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Sarcopenia and relationships between muscle mass, measured GFR and physical function in patients with CKD 3-5

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Key words: Chronic Kidney disease; glomerular filtration rate; sarcopenia; body composition;
dual-energy x-ray absorptiometry; physical function.

Abstract

Background: Sarcopenia and poor physical function are common in patients with chronic kidney disease (CKD). Our aim was to investigate the relationships between muscle mass and measured GFR, and between muscle mass and strength and balance, respectively, in patients with CKD 3-5.

Methods: This is a baseline data analysis of a randomized controlled clinical trial. 148 adult patients with an estimated $GFR < 30 \text{ ml/min/1.72 m}^2$, not on renal replacement therapy, irrespective of number of comorbidities were included from the Department of Nephrology, Skåne University Hospital, Lund, from 2011 to 2016. Body composition was measured by dual-energy x-ray absorptiometry (DEXA). GFR was measured by iohexol clearance. Balance was measured by functional reach and Berg Balance test, strength by handgrip strength and isometric quadriceps strength.

Results: Measured GFR ranged from 8 to 55 ml/min/1.73 m^2 . Lean mass ($p < 0.05$), fat mass ($p < 0.05$), appendicular skeletal muscle ($p < 0.001$) and appendicular skeletal muscle index ($p < 0.05$) were associated with GFR. Functional reach was associated with lean mass legs ($p < 0.05$), Berg balance test was associated with lean mass trunk ($p < 0.05$). Handgrip strength was associated with lean mass arms ($p < 0.001$). Isometric quadriceps strength was associated with lean mass legs ($p < 0.001$). More men (44%) suffered from low muscle mass than women (22%), while more women (36%) suffered from low muscle strength than men (26%). However, when combining both, men (16%) suffered from sarcopenia to a greater extent than women (8%).

Conclusions: Among patients with CKD 3-5, loss of lean body mass, especially appendicular skeletal muscle, was significantly related to GFR decline. Two important markers of physical function: balance and strength, were significantly related to muscle mass. Moreover, men were more prone to sarcopenia than women during kidney function decline.

Introduction

Chronic kidney disease (CKD) is a global health problem with a prevalence of about 10% [1]. Sarcopenia is common among patients with CKD, especially in patients with end stage renal disease (ESRD) [2-5]. There are multiple causes of sarcopenia such as nonspecific inflammatory processes, restriction of protein intake, metabolic acidosis, a sedentary life style as well as protein loss due to maintenance dialysis [2, 3]. Loss of muscle mass leads to a decrease in physical performance and may be associated with a decline in GFR and poor clinical outcomes [6-12]. The relationship between estimated glomerular filtration rate (eGFR) and body composition in patients with CKD and healthy people has previously been investigated [13, 14]. However, eGFR is based on estimates using plasma creatinine, which is dependent on muscle mass, thus creating a risk of inaccuracy when relating eGFR to muscle mass. To our knowledge, neither the association between body composition and measured GFR nor the association between strength and balance and their respective relationships to muscle mass has been examined in patients with CKD 3-5 not on dialysis.

Our aims are 1) to investigate the relationship between body composition and measured GFR in patients with an estimated $GFR < 30 \text{ ml/min/1.73m}^2$; 2) to investigate the frequency of sarcopenia; and 3) to investigate the relationship between physical function (balance and strength) and body composition in these patients.

Subjects and Methods

This study is part of the RENEXC trial (www.ClinicalTrials.gov NCT02041156), a consecutive, prospective, randomized, controlled and interventional exercise training study in patients with chronic kidney disease not on renal replacement therapy.

The inclusion criteria were: prevalent and incident patients with an estimated GFR < 30 ml/min/1.72m², adults ≥18 years, all renal diagnoses, any number of comorbidities. The exclusion criteria were: orthopaedic impediment, severe neurological dysfunction, inability to understand patient information and answer health related quality of life questionnaire, renal replacement therapy, estimated start of dialysis within 12 months of study start.

GFR estimation and measurement

To calculate eGFR we used the MDRD equation. To quantify measured GFR we used iohexol clearance [15, 16]. It was performed in a standardized manner at the Department of Clinical Chemistry, Laboratory Medicine Skåne, which is accredited by SWEDAC (Swedish Board for Accreditation and Conformity Assessment) according to the international standards of ISO 15189:2012.

