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Skeletal Muscle Strength and Waist-to-Height Ratio Serve as Partial Mediators in the Relationship Between Muscle Mass and Exercise Capacity in Individuals with Heart Failure: A Mediation Analysis

Kalp Yetersizliği Olan Bireylerde Kas Kütlesi ile Egzersiz Kapasitesi Arasındaki İlişkide İskelet Kası Kuvveti ve Bel/Boy Oranı Kısmi Aracı Değişkenler Olarak Rol Oynamaktadır: Bir Aracılık Analizi

ABSTRACT

Objective: Exercise intolerance is a hallmark of heart failure (HF), and skeletal muscle abnormalities and abdominal obesity are important noncardiac factors contributing to this limitation. This study aimed to investigate the mediating roles of skeletal muscle strength and waist-to-height ratio (WtHR) in the relationship between muscle mass and exercise capacity in individuals with HF.

Method: This cross-sectional study included 110 patients with HF aged over 18 years who were classified as New York Heart Association (NYHA) functional class II or III. Exercise capacity, skeletal muscle mass, muscle strength, and WtHR were assessed using the six-minute walk test, a Tanita device, a Jamar hydraulic handgrip dynamometer, and a tape measure, respectively. Mediation effects were evaluated using the bootstrapping method with a 95% confidence interval and parallel multiple mediation models. Mediation was considered significant when the intervals did not include zero.

Results: A significant correlation was observed between muscle mass and exercise capacity, with both muscle strength and WtHR acting as partial mediators in this relationship. After adjusting for age, sex, and NYHA class, the mediating effect of WtHR was greater (30.6%) than that of muscle strength (17.9%). Despite these mediating effects, muscle mass maintained a direct effect of 51.5% on exercise capacity.

Conclusion: In individuals with HF, muscle mass is associated with exercise capacity both directly and indirectly through muscle strength and WtHR. Assessing these characteristics together may help account for the impact of abdominal obesity, which is associated with reduced exercise capacity in this population.

Keywords: Abdominal obesity, heart failure, muscle strength, six-minute walk test, waist-to-height ratio

ÖZET

Amaç: Egzersiz intoleransı, kalp yetersizliğinin (KY) temel klinik özelliklerinden biridir. İskelet kası bozuklukları ve abdominal obezite ise bu kısıtlılığın önemli nonkardiyak belirleyicilerindendir. Bu çalışma, KY'li bireylerde kas kütlesi ile egzersiz kapasitesi arasındaki ilişkide kas kuvveti ve bel/boy oranının (WtHR) aracılık rollerini incelemeyi amaçlamaktadır.

Yöntem: Kesitsel olarak tasarlanan araştırmaya, NYHA fonksiyonel sınıf II–III'te olan, 18 yaş ve üzerindeki 110 KY hastası dâhil edildi. Egzersiz kapasitesi, altı dakikalık yürüme testi ile; iskelet kası kütlesi, Tanita analizörü ile; kas kuvveti, Jamar hidrolik el dinamometresi ile ve WtHR, mezura kullanılarak değerlendirildi. Aracılık analizleri, %95 güven aralıklı bootstrapping yöntemi ve paralel çoklu aracılık modelleri kullanılarak gerçekleştirildi; güven aralığının sıfırı içermemesi anlamlı aracılık olarak yorumlandı.

Bulgular: Kas kütlesi ile egzersiz kapasitesi arasında anlamlı bir ilişki gözlendi; kas kuvveti ve WtHR, bu ilişkide kısmi aracı değişkenler olarak belirlendi. Yaş, cinsiyet ve NYHA sınıflaması için düzeltme yapıldıktan sonra, WtHR'nin aracılık etkisi (%30,6), kas kuvvetinin etkisine (%17,9) kıyasla daha yüksek bulundu. Aracılık etkisine rağmen kas kütlesinin, egzersiz kapasitesi üzerinde %51,5 oranında doğrudan etkisi vardı.

ORIGINAL ARTICLE
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Sonuç: KY'li bireylerde kas kütlesi, egzersiz kapasitesi ile hem doğrudan hem de kas kuvveti ve WtHR aracılığıyla dolaylı olarak ilişkilidir. Bu faktörlerin birlikte değerlendirilmesi, KY popülasyonunda egzersiz kapasitesini önemli ölçüde azaltan abdominal obezitenin dikkate alınmasını sağlar.

