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Sarcopenia and cardiovascular risk indices in patients with chronic kidney disease on conservative and replacement therapy

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ABSTRACT

Objective: Chronic kidney disease (CKD) is a condition with high cardiovascular mortality associated with emerging risk factors, including sarcopenia. Several mechanisms can affect muscle mass, such as vitamin D deficiency, low protein intake, physical inactivity, metabolic acidosis, and inflammation leading to a worsening of cardiovascular outcomes and cognitive function.

We aimed to evaluate the prevalence of sarcopenia in CKD patients on conservative and replacement therapy and the associations between sarcopenia and markers of atherosclerosis, endothelial dysfunction, psychological and cognitive function.

Methods: We enrolled CKD patients (stage 3/5 KDIGO [Kidney Disease: Improving Global Outcomes]) and hemodialysis, peritoneal dialysis, and post–kidney transplant patients. Clinical, laboratory and instrumental assessments, including bioimpedance analysis, hand-grip strength, intima media thickness, flow-mediated dilation, and epicardial adipose tissue, were performed in addition to analysis of psychological and cognitive status by the Montreal Cognitive Assessment, Mini-Mental State Examination, and Geriatric Depression Scale.

Results: A total of 77 patients (43 male) with a mean age of 69.6 ± 9.85 y were studied. According to validated criteria (using bioimpedance analysis and hand-grip strength), the prevalence of sarcopenia was 49.4%. Sarcopenic patients had higher values of intima media thickness ($P = 0.032$) and epicardial adipose tissue ($P = 0.012$) and lower flow-mediated dilation ($P = 0.002$), total cholesterol ($P = 0.005$), and high-density lipoprotein cholesterol ($P = 0.008$) with respect to non-sarcopenic patients. We found higher Geriatric Depression Scale scores ($P = 0.04$) in sarcopenic patients, whereas we did not find differences between the two groups in Mini-Mental State Examination and Montreal Cognitive Assessment score.

Conclusion: Sarcopenia is highly prevalent in CKD/end stage renal disease patients and is associated with changes in early systemic indices of atherosclerosis and endothelial dysfunction, known as markers of worse prognosis.

Introduction

Sarcopenia is defined by the European Working Group on Sarcopenia in Older People as the presence of low muscle mass and low muscle function (strength or performance) [1,2].

Several studies, including the National Health and Nutrition Examination Survey III study, found a high prevalence of sarcopenia in patients with low estimated glomerular filtration rate (eGFR), suggesting that muscle wasting progresses as kidney function declines [3–5].

The prevalence of sarcopenia or muscle wasting among patients with end-stage renal disease (ESRD) is 20–44% and around 50% in dialysis patients [4,5]. Aging is associated with sarcopenia and chronic kidney disease (CKD), which accelerates the physiological age-related muscle wasting, determining hormonal, myocellular, and immunologic modifications through nutritional deficiency,

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metabolic acidosis, vitamin D deficiency, mineral bone disorders, insulin resistance, proteinuria, and chronic inflammation [5]. Sarcopenia may lead to physical disability, low quality of life, and psychological distress [6]. In particular, altered nutritional status in CKD and dialysis patients is often associated with psychological and cognitive impairment [7]. However, few data are available on the potential associations between sarcopenia and psychological and cognitive disorders [8,9]. Importantly, sarcopenia may increase cardiovascular risk [6], and therefore the prevention and treatment of muscle wasting in CKD patients appear as an important target for nephrologists, geriatricians, and nutritionists.

Considering the reduced survival of CKD patients on dialysis, it appears clinically relevant to stratify the morbidity and mortality risk factors, with particular attention to cardiovascular risk [10].

The association between sarcopenia and cardiovascular risk has not been completely clarified, and the assessment of sarcopenia in this population may be useful to better stratify this risk in CKD.

In this study we aimed to evaluate the associations between sarcopenia in CKD and ESRD patients and markers of atherosclerosis and endothelial dysfunction, and secondarily, with psychological and cognitive function, which may be affected during sarcopenia.

Materials and methods

Study design and participants

We conducted a prospective observational study on clinically stable CKD and ESRD patients, enrolled from January 2015 to July 2016 at the Nephrology Unit of University Hospital Policlinico Umberto I of Rome, Sapienza University of Rome, Italy. This study was approved by the Local Clinical Research Ethics Committee with protocol number 3767.15. The study conforms to the principles outlined in the Declaration of Helsinki, and we obtained a written informed consent from each patient before the enrollment. We used convenience sampling, including patients with CKD on conservative therapy (eGFR $\leq$ 60 mL/min, stage 3/5 KDIGO [Kidney Disease: Improving Global Outcomes]), patients on hemodialysis (HD), peritoneal dialysis (PD), and patients after kidney transplant (KT) (without acute renal failure, proteinuria, or renal infections). Statins, antihypertensive, antiplatelet therapies, or therapies with calcium, calcitriol, and phosphate binders were recorded (continued in all patients included in the study) in addition to any cardiac event.

