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Prevalence of obesity and obesity-associated muscle wasting in patients on peritoneal dialysis☆

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Abstract *Background and aims:* A progressive decrease in muscle mass until full-blown sarcopenia may occur in patients on peritoneal dialysis (PD) and worsen their life quality and expectancy. Here we investigate the prevalence of obesity and obesity-associated muscle wasting in PD patients.
Patients and methods: The study design was observational, cross sectional. Body composition was assessed with BIA and BIVA in 88 PD patients (53.4 ± 13.1 years; 67% male). Patients with obesity and/or with reduced muscle mass were identified using FMI and SM/BW cutoff values, respectively. Inflammatory status was assessed by measuring CRP and fibrinogen blood levels.
Results: A total of 44.3% of the patients showed a reduced muscle mass (37.5% moderate and 6.8% severe). The prevalence of obesity was 6.1%, 81.8%, and 100% in patients with normal, moderately, and severely reduced muscle mass, respectively ($p < 0.05$). Of the total, 15.2% of the patients with normal muscle mass, 18.4% of those with moderately reduced muscle mass, and 66.7% of those with severely reduced muscle mass had diabetes. The prevalence of severe muscle mass loss was higher in those with diabetes than in those without diabetes (22.2% vs. 2.8%, $p < 0.05$). Patients with obesity-associated muscle wasting showed higher fibrinogen (613.9 ± 155.1 vs. 512.9 ± 159.5 mg/dL, $p < 0.05$) and CPR (1.4 ± 1.3 vs. 0.6 ± 0.8 mg/dL, $p < 0.05$) blood concentrations than those with normal body composition.
Conclusion: Obesity and diabetes were strongly associated with muscle mass loss in our PD patients. It remains to be established whether prevention of obesity with nutritional interventions can halt the occurrence of muscle mass loss in patients on PD.

Introduction

A significant decrease in skeletal muscle mass (SM; muscle wasting) may occur in chronic kidney disease (CKD) and be complicated by dynapenia (i.e., the loss of muscle strength) until a full-blown condition of sarcopenia. In CKD, as in other chronic diseases, sarcopenia worsens patient's quality of life and reduces life expectancy [1–4]. Multiple factors contribute to muscle wasting in CKD including systemic inflammation and acidosis, indoxyl

☆ This paper is dedicated to the memory of Prof. Bruno Memoli. He will always be remembered as an exceptional scientist and teacher that dedicated his scientific life to hemo- and peritoneal dalysis.

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sulfate-induced mitochondrial dysfunction, myostatin upregulation, decrease in vitamin D and sex hormone plasma levels, and GH resistance [5,6].

Hemodialysis (HD) does not prevent the occurrence of sarcopenia and may, instead, represent an additional factor for its occurrence because it is frequently associated with malnutrition, stimulates muscle and whole-body protein loss, and alters substrate oxidation [7–9]. Clinical evidence confirmed that a significant percentage of patients on HD do develop sarcopenia and showed that this complication actually increases mortality among HD patients [10–13].

Patients on peritoneal dialysis (PD) could be even at a higher risk of developing muscle wasting than other patients with CKD because of the high glucose load from dialysing solutions and the loss of plasma proteins, mainly albumin, in the dialysate [14,15]. Nevertheless, few studies investigated muscle wasting and sarcopenia in PD patients and even less the factors associated with their development. Although it is widely accepted that sarcopenia also develops in PD and worsens its prognosis [16], controversial data are available on its prevalence, and values varying from approximately 10% up to more than 70% have been reported [16–19]. Much of this variability depends on the lack of a universal consensus both on the techniques to be used and on the thresholds to be applied to diagnose sarcopenia in patients with CKD [20]. Indeed, the current reference criteria for sarcopenia diagnosis of the European Working Group on Sarcopenia in Older People (EWGSOP) have been developed for healthy elderly people and not for younger patients with CKD [21].

In the present paper, we used the criteria proposed by Janssen et al. [22] on the basis of data from the third National Health and Nutrition Examination Survey (NHANES III) to identify patients with severe or moderate muscle mass loss among PD patients with the aim of investigating whether obesity and diabetes are associated with muscle wasting in this condition. It is well established that both obesity and diabetes increase the risk of sarcopenia by impairing insulin signaling in muscles and causing systemic inflammation [23]. Moreover, a specific form of sarcopenia, sarcopenic obesity, is characterized by an increase in body fat and by the fatty infiltration of muscle fibers. Importantly, body weight increases in many patients after starting PD [24–28]. In addition, because of the high glucose concentration in the dialyzing solution, PD also worsens glycemic control in patients with diabetes and increases the risk of developing overt diabetes in patients with prediabetes [29–31].

Even though these considerations suggest that obesity and diabetes could be associated with muscle wasting in PD, no study has specifically addressed this question thus far.

Methods

Study design and inclusion and exclusion criteria

In the present study, we used a cross-sectional, observational design to assess the prevalence of obesity and obesity-associated muscle wasting among PD patients in regular follow-up as outpatients at the Unit of Nutrition in CKD and Transplantation, Department of Medicine of the Federico II University of Naples. Inclusion criteria were age >18 years, dialysis vintage >6 months, and good compliance to medical and dialysis treatment. Exclusion criteria were malignant neoplasms, peritonitis or other acute infections, and the presence of edema. The study protocol was approved by the local ethical committee, and we obtained a signed informed consent from all the enrolled patients. The study was performed in accordance with the indications of the WMA Declaration of Helsinki.

The primary endpoint of the study was to establish whether there was any difference in the prevalence of obesity between PD patients with or without muscle mass loss. Secondary endpoints were to investigate whether there was also a difference in the prevalence of diabetes and in the plasma concentration of two main inflammation biomarkers, namely, CRP and fibrinogen.

As detailed in the next section, we used bioelectrical impedance analysis (BIA) and bioelectrical vector analysis (BIVA) to diagnose muscle wasting and/or obesity. On the day of BIA examination, a thorough clinical investigation including the assessment of the main anthropometric characteristics was performed, and a blood sample was drawn to perform a Comprehensive Metabolic Panel (CMP) and to assess blood concentrations of CRP and fibrinogen. The technical details of these clinical and laboratory investigations are reported in the next paragraphs.

Anthropometric measurements and body composition analysis

Height and weight were determined with a calibrated stadiometer and scale. Body mass index (BMI) was defined as the weight in kilograms divided by the square of the height in meters.

