European Review for Medical and Pharmacological Sciences 2024; 28: 3841-3848

Lack of association between serum apelin levels and sarcopenia in elderly malnourished subjects

D. DE LUIS[1,2], D. PRIMO[1,2], O. IZAOLA[1,2], J.J. LÓPEZ GÓMEZ[1,2]

[1]Center of Investigation of Endocrinology and Clinical Nutrition, Medicine School, University of Valladolid, Valladolid, Spain
[2]Department Endocrinology and Nutrition, Hospital Clinico Universitario, Valladolid, Spain

ABSTRACT. – OBJECTIVE: Sarcopenia is a condition characterized by muscle mass loss. Skeletal muscle is capable of producing and secreting different molecules called myokines, and apelin is one of them. The literature contains contradictory data on the relationship between apelin and sarcopenia. We decided to investigate the role of apelin in sarcopenia in subjects with disease-related malnutrition (DRM), a group of patients with a high rate of sarcopenia.

PATIENTS AND METHODS: 83 elderly patients with DRM assessed according to the Global Leadership Initiative on Malnutrition (GLIM) criteria were included in the study, with a mean age of 69.9±3.8 years. Anthropometric data, muscle mass by ultrasound at the rectus femoris quadriceps (RFQ) level, bioimpedance [skeletal muscle mass (SMM), appendicular SMM (aSMM) and aSMM index (aSMMI)], dynamometry, biochemical parameters, dietary intake, circulating apelin levels were determined in all patients.

RESULTS: A total of 33 patients (37.9%) were diagnosed with sarcopenia, while 54 patients did not present sarcopenia (60.1%). Body weight (-5.5±2.0 kg, *p*=0.01), calf circumference (-1.9±0.2 cm, *p*=0.02), phase angle (-0.6±0.2°, *p*=0.01), reactance (-6.8±2.3 Ohms, *p*=0.03), resistance (-38.8±12.3 Ohms, *p*=0.04), SMM (-2.2±0.3 kg, *p*=0.04), aSMM (-2.2±0.2 kg, *p*=0.03) and aSMMI (-0.6±0.2 kg, *p*=0.02), dominant muscle area (-0.6±0.2 cm^2, *p*=0.04), dominant Y axis (-0.4±0.1 cm, *p*=0.03), dominant X/Y axis (1.1±0.3 cm, *p*=0.04), strength (-5.1±1.3 kg, *p*=0.01), albumin (-0.9±0.1 g/dl, *p*=0.02) and prealbumin (-4.6±0.7 mg/dl, *p*=0.02) were worse in patients with sarcopenia than non-sarcopenic patients. Circulating apelin levels were similar in both groups. No significant correlation of apelin levels was detected, either with bioimpedance data or with muscle ultrasonography data. The multivariant analysis did not detect a significant association of apelin with the presence of sarcopenia.

CONCLUSIONS: Our study shows a lack of association between apelin and sarcopenia in elderly malnourished patients.

Key Words:
Apelin, Malnourished patients, Sarcopenia.

Introduction

Sarcopenia is defined by age-related loss of function and muscle mass; this entity plays a main role in the development of disability[1] and negatively impacts muscle homeostatic functions (such as immune, endocrine, and metabolic actions)[2]. Despite its high prevalence and recognition as a disease[3], several factors related to pathophysiology, related factors, and treatment/prevention/diagnostic options remain to be improved[4]. Nowadays, several blood-based molecules associated with different physiological pathways involved in muscle tissue metabolism have been proposed as sarcopenia markers[5].

Skeletal muscle is capable of producing and secreting different molecules in order to communicate with other tissues in an endocrine, either paracrine or autocrine way, named myokines. One of these myokines is apelin, the ligand of apelin protein junction (APJ) G-protein coupled receptor, which is a pleiotropic peptide that has been shown[5] to modulate several processes implied in neuroprotection, immunity, glucose metabolism, and cardiovascular regeneration. Recent data[6,7] has revealed that age-related apelin decreases might negatively impact mitochondrial amount and function, as well as local skeletal muscle regeneration, which contributes to muscle mass and function losses in the elderly[6] and a potential role in myocardial infarction and pulmonary diseases[7]. Moreover, in human investigations[7-9], the relationship between circulating apelin levels and sarcopenia remains unclear, with a lack of association in two studies[8,9] and a positive relationship in the other[10]. These investigations have been con-

