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ORIGINAL PAPER

Correlates of appendicular skeletal muscle mass in non-dialysis dependent chronic kidney disease men and the control group

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Summary *Introduction: Skeletal muscle wasting is a serious complication of chronic kidney disease (CKD) and is associated with increased mortality. However, the main determinants of muscle atrophy in CKD are not yet well known and may differ in the general and CKD populations. The aim of this study was to investigate the relationships between appendicular skeletal muscle mass (ASM) and anthropometric measurements, body composition parameters as well as laboratory results, and compare these associations in patients with estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 and participants with eGFR ≥ 60 ml/min/1.73 m^2.*

Methods: Two groups of male participants were included: 33 patients with eGFR < 60 ml/min/1.73 m^2 and 38 individuals with eGFR ≥ 60 ml/min/1.73 m^2. Muscle mass and body composition variables, including ASM, were assessed by bioimpedance spectroscopy (BIS). Blood samples were taken to evaluate serum creatinine, urea, haemoglobin, C-reactive protein (CRP) and albumin.

Results: In both groups of patients ASM positively correlated with body mass, body mass index (BMI), lean tissue mass (LTM) and lean tissue indx (LTI) ($p < 0.05$ for all parameters). ASM positively correlated with height in individuals with eGFR ≥ 60 ml/min/1.73 m^2 ($p = 0.001$). There was no statistically significant correlations between laboratory parameters and ASM in both groups.

Conclusions: ASM is associated significantly and positively with anthropometric and body composition parameters such as body mass, BMI, LTM and LTI both in patients with eGFR < 60 ml/min/1.73 m^2 and in those with eGFR ≥ 60 ml/min/1.73 m^2 which suggests that the determinants of ASM are similar in CKD and in the general population.

KEY WORDS: *Chronic kidney disease; Men; Muscle atrophy; Appendicular skeletal muscle mass.*

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INTRODUCTION

Skeletal muscle is the largest tissue in human body constituting between 30% and 50% of total body weight. Human skeletal muscle contains up to 75% of total body proteins and its mass depends on the degree of anabolic and catabolic processes (1). Various acute or chronic pathological states such as cancer, renal or heart failure, chronic obstructive pulmonary disorder, injuries, diabetes, hormonal derangements or poor nutrition may lead to the loss of skeletal muscle. Older age and sedentary lifestyle also contribute to muscle atrophy (2). Skeletal muscle wasting is more common in *chronic kidney disease* (CKD) patients than in healthy individuals. The loss of muscle mass begins at the early stages of kidney function decrease and intensifies with the progress of renal failure being the most severe in patients treated with dialysis (3). The mechanisms which reduce muscle protein synthesis, enhance muscle protein catabolism and in consequence decrease skeletal muscle mass in CKD are multivarious and include metabolic acidosis, increased inflammatory processes, oxidative stress, mitochondrial dysfunction, insulin and *insulin growth factor-1* (IGF-1) resistance, hormonal disturbances and vitamin D deficiency (4). The treatment with hemodialysis also potentiates proteolysis of skeletal muscle leading to muscle atrophy (5). Additionally, protein degradation is enhanced by elevated myostatin which is a negative regulator of muscle growth (6). Decreased skeletal muscle mass in CKD is associated with increased morbidity and mortality (7). Also, muscle atrophy is related with poor physical performance, patients with reduced muscle mass are frequently functionally dependent on assistance in performing numerous daily tasks which significantly lowers their quality of life. Additionally, patients with muscle atrophy are more prone to falls which leads to higher number of hospitalizations (8). Although the knowledge regarding the mechanisms of skeletal muscle wasting in CKD is expanding, the main determinants of muscle atrophy are not yet well known. It is still questionable why some patients with CKD develop muscle atrophy while others do not and what are the anthropometric or biochemical parameters which could indicate muscle mass loss.

According to the *European Working Group on Sarcopenia in Older People* (EWGSOP2) decreased muscle mass is a mandatory criterion, along with reduced muscle strength, to diagnose sarcopenia (9). Due to the lack of specific diagnostic criteria for sarcopenia in CKD the EWGSOP2 guidelines are used also in population with kidney function decrease. However, the determinants of muscle

strength and muscle mass may differ in the general and CKD populations.