Exclusion criteria were heart failure, chronic liver disease, chronic obstructive pulmonary disease, cerebrovascular disease, malignancy, degenerative neurologic or psychiatric diseases, and acute coronary syndrome that occurred within 3 months before the enrollment in the study. Also, we did not enroll patients who refused to give the consent and patients with missing data.

The eGFR was calculated with the abbreviated Modification of Diet in Renal Disease formula, as defined by Levey et al. [11]. Clinical, laboratory, and instrumental tests in HD patients were performed during the middle of the week, whereas PD patients were evaluated before the first replacement of the morning with an empty peritoneum at routine visits [10]. The Mini-Mental State Examination (MMSE), Geriatric Depression Scale (GDS), and Montreal Cognitive Assessment (MoCA) test were also administered in all participants.

Anthropometric assessment

Body weight was determined to the nearest 0.1 kg using a calibrated digital scale. Body mass index was calculated by the following formula: (weight [kg] / height [m^2]).

Bioelectrical impedance analysis

Bioimpedance analysis (BIA, Akern, Florence, Italy) was performed to assess body composition using an impedance plethysmograph that emits an 800-μA, 50-kHz alternating current. Measurements were taken with participants in a supine position for 5 min, according to the manufacturer's guidelines. In HD patients, we performed BIA analysis after 1 h from the end of the second HD session of the week, and all the patients maintained the supine position for this entire period, as previously described [12,13]. In summary, the analysis of the entire body involved the placement of two electrohydraulic injectors at the back of the hands and feet at the distal ends of metacarpals and metatarsals, and two measuring electrodes were placed on the dorsal surfaces of the wrists and ankles. We then proceeded recording the impedance, resistance, reactance, and phase angles and the subsequent transformation into estimates of muscle mass, cell mass, and body water [14].

Skeletal muscle mass measurement by BIA

Skeletal muscle mass (SMM) was calculated using the BIA formula validated by Janssen et al. [15,16]. Skeletal muscle index (SMI) was calculated by the following equation: skeletal muscle mass / height^2 [2].

Hand-grip strength

Hand-grip strength is the assessment of muscle mass function by means of the hand dynamometry; it is based on the determination of the strength of the finger flexor muscles performed with the use of a dynamometer. Hand-grip strength was evaluated in the upright position, with the dominant arm held away from the body, and at the request of the examiner, exerted the maximum force of contraction of the hand. The test was repeated three times, with a minimum interval of 5 min between each test and the mean of the measurements was used to determine muscle strength [12].

Definition of sarcopenia

According to the consensus of the European Working Group on Sarcopenia in Older People [2], we defined sarcopenia by the presence of SMI $\leq$10.75 kg/m^2 in men and $\leq$6.75 kg/m^2 in women and hand-grip strength $<$30 kg in men and $<$20 kg in women [2].

Laboratory measurements

Blood samples were performed in the early morning after overnight fasting for laboratory assessment. In all patients, serum metabolic, nutritional, and inflammatory parameters were assessed using standard automated techniques. Parathyroid hormone was measured using a two-site assay that measures "intact" hormone (pg/mL), and 25-hydroxyvitamin D (25-OH vitamin D) (ng/mL) was measured by radioimmunoassay. Insulin resistance was assessed using the homeostasis model assessment (HOMA-IR) [17]. Arterial blood gas was performed using a blood gas analyzer (Nova Phox Plus C).

Echocardiography and epicardial adipose tissue (EAT) assessment

M-mode 2-dimensional echocardiographic examinations by a single experienced sonographer in the echocardiography laboratory, using a standard institutional protocol, were completed. Commercially available instruments (Toshiba Aplio xV, Toshiba American Medical Systems, Inc., Tustin, CA, USA) equipped with 2.25- to 7.5-MHz imaging transducers were used. The participants were in the left decubitus position, and the sonographer was blinded to all clinical details of the patients [10]. All echocardiographic data were recorded according to the guidelines of the American Society of Echocardiography [18]. Using a protocol by Kaplan et al. [19], we performed the measurement of the EAT perpendicularly on the free wall of the right ventricle at the end of the diastole in the parasternal long-axis view in three cardiac cycles.

Common carotid intima media thickness assessment

Right and left carotid ultrasound examinations were blindly performed by an experienced sonographer who was unaware of the characteristics of the patients. Participants were studied with the high-resolution B-mode ultrasound machine Toshiba Aplio xV equipped with a 5- to 12-MHz linear transducer with a 0.01-mm resolution, following a standardized vascular protocol. Intima media thickness (IMT) was measured at three points on the far walls of both left and right distal common carotid arteries, carotid bulb, and proximal portion of the internal carotid arteries [20]. The mean IMT was computed as the average IMT on both sides. The normal IMT value was 0.55 to 0.9 mm [21].

Flow-mediated dilation brachial artery

According to the method described by Corretti et al. [22], the endothelium-dependent vasodilation (flow-mediated dilation [FMD]) of the brachial artery was assessed using a high-resolution B-mode ultrasound machine Toshiba Aplio xV equipped with a 5- to 12 MHz linear transducer with a 0.01-mm resolution, by the same blinded experienced ultrasonographer, following a standardized protocol [21]. This measurement was not assessable in HD patients. FMD was expressed as the change in poststimulus diameter as a percentage of the baseline diameter. FMD: (diameter posthyperemia − basal diameter / basal diameter) × 100. The values of FMD were considered normal if greater than 10%.