Body composition was assessed with BIA using a tetrapolar 50-kHz bioelectrical impedance analyzer (BIA 101 RJL, Akern Bioresearch, Firenze, Italy) [32]. To prevent the possible interference of liquid overload in bioimpedance measurements, which could represent a serious problem in PD, the patients were asked to empty their bladder before undergoing BIA evaluation and the peritoneal dialysate was drained out [33]. Total body water (TBW), fat mass (FM), and fat-free mass (FFM) were extrapolated from the values of Reactance (X_c) and Resistance (R_s) obtained at BIA by using specific prediction equations. To make the comparisons among patients easier, FM was expressed as Fat Mass Index (FMI) after normalization to patient height squared according to the following equation: $FMI = \frac{FM\ (Kg)}{height^2(m^2)}$. Patients were classified as obese if their FMI was ≥8.3 in males and ≥11.8 in females [34]. We used the prediction equations developed by Janssen et al. [35] to calculate SM from BIA data. SM was normalized to body weight and expressed as Skeletal Muscle/Body Weight (SM/BW) using the following equation: $SMI = \frac{SM}{BW} \cdot 100$ [22,36,37]. The SM/BW cutoff values proposed by Janssen et al. were used to identify patients with reduced muscle mass [22]. More specifically, male patients

Table 1 General characteristics of the study population.

Variable	Values
Sex, (Male/Female)	59/29
Age (years)	53.4 ± 13.2
BW (kg)	77.8 ± 15.6
BMI (kg/m^2)	28.7 (19.3–46.6)
Diabetes mellitus, %	20.5
Peritoneal dialysis modality, (% CAPD)	75
Dialysis vintage, (months)	15.9 ± 15.1
Urine volume, ml/day	1421 (200–4000)
Residual GFR, (ml/min*1.73 m^2)	4.3 ± 2.5
Kt/V	2.0 ± 0.5
nPCR (g/Kg)	1.0 ± 0.2
Resistance, (ohm)	469.2 ± 93.1
Reactance (ohm)	49.5 ± 13.0
Phase Angle (degrees)	6.0 ± 1.1
FFM (Kg, % BW)	55.8 ± 12.1 (72.5 ± 10.3)
FM (Kg, % BW)	21.9 ± 9.7 (27.7 ± 10.1)
FMI (kg/m^2)	8.2 ± 3.4
SM/BW (%)	36.3 ± 7.8

Data are reported as absolute count numbers, mean ± SD or median and interquartile range as appropriate). Abbreviations: BW = body weight, BMI = body mass index; CAPD = continuous ambulatory peritoneal dialysis, GFR = glomerular filtration rate; nPCR = normalized catabolic rate; FFM = free fat mass; FM = fat mass; FMI = fat mass index; SM/BW = skeletal Muscle/body weight ratio.

were considered having normal muscle mass if their SM/BW was greater than 37%, moderate muscle mass loss if it was between 37% and 31% and severe muscle mass loss if it was smaller than 31%. For female patients, the following cutoff values were used: higher than 28% for normal muscle mass, between 28% and 22% for moderate muscle mass loss, and below 22% for severe muscle mass loss.

Because BIA prediction equations may be biased in PD patients, especially if there is a fluid overload [33], we complemented this technique with BIVA that does not depend on prediction equations because it evaluates body composition directly from bioimpedance data [38]. More specifically, BIVA analyzes the position in the bidimensional space of the vector obtained by plotting height-normalized reactance (X_c/H) as a function of height-normalized resistance (R_s/H) [38]. Concentric reference ellipses delimit the portion of the bidimensional space in which the extremities of the 95%, 75%, and 50% of the vectors obtained in people with normal body composition are located. BIVA vectors endings that fall rightward or leftward with regard to these reference ellipses identify patients with muscle mass lower or higher than normal, respectively.

Blood chemistry tests

The following blood chemistries were determined by standard laboratory procedures: urea nitrogen, creatinine, glucose, albumin, total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, hemoglobin, glycosylated hemoglobin (HbA1c), C-reactive protein (CRP), and fibrinogen. In all patients, residual glomerular filtration rate (rGFR); normalized protein catabolic rate (nPCR); and total, renal, and peritoneal weekly dialysis dose (Kt/V) were also evaluated.

Statistical analysis and sample size calculation

Statistical analysis was performed using IBM SPSS 20.0 for Windows (Armonk, New York, USA). Data are presented as mean ± SD, or percentage. Comparisons among groups were performed with ANOVA followed by Bonferroni post-hoc test, whereas prevalence comparisons in different groups were carried out with the χ^2-test. The BMDP statistical package (Berkeley, UCLA) was used to perform vector analysis with the Hotelling's T^2 test [39].

To identify the factors affecting the severity of skeletal muscle loss, we performed an ordinal logistic regression

Table 2 Renal and bioelectrical impedance parameters in PD patients with normal, moderately, and severely reduced muscle mass.

	Normal muscle mass (n = 49)	Moderate muscle mass loss (n = 33)	Severe muscle mass loss (n = 6)
Sex (Male/Female)	37/12	19/14	3/3
Age (years)	52.5 ± 13.5	54.9 ± 13.0	53.7 ± 12.5
BW (kg)	73.3 ± 14.8	82.4 ± 14.6*	89.2 ± 17.4*
BMI (kg/m^2)	26.4 (19.3–39.6)	31.0 (24.5–37.0)*	34.1 (27.9–46.6)*
rGFR (ml/min*1.73 m^2)	4.4 ± 2.4	3.8 ± 3.3	4.9 ± 2.8
Peritoneal dialysis modality (%CAPD)	71	79	83
Dialysis vintage (months)	13.6 ± 12.6	19.8 ± 18.5	13.5 ± 10.0
Kt/V	2.1 ± 0.4	1.7 ± 0.3	2.9 ± 0.4
nPCR (g/Kg)	1.1 ± 0.2	0.9 ± 0.3	1.2 ± 0.3
Resistance (ohm)	438.7 ± 67.6	489.7 ± 82.1*	604.5 ± 172.9*†
Reactance (ohm)	45.8 ± 12.6	52.4 ± 10.7*	63.8 ± 15.8
Vector Length (ohm/m)	267.7 ± 51.8	306.3 ± 65.4*	378.9 ± 124.3*†
FFM (% BW)	78.6 ± 7.1	66.9 ± 7.3*	53.9 ± 7.2*†
FM (% BW)	21.4 ± 7.1	33.8 ± 5.7*	46.0 ± 7.2* †
Extracellular water (%)	46.8 ± 6.1	45.5 ± 4.7	45.4 ± 3.6
FMI (kg/m^2)	5.8 ± 2.6	10.4 ± 2.1*	15.8 ± 4.8*†
SM/BW (%)	41.3 ± 5.5	31.0 ± 4.5*	24.2 ± 5.3*†

Data are reported as mean ± SD or median and interquartile range as appropriate. Abbreviations: BMI = body mass index; CAPD = continuous ambulatory peritoneal dialysis, rGFR = residual glomerular filtration rate; nPCR = normalized catabolic rate; FFM = free fat mass; FM = fat mass; FMI = fat mass index; SM = skeletal muscle mass; BW = body weight. *$p < 0.05$ vs normal, †$p < 0.05$ vs. moderate muscle loss at ANOVA followed by Bonferroni test.

analysis using muscle mass score (i.e., 0 = normal muscle mass, 1 = moderate muscle mass loss, and 2 = severe muscle mass loss) as the dependent variable and age, dialysis vintage, gender, type of dialysis, and the presence or absence of diabetes and obesity as independent variables.