The aim of this study was to compare the strength of the relationships between *appendicular skeletal muscle mass* (ASM) and anthropometric measurements, body composition parameters as well as laboratory variables in patients with eGFR < 60 ml/min/1.73 m^2 and those with eGFR ≥ 60 ml/min/1.73 m^2. The article is part of a series of publications concerning the various correlates of ASM in CKD, and the current study includes the control group (10, 11).

Methods

Study design

We performed a comparative study which included two groups of male participants: patients with CKD and eGFR < 60 ml/min/1.73 m^2 not treated with dialysis (the study group) and men with eGFR ≥ 60 ml/min/1.73 m^2 (the control group).

Patients

Patients with CKD (n = 33) were recruited from the *Nephrology Outpatient Clinic of Military Institute of Medicine - National Research Institute in Warsaw*, Poland, where they visited Outpatient Clinic for a regular checkup. Participants with eGFR ≥ 60 ml/min/1.73 m^2 (n = 38) were recruited from internal medicine department. Patients with kidney function decrease were enrolled to the study between 2015 and 2017 and the control group participants - between 2018 and 2020. The inclusion criteria for all patients were 18-80 years of age, eGFR < 60 mL/min/1.73 m^2 for participants in the study group and eGFR ≥ 60 ml/min/1.73 m^2 for the control group. The exclusion criteria for both groups were infections, malignancies, acute medical conditions, the presence of metal parts in the body and for the study group renal replacement therapy or its requirement within the following 3 months. All participants signed an informed consent. Both studies were conducted in accordance with the Declaration of Helsinki. The study protocols were accepted by the local ethics committee (*Bioethics Committee in Military Institute of Medicine - National Research Institute in Warsaw, Poland, IRB acceptance number 42/WIM/2015 and 120/WIM/2018*).

Studied parameters

Muscle mass was measured by multifrequency *bioimpedance spectroscopy* (BIS) with the use of *Body Composition Monitor* (*BCM, Fresenius Medical Care, Bad Homburg, Germany*). Patients were asked to maintain a supine position with electrodes placed on one hand and one foot in a tetrapolar configuration. In order to evaluate muscle mass from BCM we used the Lin's algorithm, which derived a formula for ASM estimation based on parameters obtained from bioimpedance spectroscopy (12). BIS was also used to measure body composition parameters including *lean tissue mass* (LTM), *lean tissue index* (LTI), *fat mass* (Fat), *fat tissue index* (FTI), *relative fat* (Rel Fat), *overhydration* (OH) and *relative overhydration* (Rel OH).

Blood samples were taken after a 12-hour overnight fast. Serum parameters were analysed in the local *Departments of Laboratory Diagnostics*. Serum creatinine concentrations were evaluated with the use of Jaffe method (*Gen.2, Roche Diagnostics GmbH, Rotkreuz, Switzerland*) and plasma urea levels using urease kinetic test (*Cobas c501, Roche Diagnostics, GmbH, Rotkreuz, Switzerland*). CRP serum concentrations were determined by a nephelometry assay (*BN™ II System Siemens, USA*). Plasma albumin was measured with the use of the BCP Albumin Assay Kit (*Roche Diagnostics GmbH, Rotkreuz, Switzerland*). *Estimated glomerular filtration rate* (eGFR) (mL/min per 1.73 m^2) was calculated according to the short *Modification of Diet in Renal Disease* (MDRD) formula.

Statistical analysis

The results are presented as means ± standard deviations (SD) for normally distributed data or medians and interquartile ranges (25^{th}-75^{th} percentiles) for skewed distributions. The Kolmogorov-Smirnov test was used to evaluate distributions for normality. T-Student test or Mann-Whitney test was applied for comparisons between groups depending on assumption regarding distributions. For correlation analysis, Pearson or Spearman correlation coefficients were calculated, respectively. Partial correlations were implemented for adjustments. A p-value < 0.05 was considered to be statistically significant. Statistical analysis was performed using IBM SPSS v.29.0 software (*SPSS Inc., Chicago, IL, USA*).

Results

Two groups of male participants were included in the study: 33 patients with eGFR < 60 ml/min/1.73 m^2 (the study group) and 38 men with eGFR ≥ 60 ml/min/1.73 m^2 (the control group). The mean age of patients was similar in both groups - 65 years among participants with eGFR < 60 ml/min/1.73 m^2 and 59 years in the control group.