Dual-Energy X-ray Absorptiometry (DEXA)

DEXA scanning was conducted in a standardized manner according to the procedures recommended by the manufacturer, at the Department of Diagnostic Radiology, Skåne University Hospital, which is accredited by SWEDAC according to ISO 15189:2012. The hospital changed from Lunar Prodigy to Lunar iDEXA during the study period. Lunar iDEXA is an upgrade from Lunar Prodigy and has a superior camera and gives a more precise measurement. The analysis software is the same as Lunar Prodigy. 32 patients were analysed with Lunar iDEXA.

Definition of Sarcopenia

Sarcopenia was defined as low muscle mass [17] and low muscle strength [18], respectively, as well as both of them [19]. Appendicular skeletal muscle index (ASMI) <7.3 kg/m² for men and < 5.5 kg/m² for women were defined as low muscle mass [17]. Handgrip strength <30 kg for men and <20 kg for women were defined as low muscle strength [18]. For each indicator, cut-

off values were greater than two standard deviations below the sex-specific means from a reference population (18-40 years old and 20-102 years old, respectively).

Functional Reach

The patient stands positioned next to a wall but not touching, the arm is extended at a 90-degree angle from the shoulder, fist closed, and then asked to reach forward as far as possible without losing balance. The distance between the starting point and end point of three successive trials is recorded and the mean registered [12].

Berg Balance Test

The test comprises a set of 14 simple balance related tasks with a full score of 56, ranging from being able to sit on a chair without back support, to standing on one foot. The degree of success in achieving each task is given a score of zero (unable) to four (independent), and the final measure is the sum of all the scores [12].

Handgrip Strength

Handgrip strength is measured in kilograms by a Jamar dynamometer, in a sitting position without back support with the elbow at a 90-degree angle and the arm close to the body. For each hand, the scores of 3 successive trials were recorded and the mean registered [12].

Isometric Quadriceps Strength

Isometric quadriceps strength is tested by knee extension against resistance, and evaluated in kilograms multiplied by centimetres using the distance from the knee to the ankle. For each leg the scores of 3 successive trials were recorded and the mean registered [12].

Comorbidity

The comorbidity of each patient was evaluated by the same clinician (MH) using the Davies Comorbidity Score [20] with seven different domains: malignancy, ischemic heart disease, peripheral vascular disease, left ventricular dysfunction, diabetes mellitus, systemic collagen vascular disease or other significant pathology (a condition severe enough to have an impact

on survival in the general population). Hypertension was included in “other significant pathology” as it has a significant impact on survival. We chose the ranking system as described by Davies; patients with a cumulative score of 0, 1-2 or >3 were classified as having a comorbidity rank of 0, 1 or 2, respectively.

Nutritional assessment

Each patient was prescribed continued normal protein intake, restricted protein diet consisting of 0.8 or 0.6 g/kg body weight/day by their physician and referred to a specialized renal dietitian for dietary counselling. SGA (Subjective global assessment) [21] and PCR (Protein catabolic rate) were used to describe the patients’ nutritional status. PCR was calculated by the equation: $6.25 \times ((0.028 \times \text{urine-urea} \times 24 - \text{urine volume}) + (0.031 \times \text{weight}))$.

Statistical Analysis

Descriptive statistics are presented as mean \pm SD and/or median with interquartile range. Categorical variables were used to describe frequency and continuous variables for measurements. Data were analysed using R software (R foundation for Statistical Computing, Vienna, Austria). We chose the following references for practical reasons: female, 70 years old, with comorbidity classified as 1. These choices have no impact on the results, but were chosen to clarify and enable better understanding of the relationships between variables. Multiple linear regression analysis was performed to analyse the relationships between variables. The level of significance was set at $P < 0.05$.