Sample size was calculated depending on the primary endpoint of the study, that is, the difference in the prevalence of obesity between PD patients with and without muscle wasting. Assuming that the ratio between patients with normal and those with reduced muscle mass was 1.25 and that prevalence of obesity was 10% in patients with normal muscle mass, we estimated that a sample of at least 22 patients per group was needed to detect a 40% difference (i.e., 10% vs. 50%) in the prevalence of obesity in the two groups with a type one error of 5% and a power of 90%.

Results

The main characteristics of the study population are listed in Table 1. Briefly, we recruited 88 ESRD patients (mean age 53.4 ± 13.1 years; 67% male) on home-based PD -75% on continuous ambulatory peritoneal dialysis (CAPD) and 25% on automated peritoneal dialysis (APD). Mean dialysis vintage was 15.9 ± 15.1 months, and all patients were on PD from at least six months. There was only a minimal renal function left with an average residual GFR of 4.25 ± 2.48 ml/min*1.73 m^2, but the Kt/V ratio, which measures dialysis efficiency, averaged 2.04 ± 0.47, a value well above the minimum required of 1.7/week. In total, 20.5% of the patients had diabetes and were treated with insulin.

Using BIA and the SM/BW cutoff values reported in the *Methods section,* we found that muscle mass was normal in 55.7% of our patients (37 males and 12 females) and reduced in 44.3% (22 males and 17 females) of them. More specifically, 37.5% of the patients (19 males and 14 females) showed a moderate and 6.8% (3 males and 3 females) a severe loss of muscle mass. There was no significant difference among the three groups (normal, moderately, and severely reduced muscle mass) in variables related to renal function or dialysis (Table 2), but both fibrinogen and CRP plasma concentrations were significantly higher in patients with muscle wasting, either moderate or severe, than in patients with normal muscle mass (Fig. 1). Twenty-three percent of all PD patients with muscle wasting also had diabetes. The prevalence of diabetes was significantly higher in patients with severe muscle mass loss than in patients with moderate muscle loss and normal muscle mass (66.7% vs. 15.2%, and 18.4% respectively; $p < 0.05$). Importantly, muscle loss severity was higher in those with diabetes than in those without diabetes. Indeed, only 2.8% (2/70) of those without diabetes had severe muscle mass loss, whereas this percentage was 22.2% (4/18) in patients with diabetes; this difference in prevalence was statistically significant ($p < 0.05$ at χ^2 test).

FM and FMI were significantly higher in patients with either moderate or severe muscle loss than in those with normal muscle mass; these two parameters were also significantly higher in patients with severe muscle loss than in those with moderate muscle loss (Table 2). According to the FMI cutoff values proposed by Kyle et al. [34], 6.1% (3/49) of the patients with normal muscle mass and 86.4% (33 of 39) of those with reduced muscle mass were obese ($p < 0.01$ at χ^2 test). There was also a significant difference in the prevalence of obesity between patients with moderate and severe muscle mass loss (81.8% (27/33) vs. 100% (6/6) ($p < 0.05$ at χ^2 test)). Only 6 non-obese patients had a low muscle mass, and in all of them, muscle mass loss was only moderate. These data suggested that obesity could be associated with a low muscle mass in PD patients. Similar results were obtained also when patients with diabetes were omitted, hence suggesting that the effect of obesity was not driven by a higher prevalence of diabetes (Table 3).

The findings obtained with BIA were validated by using BIVA. In BIVA, the R_c/XH vector was displaced rightward

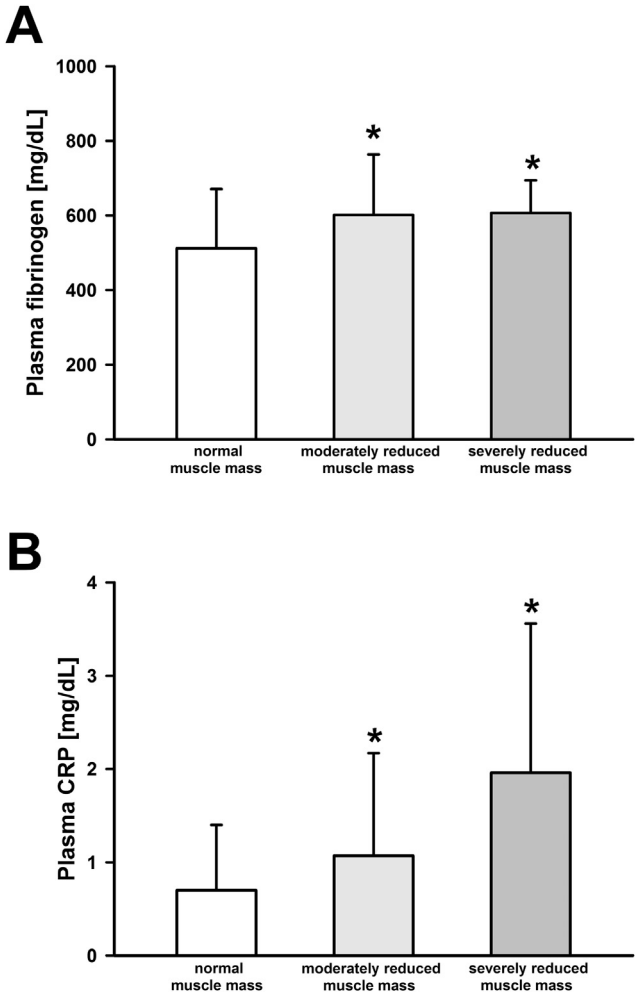

Figure 1 Fibrinogen and CRP plasma concentrations in patients with normal or reduced muscle mass. The bar graphs show fibrinogen (A) and CRP (B) plasma concentrations in PD patients with normal (white), moderately (light gray), and severely reduced (dark gray) muscle mass. See the text for details on how muscle mass was measured and on the cutoff used to discriminate patients belonging to three different groups. *$p < 0.05$ at ANOVA followed by Bonferroni post-hoc test.

Table 3 Renal and bioelectrical impedance parameters in nondiabetic PD patients with normal, moderately, and severely reduced muscle mass.

