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ABSTRACT

Introduction: FGF21 has potential functions as a key regulator in coordinating the metabolic response to protein deficiency.

Objective: the aim of our design is to explore the role of circulating FGF21 in patients with disease-related-malnutrition (DRM) and its relationship with protein dietary intake.

Material and methods: 108 DRM patients were included. Bioelectrical impedance analysis was conducted to assess skeletal muscle mass (SMM), appendicular skeletal muscle mass (aSMM), and the appendicular skeletal muscle mass index (aSMMI). Muscle mass was evaluated using ultrasound at the rectus femoris quadriceps (RFQ) level, too. Handgrip strength, biochemical parameters, dietary intake, and circulating FGF21 levels were also measured.

Results: mean age was 61.3 ± 1.1 years. A negative correlation between FGF21 levels and some parameters of rectus femoris quality (RFQ) such as dominant muscle area, reactance, SMM, aSMM and albumin levels were reported. Protein intake was negatively correlated (r = -0.55; p = 0.02), too. Patients with higher protein intake (median intake 53.7 g/day) had higher dominant muscle area RQF (0.6 ± 0.2 cm^2; p = 0.03), reactance (7.5 ± 0.3; p = 0.03), SMM (2.6 ± 0.3 kg; p = 0.03), aSMM (2.3 ± 0.8 kg; p = 0.03), albumin (0.7 ± 0.2 mg/dL; p = 0.04), prealbumin (10.1 ± 0.8 mg/dL; p = 0.02) and lower levels of FGF21 (86.5 ± 9.8 ng/dL; p = 0.01). Patients with

FGF21 levels above the median cut-off point (61.3 ng/mL) had a significantly higher risk of low protein intake (OR = 2.47, 95 % CI = 1.14-5.35; p = 0.02).

Conclusion: a significant association between increased serum FGF21 levels and low protein dietary intake is reported in patients with DRM.

Keywords: FGF21. Disease-related malnutrition. Sarcopenia. Muscle ultrasound.

RESUMEN

Introducción: el FGF21 tiene funciones como regulador clave en la coordinación de la respuesta metabólica a la deficiencia proteica.

Objetivo: el objetivo de nuestro diseño fue explorar el papel del FGF21 en pacientes con desnutrición relacionada con la enfermedad (DRE) y su relación con la ingesta de proteínas.

Material y métodos: se incluyeron 108 pacientes. Se realizó un análisis de impedancia bioeléctrica para evaluar la masa muscular esquelética (MME), masa muscular esquelética apendicular (aMME) y el índice de masa muscular esquelética apendicular (aMMEI). Se evaluaron la masa muscular mediante ecografía en el recto femoral cuádriceps (RFQ) y la fuerza de prensión manual, los parámetros bioquímicos, la ingesta dietética y FGF21.

Resultados: la edad media fue 61,3 ± 1,1 años. Se observo una correlación negativa entre los niveles de FGF21 y área muscular dominante, reactancia, SMM, aSMM y albúmina. La ingesta de proteínas también se correlacionó negativamente (r = -0,55; p = 0,02). Los pacientes con mayor ingesta proteica (mediana: 53,7 g/día) presentaron mayor área muscular dominante RQF (0,6 ± 0,2 cm^2; p = 0,03), reactancia (7,5 ± 0,3; p = 0,03), SMM (2,6 ± 0,3 kg; p = 0,03), aSMM (2,3 ± 0,8 kg; p = 0,03), albúmina (0,7 ± 0,2 mg/dL; p = 0,04), prealbúmina (10,1 ± 0,8 mg/dL; p = 0,02) y menores niveles de

FGF21 (86,5 ± 9,8 ng/dl; p = 0,01). Los pacientes con niveles de FGF21 por encima del punto de corte (mediana: 61,3 ng/mL) tuvieron un riesgo significativamente mayor de ingesta baja de proteínas (OR = 2,47; IC del 95 % = 1,14-5,35; p = 0,02).

Conclusión: existe una asociación significativa entre niveles séricos elevados de FGF21 y una ingesta dietética baja de proteínas en pacientes con DRE.

Palabras clave: FGF21. Desnutrición relacionada con enfermedades. Sarcopenia. Ecografía muscular.