Corresponding Author: D. de Luis, MD; e-mail: dluisro@saludcastillayleon.es

ducted in non-malnourished Caucasic and Asiatic patients. Disease-related malnutrition (DRM) is also an important health problem for patients[11,12]. DRM is related to the alterations associated with underlying disease, low dietary intake and decreases in body weight and muscle mass. As mentioned, sarcopenia is a condition with low muscle mass and poor functional capacity[13]. Considering the previously mentioned situation, muscle is the most important protein reserve in the human body, and its mass is one of the parameters used to evaluate DRM. The production of myokines in the skeletal muscle, such as apelin, the role of the muscle in the diagnosis of DRM and in the physiological basis of sarcopenia make this research area a promising area to investigate the potential role of this molecule, as it has already been done in murine models[14]. For example, apelin-deficient mice showed early onset of sarcopenia, whereas treatment with apelin enhanced muscle strength in this animal model[14].

Given that no studies of apelin have been conducted in patients with DRM, we decided to investigate the role of this circulating myokine in sarcopenia in this group of patients.

Patients and Methods

Study Population

This was a cross-sectional outpatient study. The participants included in the research visited the Nutrition Unit of the Hospital Clinico Universitario de Valladolid for the management of DRM. We studied all patients' nutritional status with anthropometric and biochemical parameters, including apelin levels. They were ambulatory, community-dwelling, and not in inpatient facilities. This study was approved by the Bioethical Committee of the Health Area of HCUVa (PI 23-3226, on 14 July 2023). Written informed consent was obtained and signed by all enrolled patients. The study was conducted in accordance with the principles outlined in the Helsinki Declaration.

The patient inclusion criteria were patients with DRM diagnosed by the Global Leadership Initiative on Malnutrition (GLIM) criteria[15] and aged over 65 years. The exclusion criteria were chronic heart failure, chronic obstructive pulmonary disease, active alcohol habit, decompensated liver disease, diabetes mellitus, chronic kidney disease stage IV or higher, inability to walk, and patients whose life expectancy was expected to be less than one year.

Study Variables

Anthropometric data were recorded, and a blood sample was collected during the same clinical visit. The following anthropometric data were collected [body weight, height, body mass index (BMI), calf circumference, and waist circumference]. A bioimpedance analysis (BIA) was performed, and we obtained the following parameters (resistance, reactance, and phase angle) and calculated the following data [fat mass (FM), skeletal muscle mass (SMM), appendicular muscle mass (aSMM), appendicular muscle mass index (aSMMI)][16]. Muscle mass was measured by ultrasound at the level of the rectus femoris quadriceps (RFQ). To determine the biochemical parameters, 20 ml of venous blood was aliquoted into tubes coated with ethylenediaminetetraacetic acid (EDTA) after an overnight fast of 8 hours. The following biochemical data were obtained: albumin (g/dl), C-Reactive Protein (CRP) (mg/dl), prealbumin (mg/dl), and apelin (ng/ml).

Anthropometric Parameters, Bioimpedance and Muscle Ultrasound

Height (cm) and waist circumference (cm) were determined with a non-elastic tape measure (Omrom, LA, CA, USA). Body weight was measured with a digital scale (Omrom, LA, CA, USA). BMI was calculated using body weight (kg) divided by the square of height (m). Calf circumference was measured at the point of maximum diameter of the gastrocnemius femoris muscle in the leg. From the bioimpedance analysis, we obtained two raw data: resistance (R) and the capacitance component (X). The Phase angle (PhA) was calculated using the following equation PhA = (X/R) x (180°/π). The BIA provided fat mass (FM), skeletal muscle mass (SMM), appendicular muscle mass (aSMM), and appendicular muscle mass index (aSMMI) as aSMM divided by squared height[17] (EFG BIA 101 Anniversary, Akern, Pisa, Italy).

Muscle ultrasound of the RFQ of the dominant lower extremities with a 10 to 12 MHz probe (Mindray Z60, Madrid, Spain) was performed in all patients. The probe was aligned perpendicular to the longitudinal and transverse axis of the rectus femoris quadriceps. The evaluation was performed without compression at the level of the lower third from the superior pole of the patella and the anterosuperior iliac spine. The measurements obtained with ultrasound were: rectus femoris area (cm^2), the RFQ circumference (cm), the X-axis of RFQ (cm), the Y-axis of RFQ (cm), and the X/Y index RFQ[17].

In our study, muscle strength was measured by hand grip strength using a dynamometer with the patient seated and the arm at a right angle to the forearm (JAMAR® dynamometer, Sammons Preston, Bolingbrook, IL, USA). Three measurements were taken and the average of the three measurements was calculated. The diagnostic criteria of low muscle strength proposed by the European Working Group on sarcopenia in Older People (EWGSOP2)[18] were used (<27 kg in men and <16 kg in women). Sarcopenia is diagnosed when there is low muscle strength and abnormal appendicular skeletal muscle mass index (aSMMI) on BIA (<7.0 kg/m^2 for males and <5.5 kg/m^2 for females)[18].