Patients with eGFR < 60 ml/min/1.73m^2 had lower mean serum haemoglobin concentration (p < 0.001), higher mean plasma CRP levels (p = 0.008) and lower mean serum albumin (p = 0.029) compared to participants with eGFR ≥ 60 ml/min/1.73 m^2. According to the body composition parameters individuals with eGFR < 60 ml/min/1.73 m^2 had lower mean lean mass and index (p = 0.003, p = 0.011, respectively), higher means of absolute and relative fat mass, as well as fat mass index (p = 0.024, p = 0.001, p = 0.010, respectively). We did not find statistically significant differences between these two groups in means of absolute and relative overhdration (Table 1).

In our study we did not find statistically significant correlations between ASM and age, however older participants had lower ASM in both groups (p = 0.074 in patients with eGFR < 60 ml/min/1.73 m^2 and p = 0.051 in the control group). We also observed that ASM was not associated with kidney function parameters such as creatinine, eGFR and urea in participants with kidney function decrease or in individuals from the control group. Among serum laboratory measurements we did not find significant correlations between ASM and haemoglobin, CRP and albumin in both groups (Table 2).

We observed that weight and *body mass index* (BMI) were positively related with ASM in both groups. Participants

Table 1.
Characteristics of the studied population.

	eGFR < 60 ml/min/1.73 m^2		eGFR ≥ 60 ml/min/1.73 m^2		
	n	mean ± SD	n	mean ± SD	
ASM (kg)	33	23.38 ± 3.75	38	23.87 ± 5.01	0.652
Age (years)	33	64.88 ± 12.44	38	59.05 ± 13.15	0.060
Serum creatinine (mg/dL)	33	2.94 ± 1.23	38	0.88 ± 0.16	**< 0.001**
Serum urea (mg/dL)	28	99.79 ± 38.35	38	32.10 ± 8.45	**< 0.001**
eGFR (mL/min/1.73 m^2)	33	26.55 ± 9.65	38	93.47 ± 24.45	**< 0.001**
Haemoglobin (g/dL)	31	12.72 ± 1.65	38	14.77 ± 1.14	**< 0.001**
CRP (mg/dL)	33	0.30 (0.10 - 0.75)	38	0.18 (0.05 - 0.41)	**0.008**
Serum albumin (g/dL)	32	4.18 ± 0.30	38	4.37 ± 0.39	**0.029**
Height (cm)	33	171.18 ± 5.84	38	173.46 ± 7.46	0.161
Body mass (kg)	33	92.26 ± 15.91	38	88.52 ± 20.04	0.392
BMI (kg/m^2)	33	31.62 ± 5.69	38	29.37 ± 5.98	0.110
LTM (kg)	33	39.29 ± 7.89	38	45.98 ± 10.14	**0.003**
LTI (kg/m^2)	33	13.44 ± 2.67	38	15.22 ± 2.99	**0.011**
Fat (kg)	33	37.63 ± 12.06	38	30.55 ± 13.57	**0.024**
Rel Fat (%)	33	40.12 ± 7.04	38	33.47 ± 9.30	**0.001**
FTI (kg/m^2)	33	17.56 ± 5.79	38	13.82 ± 6.03	**0.010**
OH (L)	33	0.95 ± 2.58	38	0.44 ± 1.14	0.283
Rel OH (%)	33	3.71 ± 10.15	38	2.07 ± 6.01	0.405

CKD: chronic kidney disease; ASM (BIS): appendicular skeletal muscle mass measured by bioimpedance spectroscopy; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; BMI: body mass index; LTM: lean tissue mass; LTI: lean tissue index; Fat: fat mass; Rel Fat: relative fat; FTI: fat tissue index; OH: overhydration; Rel OH: relative overhydration; p-values < 0.05 are marked in bold.