INTRODUCTION

Disease-related malnutrition (DRM) constitutes a major health issue among both hospitalized individuals and those residing in the community. Several investigations have documented a DRM prevalence of 23.7 % (1) and 32.6 % (2) in hospitalized patients. Despite ongoing preventive measures, its elevated prevalence remains. In this context, the Study on Disease-Related Malnutrition in Northern Spain (SeDREno) reported that 29.7 % of patients met the criteria for malnutrition according to the Global Leadership Initiative on Malnutrition (GLIM) guidelines (3). DRM is closely linked to the presence of inflammation, disease-induced physiological changes, reduced nutritional intake, and consequent losses in body weight and muscle mass. Within this framework, sarcopenia is recognized as a condition marked by diminished muscle mass, decreased muscle strength, and impaired physical function (4). These features substantially elevate health risks, notably increasing the incidence of falls, fractures (5), and various comorbidities (6). In light of this, skeletal muscle, serving as the principal protein reservoir in the

human body, becomes a pivotal parameter in the assessment of DRM. Moreover, skeletal muscle functions as an endocrine organ by synthesizing and secreting signalling molecules termed myokines, which mediate intercellular communication via endocrine, paracrine, or autocrine mechanisms (7). Among these molecules, Fibroblast Growth Factor 21 (FGF21), a member of the FGF family, is a hormone integral to the regulation of glucose, lipid, and amino acid metabolism, as well as to the adaptive response to various stress conditions (8-12). Although FGF21 is produced in several tissues, the liver and adipose tissue represent its predominant sources in the plasma, with minor contributions from the gastrointestinal tract, brain, skeletal muscle, and pancreas (13-14); therefore, it cannot be classified as a specific myokine. In 2014, Laeger et al. demonstrated that hepatic FGF21 expression is selectively stimulated by dietary protein restriction rather than by overall energy restriction, resulting in up to a 10-fold elevation in plasma FGF21 concentrations in rodents subjected to a low-protein diet (15). Moreover, their research revealed that FGF21-deficient mice did not show an increase in food intake compared to wild-type counterparts, nor did they exhibit changes in energy expenditure under conditions of protein restriction. These findings indicate that FGF21 acts as an endocrine mediator of protein deprivation and plays a crucial role in orchestrating the metabolic adaptations to insufficient protein intake. Similarly, in humans, adherence to a low-protein diet for 28 days resulted in elevated plasma FGF21 levels among healthy subjects (15). In further support of these results, Post et al. (16) demonstrated that higher plasma FGF21 concentrations are associated with a greater probability of low protein intake in patients undergoing haemodialysis.

To the best of our knowledge, no studies have assessed serum FGF21 concentrations in patients with Disease-Related Malnutrition (DRM) of etiologies other than chronic kidney disease. In light of this gap in the literature, the objective of our study is to investigate the

role of circulating FGF21 in patients with DRM and to examine its association with dietary protein intake

MATERIAL Y METHODS

Study population

This open-label, real-world investigation was conducted among outpatients diagnosed with disease-related malnutrition (DRM). Patients were referred to our Nutrition Unit for a nutritional assessment due to malnutrition risk, with recruitment occurring between January 2023 and July 2024. The nutritional status of all participants was evaluated through anthropometric measurements and biochemical markers. All individuals provided informed consent. The study protocol was approved by the Bioethical Committee of the Health Area of HCUVa (PI 20-2062) and complied with the ethical guidelines set forth in the Declaration of Helsinki.

The main inclusion criteria was a confirmed DRM diagnosis based on GLIM criteria (17). Exclusion criteria encompassed any stage of chronic kidney disease, alcohol consumption, active cancer, decompensated liver disease, diabetes mellitus, fluid overload resulting from decompensated cardiopulmonary disease, inability to ambulate, or refusal to provide informed consent. In all participants, anthropometric composition analysis and blood sample collection were performed. During the first clinical visit, measurements of body weight, height, body mass index (BMI), and calf circumference were recorded. Additional assessments included handgrip strength (dynamometry), bioelectrical impedance analysis, muscle mass evaluation via ultrasound at the rectus femoris quadriceps (RFQ), and venous blood sample collection. For biochemical analyses, 15 mL of venous blood were drawn into EDTA-coated tubes following a 10-hour overnight fasting period. The biochemical parameters assessed included albumin (g/dL), C-reactive protein (CRP) (mg/dL), prealbumin (mg/dL), and serum levels of FGF21.