Results

Patients

This study comprises 151 patients, aged from 19-87, with a mean age of 66 years. 148 patients (98 men and 50 women) completed the measurements at baseline. Three patients dropped out before baseline data measurement for acute medical reasons. The measured GFR ranged from 8 to 55 ml/min/1.73m², with an average of 22.5 ± 8.2 ml/min/1.73m². Of special note is that eGFR underestimated actual GFR (measured GFR) thus explaining the discrepancy between

the inclusion criteria: eGFR < 30 ml/min/1.73m², and the actual results with measured GFR. The causes of CKD were: hypertensive kidney disease (61 patients; 41%), diabetes nephropathy (24 patients; 16%), interstitial nephritis (22 patients; 15%), chronic glomerulonephritis (23 patients; 15%), polycystic kidney disease (8 patients; 5%), and others (10 patients; 7%). The patients suffered from the following comorbidities: malignancy (14%), ischemic heart disease (20%), peripheral vascular disease (21%), left ventricular dysfunction (11%), diabetes mellitus (32%), systemic collagen vascular disease (11%) and other comorbidities (77%) e.g. hypertension. The clinical characteristics of patients are presented in table 1. The characteristics of patients' nutritional status and physical function are presented in table 2.

Relationship between Body Composition and GFR, Sex, Age and Comorbidity

In table 3 the analyses of body composition variables and BMI, respectively, are given. Lean mass ($p < 0.05$), fat mass ($p < 0.05$), Appendicular skeletal muscle (ASM) ($p < 0.0001$) and ASMI ($p < 0.05$) all showed significant positive relationships with GFR, respectively, but relative lean mass and relative fat mass did not. Lean mass, ASM, ASMI and relative lean mass, were all significantly lower in women ($p < 0.001$), while fat mass ($p < 0.05$) and relative fat mass ($p < 0.001$) were significantly higher in women. Absolute values did not show significant relationships with age, however relative lean mass significantly and inversely related with age ($p < 0.05$) and relative fat mass related positively with age ($p < 0.05$). There was no significant relationship between body composition and comorbidity 0 or 2, respectively (our reference is comorbidity 1).

BMI showed a significant positive relationship with GFR ($p < 0.05$). No significant relationship was observed with sex, age or comorbidity.

In our patients, 1 ml/min/1.73m² decrease of GFR was associated with 0.15 ± 0.07 kg decrease of lean mass, 0.26 ± 0.12 kg decrease of fat mass, 0.12 ± 0.03 kg decrease of ASM, 0.03 ± 0.01

kg/m² decrease of ASMI as well as 0.11±0.05 kg/m² decrease of BMI. We found that female sex, age and more comorbidities were associated with less lean mass and more fat mass.

Prevalence of Sarcopenia

When we only used muscle mass, 54 (36%) patients were defined as having sarcopenia, 43 (44%) men and 11 (22%) women. When only using handgrip strength, 43 (29%) patients were defined as having sarcopenia, 25 (26%) men and 18 (36%) women. If both muscle mass and muscle strength were used, 20 (14%) patients were defined as having sarcopenia, 16 (16%) men and 4 (8%) women.

Relationship between Balance and Muscle Strength, respectively, and Lean Mass, Sex, Age and Comorbidity

In table 4 the results for balance, measured as functional reach and Berg balance test, are given. Functional reach showed a significant positive relationship with lean legs ($p < 0.05$), while Berg balance test showed a positive relationship with lean trunk ($p < 0.05$). Neither of them showed significant relationships with sex or comorbidity 0, but both showed significant relationships with age and comorbidity 2 ($p < 0.001$) (our reference is comorbidity 1). In our patients, 1 kg increase of leg lean mass was associated with 0.7±0.2 cm increase of functional reach. And 1 kg increase of trunk lean mass was associated with 0.3±0.1 increase of Berg balance test score. We found that age and number of comorbidities were associated with worse balance in both tests.

