued to decrease in women. Gait speed significantly reduced in both genders. Multivariable analysis identified Semaglutide dosage, baseline ASMI, and gait speed as independent predictors of muscle loss.

Conclusion: The use of Semaglutide is associated with muscle loss and functional decline in older adults with type 2 diabetes, particularly at higher doses. This effect is especially significant in patients with sarcopenia. Consequently, it is crucial to assess the risks and benefits for each elderly patient individually and to implement appropriate monitoring and interventions. The potential for nutritional supplementation and targeted exercise regimens to counteract semaglutide-associated muscle decline merits systematic investigation.

Keywords: older adults, type 2 diabetes, semaglutide, sarcopenia, muscle mass, mass strength

Introduction

Sarcopenia is a progressive disorder characterized by the loss of muscle mass and strength. And it is particularly prevalent among older adults, it might affect up to half of people aged 80 years and older, posing a significant public health challenge. In older adults with type 2 diabetes mellitus (T2DM), the prevalence of sarcopenia is 2–3 times higher than in non-diabetic peers.[1] This dual burden not only impairs physical performance and quality of life but also increases the risk of falls, frailty, and mortality.[2] In recent years, growing concerns have arisen regarding the potential impact of glucose-lowering medications on muscle health, generating significant clinical debate. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are commonly used hypoglycemic agents. They work through several mechanisms, including increasing glucose-dependent insulin secretion, inhibiting glucagon secretion during hyperglycemia, delaying gastric emptying, and reducing caloric intake. Semaglutide, a long-acting GLP-1RA, can be administered subcutaneously once weekly. It effectively lowers glucose levels and promotes significant weight loss, making it widely adopted for the treatment of diabetes and obesity.[3,4] Additionally, it has shown therapeutic effects on sarcopenic obesity.[5] However,

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concerns have been raised about the potential for muscle loss due to long-term Semaglutide use. Some studies indicate that elevated GLP-1 levels may have a detrimental effect on muscle mass.[6] Given that elderly patients are at a higher risk for sarcopenia, it is essential to further investigate how Semaglutide treatment affects skeletal muscle in this population. In this study, we examined changes in muscle mass and strength among elderly type 2 diabetes patients using Semaglutide, aiming to provide evidence-based guidance for its clinical application.

Methods

Study Design and Participants

This retrospective cohort study investigated older patients (≥65 years) with T2DM who initiated Semaglutide therapy at our hospital between January 2022 and December 2022. Propensity score matching (1:1 ratio) was performed based on age, sex, baseline BMI, diabetes duration, and comorbidities. The resulting control group had comparable baseline characteristics but was not exposed to GLP-1RAs or DPP-4 inhibitors. All participants were monitored for 24 months, with data collected at baseline (0 months), 6 months, 12 months, 18 months, and 24 months. Inclusion criteria were as follows: Age ≥65 years with T2DM (according to ADA guidelines), Body mass index (BMI) ≥24kg/m², with no prior use of GLP-1RA or DPP-4 inhibitors. The study had certain criteria that excluded individuals who had severe liver or renal impairment (defined as serum alanine transaminase (ALT) ≥ 3-fold the upper limit of normal; estimated glomerular filtration rate (eGFR)<15mL/ min/1.73 m^2) and cancer. Study subjects meeting the eligibility criteria were included after comprehensive validation of data completeness via the electronic health records system, with exclusion of any cases lacking essential variables. All participants received individualized glucose-lowering regimens supervised by endocrinology specialists. Semaglutide dosage was adjusted based on both glycemic monitoring and hemoglobin A1c levels. This study was approved by the Ethics Committee of Shijiazhuang People's Hospital (Approval No: 2025075) and conducted by the Declaration of Helsinki. All participants provided written informed consent prior to data collection. Patient confidentiality was protected by anonymizing all personal identifiers in the dataset. The reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Data Collection

Demographic and clinical parameters were systematically extracted from electronic medical records. This data included age, sex, BMI, muscle parameters, duration of diabetes, and comorbidities. The chronic diseases considered included cerebrovascular disease, coronary heart disease, kidney disease, hypertension, and chronic obstructive pulmonary disease (COPD). Due to the retrospective study design, standardized assessments of lifestyle factors (dietary intake and physical activity) were unavailable in the source dataset.

