# Muscle Mass and Muscle Strength in Non-Dialysis Dependent Chronic Kidney Disease Patients

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*Article*

# Muscle Mass and Muscle Strength in Non-Dialysis Dependent Chronic Kidney Disease Patients

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**Abstract: Background** Sarcopenia is a state with progressive and generalized loss of skeletal muscle mass and strength. It is a serious complication occurring in chronic kidney disease (CKD) patients which increases morbidity and mortality rate. Sarcopenia is diagnosed when loss of both compartments - muscle strength and skeletal muscle quality or quantity are present. However, there are still numerous patients, also with CKD, diagnosed as pre-sarcopenic individuals with low muscle strength and normal skeletal muscle quality or quantity and conversely, with correct muscle strength and decreased skeletal muscle mass, who are prone to develop sarcopenia in future life. It is crucial to examine numerous variables possibly associated with changes of skeletal muscle mass and muscle strength in terms of preventing the development of sarcopenia. The aim of the study was to investigate anthropometric and clinical correlates and sources of variation in both skeletal muscle mass and muscle strength in advanced stages of CKD. **Methods** The study sample consisted of 84 non-dialysis dependent patients of both sexes (including 45.2% of women) with eGFR < 45 ml/min/1.73m$^2$: 26.2% with eGFR 30-44 mL/min/1.73 m$^2$, 65.5% with eGFR 15-29 mL/min/1.73 m$^2$ and 8.3% with eGFR < 15 mL/min/1.73 m$^2$. Muscle strength was estimated by measuring hand grip strength (HGS) with the use of handheld hydraulic dynamometer. Muscle quantity was measured by bioimpedance spectroscopy using Body Composition Monitor. Appendicular skeletal muscle mass (ASM) was calculated according to Lin's formula. Serum creatinine, urea, uric acid and albumin were measured. **Results** In bivariate analysis we found that ASM significantly and positively correlated with anthropometric variables such as body mass (r=0.903, p<0.001), NH weight (r=0.882, p<0.001), height (r=0.694, p<0.001), body mass index (BMI) (r=0.701, p<0.001), lean tissue mass (LTM) (r=0.664, p<0.001), lean tissue index (LTI) (r=0.433, p<0.001), fat mass (r=0.614, p<0.001) and fat tissue index (FTI) (r=0.449, p<0.001), and was negatively associated with clinical variable such as hydration status (p<0.001). HGS significantly and positively correlated with anthropometric parameters such as body mass (r=0.319, p=0.003), NH weight (r=0.315, p=0.004), height (r=0.666, p<0.001), LTM (r=0.490, p<0.001), LTI (r=0.238, p=0.029), and ASM (r=0.501, p<0.001), and was negatively associated with clinical variables like uric acid (p=0.039) and urea (p<0.001). After adjustment for age, sex and height, HGS remained significantly and negatively related with uric acid (β=-1.078, p=0.041) and hydration status (β=-0.805, p=0.042). **Conclusions** In CKD patients, ASM is determined mainly by anthropometric parameters but HGS - both by anthropometric and clinical variables specific for CKD.

**Keywords:** chronic kidney disease; skeletal muscle mass; muscle strength; anthropometric variables; clinical variables

## Introduction

Low muscle strength and low skeletal muscle mass or poor skeletal muscle quality observed simultaneously are the main criteria for diagnosis of sarcopenia [1]. Sarcopenia is mainly associated with the process of aging, however it also occurs in sedentary lifestyle and numerous pathological states such as heart failure, diabetes, chronic kidney disease (CKD), acute or chronic inflammation,

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both malnutrition and obesity [2]. Low skeletal muscle mass and strength are associated with high susceptibility to injuries, increased morbidity, higher number of hospitalizations and elevated mortality [3]. Additionally, sarcopenia significantly reduces quality of life.

CKD is one of the major public health problems. Almost 13% of world population suffer from irreversible kidney damage. The prevalence of sarcopenia in CKD patients is up to 55%, especially in more advanced stages of kidney function decrease, and is negatively associated with disease progression [4]. The causes of the loss of muscle mass and muscle strength in CKD are multivariate, including low-grade inflammatory state, metabolic acidosis, insulin resistance, hyperparathyroidism, resistance to growth hormone, the derangements of adipocytokine profile and hypogonadism [5].