Dietary Intake and Physical Exercise

All malnourished patients were instructed to record their daily dietary intake for three non-consecutive days. Dietary records were determined using specific software (Dietsource®, Geneve, Switzerland), including national composition food tables as reference[19]. The average of macronutrients and micronutrients from these three days was obtained. Two weekdays and one weekend day were obtained, and the three values were averaged to improve the results. Patients recorded their daily physical activity as minutes per day. The patients collected their activity with a self-administered questionnaire in which they recorded their daily physical activity.

Biomarkers

The conventional nutritional parameters were determined with a Cobas c-711 autoanalyzer (Roche Diagnostics, Geneve, Switzerland): albumin (g/dl), CRP (mg/dl), and prealbumin (mg/dl). We used the commercial kit MILLIPLEX® Human Myokine Magnetic Bead Panel (HCYTOMAG-56K, EMD Millipore Corporation, MA, USA) to measure serum apelin levels.

Statistical Analysis

Statistical analysis was performed with SPSS statistical software for Windows version 23.0 (IBM Corp., Armonk, NY, USA). The sample size was determined to detect differences of 100 pg/ml of circulating apelin levels between both groups of patients with DRM (no sarcopenia *vs.* sarcopenia). Descriptive statistics for all variable values are presented as mean and standard deviation for continuous variables and as percentages for categorical variables. Correlation analysis was realized using Pearson's test. The variables were analyzed using the Student's *t*-test (for the variable with normal distribution) or the Kruskal-Wallis test (for the variable with non-normal distribution). The Bonferroni test is used in statistics to address the issue of multiple comparisons in order to decrease the chance of making a Type I error. We applied this correction to all the anthropometric, BIA, and ultrasound variables. The Chi-square test was used to assess the qualitative variables. Multiple logistic regression models adjusted by sex and age were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) in order to examine the relationship between apelin levels and the presence of sarcopenia (median value of apelin 76.88 pg/ml). The receptor operation characteristic curve for sarcopenia was calculated to determine apelin levels. The cutoff points were elucidated by the area under the curve (AUC) that had the best specificity and sensitivity values for the test in question. *p*-values below 0.05 were considered statistically significant.

Results

87 elderly patients diagnosed with GLIM criteria were included in the study, with a mean age of 69.9±3.8 years. There were 51 females (58.6%) and 36 males (41.4%). The cause of DRM was the following: stable oncological pathology in 34 patients (39.0%), chronic neurological pathology in 18 patients (20.7%), digestive pathology in 17 patients (19.7%) and 18 other patients (miscellany) (20.7%) being a representative sample of elderly patients with DRM who visited our Nutritional Unit. Table I reports the classical anthropometric data, ultrasound parameters, bioimpedance data and biochemical results of the studied sample, showing a normal weight population (BMI: 22.5±5.3 kg/m^2).

Of our sample of patients, a total of 33 patients (37.9%) were diagnosed with sarcopenia according to the criteria of the European Working Group on sarcopenia in older people (EWGSOP2)[18], while 54 patients did not present sarcopenia (60.1%) (Table II). The distribution by sex was similar in both the sarcopenia [18 females (54.5%) and 15 males (45.5%)] and the non-sarcopenia groups [33 females (61.1%) and 21 males (38.9%)]. As expected, Table II reports statistical differences in classical anthropometric parameters such as body weight (-5.5±2.0 kg, p=0.01) and calf circumference (-1.9±0.2 cm, p=0.02) between patients with and without sarcopenia. Bio-

Table I. Basal parameters in total group (mean±SD).

Parameters	Total group n=87
Age (years)	69.9±3.8
BMI (kg/m^2)	22.6±3
Weight (kg)	56.3±4.1
Fat mass (kg)	18.9±4.3
SMM (kg)	19.9±3.9
aSMM (kg)	15.8±2.8
aSMMI (kg)	7.7±0.8
CC (cm)	31.5±1.1
Phase angle (º)	4.9±0.8
Reactance (ohms)	51.3±6.1
Resistance (ohms)	590.1±72.1
Dominant muscle area RFQ (cm^2)	3.1±1.0
Dominant circumference area RFQ (cm)	8.3±1.2
Dominant X axis RFQ (cm)	3.4±0.7
Dominant Y axis RFQ (cm)	1.0±0.3
Dominant X/Y axis RFQ (cm)	3.4±0.2
Dominant ecointensity (gray scale units)	86.8±20.1
Strength (kg)	19.8±1.1
CRP (mg/dl)	7.2±2.0
Albumin (g/dl)	4.7±3.0
Prealbumin (mg/ml)	21.0±3.1
Apelin (pg/ml)	86.8±74.8