In table 5 the results for handgrip- and quadriceps strength are given. Handgrip strength in the right and left hand, respectively, was significantly and positively related to arm lean as well as to sex. Isometric quadriceps strength in the right and left leg, respectively, was significantly positively related to leg lean and sex ($p < 0.001$). Moreover, significant inverse relationships were observed for age and comorbidity 2 (our reference is comorbidity 1). In our patients, 1 kg

increase of arm lean mass was associated with 8 ± 1.3 kg increase of handgrip strength in the right hand and 8 ± 1.4 in the left hand. For the legs, 1 kg increase of leg lean mass was associated with 113 ± 18 kg \times cm increase of isometric quadriceps strength in the right leg and 122 ± 18 kg \times cm in the left leg. We found that female sex, age and number of comorbidities were associated with decreased strength

Discussion

In 148 patients with CKD 3-5, not on renal replacement therapy, we measured body composition and found that lean mass, ASM and fat mass, ASMI and BMI all showed positive significant relationships with GFR, especially ASM and ASMI after accounting for sex, age and number of comorbidities. This indicates that in CKD 3-5 patients' appendicular skeletal muscle loss is strongly associated with a decline in GFR. Moreover, physical function was significantly related with muscle mass. Specifically, for balance, functional reach was positively associated with leg lean mass and Berg balance test was positively associated with trunk lean mass. For strength, handgrip strength and isometric quadriceps strength were positively related with lean mass of the arm and leg, respectively. Another interesting result was that the prevalence of sarcopenia varied according to different indicators. However, no matter which indicator was used, sarcopenia was markedly more common in men than in women in our patients.

Numerous previous studies have investigated the relationship between body composition and eGFR. Some of them illustrated that creatinine based calculations of eGFR by both MDRD and CKD-EPI are strongly impacted by lean mass [22, 23]. Cystatin C based eGFR is also affected by body composition [24]. Some studies suggested that age and lean mass are strong determinants of eGFR especially in men [14]. An increase in fat mass has been shown to be associated with a decline in eGFR [25, 26]. All of these studies show that various estimates of

GFR are dependent on body composition and thus can under- or overestimate actual GFR. Therefore, using eGFR can lead to a risk of inaccurate results concerning the relationship between body composition and kidney function, due to the muscle wasting prevalent in this patient group. We measured GFR and showed that loss of body mass was associated with a decline in GFR. To our knowledge, this is the first study to show a significant relationship between body composition and measured GFR in patients with CKD 3-5. The validity of these findings is strengthened by employing ASM and ASMI as measures of muscle mass. Other studies have suggested that high BMI might be a protective factor in patients with CKD or ESRD [27-30]. Contrary to the general population, high BMI and larger body size are associated with lower mortality in these patients [27-30]. In our study BMI was positively associated with GFR.

Sarcopenia was defined by Rosenberg in 1988 [17], referring specifically to involuntary loss of skeletal muscle mass and consequently of strength. Sarcopenia is common in CKD [3, 13] and ESRD patients, especially after long-term dialysis or renal transplantation [31, 32]. It is associated with high mortality [33, 34]. However, there are an increasing number of studies suggesting that the definition of sarcopenia should include both muscle mass and muscle function [33, 35-38]. We defined sarcopenia in our patients by using either ASMI or handgrip strength only, as well as both of them together [17-19]. The prevalence of sarcopenia was highest when using muscle mass only, lower when muscle strength only was used and lowest when both were employed. Many more men suffered from low muscle mass than women, while more women suffered from low muscle strength than men. However, when combining both low muscle mass and low muscle strength, sarcopenia in men was twice that of women. Thus, men with CKD are more prone to loss of lean body mass than women, and women are more prone to loss of muscle strength as kidney function declines.

Consequently, we found evidence that body composition starts changing relatively early in the course of CKD rather than after initiation of dialysis. Thus implying that recommendations for nutrition and exercise training need to be tailored according to level of kidney function in order to counteract loss of muscle mass and maintain balance and strength. Exercise training should aim at both appendicular and trunk skeletal muscle. An important question is whether exercise training administered during CKD 3-5 can affect the development of sarcopenia and reduce the risk of accidental falls. This is being studied in the interventional part of RENEXC.