Muscle parameters were assessed through measurements of muscle mass and function. Skeletal muscle mass was estimated using bioelectrical impedance analysis (BCA-1C, Tongfang Health Technology, Beijing). Upper extremity muscle strength was evaluated through handgrip strength measurements, taken with an electronic hand dynamometer (CAMRY EH101, Guangdong). Lower limb muscle strength was evaluated using a 4-meter gait speed test, calculated as gait speed (m/s) = 4 (m) ÷ time (s).

The appendicular skeletal muscle mass index (ASMI) was calculated by dividing the appendicular lean mass of the arms and legs by the square of height (kg/m²). Sarcopenia diagnosis followed 2019 Asian Working Group for Sarcopenia (AWGS) criteria,[7] requiring both low muscle mass (ASMI <7.0 kg/m² males, <5.7 kg/m² females) and reduced muscle strength (handgrip strength <28 kg males, <18 kg females).

Statistical Analysis

Data were statistically analyzed using IBM SPSS 27.0 and GraphPad 9.0. Continuous variables with normal distribution were expressed as mean ± standard deviation (Mean ± SD). Between-group comparisons used independent samples *t*-tests, while intra-group longitudinal changes were analyzed with paired *t*-tests. Categorical variables were compared via chi-square tests. Multivariable linear regression models were constructed to identify clinical predictors of accelerated

muscle loss during Semaglutide treatment, adjusting for potential confounders. A two-tailed p-value <0.05 defined statistical significance.

Results

The analysis included 220 Semaglutide-treated patients and 212 matched controls. The baseline information of the Semaglutide treatment group is shown in Table 1. Sarcopenia prevalence was 27.73% in the study population. No significant differences were observed in baseline characteristics between the two groups. However, at the 24-month follow-up, the Semaglutide-treated group exhibited significantly lower values for BMI, ASMI, handgrip strength, and gait speed compared to the control group ($p< 0.05$). Detailed results are presented in Table 2.

Longitudinal Changes in Anthropometric and Muscle Parameters

Weight and Muscle Mass Dynamics

All subjects treated with Semaglutide showed a continuous reduction in BMI throughout the study period (p<0.001). A non-significant downward trend in ASMI emerged at 6 months, with significant reductions observed from month 12

Table 1 Baseline Characteristics of Semaglutide-Treated Patients

Variables	Female (n=112)			Male (n=108)		
	Sarcopenia (n=26)	Non-Sarcopenia (n=86)	*p*-value	Sarcopenia (n=35)	Non-Sarcopenia (n=73)	*p*-value
Age (years)	74.00±5.25	72.03±5.00	0.085	75.29±4.81	71.59±5.64	<0.001
BMI (kg/m^2)	28.12±1.69	27.03±2.25	0.024	28.65±2.05	27.51±2.76	0.033
T2DM duration (year)	15.65±5.71	15.63±7.89	0.988	13.57±8.36	13.64±7.77	0.965
Chronic diseases (n)	2.65±1.16	2.17±1.29	0.019	4.23±0.81	2.38±1.30	<0.001
Muscle parameters						
ASMI (kg/m^2)	5.55±0.13	6.53±0.51	0.001	6.74±0.22	7.73±0.56	<0.001
Hand grip strength (kg)	18.97±3.25	26.20±3.24	<0.001	28.99±2.60	35.94±3.48	<0.001
Gait speed (m/s)	0.98±0.06	1.15±0.14	<0.001	0.98±0.08	1.18±0.13	<0.001

Abbreviations: ASMI, appendicular skeletal muscle mass index; BMI, body mass index; T2DM, type 2 diabetes mellitus.