Anahtar Kelimeler: Abdominal obezite, kalp yetersizliği, kas kuvveti, altı dakika yürüme testi, bel/boy oranı

Heart failure (HF) constitutes a significant public health issue characterized by high mortality, morbidity, and hospitalization rates. Despite advances in treatment that have contributed to reduced mortality, HF remains a serious condition characterized by numerous symptoms and clinical signs.[1] Exercise intolerance is a primary symptom associated with reduced quality of life and an increased risk of mortality in individuals with HF. Exertional dyspnea, fatigue, and ambulatory difficulties are also common symptoms among non-hospitalized patients with HF.[1,2]

Individuals with HF exhibit various histological and metabolic abnormalities in skeletal muscle, including muscle atrophy, a reduction in oxidative fibers and enzymes, and decreased mitochondrial volume density and capillary-to-fiber ratio.[3] Approximately 20% of this population demonstrates reduced muscle mass, which is an independent predictor of mortality.[4,5] Previous studies have indicated that skeletal muscle atrophy and decreased lower-extremity muscle mass lead to reduced peak oxygen uptake (VO_2peak) and decreased muscle strength.[3] Furthermore, the prevalence of sarcopenia, characterized by a decline in both muscle quantity and quality, is higher in individuals with HF than in age-matched populations and is associated with poor prognosis.[5] Impaired muscle function in sarcopenia, when combined with other HF-related symptoms, is linked to an increased risk of functional limitations.[5,6]

Obesity is a significant risk factor for the development of HF. Paradoxically, a higher body mass index (BMI) has been associated with a more favorable prognosis until recently.[7] Nevertheless, the outcomes of anthropometric measurements, which provide a more accurate assessment of the distribution and quantity of ectopic fat, do not support this association, known as the obesity paradox. The waist-to-height ratio (WtHR), which assesses adiposity while accounting for sex and racial variations, has been correlated with hospitalization and mortality rates, as well as cardiorespiratory fitness.[8] Additionally, WtHR is a good predictor of metabolic and cardiovascular risk and has been linked to muscle mass, potentially acting as a confounding variable in the relationship between exercise capacity and muscle mass.[9]

Multisystem dysfunction, including peripheral, pulmonary, and cardiac dysfunctions, contributes to exercise intolerance, a key symptom in the HF population.[3,10] Skeletal muscle abnormalities, worsened by aging and the pathogenesis of HF, are critical factors leading to this exercise intolerance. There is a strong correlation between reduced exercise capacity and skeletal muscle atrophy, characterized by a decrease in muscle fiber size.[11] Furthermore, the loss of muscle mass is known to lead to muscle weakness, which further impairs exercise capacity.[3,6] Abdominal obesity is another peripheral factor that negatively impacts exercise tolerance. Research indicates that exercise capacity diminishes as the WtHR increases.[12] Skeletal muscle is among the body compartments where fatty deposits accumulate.[13] Studies have reported that WtHR values tend to rise alongside increases in skeletal muscle mass across different populations.[9,14] This suggests that the WtHR metric used to assess abdominal obesity may influence the relationship between skeletal muscle mass and exercise capacity. Given these connections, the present study aimed to identify the mediating roles of WtHR and skeletal muscle strength in the relationship between exercise capacity and muscle mass.

ABBREVIATIONS

6MWT	Six-minute walk test
BIA	Bioelectrical impedance analysis
BMI	Body mass index
DEXA	Dual-energy X-ray absorptiometry
EF	Ejection fraction
FFM	Fat-free mass
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HG	Handgrip
LVEF	Left ventricular ejection fraction
NYHA	New York Heart Association
PTCA	Percutaneous transluminal angioplasty
SMMI	Skeletal muscle mass index
WC	Waist circumference
WtHR	Waist-to-height ratio

Materials and Methods

Participants

Participants in this cross-sectional study included individuals with HF who attended the cardiology clinic of a local university hospital. The inclusion criteria were: being older than 18 years, having a diagnosis of HF with mild or reduced ejection fraction, and maintaining a stable medication regimen for at least one month. The exclusion criteria were: decompensated HF, unstable angina pectoris, severe valvulopathy, complex ventricular arrhythmias, obstructive or restrictive pulmonary disease; myocardial infarction, percutaneous transluminal angioplasty (PTCA), or cardiac surgery within the past three months; serum creatinine levels > 2.0 mg/dL; neurological and/or orthopedic conditions restricting movement; and participation in a regular exercise training program within the previous six months.

The study was approved by the Ethics Committee of Giresun Traning and Research Hospital (Approval Number: 16.10.2024/14, Date: 16.10.2024) and was conducted in accordance with the principles of the Declaration of Helsinki. Participants signed a written informed consent form prior to participation in the study.