Psychological, compliance, and cognitive tests

All individuals completed standardized psychological and cognitive tests.

The Mini-Mental State Examination

The MMSE was used to evaluate the efficiency intellectual disorders and the presence of cognitive impairment [23]. The test consists of 30 items, referring to 7 different cognitive areas: orientation in time, orientation in space, recording of words, attention and calculation, commemoration, language, and constructional praxis. The MMSE is often used as a screening tool in the investigation of patients with dementia and neuropsychological syndromes of different natures. The total score is between a minimum of 0 and a maximum of 30 points. A score ≤18 indicates severe impairment of cognitive skills, a score between 18 and 24 indicates moderate to mild impairment, 25 is considered borderline, and 26 to 30 is indicative of cognitive normality.

The Montreal Cognitive Assessment

The MoCA was used for rapid screening of mild cognitive impairment taking into account different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructive skills, abstraction, calculation, and orientation. The time of administration was approximately 10 min. The maximum score possible was 30 points; a score ≥26 was considered normal [24].

Geriatric Depression Scale

The GDS is one of the most widespread scales for the evaluation of depressive symptoms in older adults, but it can also be used in people with mild-moderate dementia [25]. This instrument was composed of 30 items excluding the detection of somatic and psychotic symptoms. The answers were reciprocating (yes/no) and the score ranged from 0 (not depressed) to 30 (maximum severity of depression), with a cutoff at 11, indicating clinically relevant depressive symptoms. The severity of depression was as follows: 0 to 10, absent; 11 to 16, mild to moderate depression; >17, severe depression [25].

Statistical analyses

The normality of variables was tested by the Shapiro-Wilk normality test. All continuous normally distributed variables were expressed as mean ± SD. Non-normally distributed variables were described using median, 25th, and 75th percentiles. Student's *t* test or-Mann-Whitney *U* test were performed to determine differences between groups. A *P* value < 0.05 was considered statistically significant. Data management and analysis were performed using R Version 3.5.0.

Results

Demographic characteristics of all the participants are shown in Table 1. There were 80 eligible patients treated at our nephrology unit; 3 patients were excluded because they declined to give informed consent. Therefore a total of 77 CKD patients (43 male) were enrolled ($n = 26$ on conservative therapy [stage 3/5 KDIGO], $n = 37$ on HD or PD, $n = 14$ KT) with a mean age of 69.6 ± 9.85 y.

In our entire cohort, according to the validated criteria [2], 38 patients were sarcopenic (49.4%; 32 male, 6 female), with a muscle mass (kg) of 24.25 ± 5.2 and an SMI (kg/m^2) of 9.25 ± 1.21.

Nutritional, metabolic, and inflammatory parameters

No differences were found between sarcopenic and non-sarcopenic patients in creatinine, serum nitrogen, intact parathyroid hormone, 25-OH vitamin D, C-reactive protein, and uric acid levels (Table 2).

Moreover, we did not identify differences between the two groups in serum transferrin, albumin, iron levels, triacylglycerol, and lymphocytes (Table 2). On the contrary, as expected, body mass index was different between the two groups ($P = 0.030$) (Table 2).

Cardiovascular indices

In sarcopenic patients we documented significantly higher values of IMT (Fig. 1) and EAT (Fig. 2) ($P = 0.032$, $P = 0.012$, respectively) and lower total cholesterol and high-density lipoprotein cholesterol ($P = 0.005$, $P = 0.008$, respectively) compared with those of non-sarcopenic patients (Table 2). In addition, FMD (%) (evaluated in all the participants with the exception of HD patients) was lower in sarcopenic with respect to non-sarcopenic patients (7.61 ± 2.74 vs 11.06 ± 4.34, $P = 0.002$).

Table 1
Patient characteristics

Clinical parameters	Patients $n = 77$
Age, y	69.6 ± 9.85
Sex, M:F	43:34
BMI, weight (kg)/height^2 (m)	26.34 ± 5.18
Waist circumference, cm	93.38 ± 12.73
Serum nitrogen, mg/dL	105.68 ± 41.42
Creatinine, mg/dL	4.81 ± 3.3
Serum uric acid, mg/dL	5.85 ± 1.42
Potassium, mEq/L	4.97 ± 0.79
Calcium, mg/dL	9.34 ± 0.64
Phosphorus, mg/dL	4.15 ± 0.99
Hb, g/dL	12.15 ± 1.56
Iron, μg/dL	68.02 ± 33.62
Transferrin, mg/dL	212.47 ± 52.35
Lymphocytes, no.	1720.05 ± 540.71
HOMA-IR	4.15 ± 2.46
Total cholesterol, mg/dL	175.64 ± 38.85
HDL cholesterol, mg/dL	50.99 ± 14.26
Triacylglycerol, mg/dL	127.21 ± 48.69
iPTH, pg/mL	179.61 ± 155.98
25-OH vitamin D, ng/mL	19.25 ± 13.83
Albumin, g/dL	3.79 ± 0.41
CRP,* mg/dL	3000 (1800; 6000)
Hand-grip strength, kg	28.19 ± 8.32
Cardiovascular risk indices	
IMT, mm	1.20 ± 0.20
FMD, %	9.7 ± 4.13
EAT, mm	5.92 ± 1.36

BMI, body mass index; CRP, C-reactive protein; EAT, epicardial adipose tissue; F, female; Hb, hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment; IMT, intima media thickness; iPTH, intact parathyroid hormone; FMD, flow-mediated dilation; M, male.
Data are show as mean ± SD.
*Median (interquartile range).