Anthropometric measurements, muscle ultrasound, bioimpedance analysis, and dietary intake

Body weight was recorded with participants in minimal clothing using a digital scale (Omron, LA, CA, USA). Following this, height (cm) and waist circumference (cm) were measured with a non-elastic tape measure (Omron, LA, CA, USA). Body mass index (BMI) was then calculated by dividing body weight (kg) by the square of height (m^2). Calf circumference was measured at the widest point of the gastrocnemius muscle using a tape measure. Bioimpedance analysis (BIA) was utilized to assess impedance components (Z), including resistance (R) and reactance (X). The phase angle (PhA) was calculated using the formula: $PhA = (X / R) \times (180° / \pi)$. BIA also estimated fat mass (FM), skeletal muscle mass (SMM), appendicular skeletal muscle mass (aSMM), and appendicular skeletal muscle mass index (aSMMI), calculated as aSMM divided by height squared (18) (EFG BIA 101 Anniversary, Akern, Italy).

Muscle ultrasound was performed to assess the rectus femoris quadriceps (RFQ) in the dominant lower limb using a 10- to 12-MHz multifrequency linear probe (Mindray Z60, Madrid, Spain), oriented perpendicularly to both the longitudinal and transverse axes of the RFQ. Measurements were taken without applying pressure at the distal third, between the superior patella pole and the anterior superior iliac spine. The recorded parameters included cross-sectional area (cm^2), circumference (cm), X-axis diameter (cm), Y-axis diameter (cm), and the X/Y ratio of the RFQ (19).

Handgrip strength was measured using a dynamometer (JAMAR®, Sammons Preston, Bolingbrook, IL) with participants seated and their forearm at a right angle. Three trials were conducted, and the average value was calculated. Muscle strength was categorized as low based on the EWGSOP2 criteria, defined as < 27 kg for men and < 16 kg for women (4). Sarcopenia was diagnosed when low muscle strength was coupled with reduced aSMMI (calculated from BIA values) of < 7.0 kg/m^2 for men and < 5.5 kg/m^2 for women (4).

Finally, participants were asked to record their daily dietary intake over three non-consecutive days (two weekdays and one weekend day). Dietary records were analyzed using specialized software (Dietsource®, Geneva, Switzerland), referencing national food composition tables (20). Participants also documented the duration of their daily physical activity in a diary.

Biochemistry

Nutritional parameters were analyzed utilizing a Cobas c-711 autoanalyzer (Roche Diagnostics, Geneva, Switzerland) to quantify albumin (g/dL), C-reactive protein (CRP) (mg/dL), and prealbumin (mg/dL). FGF21 levels were measured using the MILLIPLEX® Human Myokine Magnetic Bead Panel (HCYTOMAG-56K, EMD Millipore Corporation, MA, USA), adhering to the manufacturer's instructions. The inter-assay coefficient of variation for FGF21 was 2.6 %, while the intra-assay coefficient of variation was 3.2 %.

Statistical analysis

A sample size calculation was performed considering a difference between groups of protein dietary intakes in FGF21 levels overall 50 ng/ml, resulting in a sample size of (n = 100), with a type I error < 0.05 and a statistical power of 80 %. Statistical tests were two-tailed and conducted at a significance level of 0.05. Quantitative variables with a normal distribution were analyzed using the paired or unpaired two-tailed Student's t-test. Non-parametric variables were analyzed using the Wilcoxon test. Qualitative variables were analyzed using the Chi-square test, with Fisher’s correction applied when necessary (cells with n < 5). To reduce the likelihood of type I error in association analyses, the Bonferroni correction was applied for multiple comparisons. We estimate odds ratios (ORs) and 95 % confidence intervals (CIs), assessing the relationship between FGF21 levels and the presence of low dietary intake of protein (median level: 53.7 ng/mL). The statistical software used was SPSS

23.0 (IL, USA), and p-values < 0.05 were considered statistically significant.

RESULTS

A total of 108 patients with disease-related malnutrition (DRM), as defined by the GLIM criteria, were included in the study, with a mean age of 61.3 ± 1.1 years. The cohort comprised 64 females (59.3 %) and 44 males (40.7 %). The main causes of DRM were distributed as follows: stable oncological conditions in 34 patients (31.5 %), gastrointestinal diseases in 17 patients (15.8 %), cardiopulmonary disorders in 36 patients (33.3 %), and other causes in 21 (19.4 %) patients.

