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Original Article

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Prevalence and Risk Factors for Sarcopenia in Chronic Kidney Disease Patients Undergoing Dialysis: A Cross-Sectional Study

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ABSTRACT

Background: Chronic kidney disease (CKD) and sarcopenia are major public health problems. Dialysis patients have an increased risk of developing sarcopenia, a syndrome associated with increased risk of disability, poor quality of life, and hospitalization. The aim of this work is to investigate the risk factors associated with sarcopenia in a cohort of patients requiring dialysis, to try to prevent the onset of sarcopenia in these patients already frail by their disease.
Methods: Seventy-seven CKD patients receiving dialysis (62.7 ± 13.8 years old; 64.1% males) were enrolled. Body composition was evaluated through a whole-body DXA scan according to the diagnostic criteria suggested by the EWGSOP (European Working Group on Sarcopenia in Older People) for appendicular muscle mass. The strength of the association between factors included and the presence of sarcopenia was assessed by odds ratios (ORs) and 95% CIs using conditional logistic regression.
Results: The prevalence of sarcopenia was 53.1% (95% CI: 42.2-64.0). In the multivariate analysis, male gender (OR = 9.28; 95% CI: 1.81-47.49; $P = .008$) and low BMI (OR = 19.89; 95% CI: 4.37-90.10; $P < .0001$) were significantly associated with sarcopenia.
Conclusion: Our study confirms the high prevalence of sarcopenia in dialysis patients. Among the investigated factors, sarcopenia is negatively associated with male gender and low BMI. This result highlights the importance of a correct diet in CKD patients in order to maintain BMI in the normal range. In this context, DXA plays an important role in diagnosis of sarcopenia, and also in follow-up, giving the possibility to follow the evolution of the disease and allow adjustments in the therapy.
Keywords: Chronic kidney disease, dialysis, sarcopenia, whole-body DXA

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INTRODUCTION

Chronic kidney disease (CKD) is a condition characterized by a progressive and irreversible loss of renal function. It represents a worldwide public health problem, with a consistent estimated global prevalence between 11% and 13%.[1] In particular, severe CKD (stage 4) and kidney failure (stage 5), also called end-stage renal disease (ESRD), continue to increase, with estimated progressive growth in patients receiving dialytic maintenance treatment.[2]

From early CKD to dialysis, the kidneys, through their complex functions, can cause systemic pathophysiological processes, leading to bone and muscle changes. Several studies have shown that the most advanced stages of the disease are associated with a progressive and generalized loss of mass, strength, and function of the skeletal muscles,[3] which define the condition of sarcopenia.[4]

Muscle homeostasis is a condition of maintaining the right proportion between anabolic and catabolic

processes. In CKD, this balance is lost resulting in sarcopenia,[5] indeed ESRD is associated with protein wasting and multiple metabolic disorders due to uremia.[6] This, along with renin-angiotensin system dysregulation and growth factors—such as insulin/insulin-like growth factor 1 (IGF-1), myostatin pathway, and hormonal and immunological dysfunction[7] are primarily responsible for the close correlation between ESRD and sarcopenia.

The prevalence of sarcopenia increases in line with the progression of the stages of CKD, and it is estimated at approximately 37% in dialytic patients.[8,9] In this population, muscle weakness is a strong predictor of major clinical outcomes such as poor quality of life, disability, increased morbidity and mortality, and also mainly determined by the cardiovascular complications to which this population is at greater risk.[10,11]

However, data on the prevalence of sarcopenia and risk factors for sarcopenia in people having CKD and treated with dialysis are still limited to a few studies that illustrate the contribution of some factors, such as limited protein intake, energy deficiency, aging, insufficient or deficient exercise, chronic inflammation, and lack of vitamin D.[12]

Furthermore, CKD patients often exhibit negative variations in body composition and musculoskeletal health,[5] with an increased risk of "low energy" fracture.[13]

Moreover, impaired calcium metabolism is related to vitamin D receptor abnormalities; therefore, vitamin D deficiency is a link between osteoporosis and muscle wasting.[14]

In patients with CKD, increased muscle wasting[15] frequently causes a state of chronic low-grade systemic inflammation.[12,16] Indeed, tumor necrosis factor α (TNF-α) increases muscle wasting by activating the nuclear factor κβ pathway and inhibiting insulin-stimulated protein synthesis.[17]

In our study, we, therefore, aimed to calculate the prevalence of sarcopenia in dialytic patients with end-stage CKD and the possible risk factors associated with sarcopenia in this population.

Main Points

- Sarcopenia is directly related to the worsening of kidney function; indeed, there is a wide prevalence of end-stage renal disease (ESRD) (stage 5), in particular in patients undergoing dialysis.
- In patients with stage 5 CKD undergoing dialysis, sarcopenia is prevalent in males and in patients with a low BMI.
- All sarcopenic patients have a diagnosis of osteoporosis (low BMD); indeed, they have a greater bone fragility and a consequent increased incidence of bone fracture.