Cognitive and psychological tests

In the entire cohort we identified an MMSE score of 22.17 ± 4.76. No significant differences were found between sarcopenic and non-sarcopenic patients in MMSE (21.23 ± 4.48 versus 23.02 ± 4.90; $P = 0.12$) and MoCA score (18.8 ± 6.8 versus 21.81 ± 6.88; $P = 0.076$). A higher GDS score was documented in sarcopenic compared with non-sarcopenic patients (7.45 ± 4.75 versus 5.15 ± 5.02; $P = 0.04$).

Discussion

Sarcopenia is the progressive, generalized loss of skeletal muscle mass, often associated with reduced physical performance and muscle strength, and determines functional impairment, cardiopulmonary failure, and physical disability. Although sarcopenia is common as result of aging, it can also occur in younger adults because of an underlying acute or chronic condition [1,2]. Therefore, CKD can lead to progressive sarcopenia with a loss in kidney function. Indeed, the loss of muscle mass may be even more severe in younger patients with CKD, increasing morbidity and mortality risk [3]. Factors associated with CKD include nutritional deficiency, acidosis, mineral bone disorders, insulin resistance, proteinuria, and chronic inflammation [5].

In particular, older adults may be sarcopenic as a result of age and yet they may also have good nutritional status. Therefore, to evaluate specifically the presence of sarcopenia appears clinically important. In our clinical setting (patients with CKD on

Table 2
Characteristics of non-sarcopenic and sarcopenic patients

	Non-sarcopenic patients *n* = 39 (11 male)	Sarcopenic patients *n* = 38 (32 male)	*P*
Clinical parameters			
Age, y	68.64 ± 10.06	70.53 ± 9.8	0.408
BMI, weight (kg)/height^2 (m)	27.60 ± 6.42	25.05 ± 3.08	0.030
Waist circumference, cm	95.1 ± 14.40	91.61 ± 10.66	0.230
Serum nitrogen, mg/dL	104.49 ± 42.18	106.94 ± 41.15	0.799
Creatinine, mg/dL	4.19 ± 2.88	5.45 ± 3.62	0.095
Serum uric acid, mg/dL	5.67 ± 1.33	6.03 ± 1.51	0.270
Potassium, mEq/L	4.76 ± 0.6	5.18 ± 0.91	0.018
Calcium, mg/dL	9.32 ± 0.63	9.36 ± 0.67	0.798
Phosphorus, mg/dL	4.19 ± 0.93	4.11 ± 1.06	0.733
Hb, g/dL	12.08 ± 1.76	12.23 ± 1.34	0.671
Iron, μg/dL	69.33 ± 29.64	66.68 ± 37.64	0.732
Transferrin, mg/dL	210.95 ± 48.2	214.03 ± 56.90	0.798
Lymphocytes, no.	1710.08 ± 516.76	1730.03 ± 570.44	0.874
Total cholesterol, mg/dL	187.92 ± 42.11	163.37 ± 31.26	0.005
HDL cholesterol, mg/dL	55.35 ± 12.89	46.74 ± 14.40	0.008
Triacylglycerol, mg/dL	125.33 ± 43.69	129.20 ± 54.02	0.732
iPTH, pg/mL	148.05 ± 108.05	211.09 ± 192.02	0.07
25-OH vitamin D, ng/mL	22.06 ± 14.83	16.36 ± 12.27	0.07
Albumin, g/dL	3.84 ± 0.36	3.73 ± 0.46	0.220
CRP, mg/dL	3000 (200; 70000)	3950 (1000; 22000)	0.193
Muscle mass, kg	25.6 ± 4.66	24.25 ± 5.2	0.23
Hand-grip strength, kg	31.00 ± 9.70	25.05 ± 4.93	0.002

BMI, body mass index; CRP, C-reactive protein;Hb, hemoglobin; HDL, high-density lipoprotein; iPTH, intact parathyroid hormone.
Data are show as mean ± SD.
*Median (interquartile range).

conservative and replacement therapy), we were expecting a high prevalence and impact of sarcopenia because of the presence of the underlying chronic disease.

In the present study we found significant higher values of markers of atherosclerosis IMT, FMD, and EAT in patients with sarcopenia, as previously described by others [26].