Calf circumference (CC), skeletal muscle mass (SMM), appendicular muscle mass (aSMM), appendicular muscle mass index (aSMMI), rectus femoris quadriceps (RFQ).

impedance parameters were also worse in elderly patients with sarcopenia [Phase angle (-0.6±0.2º, p=0.01), reactance (-6.8±2.3 Ohms, p=0.03), resistance (-38.8±12.3 Ohms, p=0.04), SMM (-2.2±0.3 kg, p=0.04), aSMM (-2.2±0.2 kg, p=0.03) and aSMMI (-0.6±0.2 kg, p=0.02)] than patients without sarcopenia. Moreover, ultrasound parameters of RFQ were worse in patients with sarcopenia [dominant muscle area (-0.6±0.2 cm^2, p=0.04), dominant Y axis (-0.4±0.1 cm, p=0.03) and dominant X/Y axis (1.1±0.3 cm, p=0.04)] than non-sarcopenic patients. Finally, the strength was better in non-sarcopenic patients (5.1±1.3 kg, p=0.01) than in sarcopenic patients.

Patients with sarcopenia had worse serum protein levels [albumin (-0.9±0.1 g/dl, p=0.02) and prealbumin (-4.6±0.7 mg/dl, p=0.02)] than patients without sarcopenia. Circulating apelin levels were similar in non-sarcopenic patients than in sarcopenic patients.

When we divided the patients into two groups based on dynapenia [low force according to the European Working Group on Sarcopenia in Older People (EWGSOP2) criteria (<27 kg in males and <16 kg in females)[18]], we found that the patients with low strength had similar levels of apelin (80.3±12.3 *vs.* 88.4±112 pg/ml, p=0.41) compared to patients with normal strength (>27 kg in males and >16 kg in females).

Finally, no significant correlation between apelin levels was detected, either with bioimpedance data or with muscle ultrasonography data.

Table III reports dietary intake and physical exercise. Energy intake as well as carbohydrates, fat and protein intakes were worse in patients with sarcopenia than patients without sarcopenia. Minutes of daily exercise were similar in both groups.

Taking into account the previous data, the patients were divided into two groups according to the median value of circulating apelin (76.88 pg/ml), and the odds ratio was calculated for the risk of developing sarcopenia. Patients with a value of apelin below the median cutoff point had similar sarcopenia risk than patients under this cutoff point (OR: 0.97, 95% CI: 0.67-1.23; p=0.22). Finally, logistic regression analysis reported a similar risk of sarcopenia (OR: 0.95, 95% CI: 0.61-1.332; p=0.33) in both apelin groups as a dichotomic parameter after adjusting for BMI, sex, energy intake, and age. The ROC curve of the apelin levels for sarcopenia is shown in Figure 1. The area under the curve (AUC), according to EWGSOP2 criteria[18], showed values of 0.541 (0.411-0.661, p=0.34).

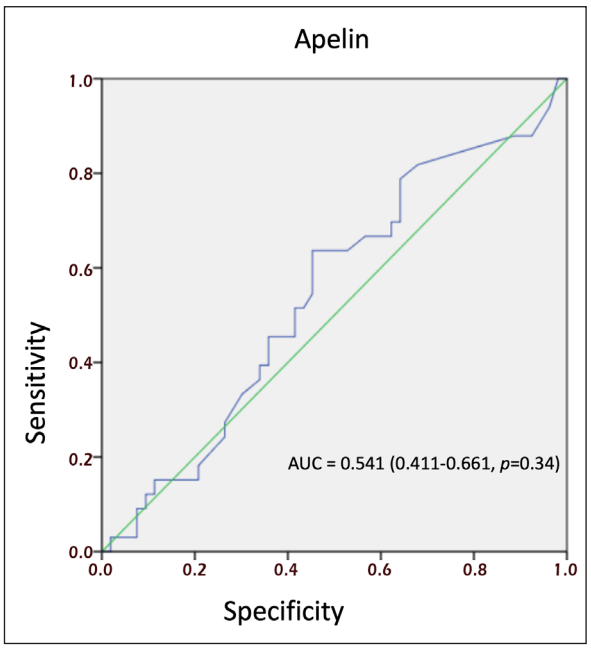

Figure 1. The ROC curve of the apelin levels for sarcopenia.