Outcomes

Descriptive Features

Participants' age, educational background, marital status, and comorbidities were recorded. Routine clinical cardiac examinations and the New York Heart Association (NYHA) classification were performed and documented. Left ventricular ejection fraction (LVEF) was assessed using echocardiography and categorized as heart failure with mildly reduced ejection fraction (HFmrEF) when LVEF was 41–49%, and heart failure with reduced ejection fraction (HFrEF) when LVEF was ≤ 40%2. All cardiac examinations and classifications were performed by a cardiologist.

Anthropometric Measures

Body weight and height were measured, and BMI was calculated by dividing body weight by height squared (m^2). Fat-free mass (FFM) was estimated using bioelectrical impedance analysis (BIA) (Tanita BC-532), with measurements performed under clinically stable and euvolemic conditions in patients who met the predefined inclusion and exclusion criteria. Skeletal muscle mass (SMM) was determined using the formula SMM = FFM * 0.566, which was validated by 24-hour creatinine excretion.[15,16] Subsequently, the skeletal muscle mass index (SMMI) was calculated by dividing SMM by height squared (kg/m^2). The cut-off values for SMMI indicating low muscle mass category were defined as < 9.2 kg/m^2 in men and 7.4 kg/m^2 in women.[16]

Waist circumference (WC) was measured horizontally using a tape measure at the midpoint between the superior iliac crest and the lower border of the 12th rib. The WtHR was calculated by dividing WC (cm) by height (cm). Abdominal obesity was defined as a WtHR ≥ 0.5, a cut-off value generally accepted in the literature as a universal indicator of abdominal obesity in adults.[17]

Skeletal Muscle Strength

Handgrip (HG) strength was measured to assess skeletal muscle strength. Participants were seated in a chair with the elbow flexed at 90°, the forearm in mid-rotation, the wrist in a neutral position, and the shoulder in neutral rotation, according to the criteria of the American Society of Hand Therapists. Measurements were performed three times at one-minute intervals using a Jamar hydraulic hand dynamometer (JLW Instruments, Chicago, IL, USA), and the mean value of the three measurements was recorded.[18] Low muscle strength was defined as HG strength < 27 kg in men and < 16 kg in women.[19]

Exercise Capacity

The six-minute walk test (6MWT) was used to evaluate exercise capacity. The test was performed according to the criteria established by the American Thoracic Society and the European Respiratory Society. Participants were instructed to walk back and forth along an empty 30-meter corridor marked by cones at both ends for six minutes. The total walking distance (m) was recorded.[20]

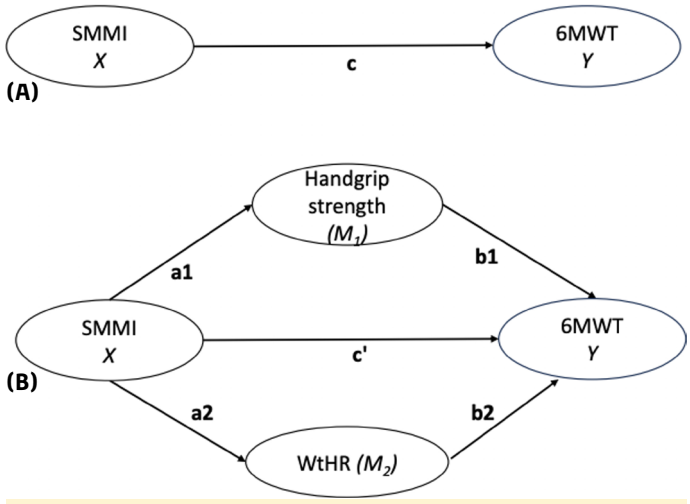


Figure 1. Path diagram showing the total effect and parallel multiple mediator models. (A) Total effect of X on Y (path c). (B) Models demonstrating the relationship between X and Y through parallel multiple mediators. In this model, path c' denotes the direct effect of X on Y after incorporating M_1 and M_2 into the regression analysis. The specific indirect effects of X on Y via M_1 and M_2 are calculated by multiplying paths a and b, with the mediator corresponding to each coefficient indicated by subscripts.

Statistical Analysis

Data analysis was performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were reported as mean ± standard deviation for continuous variables and as count (%) for categorical variables. The independent samples t-test was used to compare clinical data according to age, sex, and NYHA categories. The relationships among SMMI, HG strength, WtHR, and 6MWT distance were assessed using Pearson correlation analysis. Correlation coefficients were categorized as negligible (0–0.25), weak (0.26–0.39), moderate (0.40–0.69), high (0.70–0.89), or very strong (0.90–1.00).[21] Statistical significance was set at $P < 0.05$.