Kato et al. [27] found that decreased thigh muscle volume and increased visceral adiposity were independently associated with markers of atherosclerosis, whereas in our study the waist circumference was not different between the two groups. Beijers et al. [28] reported an association between changes in body composition and endothelial dysfunction, and in another study, authors found an association between sarcopenia and endothelial dysfunction with higher cardiovascular risk [29]. Cordeiro et al. [30] found that EAT accumulation in patients with CKD increased the risk of cardiovascular events, independent of general adiposity. This is consistent with the local pathogenic effect of EAT on heart vessels. Epicardial adipose tissue is a visceral deposit of adipose tissue located between the myocardium and visceral pericardium, predominantly on the right ventricular free wall and at the left ventricular apex, accounting for approximately 20% of the total heart weight. It is a particularly active tissue and produces many of the same proatherogenic and proinflammatory cytokines produced by the visceral abdominal fat (tumor necrosis factor, monocyte

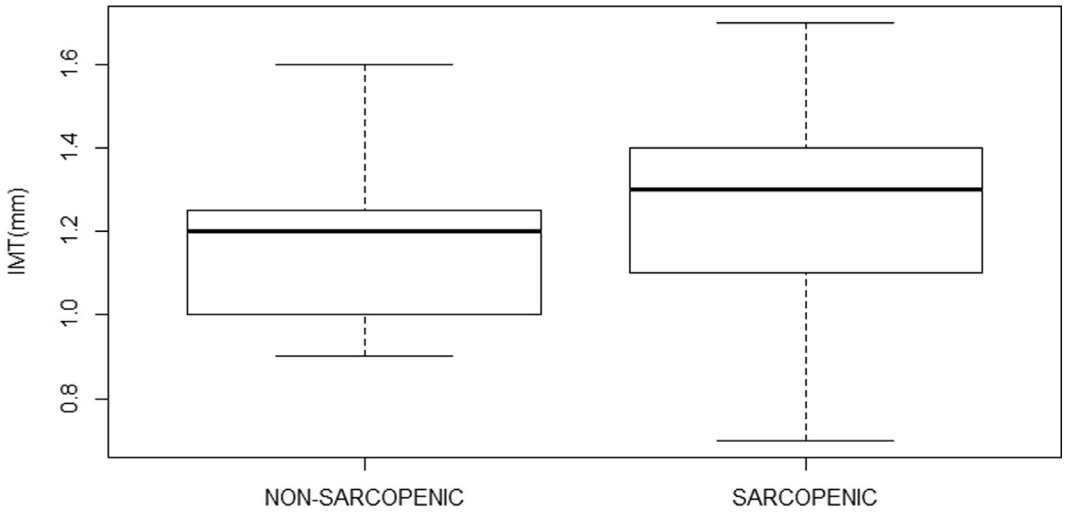

Fig. 1. Box plot of intima media thickness (IMT) in sarcopenic and non-sarcopenic patients. IMT (mm) values were higher in sarcopenic patients with respect to non-sarcopenic patients (1.25 ± 0.23 vs 1.16 ± 0.16) (p = 0.032). Lines represent the median, 25th, and 75th percentiles, and the whiskers (error bars) below and above the box indicate the minimum and maximum values.

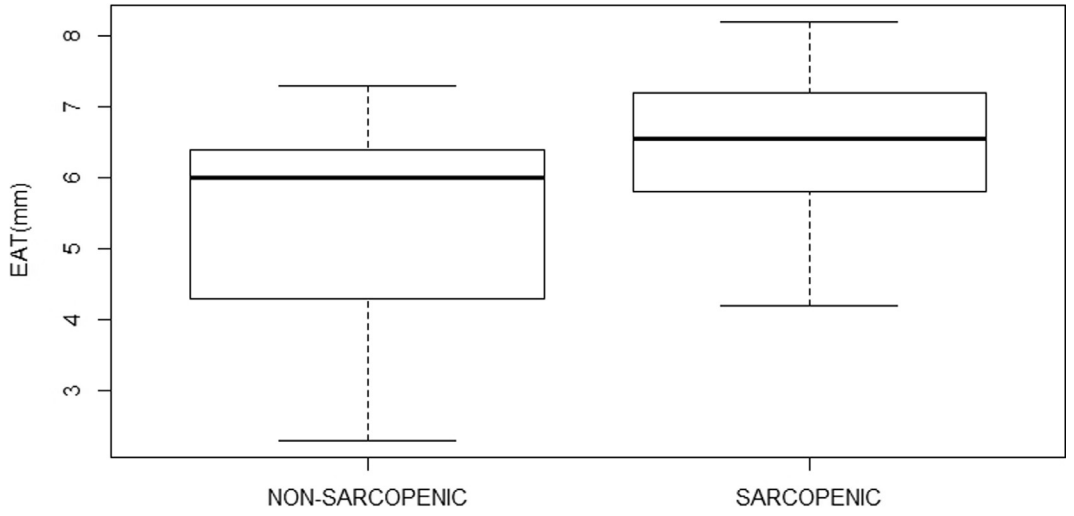

Fig. 2. Box plot of epicardial adipose tissue (EAT) in sarcopenic and non-sarcopenic patients. EAT (mm) values were higher in sarcopenic patients with respect to non-sarcopenic patients (6.46 ± 1.08 vs 5.38 ± 1.48) ($p = 0.012$). Lines represent the median, 25th, and 75th percentiles, and the whiskers (error bars) below and above the box indicate the minimum and maximum values.

chemotactic protein-1, interleukin-6, resistin, adipokines), which act locally in a paracrine or vasocrine manner to promote coronary disease [31]. Epicardial adipose tissue is an emerging novel risk factor for cardiovascular disease. Kerr et al. [31] described an association among EAT and coronary calcification, insulin resistance, inflammation, and fibroblast growth factor-23 in 93 CKD patients on conservative therapy.