Discussion

In our cross-sectional study of community-dwelling elderly malnourished subjects, we reported that serum apelin level was not associated with sarcopenia and strength. This is the first time that the effect of apelin on sarcopenia in patients with DRM has been evaluated.

Some investigations[14] from animal models report that apelin may have a main role in some age-related disorders. For example, murine models[14] lacking apelin and its receptor reported huge decreased muscle strength and muscle mass, and chronic apelin treatment decreased muscle aging. This positive effect of apelin on muscle status is mediated by the stimulation of adenosin monophospathe (AMP) activated protein kinase and Akt and the secondary mitochondriogenesis[20]. Taking into account that these physiological pathways, including musculoskeletal debility, are related to sarcopenia, apelin could be expected to be a therapeutic target to treat this entity and a clinical biomarker to diagnose sarcopenia. Despite the above-mentioned data, the effects of apelin on human health remain unclear. In our present study, we did not observe a significant association between apelin and sarcopenia in elderly patients with DRM. These results are in line with those previously obtained in other studies in the literature. For example, Sanchez-Sanchez et al[10] did not detect a relationship between this myokine and sarcopenia in older adults in the multidomain Alzheimer prevention trial (MAPT) study. This study included 168 older adults (>70 years) attending primary care centers; serum apelin was not associated with sarcopenia incidence or with the evolution of sarcopenia components over a 2-year follow-up in this Caucasian population[10]. In an Asiatic population of 80 older subjects (>60 years), Jang et al[9] reported a lack of association of serum apelin level with both functional parameters and phenotypic frailty. Only Chen et al[8] showed that apelin was associated with hand grip strength and inversely associated with the presence of sarcopenia [OR 0.54 (95% CI: 0.39-0.73)]. This study was realized in an Asiatic population of 463 older subjects (>60 years).

Although we cannot explain the exact mechanism for this discrepancy and the lack of association of apelin and sarcopenia in our study, several hypotheses might be implied. First, although the murine model is used to evaluate human illness mechanisms because of natural similarity, they are not the same. Several studies[21,22] have revealed

Table II. Differences between patients with sarcopenia *vs*. no sarcopenia (mean±SD).

Parameters	No sarcopenia n=54	Sarcopenia n=33	*p*-value
Age (years)	69.7±3.1	70.1±2.4	0.33
BMI (kg/m^2)	22.8±2.3	21.4±2.1	0.19
Weight (kg)	59.3±4.0	53.8±3.2	0.01
Fat mass (kg)	20.1±3.5	15.5±2.8	0.03
Skeletal muscle mass (kg)	21.1±1.1	18.9±1.0	0.03
Appendicular muscle mass (aSMM),	17.5±0.8	15.3±1.0	0.03
Appendicular muscle mass index (aSMMI)	8.1±0.3	7.5±0.2	0.02
CC (cm)	32.1±1.0	30.2±1.1	0.02
Phase angle (°)	5.3±0.2	4.7±3.1	0.01
Reactance (ohms)	54.6±2.0	47.8±3.1	0.03
Resistance (ohms)	575.7±14.1	613.7±51.2	0.04
Dominant muscle area RFQ (cm^2)	3.4±0.3	2.9±0.2	0.04
Dominant circumference RFQ (cm)	8.5±1.1	8.1±1.0	0.10
Dominant X axis RFQ (cm)	3.5±0.3	3.2±0.3	0.32
Dominant Y axis RFQ (cm)	1.2±0.1	0.8±0.2	0.03
Dominant X/Y axis RFQ (cm)	2.9±0.2	4.0±0.3	0.04
Dominant ecointensity (gray scale units)	90.7±22.1	89.6±18.1	0.29
Strength (kg)	23.0±2.0	17.9±2.1	0.01
CRP (mg/dl)	6.9±2.1	7.3±2.9	0.38
Albumin (g/dl)	4.9±0.3	4.0±0.4	0.02
Prealbumin (mg/ml)	23.7±2.0	19.1±1.4	0.02
Apelin (pg/ml)	77.2±16.3	90.3±23.3	0.29

Calf circumference (CC), skeletal muscle mass (SMM), appendicular muscle mass (aSMM), appendicular muscle mass index (aSMMI), rectus femoris quadriceps (RFQ).

Table III. Differences between patients with sarcopenia *vs*. without sarcopenia basal, average daily intakes, and physical activity (mean±SD).