The diagnostic criteria for sarcopenia are based on the updated guidelines of European Working Group on Sarcopenia in Older People (EWGSOP2) 2018 [1]. They are also used in research studies on CKD, however, there is still lack of specific assessment guidelines for patients with kidney function decrease. The revised European consensus on definition and diagnosis of sarcopenia in 2018 confirmed that impaired muscle strength is the most reliable tool to assess muscle function. Therefore, if low muscle strength is diagnosed, sarcopenia is probable. Sarcopenia is confirmed with the presence of low skeletal muscle quantity or quality and is severe when low physical performance also occurs [1]. However, there are patients with low muscle strength but correct muscle quality or quantity and conversely, with normal muscle strength and decreased muscle mass. These patients cannot be diagnosed as sarcopenic but are interpreted as pre-sarcopenic and are prone to develop sarcopenia in future life.

There are several methods to evaluate muscle strength and muscle quantity. Muscle strength may be evaluated with the use of hand grip strength (HGS) test or chair stand test. The measurement of HGS requires the use of calibrated dynamometer. It was proved that HGS correlates with strength in other body compartments and it may play a role as a surrogate for more accurate measurements of arm and leg strength [6]. As this method is simple it may be widely available in hospitals or outpatient clinics. The cut-off points for low muscle strength measured by HGS are < 27 kg for men and < 16 kg for women [1].

Several techniques evaluate skeletal muscle mass. According to EWGSOP2 guidelines the gold standards for measuring skeletal muscle mass are magnetic resonance imaging (MRI) and computed tomography (CT). However, the difficulties of using such methods are the high cost, not always availability and the need for specially trained personel. Moreover, cut-off points for low skeletal muscle mass are not well defined for CT and MRI. More available than MRI and CT is dual-energy X-ray absorptiometry (DXA) which is used to measure appendicular skeletal muscle mass (ASM) [1]. Another method which estimates skeletal muscle mass is bioelectrical impedance analysis (BIA). It is a simple, inexpensive and easy to use method, the equipment is portable and does not require a patient transport. Single frequency BIA uses a current of 50 kHz and by measuring the whole-body electrical conductivity estimates total body water, fat free mass (FFM) and fat mass (FM). The main disadvantage of this method is that overhydration may overestimate lean body mass [7]. Multifrequency bioimpedance spectroscopy (BIS) uses multiple current frequencies (1-1000 kHz) and provides a more precise determination of total body water (TBW) distinguishing between extracellular water (ECW) and intracellular water (ICW), lean tissue mass (LTM) and adipose tissue mass (ATM). There are numerous equations to evaluate ASM based on bioimpedance analysis in different groups of people. The EWGSOP2 recommends to use raw impedance measures along with the cross-validated Sergi equation for elderly. However, the Sergi equation uses the single operating frequency of electric current with the value of 50 kHz [8]. The cut-off points for low ASM are < 20 kg for men and < 15 kg for women, and if height squared is concerned the cut-off points are < 7 kg/m$^2$ for men and < 5.5 kg/m$^2$ for women [1].

The aim of the study is to investigate anthropometric and clinical correlates and sources of variation in skeletal muscle mass and muscle strength in advanced stages of CKD. The main analysis was preceded by validation of Lin's estimation of ASM by bioimpedance spectroscopy in Polish CKD patients.

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## Materials and Methods

*Participants and Eligibility Criteria*

We performed a cross-sectional study which included patients with eGFR < 45 mL/min/1.73 m$^2$. Patients with CKD, not treated with dialysis, who were qualified for the study visited the Nephrological Outpatient Clinic of the Military Institute of Medicine - National Research Institute in Warsaw, Poland, for a routine check-up. The inclusion criteria were age between 18 and 90 years and eGFR < 45 mL/min/1.73 m$^2$. The exclusion criteria were the lack of consent to participate in the study, clinical signs of infection, the presence of metal parts in the body and renal replacement therapy or its requirement within the following 3 months. Each participant signed an informed consent.

*Laboratory Measurements*

Blood samples for laboratory measurements such as creatinine, urea, uric acid and albumin were taken after an overnight fast and were analysed in the local Department of Laboratory Diagnostics. Serum creatinine concentrations were analyzed using Jaffe method (Gen.2, Roche Diagnostics GmbH, Rotkreuz, Switzerland), serum urea levels using urease kinetic test (Cobas c501, Roche Diagnostics, GmbH, Rotkreuz, Switzerland), and serum uric acid with the use of enzymatic colorimetric test (Cobas c501, Roche Diagnostics, GmbH, Rotkreuz, Switzerland). Plasma albumin levels were measured with the use of the BCP Albumin Assay Kit (Roche Diagnostics GmbH, Rotkreuz, Switzerland).