Table 2 Comparison of Anthropometric and Muscle Parameters Between Semaglutide-Treated and Control Patients

Variables	Female (n=221)			Male (n=211)		
	Semaglutide Group (n=112)	Control Group (n=109)	*p*-value	Semaglutide Group (n=108)	Control Group (n=103)	*p*-value
Age (years)	72.54±4.81	72.80±5.08	0.665	72.98±5.61	73.66±4.51	0.336
Baseline information						
BMI (kg/m^2)	27.28±2.18	27.80±1.95	0.065	27.68±2.57	27.88±2.23	0.545
ASMI (kg/m^2)	6.30±0.61	6.37±0.73	0.441	7.41±0.67	7.45±0.72	0.663
Hand grip strength (kg)	24.53±4.45	24.99±5.03	0.465	33.69±4.58	33.55±5.21	0.836
Gait speed (m/s)	1.11±0.15	1.10±0.17	0.728	1.11±0.15	1.14±0.18	0.252
End-of-study information						
BMI (kg/m^2)	24.46±2.18	27.71±1.97	<0.001	24.65±2.07	27.44±2.17	<0.001
ASMI (kg/m^2)	6.04±0.80	6.35±0.74	0.003	7.02±0.93	7.43±0.72	0.001
Hand grip strength (kg)	22.91±4.63	24.37±5.22	0.028	31.35±5.39	32.80±5.04	0.046
Gait speed (m/s)	1.04±0.13	1.08±0.16	0.026	1.07±0.14	1.12±0.17	0.046

Abbreviations: ASMI, appendicular skeletal muscle mass index; BMI, body mass index.

onward. Cumulative ASMI loss reached 0.39 kg/m² in females and 0.26 kg/m² in males by study end. While the control group also showed sustained ASMI decline, the magnitude was markedly smaller than in the treatment group (Figure 1).

Muscle Strength Trajectories

Handgrip strength: Males displayed a transient improvement at 6 months, followed by a progressive decline. Female participants, while showing no statistically significant change at 6 months, exhibited an upward trend that was subsequently followed by significant deterioration. Gait speed: Both genders exhibited similar patterns, with non-significant declines in intermediate phases but statistically significant overall reductions. Refer to Figure 2 for more information. Semaglutide-treated patients showed significantly greater reductions in ASMI, handgrip strength and gait speed compared to controls (see Table 2).

Influential Factors of Semaglutide-Associated Muscle Loss

To identify determinants of muscle loss, we performed correlation analysis followed by multiple linear regression. The initial correlation analysis revealed that gender, age, baseline body mass index, diabetes duration, and chronic comorbidities showed no significant association with muscle mass loss. However, significant correlations were found with Semaglutide dosage, baseline ASMI, handgrip strength, and gait speed. As shown in Table 3.

Subsequent multiple linear regression analysis, using muscle mass loss as the dependent variable and Semaglutide dosage, baseline ASMI, handgrip strength, and gait speed as independent variables, confirmed independent associations for semaglutide dosage, baseline ASMI, and gait speed, whereas handgrip strength lost statistical significance. The