Table 2.
Correlations of ASM with body composition parameters and laboratory measurements.

	eGFR < 60 ml/min/1.73 m^2		eGFR ≥ 60 ml/min/1.73 m^2	
	r	p-value	r	p-value
Age (years)	-0.315	0.074	-0.319	0.051
Serum creatinine (mg/dL)	0.175	0.330	0.089	0.596
eGFR (mL/min/1.73 m^2)	-0.247	0.165	-0.079	0.639
Serum urea (mg/dL)	0.087	0.659	0.090	0.593
Haemoglobin (g/dL)	-0.129	0.488	0.124	0.459
CRP (mg/dL)	0.263	0.140	0.151	0.367
Serum albumin (g/dL)	-0.293	0.104	-0.049	0.772
Height (cm)	0.258	0.148	0.515	**0.001**
Body mass (kg)	0.902	**< 0.001**	0.924	**< 0.001**
BMI (kg/m^2)	0.796	**< 0.001**	0.783	**< 0.001**
LTM (kg)	0.485	**0.004**	0.703	**< 0.001**
LTI (kg/m^2)	0.416	**0.016**	0.560	**< 0.001**
Fat (kg)	0.604	**< 0.001**	0.616	**< 0.001**
Rel Fat (%)	0.177	0.324	0.160	0.338
FTI (kg/m^2)	0.554	**0.001**	0.501	**0.001**
OH (L)	0.257	0.158	0.094	0.575
Rel OH (%)	0.137	0.445	0.018	0.914

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; BMI: body mass index; LTM: lean tissue mass; LTI: lean tissue index; Fat: fat mass; Rel Fat: relative fat; FTI: fat tissue index; OH: overhydration; Rel OH: relative overhydration; p-values < 0.05 are marked in bold.

with higher body weight had higher ASM in the study group and in the control group ($p < 0.001$, $p < 0.001$, respectively). Patients with higher BMI had also higher ASM ($p < 0.001$, $p < 0.001$ for both groups). We found positive association between ASM and height in individuals with eGFR ≥ 60 ml/min/1.73 m^2, taller participants had higher ASM ($p = 0.001$). According to the body composition parameters we observed significant correlation between ASM and LTM and also between ASM and LTI in both groups. Patients with higher lean mass had higher ASM ($p = 0.004$ for the study group, $p < 0.001$ for the control group), lean mass index also correlated significantly and positively with ASM ($p = 0.016$ for the study group and $p < 0.001$ for the control group). Additionally, the positive relationship between ASM and fat mass was found in both groups. We observed that individuals with increased Fat and FTI had higher ASM ($p < 0.001$, $p = 0.001$ for the study group and $p < 0.001$, $p = 0.001$ for the control group) (Table 2). However, after adjustement for BMI in partial correlation analysis, the associations between ASM and fat variables changed the direction - we observed the negative relationship between these parameters (Table 3). To visualise how the positive correlations may transform into (partial) negative correlations after controlling for BMI, unadjusted correlations between ASM and Rel Fat stratified by BMI classes are presented together with the overall bivariate correlation between BMI and Rel Fat (Figure 1). We did not find the statistically significant correlation between ASM and OH or Rel OH (Table 2).

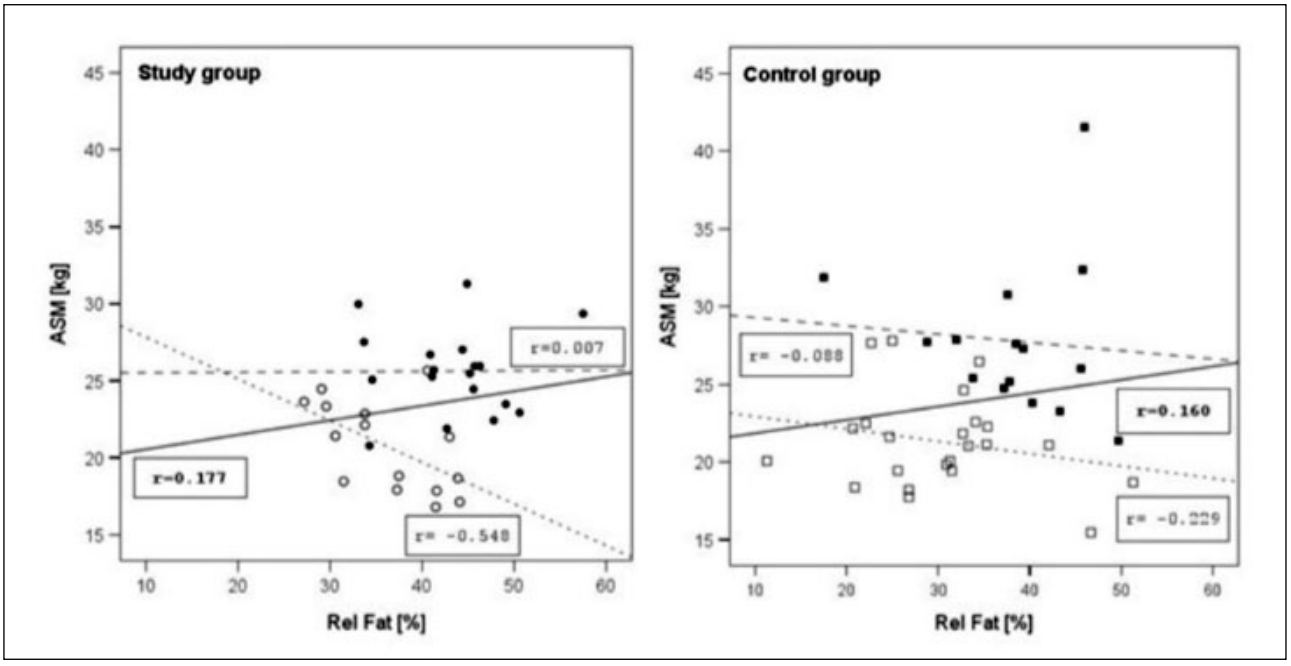
Table 3.
Partial correlations of ASM with body composition parameters adjusted for BMI.