	Normal muscle mass (n = 40)	Moderate muscle mass LOSS (n = 28)	Severe muscle mass loss (n = 2)
Sex (Male/Female)	28/12	16/12	1/1
Age (years)	50.5 ± 13.3	53.7 ± 13.6	38.0 ± 2.8
BW (kg)	73.1 ± 14.7	83.0 ± 14.7*	79.7 ± 20.7
BMI (kg/m^2)	26.6 ± 3.7	31.0 ± 3.1*	31.6 ± 4.3
rGFR (ml/min*1.73 m^2)	4.4 ± 2.4	3.1 ± 1.2	4.9 ± 2.7
Peritoneal dialysis modality (%CAPD)	72.5	75.0	50.0
Dialysis vintage (months)	13.4 ± 13.5	20.9 ± 19.4	10.5 ± 10.6
Kt/V	2.1 ± 0.4	1.5 ± 0.3	2.9 ± 0.6
nPCR (g/Kg)	1.1 ± 0.2	0.8 ± 0.3	1.2 ± 0.3
Resistance (ohm)	442.2 ± 70.1	495.3 ± 81.1*	700.5 ± 290.6*†
Reactance (ohm)	46.9 ± 13.0	52.8 ± 11.0	68.5 ± 19.1
Vector Length (ohm/m)	271.2 ± 54.8	308.6 ± 65.5	452.2 ± 212.6*†
FFM (% BW)	78.2 ± 7.1	67.0 ± 7.6*	56.5 ± 9.9*†
FM (% BW)	21.8 ± 7.1	33.9 ± 5.8*	43.5 ± 9.9*†
Extracellular water (%)	46.4 ± 6.3	45.6 ± 4.8	47.0 ± 4.0
FMI (kg/m^2)	5.9 ± 2.6	10.5 ± 2.2*	13.5 ± 1.2*
SM/BW (%)	40.8 ± 5.5	30.8 ± 4.6*	24.6 ± 7.4*

Data are reported as mean ± SD or median and interquartile range as appropriate. Abbreviations: BMI = body mass index; CAPD = continuous ambulatory peritoneal dialysis, rGFR = residual glomerular filtration rate; nPCR = normalized catabolic rate; FFM = free fat mass; FM = fat mass; FMI = fat mass index; SM= skeletal muscle mass; BW = body weight. *p < 0.05 vs. normal, †p < 0.05 vs. moderate muscle loss at ANOVA followed by Bonferroni test.

with regard to the normal reference ellipse, slightly in patients with moderate muscle mass loss and more strongly in those with severe muscle mass loss (Fig. 2). The differences in vector position among patients with normal, moderately, and severely reduced muscle mass were significant in the Hotelling's T^2 test ($p < 0.05$). Importantly, there was no change in phase angle, suggesting that the ratio between extracellular body water and TBW (ECW/TBW) was preserved and that soft tissue mass had been lost with no change in hydration.

To identify the risk factors for muscle mass loss in patients on PD, we performed an ordinal logistic regression using the aforementioned three-point muscle mass score as the dependent variable and age, dialysis vintage, sex, type of dialysis, diabetes, and obesity as covariates. The results obtained (Table 4) showed that the risk of muscle mass loss was influenced by the factors female gender, obese, or presence of diabetes, whereas it was unaffected by increasing age, longer dialysis vintage, and the type of PD. Interestingly, the risk of having a reduced muscle mass was more than 45-fold higher in patients with diabetes and obesity than in those with normal body weight and no diabetes.

To further characterize the effect of obesity on muscle mass loss, we classified our PD patients into four groups on the basis of SM/BW and FMI values: nonobese patients with normal muscle mass, obese patients with normal muscle mass, nonobese patients with low muscle mass, and obese patients with low muscle mass (Fig. 3). No significant difference in either renal or blood chemistry parameters was found among these groups (Table 5). When compared with patients with normal body composition, higher plasma concentrations of both fibrinogen and CRP were found in patients with muscle wasting and obesity but not in those with only muscle wasting or obesity (Fig. 4).

Discussion

In the present paper, we investigated the prevalence of muscle wasting in PD patients and whether this condition was associated with obesity or diabetes. We found that approximately 45% of our PD patients had muscle wasting and that 86.4% of all PD patients with muscle wasting were also obese, whereas 23% had diabetes. Interestingly, all

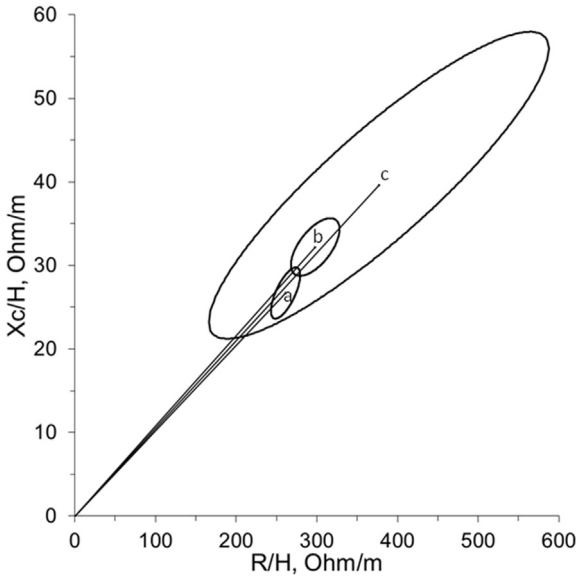

Figure 2 BIVA analysis in PD patients. The plot shows the BIVA vectors obtained in patients with normal (a), moderately (b), and severely (c) reduced muscle mass with the relative reference ellipses. Notice that as muscle mass increased, vector length also progressively increased, with no change in phase angle. The difference in position was statistically significant between a and c (Mahalabanois D = 0.91, P = 0.0003) but not between a and b (Mahalabanois D = 0.73; P = 0.076).

Table 4 Results of the ordinal logistic regression analysis.

	OR	CI (95%)	Wald	P
Age	0.98	(0.945–1.024)	.662	.416
Dialysis Vintage	1.02	(0.984–1.047)	.888	.346
Gender: female	3.82	(1.320–11.043)	6.112	.013
Gender: male	1.00			
Type of PD:CAPD	0.90	(0.283–2.883)	.030	.863
Type of PD:APD	1.00			
Obesity	13.45	(4.543–39.929)	21.993	$2.73 \cdot 10^{-6}$
No obesity	1.00			
Diabetes Mellitus	3.80	(1.095–13.213)	4.422	.035
No Diabetes Mellitus	1.00			
Diabetes * obesity	46.37	(7.26–296.13)	16.45	$5.00 \cdot 10^{-5}$
Diabetes * no obesity	1.40	(0.32–6.10)	0.20	0.65
No diabetes * obesity	8.59	(2.92–25.25)	15.27	$9.33 \cdot 10^{-5}$
No diabetes * no obesity	1.0			
Gender female * diabetes	29.36	(3.31–260.32)	9.21	0.002
Gender female* no diabetes	1.74	(0.66–4.60)	1.25	0.263
Gender male * diabetes	1.12	(0.33–3.78)	0.03	0.852
Gender male * no diabetes	1.0			
Gender female * obesity	27.60	(5.64–135.00)	16.78	$4.20 \cdot 10^{-5}$
Gender female * no obesity	5.15	(1.39–19.07)	6.03	0.014
Gender male * obesity	17.90	(4.92–65.14)	19.17	$1.20 \cdot 10^{-5}$
Gender male * no obesity	1.0			