METHODS

Participants Characteristics

From May 2015 to May 2017, 77 patients were enrolled according to the following inclusion criteria: age > 18 years, history of ESRD, on maintenance dialysis for at least 6 months. Exclusion criteria included age < 18 years or > 90 years, malignant diseases, active coronary artery disease (e.g. unstable angina, myocardial infarction) in the past 6 months, or acute diseases unrelated to CKD requiring hospitalization in the last 1 month.

All patients attended the departments of nephrology and dialysis in the hospital of San Giovanni Rotondo (FG), where they received hemodialytic treatments 2 or 3 times a week.

After providing information on the purpose of the study, all patients gave their informed consent. Ethic Commitee Approval was received from the IRCCS Foundation "Casa Sollievo della Sofferenza (Protocol Number 37/CE CSS). The research was conducted in accordance with the Declaration of Helsinki (as revised in 2008) and according to local guidelines and laws.

Comorbidities and Medications

The presence of some important comorbidities (diabetes, fractures) and medications (erythropoietin [EPO], cinacalcet, paricalcitol) was ascertained through the enrollment in a dedicated database. Similarly, time (in months) and type of dialysis were recorded. The presence of osteoporosis was assessed using dual-energy X-ray absorptiometry (DXA) on the basis of bone mineral density (BMD) assessment, according to the diagnostic criteria suggested by the World Health Organization (WHO).[18] Body mass index (BMI) was measured by a trained nurse and categorized as normal/underweight (<25 kg/m^2) vs. overweight/obese (>25 kg/m^2).[19]

Bio-humoral Exams

Biochemical data were collected from the antecubital vein of each participant after at least 12 h of fasting. Serum calcium, phosphate, and alkaline phosphatase measurements were performed on an automated chemical analyzer (Siemens Dimension Vista 1500); hemoglobin was determined via the cyanmethemoglobin method (Siemens Advia 2120i Hematology System), and total serum concentrations of 25-hydroxyvitamin D were measured by chemiluminescent immunoassay (BIO-RAD BioPlex 2200 System).

Sarcopenia Definition

The presence of sarcopenia was ascertained through a whole-body DXA scan (Lunar iDXA™; GE Healthcare, Madison, WI; enCORE™ 2011 software v. 13.6) using the appendicular skeletal muscle mass index (ASMMI), that is, the ASMM divided by the square of height (in meters).

The iDXA is a narrow-fan beam instrument that allows examining the patient with a low incident dose and is equipped with an automatic calibration and stabilization system. The precision of iDXA is reported through the coefficient of variation, which is around 1.4% for the lean body mass.

The criteria suggested by the European Working Group on Sarcopenia in Older People (EWGSOP) and 2 standard deviations (SDs) below the mean of young adults in the Rosetta study (i.e., men < 7.26 kg/m^2 and women < 5.50 kg/m^2)[4] were used.

Statistical Analysis

Continuous variables were normally distributed according to the Kolmogorov–Smirnov test. Therefore, data were shown as means and SD values for quantitative measures. Percentages were used for discrete variables. The dialysis period is reported as median (with interquartile range) for its skewed distribution. Between-group comparisons for continuous variables were performed through an independent *t*-test (except for the dialysis period for which we used the Mann–Whitney test); categorical variables were compared through the chi-square test, using the Fisher's correction when appropriate. The strength of the association between factors was included, and the presence of sarcopenia was assessed by the odds ratios (ORs) with their 95% CIs through multiple univariate analyses. Multivariate analysis included predictors having a *P*-value <.20 at the univariate analysis. Collinearity among covariates was tested using the variance inflation factor with a threshold of 2, but no covariate was excluded for this reason. All the analyses used a *P*-value < .05 and were made using Statistical Package for the Social Sciences (SPSS) version 17.0 (IBM SPSS Corp.; Armonk, NY, USA).

Information on Ethics Committee Approval

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RESULTS

The whole sample included 77 patients treated with dialysis. They had a mean age of 62.7 ± 13.8 years and were more frequently males (*n* = 64.1%). The median duration of dialysis was 28 (range: 6-289) months.

Table 1 showed the characteristics of the population by presence or absence of sarcopenia. The prevalence of sarcopenia was 53.1% (95% CI: 42.2-64.0). The 41 participants with sarcopenia did not differ in terms of age, dialysis period, or use of alpha-EPO, cinacalcet or paricalcitol compared to the 36 participants without sarcopenia. However, sarcopenic individuals were more significantly males (75.6% vs. 50.0%, *P* = .03) and had a significantly lower BMI (*P* < .0001). No significant differences emerged in terms of diabetes, fractures, or osteoporosis prevalence (Table 1).