	eGFR < 60 ml/min/1.73 m^2		eGFR ≥ 60 ml/min/1.73 m^2	
	r	p-value	r	p-value
Body mass (kg)	0.732	**< 0.001**	0.836	**< 0.001**
LTM (kg)	0.741	**< 0.001**	0.881	**< 0.001**
LTI (kg/m^2)	0.505	**0.003**	0.635	**< 0.001**
Fat (kg)	-0.282	0.118	-0.254	0.129
Rel Fat (%)	-0.611	**< 0.001**	-0.645	**< 0.001**
FTI (kg/m^2)	-0.610	**< 0.001**	-0.651	**< 0.001**
OH (L)	0.321	0.073	0.250	0.135
Rel OH (%)	0.271	0.134	0.211	0.209

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; BMI: body mass index; LTM: lean tissue mass; LTI: lean tissue index; Fat: fat mass; Rel Fat: relative fat; FTI: fat tissue index; OH: overhydration; Rel OH: relative overhydration; p-values < 0.05 are marked in bold.

related with body mass, normally hydrated weight (NH weight), height, lean and fat mass. We also did not report the association between ASM and clinical variables (11). In the current study we included the control group - male participants with eGFR ≥ 60 ml/min/1.73 m^2 and two groups of men were compared - the study group with eGFR < 60 ml/min/1.73 m^2 and the control group. We did not find the statistically significant correlations between ASM and laboratory measurements such as kidney function parameters, haemoglobin, CRP and albumin in both groups. We found that ASM was significantly associated with anthropometric parameters such as body mass and BMI in male patients with eGFR < 60 ml/min/1.73 m^2 and also in men with eGFR ≥ 60 ml/min/1.73 m^2. Height was positively associated with

Figure 1.
Bivariate correlations and BMI-specific correlation coeffcients stratified by BMI. Circles filled and squares filled – BMI ≥ 30.0 kg/m^2 for the study and the control group, respectively. Circles transparent and squares transparent – BMI < 30.0 kg/m^2 for the study and the control group, respectively. Linear regression lines: solid – unadjusted for BMI, losely dashed – specific for BMI ≥ 30.0 kg/m^2, densely dashed – specific for BMI < 30.0 kg/m^2. While overall bivariate correlations have positive signs, BMI-specific bivariate correlations – have either negative signs or equal to zero.



Discussion

The article is part of a series of our publications focused on correlates of ASM in CKD. In the study of Romejko we found that ASM in CKD men with eGFR < 60 ml/min/1.73 m^2 was significantly associated with anthropometric and body composition parameters such as weight, height, BMI, lean and fat mass, we did not observe relationships between ASM and kidney, nutritional, metabolic and inflammatory variables (10). In the second of our studies concerning various associations of ASM in CKD population (men and women with eGFR < 45 ml/min/1.73 m^2) we also reported that ASM significantly and positively correlated with skeletal muscle mass, however such a relationship was found statistically significant in the control group only, possibly due to higher variability of height in this group. We observed that ASM was positively and significantly related with body composition parameters like LTM and LTI both in participants with eGFR < 60 ml/min/1.73 m^2 and those with eGFR ≥ 60 ml/min/1.73 m^2.