*The Assessment of eGFR*

eGFR (mL/min per 1.73 m$^2$) was calculated according to the short Modification of Diet in Renal Disease (MDRD) formula:

$$\text{eGFR} = 175 \times \text{SerumCr}^{-1.154} \times \text{age}^{-0.203} \times 1.212 \text{ (if patient is black)} \times 0.742 \text{ (if female)}$$

*The Diagnosis of Diabetes Mellitus Type 2*

Diabetes mellitus type 2 was diagnosed based on the patient's medical history and on the results of oral glucose tolerance test (OGTT) with the value of serum glucose concentration ≥ 200 mg/dL after 120 minutes of 75 g oral glucose load.

*The Assessment of Muscle Strength*

Muscle strength was estimated by measuring HGS with the use of handheld hydraulic dynamometer (Saehan Corporation, South Korea). Subjects were asked to stay in a seated position, with the elbow flexed at a 90° angle, the forearm and wrist in a neutral position, and to grip dynamometer with both dominant and non-dominant hand as hard as possible for three times with intervals lasting 30 seconds. Then the arithmetic mean for each hand was measured. The final result for HGS was the arithmetic mean of the measurements for both hands.

*The Assessment of Skeletal Muscle Mass*

Muscle quantity was measured by bioimpedance spectroscopy (BIS) using Body Composition Monitor (BCM, Fresenius Medical Care). Patients were asked to stay in supine position after a five-minute rest 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 (kg) based on parameters obtained from bioimpedance spectroscopy and the sum of fat-free soft tissues in the arms and legs assessed from DXA [9]:

$$ASM_{BCM} = -1.838 + 0.395 \times \text{TBW} + 0.105 \times \text{body weight} - 0.026 \times \text{age} + 1.231(\text{if male})$$

Lin applied his prediction model to the validation group of 108 CKD Taiwanese patients obtaining Pearson correlation coefficient r=0.953 between estimated $ASM_{BCM}$ and $ASM_{DXA}$ ($p<0.001$).

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The limit of agreement in Bland-Altman analysis of model-derived ASM compared to DXA-derived ASM was 0.098±2.440 kg.

In order to validate Lin's prediction model in Polish CKD patients we applied Lin's formula to the independent sample of 109 CKD patients (eGFR<30 ml/min/1.73 m²) in which both DXA and BCM measurements were collected. This study design has been previously described [10]. The Pearson correlation coefficient between estimated $ASM_{BCM}$ and $ASM_{DXA}$ was 0.954 (p<0.001). The limit of agreement in Bland-Altman analysis of model-derived ASM compared to DXA-derived ASM was 0.949±2.698 kg.

*Statistical Analysis*

The results are presented as means±standard deviations (SD) and proportions. Bivariate associations between continuous variables were assessed by Pearson correlation coefficient, between continuous and categorical variables - by t-Student test or analysis of variance depending on the number of categories, and between categorical variables – by chi-square test. For multivariate analysis, stepwise forward linear regression was applied. A P value <0.05 was considered to be statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.

## Results

The study sample consisted of 84 patients - 38 women (45.2%) and 46 men (54.8%) with eGFR < 45 mL/min/1.73 m²: 22 patients (26.2%) had eGFR 30-44 mL/min/1.73 m², 55 patients (65.5%) had eGFR 15-29 mL/min/1.73 m² and 7 individuals (8.3%) had eGFR < 15 mL/min/1.73 m². The mean age of patients was 68.7±14.6 years, range 24-90 years. 86.9% of patients were overweight or obese: 41,7% of participants had BMI 25.0-29.9 kg/m² and 45.2% of patients had BMI ≥ 30.0 kg/m².

Men had higher HGS and higher ASM compared to women (p<0.001, p<0.001). Men were taller and heavier than women (p<0.001, p=0.018). Lean tissue mass (LTM), lean tissue index (LTI) and relative fat (Rel Fat) significantly differed between men and women with higher LTM and LTI in men (p<0.001, p=0.037) but increased relative fat (Rel Fat) in women (p=0.010) (Table 1).