Parameters	Total group n=87	No sarcopenia n=54	Sarcopenia n=33	*p*-value
Calorie intake (kcal/day)	1,590.1±323.2	1,698.1±218.9	1,401.9±209.2	*p*=0.01
Carbohydrate intake (g/day)	164.9±51.1	174.5±50.1	150.4±43.1	*p*=0.02
(PTC %)	(43.9%)	(44.2%)	(43.5%)	
Fat intake (g/day)	69.3±10.1	75.3±12.2	67.6±10.9	
(PTC %)	(39.9%)	(39.5%)	(40.0%)	*p*=0.03
Protein intake (g/day)	68.3±8.1	71.3±7.0	67.3±5.1	
(PTC %)	(16.2%)	(16.3%)	(16.5%)	*p*=0.02
Fiber intake (g/day)	13.7±5.0	13.4±5.1	13.8±4.1	*p*=0.31
Physical activity (min/day)	59.9±6.2	60.3±9.1	58.5±6.1	*p*=0.39

Percentage of total calories (PTC).

a large degree of difference in sequences related to transcriptional regulation, chromatin state, and higher-order chromatin organization. This could explain why some processes in mice metabolism and aging are significantly different from those in humans. Second, the physiologic apelin level detected in humans may not be high enough to explain the phenotypic changes. The apelin expression is almost completely stopped in murine models, and the concentration of apelin used was relatively high and had a long period[22]. Only one study[8] has demonstrated a relationship between apelin levels and sarcopenia; in this study, the average of patients was higher than our study, and patients were from an Asiatic area. Finally, the nutritional status of the patients was not described, although they had a lower average SMI than our patients; perhaps not all the patients were as malnourished as our design. All these data mean that this study[8] is not comparable with ours. In any case, given the lack of well-powered and designed longitudinal studies, further research is needed to evaluate the potential of apelin as a diagnosis biomarker or interventional target in the area of sarcopenia. The absence of a relationship between circulating apelin levels in our study and the presence of sarcopenia may be due to the population studied in our work, which is an entire population with DRM, unlike the only study[8] in humans in the literature that has shown this relationship, conducted in a population without demonstrated DRM. On the other hand, the absence of a relationship with circulating levels does not mean that apelin may have a paracrine action, which, in our study, is impossible to evaluate by determining only the circulating levels of apelin.

Limitations and Strengths

Our design has some limitations. First, the sample size is relatively small, which may affect the robustness and generalizability of our findings. A larger sample size would provide more statistical power and potentially more reliable results. Second, because our study is cross-sectional, we are unable to establish causal relationships between the variables. Longitudinal studies would be needed to determine causality and understand the temporal sequence of events. Third, our design only included patients with DRM, meaning that our results cannot be generalized to the broader population. Including a more diverse range of participants would provide a more comprehensive understanding of the issue. Fourth, our study population was exclusively Caucasian, limiting the applicability of our findings to other ethnic groups. Research that includes various ethnic backgrounds would enhance the external validity of the results. Additionally, we cannot rule out the possibility that biased information or uncontrolled factors, such as dietary habits or physical activity levels, might influence sarcopenia and apelin levels, thereby affecting our conclusions. Despite these limitations, our study has notable strengths. We utilized multiple techniques to measure muscle mass, including impedance and RFQ ultrasound, which provide

a more accurate and reliable assessment. This methodological rigor strengthens the validity of our findings. Furthermore, the spectrum of subjects with DRM in our study is wide, reflecting the diversity seen in real clinical practice. This broad inclusion enhances the relevance and applicability of our findings to typical clinical settings, ensuring that our results are meaningful for healthcare practitioners dealing with a variety of cases in real-world environments.

Conclusions

In conclusion, our study shows a lack of association between apelin and sarcopenia in elderly malnourished patients. Considering the limitations, this study might serve as a proof of concept on this topic area, and additional well-designed large-scale longitudinal studies are necessary to understand the role of apelin in sarcopenia. It is necessary to take into account that it has been suggested[23] that apelin induces protein synthesis and inhibits age-related proteolysis in myotubes. It is evident that sarcopenia is an area of high interest in research, given its clinical significance in our patients[24].

Conflict of Interest
The authors declare no conflict of interest.

Ethics Approval
This study protocol was reviewed and approved by the HCVUA Committee [approval number (PI 23-3226, 14 July 2023)]. This research complies with the guidelines for human studies in accordance with the Declaration of Helsinki.

Informed Consent
Signed informed consent was obtained from all participants.

Funding
No funding was received for this study.

Authors' Contributions
D. de Luis designed the study and wrote the article. J.J. Lopez Gomez and O. Izaola performed the nutritional evaluation. D. Primo and D. de Luis performed the biochemical evaluation.