Two parallel mediation models were constructed with two potential mediator variables, HG strength and WtHR, to investigate the effect of muscle mass on exercise capacity (Figure 1). Accordingly, three potential paths were examined in both models: indirect path 1 (a1b1), representing the pathway from muscle mass to muscle strength to exercise capacity; indirect path 2 (a2b2), representing the pathway from muscle mass to WtHR to exercise capacity; and the direct path (c'), representing the pathway from muscle mass to exercise capacity. Model 1 included the 6MWT distance as the dependent variable, SMMI as the independent variable, and WtHR and HG strength as potential mediators. Model 2 was constructed by adding age, sex, and NYHA status as covariates to Model 1.

The SPSS PROCESS macro (Model 4) was used to assess the significance of the mediation models.[22] A bootstrapping approach with 5,000 resamples was employed to determine the 95% confidence interval (CI). For the point estimate to be considered statistically significant, the 95% CI should not include zero.[23] The G*Power 3.1 program indicated that, to achieve a medium effect size (f2 = 0.15) with 80% power and a 5% type error for a

multiple regression fixed model with three variables, a minimum of 77 participants was required.[24] For all statistical tests, the level of significance was set at $P < 0.05$.

Results

A total of 122 individuals with HF were evaluated for eligibility. Of these, 12 individuals were excluded: seven had changes in their medication during their last medical visit, three had undergone PTCA within the previous two months, and two had a history of lumbar disc herniation that could impair walking performance. Ultimately, 110 eligible participants with a mean age of 64.25 ± 9.54 years were recruited. Of the sample, 53.6% were aged 65 years or older, and 29.1% were female. Participants were classified as NYHA class II and III, with 73.6% falling into the HFrEF category. The participants' sociodemographic and clinical characteristics are presented in Table 1.

Table 2 presents comparative data on anthropometric measures, muscle strength, and exercise capacity categorized by age, sex, NYHA class, and LVEF category. SMMI showed significant differences only across the sex category, whereas WtHR demonstrated significant differences across both age and sex categories. HG strength and 6MWT distance showed significant differences across age, sex, and NYHA categories.

According to the correlation analysis among SMMI, 6MWT distance, HG strength, and WtHR, a strong association was observed only between 6MWT distance and HG strength ($r = 0.569$, $P < 0.001$). No relationship was found between HG strength and WtHR ($r = -0.127$, $P = 0.187$). Other variables in the correlation matrix showed weak to moderate correlations with each other (Table 3).

The total effect of SMMI on 6MWT distance, without considering any mediators or covariates, was significant ($F(1,108) = 8.884$, $P = 0.004$), with the model explaining 8% of the variance in 6MWT distance. In Model 1, which incorporated HG strength and WtHR as potential mediators, the direct effect of SMMI (B = 10.517) on 6MWT distance remained significant, with HG strength (B = 9.157) and WtHR (-5.496) acting as partial mediators. The 95% bootstrap CI for both direct and indirect effects did not include zero, confirming these findings. The mediation analysis indicated that higher muscle mass was significantly associated with greater HG strength, and greater HG strength was associated with longer 6MWT distances. Consequently, when accounting for SMMI and WtHR, indirect path 1 (a1b1) explained 36.4% of the total effect on 6MWT distance.

Conversely, a positive relationship was observed between SMMI and WtHR (B = 0.016), while a negative relationship was found between WtHR and 6MWT distance (B = -336.414). When considering SMMI and HG strength, indirect path 2 (a2b2) accounted for 21.8% of the total effect on 6MWT distance in a negative direction.

According to Model 2, which included age, sex, and NYHA class as covariates in addition to Model 1, the total effect was significant, with SMMI accounting for 41% of the variation in 6MWT distance ($F(4,105) = 18.82$, $P < 0.001$). Compared with Model 1, the mediating effect of HG strength decreased to 17.9%, whereas the mediating effect of WtHR increased to 30.6%. The direct effect also increased, explaining 51.5% of the variation in 6MWT distance. Overall, more than half of the variance in 6MWT distance was explained by Model 2 ($R2 = 0.53$, $P < 0.001$). In both Model 1 and Model 2, HG strength acted as a positive statistical mediator in the association between SMMI and 6MWT distance, whereas WtHR acted as a negative statistical mediator. When age, sex, and NYHA class were considered, the roles of SMMI and the other mediators in relation to 6MWT distance became clearer. All mediation analysis results are presented in Table 4 and Figure 2.