Tables IA and IB provide an overview of the anthropometric, muscle ultrasound, bioimpedance, and biochemical characteristics of the study population, showing that the average BMI and body weight fell within normal ranges. Based on the criteria established by the European Working Group on Sarcopenia in Older People (EWGSOP2), 54 patients (50.0 %) were classified as sarcopenic (Table II). The gender distribution was comparable between groups: the sarcopenic group included 33 females (66.0 %) and 21 males (34.0 %), while the non-sarcopenic group comprised 31 females (62.0 %) and 23 males (48.0 %).

Table II highlights statistically significant differences in anthropometric, bioimpedance, and muscle ultrasound parameters between sarcopenic and non-sarcopenic patients. Among anthropometric measures, sarcopenic patients exhibited a notably smaller calf circumference (-1.7 ± 0.2 cm; p = 0.02). Bioimpedance analysis revealed lower values in this group, characterized by a decreased phase angle (-0.9 ± 0.2°; p = 0.01), reduced reactance (-5.3 ± 2.1 ohms; p = 0.03), skeletal muscle mass (SMM) (-3.3 ± 0.2 kg; p = 0.03), appendicular skeletal muscle mass (aSMM) (-2.7 ± 0.3 kg; p = 0.03), and appendicular skeletal muscle mass index (aSMMI) (-1.1 ± 0.2 kg; p = 0.04). Muscle assessments with

ultrasound also indicated lower in rectus femoris parameters among sarcopenic individuals, with reductions in dominant muscle area (-0.6 ± 0.1 cm^2; p = 0.04) and dominant Y-axis thickness (-0.5 ± 0.1 cm; p = 0.03), alongside an increase in the dominant X/Y axis ratio (0.7 ± 0.2; p = 0.04). Additionally, muscle strength was significantly greater in non-sarcopenic patients (9.9 ± 1.3 kg; p = 0.02) than patients with sarcopenia. Table II also presents biochemical parameters, revealing significant differences between sarcopenic and non-sarcopenic patients. Patients with sarcopenia displayed lower serum protein concentrations; albumin (-0.6 ± 0.1 g/dL; p = 0.04) and prealbumin (-9.5 ± 0.8 mg/dL; p = 0.02). Additionally, circulating levels FGF21 were similar in both groups, without statistical differences.

Table III provides an overview of dietary intake and physical activity levels. Patients with sarcopenia engaged in fewer minutes of physical activity per week (35.8 ± 8.1 min/week; p = 0.02). Additionally, their overall energy intake, along with the consumption of carbohydrates, fats, and proteins, were lower compared to non-sarcopenic individuals. The correlation analysis identified a significant negative association between FGF21 levels and some parameters of rectus femoris quality (RFQ) such as dominant muscle area, as well as bioimpedance parameters such as reactance and derived parameters (SMM and aSMM) and albumin levels (Table IV). Protein intake was also significantly and negatively correlated (r = -0.55; p = 0.02) with FGF21 levels. No significant relationships were observed between FGF21 levels and other dietary parameters or weekly physical activity duration.

The patients were divided into two groups taking into account the median value of daily protein intake (53.7 g/day). Patients with higher protein intake had higher dominant muscle area RQF (0.6 ± 0.2 cm^2; p = 0.03), reactance (7.5 ± 0.3°; p = 0.03), SMM (2.6 ± 0.3 kg; p = 0.03), aSMM (2.3 ± 0.8 kg; p = 0.03), albumin (0.7 ± 0.2 mg/dL; p =

0.04), prealbumin (10.1 ± 0.8 mg/dL; p = 0.02) and lower levels of FGF21 (86.5 ± 9.8 ng/dL; p = 0.01) (Table V).

Based on the preceding data, patients were divided into two groups according to the median FGF21 value (61.3 ng/mL), and the odds ratio (OR) adjusted by age, sex and etiologies for the risk of low intake of protein was calculated. Patients with FGF21 levels above the median cut-off point had a significantly higher risk of low protein intake compared to those below the cut-off (OR = 2.47, 95 % CI = 1.14-5.35; p = 0.02). Finally, patients with low intake of proteins had a significantly higher risk of sarcopenia compared to those above the cut-off (OR = 2.89, 95 % CI = 1.32-6.31; p = 0.01). The remaining analyses in relation to macronutrient intake and total energy did not show significant ORs in relation to FGF21 values or the presence of sarcopenia.