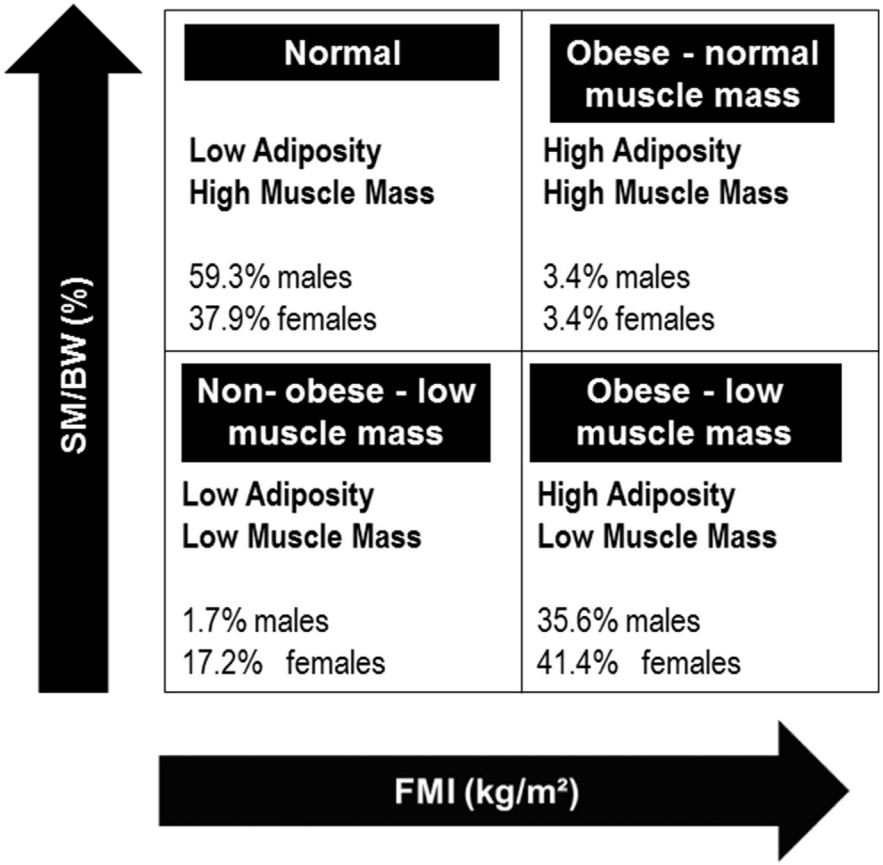

Figure 3 Schematic drawing of PD patient classification based on fat mass and muscle mass determination at BIA. The drawing shows how we classified our PD patients into four categories according to the SM/BW and FMI cutoff reported in the Methods section of the manuscript: patients with normal body composition (upper left quadrant), obese patients (upper right quadrant), patients with muscle wasting (lower left quadrant), and patients with obesity-associated muscle wasting (lower right quadrant). The percentage of male and female patients in each category is also reported in the respective quadrant. Notice that more than 90% of male and more than 70% of female patients fall either in the upper left (normal body composition) or in the lower right (obesity-associated muscle wasting) quadrants.

Table 5 Body composition and metabolic parameters in PD patients with normal body composition, obesity, and muscle wasting with or without obesity.

	Normal (n = 46)	Obesity (n = 3)	Muscle mass loss (n = 6)	Muscle mass loss and obesity (n = 33)
BMI (Kg/m^2)	25.9 ± 3.0	34.4 ± 4.8*	27.0 ± 1.9	32.2 ± 3.6*
FFM (%BW)	79.4 ± 6.3	65.4 ± 6.0*	66.1 ± 5.9*	64.7 ± 9.0*
FM (%BW)	20.5 ± 6.3	34.6 ± 6.0*	33.8 ± 5.9*	36.0 ± 7.6*
FMI (kg/m^2)	5.4 ± 2.0	11.8 ± 3.3*	8.9 ± 1.9*	11.6 ± 3.3*
SM/BW (%)	41.5 ± 5.5	38.2 ± 6.9	28.4 ± 3.3*	30.3 ± 5.5*
Vector Length (ohm/m)	271.5 ± 51.1	209.5 ± 13.1	371.6 ± 60.2*†	307.6 ± 79.5
Albumin (g/dL)	3.7 ± 0.5	3.4 ± 0.7	4.0 ± 0.4	3.8 ± 0.4
Total cholesterol (mg/dL)	180.5 ± 49.7	164.7 ± 48.8	185.3 ± 32.2	168.0 ± 44.0
HDL-cholesterol (mg/dL)	45.1 ± 10.5	45.0 ± 1.7	58.6 ± 24.4	41.9 ± 12.4
Triglycerides (mg/dL)	165.7 ± 105.8	127.0 ± 55.6	173.0 ± 86.8	172.1 ± 91.7
Glycated Hemoglobin (mg/dL)	5.5 ± 1.4	6.9 ± 1.5	5.6 ± 1.1	6.0 ± 1.3

Data are reported as mean ± SD or median and interquartile range as appropriate. Abbreviations: BMI = body mass index; FFM = free fat mass; FM = fat mass; FMI = fat mass index; SM = Skeletal Muscle Mass; BW = Body weight. *$p < 0.05$ vs. normal, †$p < 0.05$ vs. obesity at ANOVA followed by Bonferroni test.

patients with both diabetes and muscle wasting were also obese. Ordinal regression analysis confirmed that obesity and diabetes were strongly associated with muscle wasting and identified female gender as a significant predictor, whereas it excluded that patient age and dialysis vintage were involved.

Our finding of high prevalence of obesity among PD patients with muscle loss is in contrast with the findings reported by the few publications that addressed this issue in the past. For instance, in a large series of 325 PD patients reported by Hung et al. [19], less than 5% of females and approximately 7% of the males had both obesity and muscle wasting. Likewise, Yoowannakul et al. [45] reported a prevalence of obesity lower than 3% in a population of 434 PD patients of different ethnicity, whereas according to Greenhall and Davenport [18], the percentage of body fat was higher than normal in 20–30% of PD patients depending on the severity of muscle wasting. Several factors could account for the higher prevalence of obesity in our patients than that in these previous studies. First, the prevalence of obesity or overweight even before starting dialysis could have been higher in our patient population than in the populations of other studies. Different criteria are used, indeed, in different institutions to select patients for HD or PD and some centers strictly exclude overweight or obese patients from PD. A second possibility is related to longer dialysis vintage in our patients than in those evaluated in the studies that we mentioned before. In fact, evidence obtained in HD patients suggests that the longer the vintage is, the higher will be the risk of systemic inflammation, of a bad nutritional status and, consequently of changes in body composition [40,41]. However, the most important factor responsible for the differences in the prevalence of muscle wasting and obesity-associated muscle wasting in our study and in previous studies was presumably represented by the use of different criteria to identify muscle mass loss. The lack of an international consensus on the techniques to be used and the thresholds to be applied to identify patients with muscle wasting in CKD is emerging as a major problem for clinical research in the field because it