Table 1. Sociodemographic and clinical characteristic of participants with heart failure

Characteristic	Values
Age, years	64.25 ± 9.54
<65 years	51 (46.4)
≥65 years	59 (53.6)
Sex, n (%)	
Female	32 (29.1)
Male	78 (70.9)
Educational background, n (%)	
Illiterate	15 (13.6)
literate	7 (6.4)
Primary school	32 (29.1)
Secondary school	25 (22.7)
High school	22 (20.0)
College or equivalent	9 (8.2)
Marital status	
Single	3 (2.7)
Married	88 (80.0)
Widowed or divorced	19 (17.3)
NYHA class	
Class II	75 (68.2)
Class III	35 (31.8)
LVEF category, %	
≤40%	81 (73.6)
41–49%	29 (26.4)
Diabetes mellitus history	45 (40.9)
Hypertension history	90 (81.8)
PTCA history	87 (79.1)
CABG history	21 (19.1)
CAD history	93 (84.5)
Pacemaker history	10 (9.1)

Data are presented as means ± standard deviation or n (%). CABG, Coronary arterial bypass graft; CAD, Coronary artery disease; LVEF, Left ventricular ejection fraction; NYHA, New York Heart Association; PTCA, Percutaneous transluminal coronary angioplasty.

Discussion

This study investigated muscle strength and WtHR as potential mediators in the relationship between muscle mass and exercise capacity in individuals with HF. The findings support our hypothesis and indicate that skeletal muscle strength acts as a positive

Table 2. Comparison of body composition, muscle strength, and exercise capacity according to age, sex, New York Heart Association (NYHA) class, and ejection fraction (EF) categories in participants with heart failure

	Age category			Sex category			NYHA class			LVEF category		
	<65 years (n = 51)	≥65 years (n = 59)	*P*	Female (n = 32)	Male (n = 78)	*P*	Class II (n = 75)	Class III (n = 35)	*P*	HFrEF (n = 81)	HFmrEF (n = 29)	*P*
Height, m	1.67 ± 0.09	1.65 ± 0.08	0.280	1.56 ± 0.06	1.70 ± 0.05	**< 0.001**	1.66 ± 0.08	1.64 ± 0.09	0.162	**1.66 ± 0.09**	**1.65 ± 0.09**	**0.714**
BMI, kg/m²	27.40 ± 4.22	29.58 ± 4.76	**0.013**	31.02 ± 6.09	27.56 ± 3.44	**0.004**	28.65 ± 4.20	28.41 ± 5.49	0.802	**28.30 ± 4.37**	**29.32 ± 5.30**	**0.309**
SMMI	10.80 ± 1.58	10.67 ± 1.39	0.657	10.07 ± 1.67	10.99 ± 1.30	**0.003**	10.74 ± 1.46	10.69 ± 1.51	0.873	**10.67 ± 1.44**	**10.89 ± 1.56**	**0.481**
Low muscle mass, n (%)	7 (13.7)	8 (13.6)	0.598	5 (15.6)	10 (12.8)	0.454	10 (13.3)	5 (14.3)	0.554	**12 (14.8)**	**3 (10.3)**	**0.755**
WtHR, m/cm	0.57 ± 0.06	0.60 ± 0.08	**0.020**	0.61 ± 0.09	0.57 ± 0.05	**0.019**	0.58 ± 0.06	0.59 ± 0.08	0.541	**0.58 ± 0.07**	**0.59 ± 0.08**	**0.201**
Abdominal obesity, n (%)	47 (92.2)	53 (89.8)	0.467	27 (84.4)	73 (93.6)	0.124	69 (92.0)	31 (88.6)	0.398	**72 (88.9)**	**28 (96.6)**	**0.286**
HG strength, kg	31.88 ± 9.93	26.14 ± 7.05	**0.001**	20.25 ± 4.66	32.31 ± 7.84	**< 0.001**	30.05 ± 9.08	26.11 ± 8.10	**0.031**	**28.72 ± 8.27**	**29.03 ± 10.75**	**0.870**
Low muscle strength, n (%)	4 (7.8)	18 (30.5)	**0.003**	8 (25.0)	14 (17.9)	0.277	11 (14.7)	11 (31.4)	**0.039**	**15 (18.5)**	**7 (24.1)**	**0.590**
6MWT, m	415.71 ± 66.76	371.85 ± 77.72	**0.002**	347.87 ± 71.79	410.36 ± 70.01	**< 0.001**	416.32 ± 61.84	340.46 ± 77.74	**< 0.001**	**388.19 ± 70.13**	**403.31 ± 90.13**	**0.359**

Data are presented as mean ± standard deviation. HG strength, Handgrip strength; HFmrEF, Heart failure with mildly reduced ejection fraction; HFrEF, Heart failure with reduced ejection fraction; LVEF, Left ventricular ejection fraction; NYHA, New York Heart Association; WtHR, Waist-to-height ratio; 6MWT, Six-minute walk test.