Data Availability
All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

ORCID ID
David Primo Martin: 0000-0002-3474-0766
Olatz Izaola Jauregui: 0000-0003-1201-4875
Juan jose Lopez Gomez: 0000-0003-3144-343X
Daniel de Luis Román: 0000-0002-1745-9315

References

1) Cruz-Jentoft AJ, Sayer AA. Sarcopenia. Lancet 2019; 393: 2636-2646.
2) Angulo J, El Assar M, Rodríguez-Mañas L. Frailty and sarcopenia as the basis for the phenotypic manifestation of chronic diseases in older adults. Mol Aspects Med 2016; 50: 1-32.
3) Locquet M, Beaudart C, Hajaoui M, Petermans J, Reginster JY, Bruyère O Three-Year Adverse Health Consequences of Sarcopenia in Community-Dwelling Older Adults According to 5 Diagnosis Definitions. J Am Med Dir Assoc 2019; 20: 43-46.
4) Laosa O, Alonso C, Castro M, Rodriguez-Manas L. Pharmaceutical interventions for frailty and sarcopenia. Curr Pharm Des 2014; 20: 3068-3082.
5) Kwak SE, Cho SC, Bae JH, Lee J, Shin HE, Di Zhang D, Lee YI, Song W Effects of exercise-induced apelin on muscle function and cognitive function in aged mice. Exp Gerontol 2019; 127: 110710.
6) Vinel C, Lukjanenko L, Batut A. The exerkine apelin reverses age-associated sarcopenia. Nat Med 2018; 24: 1360-1371.
7) Gao S, Chen H. Therapeutic potential of apelin and Elabela in cardiovascular disease. Biomed Pharmacother 2023 8; 166: 115268.
8) Chen YY, Chiu YL, Kao TW, Peng TC, Yang HF, Chen WL. Cross-sectional associations among P3NP, HtrA, Hsp70, Apelin and sarcopenia in Taiwanese population. BMC Geriatr 2021; 21: 192.
9) Jang IY, Lee S, Kim JH, Lee E, Lee JY, Park SJ, Kim DA, Hamrick MW, Park JH, Kim BJ. Lack of association between circulating apelin level and frailty-related functional parameters in older adults: a cross-sectional study. BMC Geriatr 2020; 20: 420.
10) Sanchez-Sanchez JL, He L, Virecoulon Giudici K, Guyonnet S, Parini A, Dray C, Valet P, Pereira O, Vellas B, Rolland Y, de Souto Barreto P. Circulating Levels of Apelin, GDF-15 and Sarcopenia: Lack of Association in the MAPT Study. J Nutr Health Aging 2022; 26: 564-570.
11) Sorensen J, Kondrup J, Prokopowicz J, Schiesser M, Krähenbühl L, Meier R, Liberda M; EuroOOPS study group. EuroOOPS: An international, multicentre study to implement nutritional risk screening and evaluate clinical outcome. Clin Nutr 2008; 27: 340-349.
12) Zugasti Murillo A, Petrina-Jáuregui ME, Ripa-Ciáurriz C, Sánchez Sánchez R, Villazón-González F, González-Díaz Faes Á. SeDREno study — prevalence of hospital malnutrition according to GLIM criteria, ten years after the PREDyCES study. Nutr Hosp 2021; 38: 1016-1025.

13) Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M, Zamboni M; Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: European consensus on definition and diagnosis. Age Ageing 2018; 39: 412-423.

14) Vinel C, Lukjanenko L, Batut A, Deleruyelle S, Pradère JP, Le Gonidec S, Dortignac A, Geoffre N, Pereira O, Karaz S, Lee U, Camus M, Chaoui K. The exerkine apelin reverses age-associated sarcope-nia. Nat Med 2018; 24: 1360-1371.

15) Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, Baptista G, Barazzoni R, Blaauw R, Coats A, Crivelli A, Evans DC, Gramlich L, Fuchs-Tarlovsky V, Keller H, Llido L, Malone A, Mogensen KM, Morley JE, Muscaritoli M, Nyulasi I, Pirlich M, Pisprasert V, de van der Schueren MAE, Siltharm S, Singer P, Tappenden K, Velasco N, Waitzberg D, Yamwong P, Yu J, Van Gossum A, Compher C; GLIM Core Leadership Committee; GLIM Working Group. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. Clin Nutr 2019; 38: 1-9.

16) Lukaski H, Johson PE. Assessment of fat-free mass using bioelectrical impedance measurements of the human body. Am J Clin Nutr 1985; 41: 810-817.