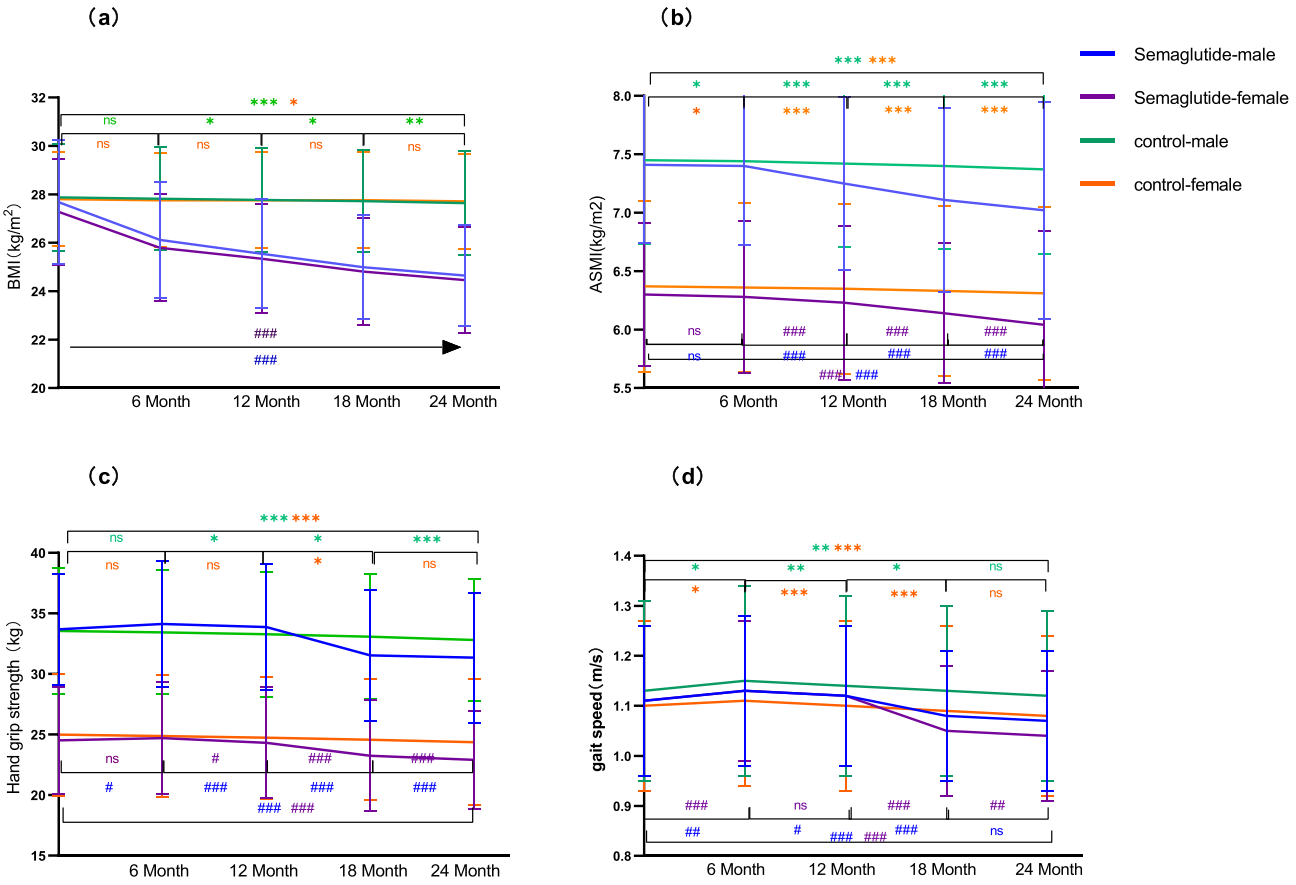

Figure 1 Longitudinal changes in BMI and muscle parameters during the study period. (**a**) BMI trajectories. (**b**) AMSI changes. (**c**) Handgrip strength variations. (**d**) Gait speed dynamics. Compare of Semaglutide group: male #<0.05, ##<0.01, ####<0.001; female #<0.05, ##<0.01, ####<0.001. Compare of control group: male *<0.05, **<0.01, ***<0.001; female *<0.05, **<0.01, ***<0.001.