Appendicular skeletal muscle mass and BMI

BMI is a simple parameter with cut-off points determined by the *World Health Organization* (WHO) and is useful to assess malnutrition (< 18.5 k/m^2), normal weight (18.5 -

24.9 kg/m^2), overweight (25.0-29.9 kg/m^2) or obesity (above 30 kg/m^2) which is divided into moderate obesity - class 1 (30.0 to 34.9 kg/m^2), severe obesity - class 2 (35.0 to 39.9 kg/m^2) and morbid obesity - class 3 (≥ 40.0 kg/m^2) (13). In the general population BMI is associated with all-cause mortality, undernourished and overweight or obese individuals have higher mortality than those with normal BMI (14). Among CKD patients, similarly to the general population, low BMI is found to be associated with higher mortality rate, however overweight, obese class 1 and 2 patients have lower mortality compared to those with normal BMI (15). Moreover, obesity class 3 is not related with increased mortality among CKD patients (16). Similar results were also observed in CKD dialysis dependent population: patients treated with dialysis - both peritoneal and hemodialysis with BMI above 30 kg/m^2 had lower all-cause mortality (17). Better outcome in CKD patients with higher BMI is known as obesity paradox or reverse epidemiology (18). Some authors found that CKD patients with BMI > 30 kg/m^2 had larger stores of both muscle and fat mass, and were better nourished according to *subjective global assessment* (SGA) (19). The results of our study are similar - patients with CKD and higher BMI had also higher ASM, what was also observed in the control group. Since muscle atrophy is associated with worse outcomes in CKD, the obesity paradox in CKD according to which overweight and obese individuals have lower morbidity and mortality may be associated with larger stores of skeletal muscle and their protective role in those with higher BMI. Tomborelli Bellafronte also assumed that the obesity paradox in CKD population may result from the protective role of lean mass even in patients with the presence of greater adiposity (20). In addition to BMI participants with higher body mass had also larger ASM in both groups.

Appendicular skeletal muscle mass and body composition parameters

According to the body composition parameters, lean and fat mass were significantly and positively associated with ASM in both groups. Lean mass reflects muscle mass and their positive association with ASM in our study is rather understandable. Fluid excess may overestimate lean mass, but in our study the level of overhydration was low in both groups, so the impact of fluid overload on the relationships between LTM and ASM was rather negligible. More confusing was the positive bivariate correlation between ASM and fat mass. Patients with larger fat stores had higher ASM, both in participants with eGFR < 60 ml/min/1.73 m^2 and those with eGFR ≥ 60 ml/min/1.73 m^2. After adjustement for BMI, we observed the negative relationship between ASM and all variables representing fat mass. Since BMI is associated both with fat-related parameters and ASM, it is likely that BMI played a role here as a confounding variable. As it was mentioned before, Gracia-Iguacel found that obese CKD patients had higher muscle mass, as well as fat mass (19). However, it does not mean that muscle mass and fat mass are positively related, as stated above. Greater muscle mass in overweight and obese individuals in the general population may result from the necessity of muscle strenghtening in the case of increased body mass (21).

In summary, the strength of the relationships between most anthropometric parameters and ASM was similar in patients with eGFR < 60 ml/min/1.73 m^2 and those with eGFR ≥ 60 ml/min/1.73 m^2, especially in case of body mass, BMI, LTI, Fat and FTI. It suggests that the determinants of ASM are not specific for CKD patients.