17) García-Almeida JM, García-García C, Vegas-Aguilar IM, Ballesteros Pomar MD, Cornejo-Pareja IM, Fernández Medina B, de Luis Román DA, Bellido Guerrero D, Bretón Lesmes I, Tinahones Madueño FJ. Nutritional ultrasound®: Conceptualisation, technical considerations and standardisation. Endocrinol Diabetes Nutr 2022: 1: 74-84.

18) Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M, Zamboni M; Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019; 48: 601.

19) Mataix J, Mañas M. Tablas de composición de alimentos españoles. Ed: University of Granada, 2003.

20) Dray C, Knauf C, Daviaud D, Waget A, Boucher J, Buléon M, Cani PD, Attané C, Guigné C, Carpéné C, Burcelin R, Castan-Laurell I, Valet P. Apelin stimulates glucose utilization in normal and obese in-sulin-resistant mice. Cell Metab 2008; 8: 437-445.

21) Yue F, Cheng Y, Breschi A, Vierstra J, Wu W, Ryba T, Sandstrom R, Ma Z, Davis C, Pope BD, Shen Y, Pervouchine DD, Djebali S, Thurman RE, Kaul R, Rynes E, Kirilusha A, Marinov GK, Wil-liams BA, Trout D, Amrhein H, Fisher-Aylor K, Antoshechkin I, DeSalvo G, See LH, Fastuca M, Drenkow J, Zaleski C, Dobin A, Prieto P, Lagarde J, Bussotti G, Tanzer A, Denas O, Li K, Bender MA, Zhang M, Byron R, Groudine MT, McCleary D, Pham L, Ye Z, Kuan S, Edsall L, Wu YC, Rasmussen MD, Bansal MS, Kellis M, Keller CA, Morrissey CS, Mishra T, Jain D, Dogan N, Harris RS, Cayting P, Kawli T, Boyle AP, Euskirchen G, Kundaje A, Lin S, Lin Y, Jansen C, Malladi VS, Cline MS, Erickson DT, Kirkup VM, Learned K, Sloan CA, Rosenbloom KR, Lacerda de Sousa B, Beal K, Pignatelli M, Flicek P, Lian J, Kahveci T, Lee D, Kent WJ, Ramalho Santos M, Herrero J, Notredame C, Johnson A, Vong S, Lee K, Bates D, Neri F, Diegel M, Canfield T, Sabo PJ, Wilken MS, Reh TA, Giste E, Shafer A, Kutyavin T, Haugen E, Dunn D, Reynolds AP, Neph S, Humbert R, Hansen RS, De Bruijn M, Selleri L, Rudensky A, Josefowicz S, Samstein R, Eichler EE, Orkin SH, Levasseur D, Papayannopoulou T, Chang KH, Skoultchi A, Gosh S, Disteche C, Treuting P, Wang Y, Weiss MJ, Blobel GA, Cao X, Zhong S, Wang T, Good PJ, Lowdon RF, Adams LB, Zhou XQ, Pazin MJ, Feingold EA, Wold B, Taylor J, Mortazavi A, Weissman SM, Stamatoyannopoulos JA, Snyder MP, Guigo R, Gingeras TR, Gilbert DM, Hardison RC, Beer MA, Ren B; Mouse ENCODE Consortium. A comparative encyclopedia of DNA elements in the mouse genome. Nature 2014; 515: 355-364.

22) Rai R, Ghosh AK, Eren M, Mackie AR, Levine DC, Kim SY, Cedernaes J, Ramirez V, Procissi D, Smith LH, Woodruff TK, Bass J, Vaughan DE. Downregulation of the Apelinergic Axis accelerates aging, whereas its systemic restoration improves the mammalian Healthspan. Cell Rep 2017; 21: 1471-1480.

23) Vinel C, Lukjanenko L, Batut A, Deleruyelle S, Pradère JP, Le Gonidec S, Dortignac A, Geoffre N, Pereira O, Karaz S, Lee U, Camus M, Chaoui K, Mouisel E, Bigot A, Mouly V, Vigneau M, Pagano AF, Chopard A, Pillard F, Guyonnet S, Cesari M, Burlet-Schiltz O, Pahor M, Feige JN, Vellas B, Valet P, Dray C. The exerkine apelin reverses age-associated sarcopenia. Nat Med 2018; 24: 1360-1371.

24) Wu JF, Jia J, Chen P, Wang XF, Yang FX, Liu Y, Ma YM, Jin JW. Sarcopenia and its clinical corre-lation in elderly chronic obstructive pulmonary disease: a prospective cohort study. Eur Rev Med Pharmacol Sci 2023; 27: 9762-9772.

3848