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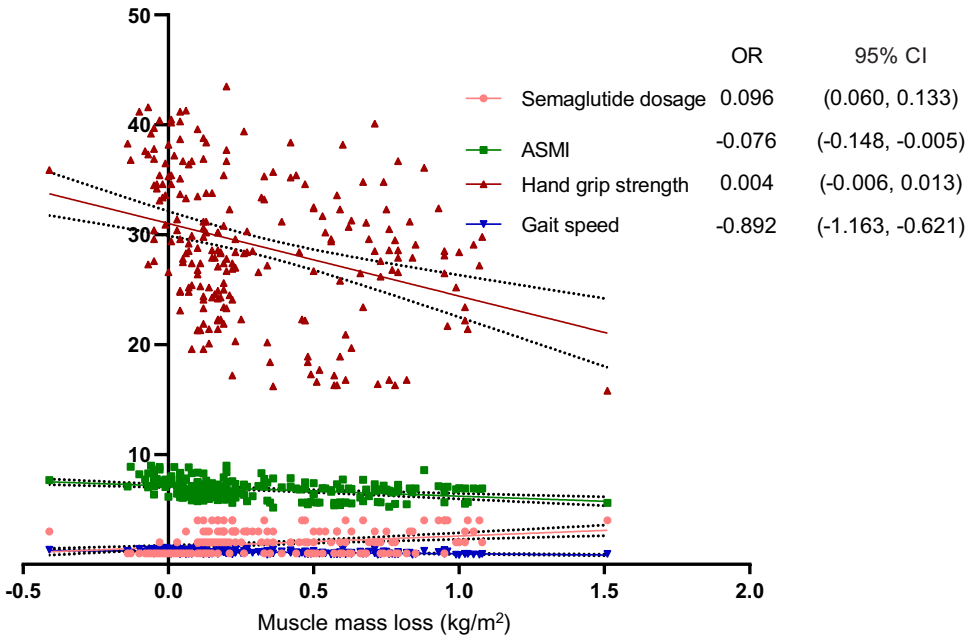

Figure 2 Multivariable regression analysis of predictors for muscle mass loss following semaglutide treatment. Semaglutide dosage, ASMI, and Gait speed were significant influences. Muscle mass loss (kg/m^2) =1.536 + 0.096 × Semaglutide dosage – 0.076 × ASMI + 0.004 × Hand grip strength – 0.892 × Gait speed (R^2=0.337).

regression model (R^2 = 0.337) predicted muscle mass loss as: Muscle mass loss (kg/m^2) =1.536+0.096×Semaglutide dosage-0.076× ASMI+0.004×Hand grip strength-0.892×Gait speed, R^2=0.337. As displayed in Figure 2.

Discussion

Sarcopenia is an age-related condition characterized by the progressive loss of skeletal muscle mass and strength. It typically begins after the age of 30, at a rate of 0.1% to 0.5% annually, and accelerates beyond the age of 65 due to physiological and metabolic changes in aging populations.[8] In this study, we investigated the effects of Semaglutide on muscle health in elderly patients with T2DM. Our analysis reveals that while Semaglutide effectively reduces body weight in elderly T2DM patients, it paradoxically accelerates this physiological muscle decline, particularly at higher doses and in individuals with pre-existing low muscle mass and function.

The weight-loss effects of Semaglutide, a long-acting GLP-1RA, are well-established,[9] and this was confirmed in our elderly cohort. This weight loss may be linked to its ability to suppress appetite, delay gastric emptying, and regulate satiety signaling in the central nervous system.[10] In older patients with T2DM, weight loss not only improves glycemic control but also reduces the risk of cardiovascular disease,[11] which is especially important in this population. However, despite the metabolic benefits of weight loss, it is crucial to consider the components of that weight loss. Our study found that weight loss was accompanied by a reduction in muscle mass and a decline in muscle function, which could

Table 3 Correlation Analysis of the Variables with Muscle Loss

Variables	*p*-value	OR	95% CI	Variables	*p*-value	OR	95% CI
Demographics				Baseline Measures			
Sex	0.931	−0.006	(−0.142, 0.130)	BMI (kg/m^2)	0.322	0.067	(−0.066, 0.198)
Age (years)	0.069	0.123	(−0.009, 0.251)	Hand grip strength (kg)	<0.001	−0.399	(−0.474, −0.244)
Semaglutide dosage (mg)	<0.001	0.293	(0.167, 0.409)	Gait speed (m/s)	<0.001	−0.485	(−0.586, −0.385)
Chronic diseases (n)	0.120	0.105	(−0.032, 0.238)	ASMI (kg/m^2)	<0.001	−0.436	(−0.499, −0.275)
T2DM duration (year)	0.582	0.037	(−0.079, 0.192)				

Abbreviations: ASMI, appendicular skeletal muscle mass index; BMI, body mass index; CI, confidence interval; OR, Odds ratio.