DISCUSSION

Our study identified an inverse relationship between circulating fibroblast growth factor 21 (FGF21) levels and protein dietary intake in patients with disease-related malnutrition (DRM). In this population, individuals with low protein intake exhibited significantly higher FGF21 levels. A relationship between low protein intake and sarcopenia was also observed. However, the association between circulating FGF21 and sarcopenia risk was not detected.

FGF21 functions as a key metabolic regulator primarily produced in the liver, with additional expression in adipose tissue, skeletal muscle, and the pancreas. Its biological effects require binding to the co-receptor β-Klotho, which facilitates activation of specific receptor complexes in target tissues. FGF21 plays an essential role in regulating lipid, carbohydrate, and protein metabolism, as well as maintaining energy homeostasis and modulating body weight (21). Its expression is upregulated in response to various physiological and pathological stimuli, including fasting, excessive caloric intake, inflammatory conditions, and other unidentified factors (22).

FGF21 exerts its actions through endocrine, paracrine, and autocrine pathways (22). During periods of fasting, FGF21 enhances gluconeogenesis, ketogenesis, and fatty acid oxidation to preserve energy balance (23). Moreover, FGF21 can cross the blood-brain barrier and modulate central nervous system pathways involved in glucose regulation and body weight control (24). In our study, no association was observed between FGF21 levels and inflammatory markers such as C-reactive protein, contrasting with the findings of Lukawska et al. (25), likely due to differences in study populations, as their cohort included patients with active inflammatory bowel disease —a condition characterized by chronic and acute inflammatory activity. In that study, FGF21 levels were inversely correlated with anthropometric variables such as BMI and biochemical markers including albumin (25). Our results are partially consistent, although we identified a negative correlation specifically with muscle mass, assessed through bioimpedance and ultrasound techniques. Furthermore, a meta-analysis has demonstrated that FGF21 analogues significantly reduce body weight (26), and experimental studies have reported that FGF21 overexpression may contribute to reductions in both muscle mass and strength (27). Mitochondrial dysfunction has been proposed as a potential mechanism underlying this association, as suggested by Amado et al. (28) in patients with chronic bronchopathy, where FGF21 levels inversely correlated with functional performance tests, such as the 6-minute walk test. In contrast, our study did not find an association between FGF21 levels and handgrip strength measured by dynamometry, but we did observe significant correlations with muscle mass parameters assessed by bioimpedance and ultrasound. Differences in the functional assessment methods and the characteristics of the study populations may explain these discrepancies.

Another interesting finding in our article is the inverse relationship between dietary protein intake and circulating levels of FGF21, this

association has only been previously published by the group of Post et al. (16). In this investigation, the authors evaluated patients on haemodialysis, with a very high inflammatory situation, presenting protein energy wasting (PEW) and that could bias this obtained relationship. In this study (16), patients with low protein intake had almost double the circulating levels of FGF21 than those with a normal intake, and elevated levels of FG21 were also associated with low muscle mass, in this case determined by a slight indirect test on the creatinine excretion rate. These findings have also been apparently replicated in healthy adults (14). The key differences between previous studies and our investigation are notable. In the first study, the participants had chronic kidney disease, a condition known to independently elevate circulating FGF21 levels (16). In contrast, the second study involved healthy adults whose protein intake exceeded recommended levels (14). Our study demonstrates that, even in patients with preserved renal function and compromised protein intake due to disease-related malnutrition (DRM), the association between low protein intake and elevated FGF21 levels remains evident. Furthermore, in our cohort, no significant correlations were observed between FGF21 concentrations and the intake of other macronutrients or overall energy intake, reinforcing the notion that dietary protein intake specifically drives the observed relationship. This finding aligns with the results previously reported by Laeger et al. (14). Similarly, Bray et al. (29) demonstrated, in a study utilizing various dietary intervention arms with either caloric and/or protein restriction, that elevations in FGF21 levels occurred exclusively in response to protein restriction, further supporting the specificity of this association.