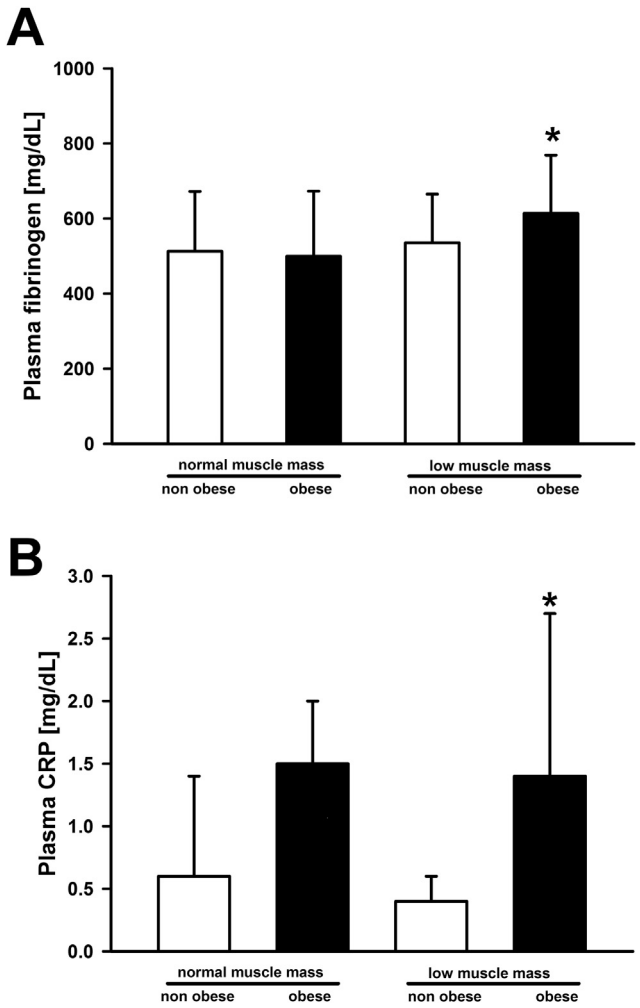

Figure 4 Fibrinogen and CRP plasma concentrations in patients with obesity, muscle wasting, and obesity-associated muscle wasting. The bar graphs show fibrinogen (A) and CRP (B) plasma concentrations in obese (black) and nonobese (white) PD patients with normal or reduced muscle mass as indicated. See the text for details on how muscle mass was measured and on the cutoff used to discriminate patients belonging to the different groups. *$p < 0.05$ at ANOVA followed by Bonferroni post-hoc test.

makes difficult or impossible the comparisons among different studies. Greenhall and Davenport [18] reported that when bioimpedance with the NANHES criteria was used to diagnose muscle mass loss, 98.5% of PD patients showed this condition, whereas this percentage decreased to 6.3%–28.8% when a grading correlated with functional disability was used. Similarly, according to Hung et al. [19] the prevalence of muscle wasting varied between 25.1% and 75.6% of male and 2.2% and 31.3% of female PD patients depending on the diagnostic criteria applied. Moreover, Abro et al. [20] showed that the prevalence of both dynapenia and muscle mass loss in PD patients showed significant difference when estimated with the cutoff values of the Foundation for the National Institutes of Health Biomarkers Consortium Sarcopenia Project (FNIH), European Working Group on Sarcopenia in Older People (EWGSOP), and the Asian Working Group for Sarcopenia (AWGS) definitions. In the present study, we used BIA complemented with BIVA to identify patients with a lower than normal muscle mass and/or with a high FM. Even though many studies on sarcopenia in CKD used dual-energy X-ray absorptiometry (DXA) measurements of appendicular lean mass [42], it is now widely accepted that BIA can also be reliably used for this aim, especially if BIVA is also used, as we did, to exclude major differences in hydration [43]. Importantly, the results obtained with DXA and BIA/BIVA are in good agreement with each other [44,45]. In addition, good reproducibility of the results obtained with BIA has also been demonstrated [33,46]. Previous studies used SM indexed to height-squared to quantify muscle mass and diagnose sarcopenia [22,36]. However, such approach may underestimate the prevalence of low muscle mass, especially in the obese patients [37]. Therefore, in the present study, we used SM/BW, that is, the percent ratio between SM and body weight, whose changes are considered a more reliable predictor of not only muscle mass loss but also functional impairment [11,22,37]. Because of the difference in the diagnostic criteria for sarcopenia our sarcopenic patient could have been actually different from those of the previous studies. In addition, our obese patients could have also been different. Indeed, another important methodological difference between our study and the study of Hung et al. [19] is that we used the BIA-derived parameter FMI and the FMI thresholds proposed by Kyle et al. [34] instead of BMI to identify patients with obesity. The use of BMI has been strongly criticized because this parameter not only reflects fat accumulation but is also influenced by changes in lean mass [47] and, therefore, may lead to the misclassification of patients with fat excess as “normal” when sarcopenia is present [48]. Importantly, the unreliability of BMI for the diagnosis of obesity in the specific setting of CKD patients has been demonstrated in comparative studies with DXA [49,50]. Therefore, with the use of FMI, our study could have detected many cases of sarcopenic obesity that could have been misdiagnosed with the use of BMI.

The strong association that we found between muscle wasting and obesity in PD suggests a possible causal link between these two conditions. An obvious, simplistic hypothesis to explain this association is that glucose overload caused by its absorption from the PD dialysate could cause obesity, insulin resistance, and, consequently, muscle mass loss [51–54]. In addition, obesity promotes inflammation and systemic cytokine release and, when fat accumulation takes place in muscle fibers as in sarcopenic obesity, muscle fibers could be damaged by the high local cytokine concentrations. Cesari et al. [55] showed that CRP and IL-6 correlate directly with BMI and indirectly with appendicular lean mass and that obesity remains positively related to these inflammatory markers after correction for muscle loss. Based on these results, they proposed that CRP and IL-6 could have a role in the development of sarcopenic obesity. Interestingly, in the present study, we obtained similar results in PD patients as we observed higher fibrinogen and CRP plasma levels in patients with muscle wasting and obesity. It has to be mentioned, however, that criticisms have been raised on the inflammatory hypothesis of the genesis of sarcopenic obesity and that some authors consider cytokine plasma levels only as confounders of the real pathogenetic mechanism of this condition [56].

Our finding that diabetes was associated with muscle mass loss in patients on PD was not surprising considering that PD is known to increase the risk of obesity and diabetes possibly because of the high glucose concentration in the dialyzing solution and that diabetes is per se an important risk factor of sarcopenia [29–31]. We can, however, exclude that obesity was linked with muscle loss in our PD patients only because being obese increases the chance of having diabetes. Obesity was, indeed, still associated with muscle loss when only patients without diabetes were included in the analysis. Moreover, in the presence of both diabetes and obesity, the OR of muscle mass loss strongly increased as the two factors were reciprocally potentiating each other.