Appendicular skeletal muscle mass and serum albumin

In our study ASM was not associated with serum albumin. It is assumed that plasma albumin may play a role as a marker of poor nutritional status (22). Additionally, low plasma albumin was also found to be associated with decreased skeletal muscle mass (23). However, there are studies which do not confirm the association between albumin and malnutrition or between albumin and skeletal muscle mass (24, 25). Also, many researchers emphasize that albumin may be a confounding variable in the assessment of malnutrition due to its role as a negative acute phase reactant, the concentrations of which increase during an inflammatory response. Additionally, serum albumin depends on hepatic function and its plasma levels may decrease in case of liver derangements (26). In individuals with nephrotic syndrome serum albumin concentrations may be low due to protein kidney losing and in enteropathies albumin may be lost through gastrointestinal track (27). In patients treated with dialysis hypoalbuminemia may be caused by the loss of protein during renal replacement therapy (28). Besides, patients with CKD on restricted protein and energy diet did not reveal the significant decrease of serum albumin (29). In our study we also did not observe the significant relationship between serum albumin and ASM both in participants with eGFR < 60 ml/min/1.73 m^2 and those with eGFR ≥ 60 ml/min/1.73 m^2. Therefore, we may conclude that serum albumin is rather a poor marker of ASM.

Appendicular skeletal muscle mass and C-reactive protein

Chronic inflammation in CKD also contributes to muscle wasting. The main inflammatory factors which trigger muscle atrophy in CKD are *tumor necrosis factor-alpha* (TNF-alpha), *C-reactive protein* (CRP), *interleukin-6* (IL-6) and interleukin-1β (IL-1β) (30). Inflammation enhances muscle protein degradation and thus potentiates muscle atrophy by activating the *ubiquitin-proteasome system* (UPS). Inflammatory cytokines increase myostatin expression which leads to inhibition of muscle protein synthesis (6). Moreover, increased systemic inflammatory status in CKD causes the derangements of hypothalamic response to apetite-regulating hormones such as leptin or melanocortin which in consequence reduces food intake and develops anorexia (31). The negative relationship between ASM and CRP was reported for the general population (32), however such observations are scarce in CKD patients. For example Wong observed that higher CRP/albumin ratio was associated with lower skeletal muscle mass in CKD patients treated with hemodialysis (33). In our study we did not find the relationship between CRP and ASM both in patients with eGFR < 60 ml/min/1.73 m^2 and in participants with eGFR ≥ 60 ml/min/1.73 m^2.

Appendicular skeletal muscle mass and haemoglobin

We also found no associations between serum haemoglobin and ASM. The causes of anemia in CKD are multifactorial. Increased inflammatory state, kidney dysfunction, malnutrition, reduced nutrients intestinal absorption, overhydration, iron deficiency and also older age contribute to this complication (34). There are studies which revealed that anemia was associated with lower muscle mass but also muscle strength in CKD (35).

Appendicular skeletal muscle mass and kidney function parameters

In our study we did not find the association between ASM and kidney function parameters such as serum creatinine, urea and eGFR. We also observed no difference in ASM between patients with eGFR < 60 ml/min/1.73 m^2 and individuals with eGFR ≥ 60 ml/min/1.73 m^2. Muscle wasting in CKD potentiates with the progress of kidney function decrease being most severe in individuals treated with dialysis. However, the pathogenesis of muscle atrophy in CKD is complex and depends on numerous metabolic, inflammatory and hormonal derangements which are not necessarily present in each CKD patient or which may be extended to varying degrees in different individuals. Therefore, although CKD patients are prone to muscle wasting and muscle atrophy is a frequent state in this group it does not necessarily affect all CKD individuals and may not be strictly associated with eGFR. However, since approximately 98% of serum creatinine derives from muscle, thus interpretation of the relationship between serum creatinine and muscle mass should be cautious (36). Serum creatinine is also inversely related with eGFR, therefore low muscle mass and consequently lower serum creatinine may be associated with higher eGFR (37).

Appendicular skeletal muscle mass versus muscle strength in prediction of sarcopenia in chronic kidney disease