Of special interest is our novel finding of a relationship between different balance functions and muscle mass. Accidental falls and fractures are common both in patients on maintenance haemodialysis and peritoneal dialysis [39-43]. There are a number of causes such as deranged calcium-phosphate-vitamin D-parathyroid hormone homeostasis, osteoporosis, neuropathy, muscle weakness and general frailty [44-48]. In previous studies we have shown that balance was impaired in patients with CKD 3-5 and was a predictor for mortality after starting dialysis [12, 49]. In the present study, we found that balance was associated with lean mass: functional reach showed a significant relationship with lean mass of the legs and Berg balance test with lean mass of the trunk. In consequence, in order to improve balance both core exercises for the trunk and strength exercise for the legs should be part of the exercise training program. Moreover, we showed that limb muscle mass was strongly associated with limb strength, which is consistent with previous studies [7, 8, 10, 34]. Some strengths of our study: firstly, we used measured GFR instead of eGFR to avoid the influence of muscle mass on estimated GFR. Secondly, we used different methods and cut-off values to measure and define body composition and sarcopenia. Finally, physical function was defined by both balance and strength. Some limitations: The average age of our patients was 66 and 75% were over 60 years old. Thus, our results might be biased towards the aged CKD population. This could also be a strength, as the majority of patients with CKD are over 60 years of age [50, 51]. Finally, because

this is a baseline data analysis of a prospective trial, we cannot comment on longitudinal changes in body composition as GFR declines.

In conclusion, among patients with CKD 3-5, loss of lean body mass, especially appendicular skeletal muscle, was significantly related to GFR decline. Balance and strength were significantly related to muscle mass. Moreover, men were more prone to sarcopenia than women during kidney function decline. All these results provide a better understanding of changes in nutritional status with the decline of GFR in the CKD 3-5 population and have important implications for future studies about body composition, GFR, physical function and exercise training.

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Conflict of Interest Statement

We have had no involvements that might raise the question of bias in the work reported or in the conclusions, implications or opinions stated. The results presented in this paper have not been published previously in whole or part.

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Tables

Table 1. Clinical characteristics of 148 patients with CDK 3-5

Characteristics	Units	Mean±SD or Median (25th-75th percentile)
Weight	kg	82±18
Height	m	1.72±0.09
BMI	kg/m ²	28±5
GFR	ml/min/1.73m ²	22.5±8.2
P-creatinine	µmol/L	254±104
P-urea	mmol/L	16±5
PTH	pmol/L	12 (8.8-18)
Albumin	g/L	37±4
Hemoglobin	g/L	127±14
Potassium	mmol/L	4.2±0.5
Calcium	mmol/L	2.3±0.1
Phosphate	mmol/L	1.2±0.3
Base excess	µmol /L	-1.2 (3.2-0.1)
CRP	mg/L	3 (1.5-6.1)

BMI=Body mass index; GFR= Glomerular Filtration Rate; P-creatinine=Plasma creatinine; P-urea=Plasma urea; PTH= Parathyroid hormone; CRP= C-reactive protein.

Table 2. Data on nutritional status and physical function in 148 patients with CDK 3-5

Characteristics	Units	Mean± SD or Median (25th-75th percentile)
SGA	Score (A/B/C)	132 A, 13 B, 0 C; (3 not done)
PCR	g/kg/day	79±35
Functional reach	cm	33±9
Berg balance test	Score	51±8
Handgrip strength left	kg	29±10.6
Handgrip strength right	kg	31.7±10.5
Isometric Quadriceps Strength left	kg× cm	1132.3±421.4
Isometric Quadriceps Strength right	kg× cm	1144±408.7

SGA= Subjective global assessment; PCR= Protein catabolic rate.

Table 3. Multiple linear regression analyses with variables of body composition and GFR, sex, age and comorbidity

	GFR		Sex		Age		Comorbidity		Comorbidity	
	1ml/min/1.73m ²		Male		1 year increase		0		2	
	Eff±SE	P	Eff±SE	P	Eff±SE	P	Eff±SE	P	Eff±SE	P
DEXA										
Lean mass(kg)	0.15±0.07	0.04	11.86±1.22	<0.001	-0.07±0.04	0.1	0.47±1.79	0.8	2.04±1.41	0.2
Fat mass(kg)	0.26±0.12	0.04	-4.23±2.15	0.04	0.08±0.08	0.3	0.12±3.14	0.9	3.67±2.48	0.1
ASM (kg)	0.12±0.03	<0.001	6.49±0.56	<0.001	-0.04±0.02	0.05	0.33±0.82	0.7	0.43±0.65	0.5
ASMI (kg/m²)	0.03±0.01	0.002	1.22±0.17	<0.001	-0.003±0.01	0.6	-0.11±0.25	0.7	0.10±0.20	0.6
Relative Lean mass (%)	-0.10±0.08	0.2	9.29±1.46	<0.001	-0.12±0.05	0.03	-1.16±2.13	0.6	-1.66±1.68	0.3
Relative Fat mass (%)	0.10±0.08	0.2	-9.29±1.461	<0.001	0.12±0.05	0.03	1.16±2.13	0.6	1.66±1.68	0.3
BMI (kg/m²)	0.11±0.05	0.04	-1.32±0.92	0.2	0.03±0.03	0.3	-0.64±1.34	0.6	1.66±1.03	0.1