Table 3. Correlations among muscle mass, waist-to-height ratio (WtHR), muscle strength, and exercise capacity in participants with heart failure

	SSMI (kg/m²)	6MWT distance (m)	HG strength (kg)
6MWT distance (m)	R = 0.276 P = 0.004		
HG strength (kg)	R = 0.397 P < 0.001	R = 0.569 P < 0.001	
WtHR (cm/cm)	R = 0.343 P < 0.001	R = -0.298 P = 0.002	R = -0.127 P = 0.187

Data are presented as mean ± standard deviation. HG strength, Handgrip strength; SSMI, Skeletal muscle mass index; WtHR, Waist-to-height ratio; 6MWT, Six-minute walk test.

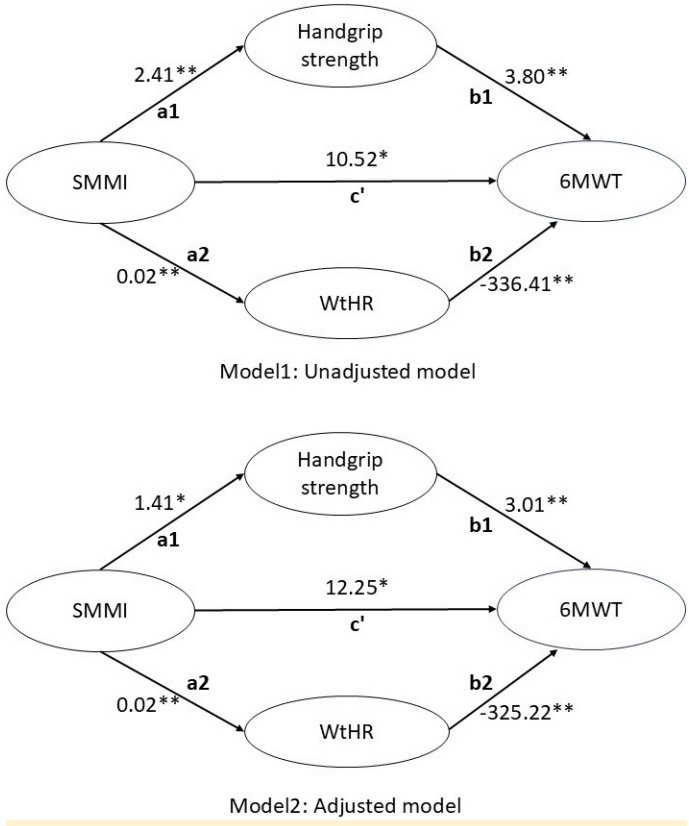


Figure 2. Results of the mediation analysis examining the effects of skeletal muscle mass on exercise capacity in the heart failure (HF) population. Direct and indirect effects of the skeletal muscle mass index on exercise capacity are shown. Unstandardized regression coefficients were used to quantify all paths.

***P < 0.05; **P < 0.001.**

partial mediator, whereas WtHR functions as a negative partial mediator in the association between muscle mass and exercise capacity. Despite these mediating pathways, more than half of the relationship between muscle mass and exercise capacity is attributable to muscle mass itself, even after accounting for age, sex, and the functional status of the participants.

Table 4. Path coefficients, indirect effects, and 95% confidence intervals for each model predicting exercise capacity in participants with heart failure

	Model 1					Model 2				
	Unstandardized B	SE	LLCI	ULCI	Mediation proportion	Unstandardized B	SE	LLCI	ULCI	Mediation proportion
Total effect	14.178	4.756	4.749	23.607	100%	9.240	3.40	1.311	17.170	100%
Direct effect	10.517	4.656	1.285	19.748	41.8%	12.254	4.272	3.782	20.726	51.5%
a1	2.410	0.536	1.347	3.472		1.412	0.421	0.578	2.246	
b1	3.800	0.726	2.359	5.240		3.011	0.839	1.348	4.675	
a2	0.016	0.004	0.007	0.024		0.022	0.004	0.0145	0.030	
b2	-336.414	90.416	-515.673	-157.154		-325.222	88.626	-500.991	-149.453	
Indirect effects										
a1b1	9.157	2.66	4.243	14.629	36.4%	4.252	1.840	1.1456	8.3435	17.9%
a2b2	-5.496	2.321	-10.474	-1.5485	21.8%	-7.266	2.385	-12.120	-2.783	30.6%
Total indirect effect	3.661	4.136	-4.719	11.737		-3.014	2.955	-8.878	2.780	
	R^2 = 0.40, P < 0.001, F = 24.012					R^2 = 0.53, P < 0.001, F = 19.641				

LLCI, Lower limit of the confidence interval; SE, Standard error; ULCI, Upper limit of the confidence interval.