Our finding of an association between obesity and reduced muscle mass suggests that becoming obese could negatively impact the prognosis of PD patients by increasing the risk of muscle wasting. The effect of obesity in PD patients has been the matter of debate, and evidence has been reported that it could be associated with a better preservation of total body protein in these patients than in nonobese PD patients [57]. However, both in patients with normal renal function and in those with CKD not yet on dialysis, risk of both morbidity and mortality becomes higher when muscle mass decreases in combination with an increase in FM [58,59]. Further, long-term prospective studies will be needed to establish whether sarcopenic obesity actually affects prognosis in PD patients and to provide rationale basis for implementing specific nutritional interventions that reduce obesity and not cause malnutrition but, instead, promote muscle mass.

Our study has some limitations. First, we measured the prevalence of muscle wasting and not of sarcopenia, which is considered as a negative prognostic factor in patients with renal insufficiency. However, we did this on purpose because, as we discussed before, no universally

accepted definition of sarcopenia is available yet for CKD. A second important limitation of our study is that we do not have data on the body composition of our PD patients before starting PD, and therefore, our data could actually reflect changes in body composition unrelated to dialysis. Finally, because of the cross-sectional observational design, we can only state that obesity and muscle mass loss are associated with each other in PD patients, but no formal causal relationship can be established between them.

In conclusion, we showed that the majority of the PD patients with low muscle mass are obese. Moreover, our data showed a close association between low muscle mass and inflammation in PD patients. These characteristics may contribute to the development of physical disability and mortality and pave the way to specific nutritional intervention to reduce fat and increase muscle mass in PD patients.

Conflicts of interest

None declared.

References

[1] Isoyama N, Qureshi AR, Avesani CM, Lindholm B, Bàràny P, Heimbürger O, et al. Comparative associations of muscle mass and muscle strength with mortality in dialysis patients. Clin J Am Soc Nephrol 2014;9:1720–8.

[2] 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.

[3] Souza VA, Oliveira D, Barbosa SR, Corrêa JODA, Colugnati FAB, Mansur HN, et al. Sarcopenia in patients with chronic kidney disease not yet on dialysis: analysis of the prevalence and associated factors. PLoS One 2017;12:e0176230.

[4] Pereira RA, Cordeiro AC, Avesani CM, Carrero JJ, Lindholm B, Amparo FC, et al. Sarcopenia in chronic kidney disease on conservative therapy: prevalence and association with mortality. Nephrol Dial Transplant 2015;30:1718–25.

[5] Fahal IH. Uraemic sarcopenia: aetiology and implications. Nephrol Dial Transplant 2014;29:1655–65.

[6] Moorthi RN, Avin KG. Clinical relevance of sarcopenia in chronic kidney disease. Curr Opin Nephrol Hypertens 2017;26:219–28.

[7] Ikizler TA, Pupim LB, Brouillette JR, Levenhagen DK, Farmer K, Hakim RM, et al. Hemodialysis stimulates muscle and whole body protein loss and alters substrate oxidation. Am J Physiol Endocrinol Metab 2002;282:E107–16.

[8] Kaizu Y, Ohkawa S, Odamaki M, Ikegaya N, Hibi I, Miyaji K, et al. Association between inflammatory mediators and muscle mass in long-term hemodialysis patients. Am J Kidney Dis 2003;42:295–302.

[9] Qureshi AR, Alvestrand A, Danielsson A, Divino-Filho JC, Gutierrez A, Lindholm B, et al. Factors predicting malnutrition in hemodialysis patients: a cross-sectional study. Kidney Int 1998;53:773–82.

[10] Kim JK, Kim SG, Oh JE, Lee YK, Noh JW, Kim HJ, et al. Impact of sarcopenia on long-term mortality and cardiovascular events in patients undergoing hemodialysis. Korean J Intern Med 2017 Nov 23. https://doi.org/10.3904/kjim.2017.083 [Epub ahead of print].

[11] Kittiskulnam P, Chertow GM, Carrero JJ, Delgado C, Kaysen GA, Johansen KL. Sarcopenia and its individual criteria are associated, in part, with mortality among patients on hemodialysis. Kidney Int 2017;92:238–47.

[12] Lamarca F, Carrero JJ, Rodrigues JC, Bigogno FG, Fetter RL, Avesani CM. Prevalence of sarcopenia in elderly maintenance hemodialysis patients: the impact of different diagnostic criteria. J Nutr Health Aging 2014;18:710–7.

[13] Ren H, Gong D, Jia F, Xu B, Liu Z. Sarcopenia in patients undergoing maintenance hemodialysis: incidence rate, risk factors and its effect on survival risk. Ren Fail 2016;38:364–71.

[14] Krediet RT, Zuyderhoudt FM, Boeschoten EW, Arisz L. Peritoneal permeability to proteins in diabetic and non-diabetic continuous ambulatory peritoneal dialysis patients. Nephron 1986;42:133–40.

[15] Rajakaruna G, Caplin B, Davenport A. Peritoneal protein clearance rather than faster transport status determines outcomes in peritoneal dialysis patients. Perit Dial Int 2015;35:216–21.

[16] Kang SH, Park JW, Yoon KW, Do JY. Limb/trunk lean mass ratio as a risk factor for mortality in peritoneal dialysis patients. J Ren Nutr 2013;23:315–23.

[17] As'habi A, Najafi I, Tabibi H, Hedayati M. Prevalence of sarcopenia and dynapenia and their determinants in Iranian peritoneal dialysis patients. Iran J Kidney Dis 2018;12:53–60.

[18] Greenhall GH, Davenport A. Screening for muscle loss in patients established on peritoneal dialysis using bioimpedance. Eur J Clin Nutr 2017;71:70–5.

[19] Hung R, Wong B, Goldet G, Davenport A. Differences in prevalence of muscle wasting in patients receiving peritoneal dialysis per dual-energy X-ray absorptiometry due to variation in guideline definitions of sarcopenia. Nutr Clin Pract 2017;32:539–44.

[20] Abro A, Delicata LA, Vongsanim S, Davenport A. Differences in the prevalence of sarcopenia in peritoneal dialysis patients using hand grip strength and appendicular lean mass: depends upon guideline definitions. Eur J Clin Nutr 2018;72:9939.

[21] Cruz-Jentoft AJ, Baeyens 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.

[22] 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 May;50:889–96.

[23] Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 1993;259:87–91.

[24] Bergia R, Bellini ME, Valenti M, Berto IM, Caramello E, Dionisio P, et al. Longitudinal assessment of body composition in continuous ambulatory peritoneal dialysis patients using bioelectric impedance and anthropometric measurements. Perit Dial Int 1993;13(Suppl. 2):S512–4.

[25] Fernström A, Hylander B, Moritz A, Jacobsson H, Rössner S. Increase of intra-abdominal fat in patients treated with continuous ambulatory peritoneal dialysis. Perit Dial Int 1998;18:166–71.

[26] Lo WK. Metabolic syndrome and obesity in peritoneal dialysis. Kidney Res Clin Pract 2016;35:10–4.

[27] Mehrotra R, de Boer IH, Himmelfarb J. Adverse effects of systemic glucose absorption with peritoneal dialysis: how good is the evidence? Curr Opin Nephrol Hypertens 2013;22:663–8.