Our reference is female, 70 years old and with one comorbidity

DEXA= Dual-energy X-ray absorptiometry; ASM= Appendicular skeletal muscle; ASMI= Appendicular skeletal muscle index; BMI= Body mass index; GFR= Glomerular Filtration Rate. ASM= Arm lean mass+ leg lean mass; ASMI= ASM/ Height²; Relative Lean mass= [Lean mass/ Lean mass+ Fat mass] ×100%; Relative Fat mass= [Fat mass/ (Lean mass+ Fat mass)] ×100%; BMI= Body weight/ Height². Eff= Efficiency; SE= Standard Error.

Table 4 Multiple linear regression analyses with balance function and lean mass, sex, age and comorbidity

	Lean mass		Lean Trunk mass		Lean Legs mass		Sex		Age		Comorbidity		Comorbidity	
	kg		kg		kg		male		1 year increase		0		2	
	Eff±SE	p	Eff±SE	P	Eff±SE	P	Eff±SE	P	Eff±SE	P	Eff±SE	P	Eff±SE	P
Functional Reach (cm)	0.13±0.09	0.2					0.18±1.69	0.9	-0.29±0.05	<0.001	2.26±1.88	0.2	-6.72±1.54	<0.001
			0.05±0.16	0.7			1.42±1.51	0.4	-0.30±0.05	<0.001	2.37±1.90	0.2	-6.50±1.55	<0.001
					0.69±0.24	0.01	-1.26±1.63	0.4	-0.29±0.05	<0.001	1.94±1.85	0.3	-6.73±1.49	<0.001
Berg Balance Test (Score)	0.08±0.08	0.3					1.28±1.57	0.4	-0.16±0.05	<0.001	1.43±1.73	0.4	-6.92±1.43	<0.001
			0.30±0.14	0.04			1.78±1.37	0.2	-0.16±0.04	<0.001	1.54±1.71	0.4	-6.65±1.42	<0.001
					0.19±0.23	0.4	-0.48±1.56	0.8	-0.15±0.05	<0.001	1.19±1.74	0.5	-7.26±1.43	<0.001

Eff= Efficiency; SE= Standard Error.

Table 5 Multiple linear regression analysis with strength function and limb lean mass, sex, age and comorbidity

	Limb Lean mass (arm/leg, right/left)		Sex		Age		Comorbidity		Comorbidity	
	kg		male		1 year increase		0		2	
	Eff±SE	p	Eff±SE	p	Eff±SE	p	Eff±SE	p	Eff±SE	p
<i>Handgrip right (kg)</i>	7.98±1.32	< 0.001	5.77±1.85	0.002	-0.19±0.04	< 0.001	2.82±1.72	0.1	-4.23±1.39	0.003
<i>Handgrip left (kg)</i>	8.03±1.39	< 0.001	6.28±1.85	< 0.001	-0.18±0.05	< 0.001	2.74±1.81	0.1	-3.76±1.48	0.01
<i>Isometric Quadriceps Strength right (kg× cm)</i>	113.20±18.10	< 0.001	204.07±62.73	0.001	-10.51±1.81	< 0.001	134.65±70.30	0.06	-179.08±59.08	0.003
<i>Isometric Quadriceps Strength left (kg× cm)</i>	121.90±18.01	< 0.001	214.54±61.32	0.001	-10.08±1.77	< 0.001	206.23±69.26	0.003	-158.61±57.96	0.007

Eff= Efficiency; SE= Standard Error.