Skeletal muscle abnormalities, such as muscle atrophy, muscle weakness, mitochondrial dysfunction, and fiber-type transition, play a significant role among the non-cardiac factors contributing to exercise intolerance in the HF population. Previous studies have reported a correlation between skeletal muscle mass and peakVO_2[25,26] in this population. In accordance with the existing literature, the present study identified a significant association, showing that greater muscle mass is associated with longer 6MWT distance in individuals with HF.

Handgrip strength has been identified as a significant predictor of clinical outcomes in patients with HF, with decreases in HG strength being associated with reduced exercise capacity.[27] Studies indicate that alterations in skeletal muscle may have a greater impact on exercise capacity than central hemodynamic changes.[6] The effort required to generate force in weakened muscles has been reported to be higher; however, when muscle strength is reduced, maximal effort often fails to produce optimal power output.[28] Moreover, at an equal work rate, individuals with weaker muscles experience higher levels of fatigue.[29] Considering that HG strength is representative of overall muscle strength in the body,[30] lower muscle strength may contribute to reduced exercise capacity through increased fatigue and diminished power output.

Muscle strength is closely correlated with muscle mass,[11] and the present study confirmed that this relationship is also evident in the HF population. An imbalance favoring protein degradation over protein synthesis in muscle cells has been linked to muscle loss and muscle weakness.[11] Our findings indicate that incorporating HG strength alongside muscle mass improves the prediction of changes in 6MWT distance. This finding aligns with the detrimental clinical outcomes associated with sarcopenia, defined as a decrease in both muscle mass and muscle strength. Sarcopenia has been linked to poor prognosis and reduced physical performance.[31] Our results suggest that, within the present model, 6MWT distance is partly explained by the a1b1 indirect pathway—representing the interaction between muscle strength and muscle mass—which accounted for 36.4% of the total effect. However, after adjusting for factors including age, sex, and functional status, this effect was reduced. This attenuation might be related to the strong association of these confounding factors with muscle strength.

Muscle tissue contains fatty deposits located within the fascia, muscle fibers, and intramuscular areas.[13] Therefore, it is not surprising to observe an increase in adipose tissue alongside an increase in muscle mass. Consistent with our findings, WtHR has been shown to correlate positively with muscle mass in patients with type 2 diabetes mellitus.[14] Another study involving elderly participants revealed that individuals with a high BMI had greater muscle mass, and a strong positive correlation was identified between WtHR and BMI.[32] Conversely, elevated fat levels have been associated with reduced insulin sensitivity, increased inflammatory responses, and higher cardiovascular risk.[33] Excessively high fat levels have also been linked to lower muscle mass. A study involving healthy middle-aged and older women identified a WtHR cut-off value of 0.64 for detecting low muscle mass.[34] In our investigation, the average WtHR values did not exceed this threshold in any group. Therefore,

the weak association observed between WtHR and muscle mass may reflect normal muscle physiology within this range. However, due to the cross-sectional design of the study, causal inferences cannot be made.

WtHR is used as a measure of abdominal adiposity and has been associated with mortality risk in patients with HF.[8] In individuals with abdominal obesity, abdominal pressure increases during breathing due to lung inflation and diaphragm descent. This condition is thought to contribute to reduced cardiovascular fitness.[8] Previous studies have examined the association between WtHR and exercise capacity in healthy males and in patients with HF with preserved ejection fraction (EF), demonstrating a significant negative association between WtHR and peak VO_2.[12] The present study is consistent with these findings and further demonstrates that, within the proposed model, WtHR partially and statistically explains the association between muscle mass and exercise capacity in the HF population.