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negatively affect the long-term health of elderly patients. This finding contrasts with results from previous studies,[12] possibly because our follow-up population consisted entirely of elderly individuals. Skeletal muscle is the largest organ system in adults, accounting for approximately 30–45% of body weight in young adults, and it plays a vital role in protein homeostasis, as it contains the largest amount of body protein. Maintaining protein homeostasis, or net protein balance, is essential for muscle health. Under certain conditions, such as prolonged fasting, starvation, or inadequate protein intake, skeletal muscle can break down its proteins to mobilize amino acids.[13] Semaglutide reduces body weight by suppressing appetite and decreasing energy intake; this diminished protein intake may lead to the body breaking down muscle proteins to provide necessary amino acids.[10] Thus, using Semaglutide in older patients with T2DM may exacerbate the development of sarcopenia due to negative energy balance. Moreover, high doses of Semaglutide may more robustly suppress appetite and energy intake,[14] leading to exacerbated muscle mass loss. The precise molecular mechanisms underlying this phenomenon require further investigation. These findings prompt critical inquiry into whether targeted protein supplementation may attenuate these effects in older populations - a promising avenue for future investigation.

Interestingly, we observed that Semaglutide initially improved muscle function, although in female participants this improvement only manifested as an upward trend. This effect may be mediated through the reduction of intramuscular fat infiltration, which is characteristically elevated in obese individuals. The accumulation of lipids and their metabolic byproducts within and between muscle cells can lead to mitochondrial dysfunction and subsequent declines in muscle strength and function.[15] Previous studies have confirmed that GLP-1RA treatment significantly reduces this pathological fat infiltration.[16] However, our data demonstrate that long-term administration results in gradual muscle mass loss, ultimately attenuating the initial functional improvements.

Our regression analysis identified baseline ASMI and gait speed as independent predictors of muscle loss, without significant gender or age differences. This suggests that reduced physical activity, resulting from declining muscle function, may create a vicious cycle of further muscle deterioration.[17] Current research has shown that physical activity, particularly resistance training, has therapeutic effects on sarcopenia.[18] Whether muscle loss can be prevented in Semaglutide users by increasing exercise participation needs further investigation.

The findings of this study have significant implications for clinical practice. While Semaglutide has notable benefits in improving glycemic control and promoting weight loss, its adverse effects on muscle mass should not be overlooked, especially in elderly patients. Clinicians should consider the following points when prescribing Semaglutide: (1) Patient selection: Carefully evaluate the risks and benefits of Semaglutide in elderly patients or those with pre-existing sarcopenia. (2) Dose adjustment: Start elderly patients on a low dose and gradually adjust according to their tolerance and response, avoiding high doses. (3) Monitoring and intervention: Regularly monitor muscle mass, physical function, and quality of life during Semaglutide treatment. This could be combined with moderate resistance training and optimized protein intake,[19] if needed, to help slow muscle loss.

This study has several limitations. The relatively small sample size may limit the generalizability of the findings. While we accounted for major known confounders, we were unable to assess nutritional intake and physical activity patterns, which could influence muscle outcomes. Additionally, the observational nature of the study prevents causal conclusions. These limitations highlight the need for future prospective studies with standardized assessments of diet and exercise.

Conclusion

The use of Semaglutide is associated with muscle loss and functional decline in older adults with type 2 diabetes, particularly at higher doses. This effect is especially significant in patients with sarcopenia. Consequently, it is crucial to assess the risks and benefits for each elderly patient individually and to implement appropriate monitoring and interventions. The potential for nutritional supplementation and targeted exercise regimens to counteract semaglutide-associated muscle decline merits systematic investigation.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Shijiazhuang People's Hospital (Approval No: 2025075). All methods were performed by the Declaration of Helsinki, and the reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

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Disclosure

The authors declare that they have no competing interests in this work.

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