In our study we found low 25-OH vitamin D levels in the entire cohort, which tended to be lower in sarcopenic patients than non-sarcopenic patients, although at the limit of significance.

An inverse correlation between vitamin D levels and markers of general and abdominal obesity has been noted previously; indeed, experimental data indicated that vitamin D deficiency induces inflammatory cellular infiltration and increases proinflammatory adipokine expression in EAT, supporting the concept that this may be an alternative pathway linking vitamin D deficiency and cardiovascular disease in CKD patients [6]. In fact, the muscle is a target organ for vitamin D, and when vitamin D binds to the vitamin D receptor in skeletal muscle, muscular protein synthesis and calcium influx from cellular membranes increase. A low vitamin D level is associated with atrophy, particularly in type 2 muscle fibers, and sarcopenia [6]. Although vitamin D supplementation improves muscular strength, reduces falls, prevents fractures, and possibly affects muscle fibers composition and morphology [32], there is a lack of consensus in the literature regarding the possible benefit of vitamin D supplementation on muscle mass and strength.

As in individuals with normal renal function and vitamin D deficiency, patients with CKD have prolongation of the relaxation phases of muscle contraction, independent of serum calcium, parathyroid hormone, or serum phosphorus levels [32]. These observations suggest a possible role for vitamin D in the myopathy of CKD [32]. In addition, muscle biopsies in adults with vitamin D deficiency have shown type II fibers atrophy, enlarged interfibrillar spaces, and infiltration of fat, fibrosis, and glycogen granules. These morphologic features are not dissimilar from those found in patients with CKD, with type II muscle fiber atrophy, lipofuscin, and glycogen deposition [33].

Sarcopenia is also associated with higher risk of cognitive decline, depressive symptoms, and worse prognosis [34]. Indeed, it was recently documented that body composition modifications might play a role in the development of depression and anxiety [35,36]. The mechanisms underlying the association between depressive symptoms and sarcopenia remain largely unknown.

Ishii et al. [37] reported that leptin resistance might be implicated as a mediating factor between sarcopenic obesity and depression. Previous studies reported the association of depression with low physical performance [36], assessed by gait speed or hand-grip strength [37]. Pasco et al. [35] supported the hypothesis that shared pathophysiological pathways for sarcopenia and the common mental disorders constitute links between skeletal muscle and brain function. The contraction of skeletal muscle releases neurotrophic factors that are known to play a role in mood changes and anxiety and have the dual role of nourishing neuronal growth and differentiation while protecting the size and number of motor units in skeletal muscle [35]. Furthermore, skeletal muscle activity has important immune and redox effects, affecting behavior and reducing muscle catabolism [35,36].

In our cohort we found a higher level of depression in patients with sarcopenia, with a significant difference in GDS results. Moreover, MoCA scores tended to be lower in sarcopenic versus non-sarcopenic patients, suggesting a possible cognitive decline, although we did not find significant differences in MMSE results. These differences could be explained by the different content of the two tests. In fact, MoCA is a test that allows an early diagnosis of mild cognitive decline, whereas MMSE identifies the presence of advanced cognitive impairment [38]. Moreover, depression is one of the reasons for reduced appetite and hence for low energy/protein intake. Another important cause of muscle wasting in patients with CKD is the permanent low-grade inflammation that is common in CKD even in early stages, although in our sample we did not find significant differences in C-reactive protein levels between sarcopenic and non-sarcopenic patients.

In addition to the protein loss and reduction of muscle mass, another negative phenomenon is the change of the quality of the muscular compartment. In patients with CKD, some authors identified an accumulation of fat in the striated muscle cells and in the form of intermuscular adipose tissue [39]. The current state of knowledge indicates that kidney disease predisposes to the development of sarcopenia [32], although other studies have found that patients with CKD exhibit mitochondrial dysfunction within the skeletal muscle compared with healthy individuals [40,41] and that the reduction of mitochondria in skeletal muscle might precede the development of sarcopenia [42]. Mitochondrial

dysfunction is associated with increased oxidative stress, inflammation [43], and atherosclerosis [44], suggesting that impaired mitochondrial function may also contribute to the pathogenesis of cardiovascular diseases [40].

Limitations of the study

The limitations of our study are mainly represented by the relatively small number of participants, in particular in the HD/PD and KT groups, and the cross-sectional design of the study. Also, we used convenience sampling, which may limit the interpretation of our results. Therefore, additional prospective multicenter studies are necessary to confirm associations between sarcopenia and cardiovascular risk. We used BIA to estimate muscle mass also in CKD patients, representing a limiting factor as a result of potential excess in extracellular water in this clinical setting. Moreover, our study is based on associations with surrogate end points, not clarifying a causal relationship.