Several limitations of this study must be considered. A primary limitation is that the investigation was confined to patients with disease-related malnutrition (DRM), thereby limiting the generalizability of the results to other populations. Additionally, the relatively modest sample size may reduce the statistical power and

robustness of the findings. The cross-sectional design further restricts the ability to infer causal relationships between the variables analyzed. Another limitation is the reliance on self-reported dietary intake, which introduces the potential for reporting bias. Despite these limitations, the study also has notable strengths. It included a heterogeneous cohort of DRM patients, closely mirroring the variability typically encountered in clinical practice, thereby enhancing the external validity of the findings. Moreover, muscle mass was assessed using multiple techniques—bioelectrical impedance analysis and rectus femoris ultrasound—both of which are non-invasive, do not involve ionizing radiation, and allow for rapid, practical evaluation. Importantly, this study assessed circulating FGF21 levels in a population without chronic kidney disease, a condition known to independently elevate FGF21 concentrations, thereby minimizing a significant confounding factor.

In summary, our study revealed a significant association between increased serum FGF21 levels and low protein dietary intake in patients with disease-related malnutrition (DRM). Based on our findings, fibroblast growth factor 21 (FGF21) emerges as a promising biomarker in the clinical assessment of disease-related malnutrition (DRM), particularly in identifying patients at risk of low protein intake. Compared to traditional markers such as albumin and prealbumin, FGF21 offers a unique advantage by specifically reflecting alterations in dietary protein intake, independent of inflammatory status. Our study demonstrated a significant inverse correlation between FGF21 levels and protein consumption, with elevated FGF21 concentrations associated with a greater likelihood of low protein intake. This suggests that FGF21 could complement traditional parameters, providing an earlier and more sensitive indication of nutritional risk before significant changes in serum protein markers occur. Furthermore, given the strong association between low protein intake, sarcopenia, and adverse clinical outcomes, the measurement of circulating FGF21 could become a valuable tool in routine clinical

practice, facilitating early identification and intervention in malnourished patients. However, further prospective studies are warranted to validate FGF21 as a diagnostic marker and to define optimal cutoff points for its clinical application alongside conventional nutritional assessments (30).

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Table IA. Anthropometric and BIA data of the total sample (mean ± SD)

Parameters	**Total group** ***n*** **= 108**
Age (years)	61317
BMI (kg/m^2)	223 21
Body weight (kg)	568 10 7
Fat mass (kg)	180 30
SMM (kg)	201 1 2
aSMM (kg)	162 20
aSMMI (kg)	77 03
CC (cm)	31110
Phase angle (°)	4903
Reactance (ohms)	51140
Resistance (ohms)	5921221
Strength (kg)	22331

CC: calf circumference; SMM: skeletal muscle mass; aSMM: appendicular muscle mass; aSMMI: appendicular muscle mass index.

Table IB. Biochemical parameters and US measurements of the total sample (mean ± SD)

Parameters	**Total group** ***n*** **= 108**
Dominant muscle area RFQ (cm^2)	3211
Dominant circumference area RFQ (cm)	8214
Dominant X axis RFQ (cm)	3102
Dominant Y axis RFQ (cm)	11 02
Dominant X/Y axis RFQ (cm)	33 02
Dominant echo-intensity (points)	915121
CRP (mg/dl)	7111
Albumin (g/dl)	4520
Prealbumin (mg/ml)	21668
FGF21 (ng/ml)	1344216

RFQ: rectus femoris quadriceps.

Table II. Comparison of epidemiological, anthropometric and biochemical parameters between sarcopenic and non-sarcopenic patients (mean ± SD)

Parameters	**No sarcopenia** ***n*** **= 54**	**Sarcopenia** ***n*** **= 54**	***p*-value**
Age (years)	61121	62910	0.29
BMI (kg/m^2)	224 20	222 11	0.31
Weight (kg)	579 5 1	561 3 2	0.18
CC (cm)	32810	31003	0.02
Strength (kg)	261 3 0	168 2 0	0.02
Ultrasound parameters			
Dominant muscle area RFQ (cm^2)	3502	2804	0.04
Dominant circumference RFQ (cm)	8312	7810	0.23
Dominant X axis RFQ (cm)	3407	3202	0.49
Dominant Y axis RFQ (cm)	14 02	09 01	0.03
Dominant X/Y axis RFQ (cm)	31 01	38 03	0.04
Dominant echo-intensity (points)	901111	955121	0.23
BIA parameters			
Fat mass (kg)	189 31	175 23	0.16
Skeletal muscle mass (kg)	208 1 4	175 0 9	0.03
Appendicular muscle mass (aSMM)	169 11	142 10	0.03
Appendicular muscle mass index (aSMMI)	78 03	67 04	0.04
CC (cm)	32810	31003	0.02
Phase angle (°)	5502	4603	0.01
Reactance (ohms)	53110	47820	0.03
Resistance (ohms)	5998241	4983502	0.07

Biochemical parameters			
CRP (mg/dl)	67 22	73 39	0.35
Albumin (g/dl)	47 02	42 03	0.04
Prealbumin (mg/ml)	287 20	192 20	0.02
FGF21 (ng/ml)	130242	140539	0.31

CC: calf circumference; SMM: skeletal muscle mass; aSMM: appendicular muscle mass; aSSMI: appendicular muscle mass index; RFQ: rectus femoris quadriceps.