Table 1. Descriptive Characteristics by Presence or Absence of Sarcopenia

	Sarcopenia (*n* = 41)	No Sarcopenia (*n* = 36)	*P*
General characteristics			
ASMMI	2.94 (1.00)	7.52 (1.20)	<.0001
Age (years)	63.3 (15.0)	61.8 (12.6)	.65
Males (*n*, %)	31 (75.6)	18 (50.0)	.03
BMI (kg/m^2)	22.6 (2.8)	29.0 (6.3)	<.0001
Dialysis period (months)	26 (8-85)	29 (9-50)	.76
HD-HCO_3 (*n*, %)	36 (87.8)	27 (75.0)	.35
Use of alpha-EPO (*n*, %)	24 (70.6)	20 (62.5)	.60
Use of cinecalcet (*n*, %)	9 (22.0)	8 (22.2)	1.00
Comorbidities			
Diabetes (*n*, %)	5 (12.2)	5 (13.9)	1.00
Fractures (*n*, %)	4 (10.0)	3 (8.3)	1.00
Osteoporosis (*n*, %)	41 (100)	34 (94.4)	.22
Bio-humoral exams			
Hemoglobin (g/dL)	11.4 (1.0)	11.3 (1.1)	.43
Serum calcium (mg/dL)	9.1 (0.9)	9.1 (0.7)	.91
Serum phosphorus (mg/dL)	5.4 (1.4)	6.0 (1.9)	.12
ALP (U/L)	86.0 (47.7)	78.5 (31.6)	.43
PTH (ng/L)	285.9 (176.7)	328.0 (200.3)	.33
25OHD (ng/mL)	14.9 (11.0)	15.8 (16.2)	.77

The data are presented as mean (with standard deviations) for continuous and as number (and percentages) for categorical variables, respectively. Dialysis period is reported as median (with interquartile range) for its skewed distribution. Continuous variables are analyzed through independent *t*-test (except for dialysis period for which we used the Mann–Whitney test); categorical variables were compared through the chi-square test, using the Fisher's correction when appropriate.
ASMMI, appendicular skeletal muscle mass index; BMI, body mass index; HD-HCO_3, bicarbonate hemodialysis; EPO, erythropoietin; ALP, alkaline phosphatase level; PTH, parathprmone; 25OHD, 25-hydroxy vitamin D.

Table 2 reported univariate and multivariate analyses, taking sarcopenia as an outcome. In the univariate analyses, male sex and low BMI were associated with a significantly higher presence of sarcopenia. Interestingly, all the sarcopenic patients had a diagnosis of osteoporosis. These factors, in the multivariate analysis, remain associated with sarcopenia with an OR = 9.28 (95% CI: 1.81-47.49; *P* = .008) for male gender, OR = 19.89 (95% CI: 4.37-90.10; *P* < .0001) for people having normal or low BMI.

DISCUSSION

Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength, which

Table 2. Predictors of Sarcopenia in Univariate and Multivariate Analyses

	Reference Group	Univariate	*P*	Multivariate	*P*
General characteristics					
Age > 65 years	Age < 65 years	1.19 (0.49-2.92)	.70		
Males	Females	3.10 (1.18-8.15)	.02	9.28 (1.81-47.49)	.008
Normal/underweight	Overweight/obese	10.73 (3.71-31.0)	<.0001	19.89 (4.37-90.1)	<.0001
Dialysis period > 28 months	Dialysis period < 28 months	0.86 (0.35-2.12)	.75		
HD-HCO3	Other types of HD	1.33 (0.25-7.13)	.74		
Use of alpha-EPO (*n*, %)	Beta-EPO/no EPO	0.69 (0.25-1.94)	.49		
Use of cinecalcet (*n*, %)	No use	0.98 (0.34-2.90)	.98		
Comorbidities					
Diabetes (*n*, %)	No diabetes	0.86 (0.23-3.25)	.83		
Fractures (*n*, %)	No fractures	1.22 (0.25-5.87)	.80		
Osteoporosis (*n*, %)	No osteoporosis	All people with sarcopenia had osteoporosis		-	-
Bio-humoral exams					
Anemia	Normal values of Hb	1.14 (0.47-2.81)	.77		
Serum calcium > 9 (mg/dL)	Serum calcium < 9 (g/dL)	1.29 (0.53-3.17)	.57		
Serum phosphorus > 4.5 (mg/dL)	Serum phosphorus < 4.5 (g/dL)	0.69 (0.25-1.94)	.48		
ALP > 74 (U/L)	ALP < 74 (U/L)	0.99 (0.40-2.45)	.99		
PTH > 288 (ng/L)	PTH < 288 (ng/L)	0.95 (0.39-2.33)	.92		
25OHD (ng/mL) < 30 (ng/mL)	25OHD (ng/mL) > 30 (ng/mL)	0.26 (0.03-2.57)	.26		

$HD\text{-}HCO_3$, bicarbonate hemodialysis; EPO, erythropoietin; ALP, alkaline phosphatase level; PTH, parathprmone; 25OHD, 25-hydroxy vitamin D.

leads to a decline in muscle function and physical performance. It is associated with the aging process, and also with chronic diseases, including CKD.