Conclusions

In our study we found a high prevalence of sarcopenia in CKD/ESRD patients. In patients with sarcopenia, we found changes in early systemic markers of atherosclerosis and endothelial dysfunction (IMT, FMD, and EAT), in addition to a reduction in high-density lipoprotein levels known as negative prognostic markers. Moreover, sarcopenic patients had altered cognitive function and mood.

Sarcopenia is a condition underestimated in CKD patients, and therefore skeletal muscle involvement should be systematically investigated by simple, inexpensive, and non-invasive methods, such as BIA. The systematic assessment of the muscular component may be useful to define the prognosis and the cardiovascular risk in patients with CKD on conservative and replacement therapy.

References

[1] Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB. International Working Group on Sarcopenia. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. J Am Med Dir Assoc 2011;12:249–56.

[2] Cruz-Jentof AJ, Baeyns JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. Age Ageing 2010;39:412–23.

[3] Foley RN, Wang C, Ishani A, et al. Kidney function and sarcopenia in the United States general population: NHANES II. Am J Nephrol 2007;27:279–86.

[4] Molfino A, Chiappini MG, Laviano A, Ammann T, Bollea MR, Alegiani F, et al. Effect of intensive nutritional counseling and support on clinical outcomes of hemodialysis patients. Nutrition 2012;28:1012–5.

[5] Muscaritoli M, Molfino A, Bollea MR, Rossi Fanelli F. Malnutrition and wasting in renal disease. Curr Opin Clin Nutr Metab Care 2009;12:378–83.

[6] Ozkayar N, Altun B, Halil M, Kuyumcu ME, Arik G, Yesil Y, et al. Evaluation of sarcopenia in renal transplant recipients. Nephrourol Mon 2014;6:e20055.

[7] Gerogianni G, Kouzoupis A, Grapsa E. A holistic approach to factors affecting depression in haemodialysis patients. Int Urol Nephrol 2018;50:1467–76.

[8] Alston H, Burns A, Davenport A. Loss of appendicular muscle mass in haemodialysis patients is associated with increased self-reported depression, anxiety and lower general health scores. Nephrology (Carlton) 2018;23:546–51.

[9] Kim JK, Choi SR, Choi MJ, Kim SG, Lee YK, Noh JW, et al. Prevalence of and factors associated with sarcopenia in elderly patients with end-stage renal disease. Clin Nutr 2014;33:64–8.

[10] Lai S, Molfino A, Russo GE, Testorio M, Galani A, Innico G, et al. Cardiac, inflammatory and metabolic parameters: hemodialysis versus peritoneal dialysis. Cardiorenal Med 2015;5:20–30.

[11] Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S. Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145:247–54.

[12] Molfino A, Amabile MI, Ammann T, Farcomeni A, Lionetto L, Simmaco M, et al. The metabolite beta-aminoisobutyric acid and physical inactivity among hemodialysis patients. Nutrition 2017;34:101–7.

[13] Jankowska M, Debska-Slizien A, Rutkowski B. Bioelectrical impedance analysis before versus after a hemodialysis session in evaluation of nutritional status. J Ren Nutr 2006;16:137–40.

[14] Lai S, Molfino A, Coppola B, De Leo S, Tommasi V, Galani A, et al. Effect of personalized dietary intervention on nutritional, metabolic and vascular indices in patients with chronic kidney disease. Eur Rev Med Pharmacol Sci 2015;19:3351–9.

[15] Janssen I, Heymsfield SB, Baumgartner RN, Ross R. Estimation of skeletal muscle mass by bioelectrical impedance analysis. J Appl Physiol 2000;89:465–71.

[16] Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. J Am Geriatr Soc 2002;50:889–96.

[17] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.

[18] Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography: recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.

[19] Kaplan O, Kurtoglu E, Nar G, Yasar E, Gozubuyuk G, Dogan C, et al. Evaluation of electrocardiographic T-peak to T-end interval in subjects with increased epicardial fat tissue thickness. Arq Bras Cardiol 2015;105:566–72.

[20] Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, et al. BHS guidelines working party, for the British Hypertension Society: British hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. BMJ 2004;328:634–40.

[21] Lai S, Mariotti A, Coppola B, Lai C, Aceto P, Dimko M, et al. Uricemia and homocysteinemia: nontraditional risk factors in the early stages of chronic kidney disease—preliminary data. Eur Rev Med Pharmacol Sci 2014;18:1010–7.

[22] Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol 2002;39:257–65.

[23] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.

[24] Julayanont P, Tangwongchai S, Hemrungrojn S, Tunvirachaisakul C, Phanthumchinda K, Hongsawat J, et al. The Montreal Cognitive Assessment-Basic: a screening tool for mild cognitive impairment in illiterate and low-educated elderly adults. J Am Geriatr Soc 2015;63:2550–4.

[25] Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982;17:37–49. -1983.