In the present study, after controlling for age, sex, and functional status, WtHR demonstrated a stronger statistical mediating role in the association between muscle mass and 6MWT distance than HG strength. Although no study has specifically examined these relationships in the HF population, abdominal obesity has been reported to have a stronger correlation with functional capacity than HG strength in active women over the age of 50, which parallels our findings. Despite the different methodologies used to assess functional capacity, the results of that study, conducted in a specific population, are consistent with our findings.[35] The association between skeletal muscle weakness and exercise capacity may be related to muscle mass loss but may also occur independently of it.[36] Dynapenia, characterized by a decline in muscle strength without concurrent loss of muscle mass, has been associated with lower exercise capacity in the HF population.[37] This association has been linked to factors including inadequate power generation during exertion, insufficient oxygen consumption, and an earlier onset of fatigue in the context of neuromotor system deficits.[36,38] Abdominal fat has been associated with exercise capacity through metabolic pathways[39] but has also been linked to biomechanical limitations in mobility.[40] Central adipose tissue accumulation has been associated with shifts in the center of gravity, altered knee-joint momentum, and changes in lower-extremity alignment.[40-42] These biomechanical changes may be associated with a higher energy demand for movement and stabilization, which could contribute to exercise intolerance. Moreover, the negative effects of abdominal obesity on respiratory functions in elderly individuals,[43] combined with the association between exercise capacity and dyspnea in the HF population with, irrespective of respiratory muscle strength,[44] may help explain the pronounced mediating role of WtHR on exercise capacity observed in the present model.

In the present investigation, after accounting for clinical variables including functional status, age, and sex, muscle mass exhibited a statistically estimated direct effect, accounting for 51% of the total effect on the 6MWT distance within the mediation model. In the pathophysiological process of HF, early alterations in skeletal muscles have been described as involving disruptions in mitochondrial metabolism. According to a previous study, mitochondrial abnormalities lead to myocyte atrophy and apoptosis, playing a pivotal role in the pathogenesis of muscle dysfunction.[10] Another study involving patients with HF identified skeletal muscle mass as a primary factor associated with peak VO_2, potentially reflecting impairments in oxygen consumption mechanisms.[45] In this context, considering that the 6MWT is an assessment of aerobic exercise capacity, the observed 51% direct effect within the mediation model may be statistically related to alterations in skeletal muscle oxygen consumption mechanisms rather than to the influence of contractile fibers or adipose tissue accumulation. However, this remains a topic for further investigation. On the other hand, our findings indicate that focusing solely on skeletal muscle mass appears insufficient to account for the variation in the 6MWT distance (R^2 = 0.07). In contrast, when assessed together with muscle strength and WtHR, muscle mass contributes significantly to the statistical prediction of the 6MWTdistance (R^2 = 0.53).

From a clinical perspective, these findings may have implications for cardiac rehabilitation (CR) programs in patients with HF. The observed mediation patterns suggest that interventions addressing not only skeletal muscle mass and strength but also abdominal adiposity may be relevant for improving exercise capacity. In this context, comprehensive rehabilitation strategies that consider both muscle-related parameters and central adiposity could be beneficial. Additionally, simple clinical measures such as HG strength and WtHR may serve as useful tools for identifying patients at risk of reduced exercise capacity.

Strength and Limitations

Our study provides a novel contribution to the literature by investigating the relationship between skeletal muscle mass and exercise capacity in symptomatic ambulatory individuals with HF, while considering both facilitating and constraining mediating pathways. By applying a mediation framework, the present model allows for a more comprehensive evaluation of the interrelationships among muscle mass, muscle strength, abdominal adiposity, and exercise capacity.

However, the study has some limitations. First, although an a priori power analysis indicated that the sample size was adequate for the primary regression analyses, the data were collected from a single center, and the sample size may still be considered relatively limited for mediation analysis, particularly with respect to the precision of the estimated indirect effects. This limitation may, in turn, affect the generalizability of the findings. Second, the present study assessed muscle mass using a bioimpedance device commonly used in the literature;[16,46] nevertheless, further research using multi-frequency, multi-electrode bioelectrical impedance analysis (BIA) or dual-energy X-ray absorptiometry (DEXA) may provide greater clarity regarding our findings. Although measurements were performed under clinically stable and euvolemic conditions, and patients with serum creatinine levels > 2.0 mg/dL were excluded, BIA–derived estimates may still be influenced by minor variations in fluid distribution inherent to HF populations. Moreover, although the applied equation has been widely used in sarcopenia research, including studies conducted in clinically heterogeneous geriatric populations with multiple comorbidities, it has not yet been specifically validated in HF–specific cohorts.

Conclusion

Muscle mass accounted for 51% of the total association with exercise capacity in patients with HF when age, sex, and functional status were considered within the mediation model. This finding suggests that maintaining and/or increasing muscle mass may represent an important consideration for exercise capacity in the context of non-cardiac variables. Additionally, increasing skeletal muscle strength and reducing abdominal fat may enhance the influence of muscle mass on exercise capacity. The study also demonstrated that WtHR had a larger mediating role than muscle strength, which represents an important consideration. Overall, these findings highlight the importance of considering both muscle-related parameters and abdominal adiposity when interpreting exercise capacity in patients with HF.

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