In CKD, the predisposition to the condition of sarcopenia is favored by multiple metabolic and nutritional anomalies. Several studies have shown that the prevalence of sarcopenia is directly related to the worsening of kidney function, with a wide prevalence in patients undergoing dialysis. In the latter, moreover, sarcopenia progressed in accordance with the duration of hemodialysis.[20]

In fact, ESRD patients receiving dialysis present additional factors concurring to sarcopenia progression, compared to CKD patients in the pre-dialysis stage: loss of amino-acids and albumin in the dialysate, systemic inflammation induced by contact with an artificial dialysis membrane and circuits, and decreased physical activity due to rest during dialysis.[21]

In the assessment of these patients, evaluating and quantifying the prevalence of sarcopenia is very important because it represents a strong prognostic factor, being associated with an increased risk for other medical conditions (such as cardiovascular conditions) and mortality.[10,11]

In our study, all participants attended dialytic treatments for 26 months on average. According to the EWGSOP criteria published in 2010, we observed a high prevalence of sarcopenia, of about 53%, higher than the average prevalence reported in the literature. Indeed other international studies in the past years have reported a prevalence of sarcopenia or muscle wasting among patients with ESRD ranging from 20% to 44%,[8,9,11] lower than our finding. We can argue that the difference in the diagnostic criteria used for the diagnosis of sarcopenia (the lack of an international consensus on the techniques to be used in the identification of the patients with muscle wasting in CKD is a problem for research in this field) and the duration of the dialysis may in part explain these not univocal findings. However, we need other studies reporting the prevalence of sarcopenia in this population.

Among the risk factor investigated for sarcopenia in these patients, a higher prevalence of muscle weakness was found in male patients and in people with a low BMI. Data from the Korean National Health and Nutrition Examination Surveys found that in the most advanced stages (CKD 3-5) sarcopenia was significantly associated with an increase in the prevalence of sarcopenia in men.[22]

As for the lower BMI, it is likely that in people in the ESRD stage, a low BMI may reflect a low amount of muscle mass. This can be said as some studies on obesity in populations with CKD and ESRD[23] have correlated higher BMI with better survival, presumably because it is associated with better maintained nutritional status.

Even if DXA allows the analysis of body composition, basing on a 3-compartment model (fat mass, lean mass, and body mineral content),[24] in this case, high BMI could be related not to fat mass but to the presence of higher muscle mass because this value confers a protective effect on these patients.

Interestingly, all sarcopenic patients had a diagnosis of osteoporosis. Several studies have shown the close pathophysiological links between muscle and bone at the genetic, cellular, biochemical, and biomechanical levels, which are enclosed in the term of "bone and muscle pleiotropy."[25] In particular, the functional muscle-bone unit was studied in subjects of varying BMD, observing that it decreased in subjects with lower BMI regardless of age.[25]

Compared to the general population, CKD patients have greater bone fragility and, consequently, an increased incidence of bone fracture due to both CKD-mineral bone disorder and uremic osteoporosis.[26] Moreover, the decreased skeletal muscle mass causes a reduction in mechanical stress to bone (generated by muscle contraction) and lower production of pro-osteogenic cytokines. This concurs to reduce BMD and to impair bone quality.[26]

This study had some limitations. First, the limited sample size. Second, the prevalence of sarcopenia was assessed only by measuring the ASMMI using a total-body DXA scan and not by a physical performance test as suggested by common guidelines on this topic. Third, the nutritional status of the patients wasn't evaluated.

In conclusion, our study confirms that there is a high prevalence of sarcopenia in patients on chronic hemodialysis, regardless of age or comorbidity such as diabetes or osteoporosis, but probably linked only to the metabolic and nutritional abnormalities induced by this pathological condition and, in particular, from the dialytic treatment. This seems to be the same cause of the increased incidence of osteoporosis in hemodialysis (HD) patients, which resulted to be closely associated with sarcopenia in our population.

Furthermore, our study shows a high prevalence of sarcopenia in male patients with low BMI, the latter obtained by DXA evaluation. This finding can be used to carry out further DXA studies on both the prevention of sarcopenia in CKD patients through diet and exercise, as well as the follow-up of disease evolution and mortality risk.

Ethics Committee Approval: Ethic Commitee Approval was received from the IRCCS Foundation Casa Sollievo della Sofferenza (Protocol Number 37/CE CSS).

Informed Consent: Informed consent was obtained from all participants who participated in this study.

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