[28] Fernandes NM, Bastos MG, Franco MR, Chaoubah A, Lima Mda G, Divino-Filho JC, et al. Brazilian Peritoneal Dialysis Multicenter Study (BRAZPD) Group Body size and longitudinal body weight changes do not increase mortality in incident peritoneal dialysis patients of the Brazilian peritoneal dialysis multicenter study. Clinics 2013;68:51–8.

[29] Dong J, Yang Z-K, Chen Y. Older age, higher body mass index and inflammation increase the risk for new-onset diabetes and impaired glucose tolerance in patients on peritoneal dialysis. Perit Dial Int 2016;36(3):277–83.

[30] Li PKT, Dorval M, Johnson DW, Rutherford P, Shutov E, Story K, et al. The benefit of a glucose-sparing PD therapy on glycemic control measured by serum fructosamine in diabetic patients in a randomized, controlled trial (IMPENDIA). Nephron 2015;129:233–40.

[31] Liao CT, Kao TW, Chou YH, Wu MS, Chen YM, Chuang HF, et al. Associations of metabolic syndrome and its components with cardiovascular outcomes among non-diabetic patients undergoing maintenance peritoneal dialysis. Nephrol Dial Transplant 2011;26:4047–54.

[32] Guida B, Cataldi M, Maresca ID, Germanò R, Trio R, Nastasi AM, et al. Dietary intake as a link between obesity, systemic inflammation, and the assumption of multiple cardiovascular and antidiabetic drugs in renal transplant recipients. Biomed Res Int 2013;2013:363728.

[33] Davenport A. Does peritoneal dialysate affect body composition assessments using multi-frequency bioimpedance in peritoneal dialysis patients? Eur J Clin Nutr 2013;67:223–5.
[34] Kyle UG, Pirlich M, Lochs H, Schuetz T, Pichard C. Increased length of hospital stay in underweight and overweight patients at hospital admission: a controlled population study. Clin Nutr 2005;24:133–42.
[35] Janssen I, Heymsfield SB, Baumgartner RN, Ross R. Estimation of skeletal muscle mass by bioelectrical impedance analysis. J Appl Physiol (1985) 2000;89:465–71.
[36] Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol 1998;147:755–63.
[37] Cawthon PM, Peters KW, Shardell MD, McLean RR, Dam TT, Kenny AM, et al. Cutpoints for low appendicular lean mass that identify older adults with clinically significant weakness. J Gerontol A Biol Sci Med Sci 2014;69:567–75.
[38] Piccoli A, Rossi B, Pillon L, Bucciante G. A new method for monitoring body fluid variation by bioimpedance analysis: the RXc graph. Kidney Int 1994;46:534–9.
[39] Dixon WJ, Brown MB, Engelman L, Jennrich RJ. BMDP: statistical software manual. Berkeley: UCLA; 1992.
[40] Carrero JJ, Chmielewski M, Axelsson J, Snaedal S, Heimbürger O, Bárány P, et al. Muscle atrophy, inflammation and clinical outcome in incident and prevalent dialysis patients. Clin Nutr 2008;27:557–64.
[41] Chertow GM, Johansen KL, Lew N, Lazarus JM, Lowrie EG. Vintage, nutritional status, and survival in hemodialysis patients. Kidney Int 2000;57:1176–81.
[42] Kelly TL, Wilson KE, Heymsfield SB. Dual energy X-ray absorptiometry body composition reference values from NHANES. PLoS One 2009;4:e7038.
[43] Guida B, Trio R, Pecoraro P, Gerardi MC, Laccetti R, Nastasi A, et al. Impedance vector distribution by body mass index and conventional bioelectrical impedance analysis in obese women. Nutr Metab Cardiovasc Dis 2003;13:72–9.
[44] Fürstenberg A, Davenport A. Comparison of multifrequency bioelectrical impedance analysis and dual-energy X-ray absorptiometry assessments in outpatient haemodialysis patients. Am J Kidney Dis 2010;57:123–9.
[45] Fürstenberg A, Davenport A. Assessment of body composition in peritoneal dialysis patients using bioelectrical impedance and dual-energy x-ray absorptiometry. Am J Nephrol 2011;33:150–6.
[46] Davenport A. Effect of intra-abdominal dialysate on bioimpedance-derived fluid volume status and body composition measurements in peritoneal dialysis patients. Perit Dial Int 2013;33:578–9.
[47] Pischon T. Commentary: use of the body mass index to assess the risk of health outcomes: time to say goodbye? Int J Epidemiol 2010;39:528–9.
[48] Gonzalez MC, Pastore CA, Orlandi SP, Heymsfield SB. Obesity paradox in cancer: new insights provided by body composition. Am J Clin Nutr 2014;99:999–1005.
[49] Sharma D, Hawkins M, Abramowitz MK. Association of sarcopenia with eGFR and misclassification of obesity in adults with CKD in the United States. Clin J Am Soc Nephrol 2014;9:2079–88.
[50] Ziolkowski SL, Long J, Baker JF, Simard JF, Chertow GM, Leonard MB. Sarcopenia, relative sarcopenia and excess adiposity in chronic kidney disease. JCSM Clin Rep Feb 01, 2018.
[51] Burkart J. Metabolic consequences of peritoneal dialysis. Semin Dial 2004;17:498–504.
[52] Gallieni M, Musetti C, Granata A, Olivi L, Bertoli S. Metabolic consequences of peritoneal dialysis treatment. Panminerva Med 2009;51:175–85.
[53] Kim YL, Cho JH, Choi JY, Kim CD, Park SH. Systemic and local impact of glucose and glucose degradation products in peritoneal dialysis solution. J Ren Nutr 2013;23:218–22.
[54] Jolly S, Chatatalsingh C, Bargman J, Vas S, Chu M, Oreopoulos DG. Excessive weight gain during peritoneal dialysis. Int J Artif Organs 2001;24:197–202.
[55] Cesari M, Kritchevsky SB, Baumgartner RN, Atkinson HH, Penninx BW, Lenchik L, et al. Sarcopenia, obesity, and inflammation–results from the trial of angiotensin converting enzyme inhibition and novel cardiovascular risk factors study. Am J Clin Nutr 2005;82:428–34.
[56] Kob R, Bollheimer LC, Bertsch T, Fellner C, Djukic M, Sieber CC, et al. Sarcopenic obesity: molecular clues to a better understanding of its pathogenesis? Biogerontology 2015;16:15–29.
[57] Pellicano R, Strauss BJ, Polkinghorne KR, Kerr PG. Longitudinal body composition changes due to dialysis. Clin J Am Soc Nephrol 2011;6:1668–75.
[58] Prado CM, Wells JC, Smith SR, Stephan BC, Siervo M. Sarcopenic obesity: a critical appraisal of the current evidence. Clin Nutr 2012;31:583–601.
[59] Wu HC, Tseng SF, Wang WJ, Chen HJ, Lee LC. Association between obesity with low muscle mass and dialysis mortality. Intern Med J 2017;47:1282–91.