[26] Ochi M, Kohara K, Tabara Y, Kido T, Uetani E, Ochi N, et al. Arterial stiffness is associated with low thigh muscle mass in middle-aged to elderly men. Atherosclerosis 2010;212:327–32.

[27] Kato A, Ishida J, Endo Y, Takita T, Furuhashi M, Maruyama Y, et al. Association of abdominal visceral adiposity and thigh sarcopenia with changes of arteriosclerosis in haemodialysis patients. Nephrol Dial Transplant 2011;26:1967–76.

[28] Beijers HJ, Ferreira I, Bravenboer B, Henry RM, Schalkwijk CG, Dekker JM, et al. Higher central fat mass and lower peripheral lean mass are independent determinants of endothelial dysfunction in the elderly: the Hoorn study. Atherosclerosis 2014;233:310–8.

[29] Delgado-Frías E, González-Gay MA, Muñiz-Montes JR, Gómez Rodríguez-Bethencourt MA, González-Díaz A, Díaz-González F, et al. Relationship of abdominal adiposity and body composition with endothelial dysfunction in patients with rheumatoid arthritis. Clin Exp Rheumatol 2015;33:516–23.

[30] Cordeiro AC, Amparo FC, Oliveira MA, Amodeo C, Smanio P, Pinto IM, et al. Epicardial fat accumulation, cardiometabolic profile and cardiovascular events in patients with stages 3-5 chronic kidney disease. J Intern Med 2015;278:77–87.

[31] Kerr JD, Holden RM, Morton AR, Nolan RL, Hopman WM, Pruss CM, et al. Associations of epicardial fat with coronary calcification, insulin resistance, inflammation, and fibroblast growth factor-23 in stage 3-5 chronic kidney disease. BMC Nephrol 2013;14:26.

[32] Domański M, Ciechanowski K. Sarcopenia: a major challenge in elderly patients with end-stage renal disease. J Aging Res 2012;2012:754739.

[33] Lee YH, Kim JE, Roh YH, Choi HR, Rhee Y, Kang DR, et al. The combination of vitamin D deficiency and mild to moderate chronic kidney disease is associated with low bone mineral density and deteriorated femoral microarchitecture: results from the KNHANES 2008-2011. J Clin Endocrinol Metab 2014;99:3879–88.

[34] Hsu YH, Liang CK, Chou MY, Liao MC, Lin YT, Chen LK, et al. Association of cognitive impairment, depressive symptoms and sarcopenia among healthy older men in the veterans retirement community in southern Taiwan: a cross-sectional study. Geriatr Gerontol Int 2014;14:102–8.

[35] Pasco JA, Williams LJ, Jacka FN, Stupka N, Brennan-Olsen SL, Holloway KL, et al. Sarcopenia and the common mental disorders: a potential regulatory role of skeletal muscle on brain function? Curr Osteoporos Rep 2015;13:351–7.

[36] Roberts HC, Syddall HE, Sparkes J, Ritchie J, Butchart J, Kerr A, et al. Grip strength and its determinants among older people in different healthcare settings. Age Ageing 2014;43:241–6.

[37] Ishii S, Chang C, Tanaka T, Kuroda A, Tsuji T, Akishita M, et al. The association between sarcopenic obesity and depressive symptoms in older Japanese adults. PLoS One 2016;11:e0162898.
[38] Ciesielska N, Sokołowski R, Mazur E, Podhorecka M, Polak-Szabela A, Kędziora-Kornatowska K. Is the Montreal Cognitive Assessment (MoCA) test better suited than the Mini-Mental State Examination (MMSE) in mild cognitive impairment (MCI) detection among people aged over 60? Meta-analysis. Psychiatr Pol 2016;50:1039–52.
[39] Cheema B, Abas H, Smith B, O'Sullivan AJ, Chan M, Patwardhan A, et al. Investigation of skeletal muscle quantity and quality in end-stage renal disease. Nephrology (Carlton) 2010;15:454–63.
[40] Gamboa JL, Billings 4th FT, Bojanowski MT, Gilliam LA, Yu C, Roshanravan B, et al. Mitochondrial dysfunction and oxidative stress in patients with chronic kidney disease. Physiol Rep 2016;4.
[41] Kemp GJ, Crowe AV, Anijeet HKI, Gong QY, Bimson WE, Frostick SP, et al. Abnormal mitochondrial function and muscle wasting, but normal contractile efficiency, in haemodialysed patients studied non−invasively in vivo. Nephrol Dial Transplant 2004;19. 1520−17.
[42] Tamaki M, Miyashita K, Wakino S, Mitsuishi M, Hayashi K, Itoh H. Chronic kidney disease reduces muscle mitochondria and exercise endurance and its exacerbation by dietary protein through inactivation of pyruvate dehydrogenase. Kidney Int 2014;85:1330–9.
[43] López-Armada MJ, Riveiro-Naveira RR, Vaamonde-García C, Valcárcel-Ares MN. Mitochondrial dysfunction and the inflammatory response. Mitochondrion 2013;13:106–18.
[44] Madamanchi NR, Runge MS. Mitochondrial dysfunction in atherosclerosis. Circ Res 2007;100:460–73.