According to EWGSOP2 sarcopenia may be diagnosed if low muscle strength along with low muscle mass are present (9). Due to the lack of specific diagnostic criteria for sarcopenia in CKD, the EWGSOP2 guidelines are used also for the population with kidney function decrease. In our previous studies we observed that ASM was associated with anthropometric and body composition parameters, but not with kidney, nutritional, metabolic and inflammatory variables (10, 11). In our current report we also found statistically significant relationships between ASM and anthropometric, as well as body composition variables, both in CKD patients with eGFR < 60 ml/min/1.73 m^2 and individuals with eGFR ≥ 60 ml/min/1.73 m^2. However, in CKD, the inflammatory and metabolic derangements are more intensified than in the general population and these disorders are observed to be associated with decreased muscle strength both in CKD and non-CKD (38, 39). Thus, the mechanisms which lead to muscle strength lowering may differ from the processes which cause the reduction of ASM. Because in our study the correlates of ASM were similar in participants with eGFR < 60 ml/min/1.73 m^2 and eGFR ≥ 60 ml/min/1.73 m^2, and ASM was not associated with clinical variables, we may thus assume that it is decreased muscle strength, not necessarily along with reduced muscle mass, that should be the main criterion in the diagnostic process of sarcopenia in CKD population. The study of Chatrenet for the first time prospectively evaluated the relationship between muscle mass and muscle strength across the CKD stages. They demonstrated that in CKD patients muscle strength deteriorates progressively with the decline of renal function, even when skeletal muscle mass remains stable. Also, the association between muscle mass and muscle strength diminished with the decrease of eGFR (40). This indicates that CKD progression negatively affects the quality rather than the quantity of muscle and that the disturbances which affect muscle strength and muscle mass in CKD may not be the same. These findings also support the concept that the inflammatory, metabolic and hormonal derangements in CKD which contribute to the reduction of muscular contractile efficiency, cause neuromuscular dysfunction and enhance intramuscular fat infiltration, primarily lead to the reduction of muscle strength, not always causing the decline of muscle mass. The results of Chatrenet report confirm our observations that reduced muscle strength, not inevitably accompanied by decreased muscle mass, determines the diagnosis of sarcopenia in CKD (10, 11, 40).

Limitations of the study

The main limitation of our study is the inclusion of relatively small samples, only male patients. The higher number of participants of both sexes would allow for more in-depth analyses.

Another limitation of our study is that muscle mass was

Declarations

Ethical approval and consent for participate: *Data used in this paper were obtained from two different studies that had separate ethical approval. Both studies were conducted in accordance with the Declaration of Helsinki established in the 1964 and its later amendments. The study protocols were accepted by the Bioethics Committee in Military Institute of Medicine – National Research Institute in Warsaw, Poland, IRB acceptance number 42/WIM/2015 and 120/WIM/2018. All participants signed an informed consent.*

Consent for publication: *Not applicable.*

Availability of data and material: *The original dataset is available from the corresponding author upon reasonable request.*

Competing interests: *The authors declare that they have no competing interests.*

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Authors' contributions: *Conceptualization, K.R. and K.S.; data curation, K.R.; formal analysis, K.S.; funding acquisition, S.N.; investigation, K.R. and A.R; methodology, K.R. and K.S.; project administration, A.R. and S.N.; resources, S.N.; supervision, S.N.; visualization, K.S.; writing - original draft preparation, K.R.; writing - review and editing, K.R.; K.S.; and S.N. All authors have approved the final version of the manuscript.*

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assessed by BIS rather than by *magnetic resonance imaging* (MRI) or *computed tomography* (CT), which are, according to EWGSOP2 guidelines, considered as gold standards for muscle mass assessment. *Dual-energy X-ray absorptiometry* (DXA) would also be more precise method to measure muscle mass comparing to BIS.
Additionally, instead of MDRD formula, CKD-EPI equation would be more appropriate to estimate eGFR.

Conclusions

We may conclude that in our study in the group of patients with eGFR < 60 ml/min/1.73 m^2 and in individuals with eGFR ≥ 60 ml/min/1.73 m^2 ASM was associated significantly and positively mainly with anthropometric and body composition parameters such as body mass, BMI, height (in individuals with eGFR ≥ 60 ml/min/1.73 m^2 only), LTM and LTI. We did not find the significant relationships between ASM and kidney function parameters, as well as between ASM and serum albumin, CRP and haemoglobin both in patients with eGFR < 60 ml/min/1.73 m^2 and in participants with eGFR ≥ 60 ml/min/1.73 m^2, which suggests that the determinants of ASM are similar in CKD and in the general population, and are not specific for CKD patients. Therefore studying the determinants of sarcopenia in CKD should be focused on its other component which is muscle strength.
From the clinical point of view, as ASM correleates of with anthropometric and body composition variables, the monitoring of these parametres should be a routine practice in order to implement preventive or therapeutic methods which would allow to slow down the development of sarcopenia.

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