Table III. Comparison of baseline characteristics, average daily intakes, and physical activity (mean ± SD)

Parameters	**Total group *n* = 108**	**No sarcopenia *n* = 54**	**Sarcopenia *n* = 54**	***p*-value**
Calorie intake (kcal/day)	1584.3 ± 419.2	1699.2 ± 102.1	1445.1 ± 103.9	$p = 0.02$
Carbohydrate intake (g/day) (PTC %)	167.6 ± 50.0 (43.2 %)	169.3 ± 51.1 (43.2 %)	151.3 ± 22.1 (42.3 %)	$p = 0.02$
Fat intake (g/day) (PTC %)	68.0 ± 9.1 (39.1 %)	70.9 ± 10.2 (39.7 %)	60.5 ± 8.3 (38.8 %)	$p = 0.02$
Protein intake (g/day) (PTC %)	67.3 ± 4.1 (18.6 %)	69.8 ± 3.1 (17.1 %)	66.2 ± 3.0 (19.9 %)	$p = 0.03$
Fiber intake (g/day)	13.0 ± 3.0	13.3 ± 2.1	12.9 ± 2.2	$p = 0.39$
Physical activity (min/day)	76.3 ± 5.2	85.2 ± 4.2	50.4 ± 3.1	$p = 0.02$

PTC: percentage of total calories.

Table IV. Correlation analysis of FGF21 levels

Parameters	**FGF21**
Dominant muscle area RFQ (cm^2)	r = -0.30, p = 0.03
aSMM (kg)	r = -0.21, p = 0.04
SMM (kg)	r = -0.22, p = 0.03
Reactance (ohms)	r = - 0.24, p = 0.04
Protein intake (g/day)	r = -0.55, p = 0.02
Albumin (g/dl)	r = -0.28, p = 0.02

SMM: skeletal muscle mass; aSMM: appendicular muscle mass; RFQ: rectus femoris quadriceps.

Table V. Comparison of epidemiological, anthropometric and biochemical parameters between low protein intake and high protein intake (mean ± SD)

Parameters	**Low intake *n* = 54**	**High intake *n* = 54**	***p*-value**
Age (years)	61.3 ± 2.3	62.1 ± 1.3	0.31
BMI (kg/m^2)	223 19	220 12	0.38
Weight (kg)	559 5 0	571 3 0	0.19
CC (cm)	31812	33205	0.12
Strength (kg)	211 2 0	271 2 4	0.32
Ultrasound parameters			
Dominant muscle area RFQ (cm^2)	2902	3504	0.03
Dominant circumference RFQ (cm)	7912	8110	0.29
Dominant X axis RFQ (cm)	3309	3502	0.43
Dominant Y axis RFQ (cm)	10 02	14 02	0.04
Dominant X/Y axis RFQ (cm)	37 01	32 06	0.12
Dominant echo-intensity (points)	90191	924101	0.53
Bioimpedance parameters			
Fat mass (kg)	179 32	185 23	0.34
Skeletal muscle mass (kg)	178 1 2	205 0 8	0.03
Appendicular muscle mass (aSMM)	143 11	169 08	0.03
Appendicular muscle mass index (aSMMI)	68 06	77 07	0.10
Phase angle (°)	4502	5308	0.23
Reactance (ohms)	48110	55812	0.03
Resistance (ohms)	4898971	5583812	0.17
Biochemical parameters			
CRP (mg/dl)	68 21	71 39	0.35

Albumin (g/dl)	41 02	48 02	0.04
Prealbumin (mg/ml)	187 21	292 10	0.02
FGF21 (ng/ml)	168032	82952	0.01

CC: calf circumference; SMM: skeletal muscle mass; aSMM: appendicular muscle mass; aSSMI: appendicular muscle mass index; RFQ: rectus femoris quadriceps