**Table 1.** Anthropometric characteristics of the studied population.

| | Total | | Women | | Men | | $P_{men\ vs\ women}$ |
|---|---|---|---|---|---|---|---|
| | n | mean±SD | n | mean±SD | n | mean±SD | |
| HGS [kg] | 84 | 25.27±10.09 | 38 | 18.88±5.31 | 46 | 30.55±10.07 | **<0.001** |
| ASM (BIS) | 84 | 19.72±4.89 | 38 | 16.90±4.42 | 46 | 22.04±3.97 | **<0.001** |
| Age [years] | 84 | 68.71±14.61 | 38 | 66.53±15.27 | 46 | 70.52±13.94 | 0.214 |
| Body mass [kg] | 84 | 82.87±18.88 | 38 | 77.58±20.57 | 46 | 87.25±16.33 | **0.018** |
| NH Weight [kg] | 84 | 82.20±19.04 | 38 | 77.54±21.10 | 46 | 86.04±16.40 | **0.041** |
| Height [cm] | 84 | 164.65±8.57 | 38 | 158.11±6.86 | 46 | 170.07±5.54 | **<0.001** |
| BMI [kg/m²] | 84 | 30.45±6.02 | 38 | 30.74±6.66 | 46 | 30.21±5.49 | 0.685 |
| LTM [kg] | 84 | 33.39±8.71 | 38 | 28.80±7.61 | 46 | 37.18±7.74 | **<0.001** |
| LTI | 84 | 12.26±2.91 | 38 | 11.53±3.19 | 46 | 12.87±2.55 | **0.037** |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Fat [kg] | 84 | 35.24±13.17 | 38 | 35.42±14.93 | 46 | 35.09±11.69 | 0.909 |
| Rel Fat [%] | 84 | 41.64±8.53 | 38 | 44.24±9.52 | 46 | 39.49±7.00 | **0.010** |
| FTI | 84 | 17.65±6.40 | 38 | 19.02±7.18 | 46 | 16.53±5.50 | 0.075 |

HGS, hand grip strength; ASM (BIS), appendicular skeletal muscle mass measured by bioimpedance spectroscopy; BMI, body mass index; LTM, lean tissue mass; LTI, lean tissue index; Rel Fat, relative fat; FTI, fat tissue index; p-values < 0.05 are marked in bold.

We found that 19.5% of participants were anemic with serum hemoglobin concentrations below 11.0 g/dL. The majority of patients – 88.9% had correct plasma albumin concentrations and 11.1% of individuals had decreased serum albumin. 62.3% of patients showed elevated plasma uric acid. Overhydration was observed in 33.3% of patients. Diabetes mellitus was diagnosed in 25.0% of individuals (Table 2).

**Table 2.** Clinical characteristics of the studied population.

| | Total | | Women | | Men | | $P_{men\ vs\ women}$ |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | |
| Serum albumin [g/dL] | | | | | | | |
| < 3.9 | 9 | 11.1% | 3 | 8.3% | 6 | 13.3% | 0.722 |
| 3.9 - 4.9 | 72 | 88.9% | 33 | 91.7% | 39 | 86.7% | |
| Hemoglobin [g/dL] | | | | | | | |
| < 11.0 | 16 | 19.5% | 8 | 21.1% | 8 | 18.2% | 0.744 |
| 11.0 - 18.0 | 66 | 80.5% | 30 | 78.9% | 36 | 81.8% | |
| eGFR [mL/min/1.73 m$^2$] | | | | | | | |
| ≤ 29 | 62 | 73.8% | 28 | 73.7% | 34 | 73.9% | 0.981 |
| 30-44 | 22 | 26.2% | 10 | 26.3% | 12 | 26.1% | |
| Serum creatinine [ULN] | | | | | | | |
| <1.5 | 18 | 21.4% | 15 | 39.5% | 3 | 6.5% | **0.001** |
| 1.5 - 2.0 | 31 | 36.9% | 14 | 36.8% | 17 | 37.0% | |
| 2.0 - 3.0 | 27 | 32.1% | 6 | 15.8% | 21 | 45.7% | |
| > 3.0 | 8 | 9.5% | 3 | 7.9% | 5 | 10.9% | |
| Serum urea [ULN] | | | | | | | |
| ≤ 1 | 3 | 4.2% | 0 | 0.0% | 3 | 7.7% | **0.012** |
| 1 - 1.5 | 20 | 27.8% | 11 | 33.3% | 9 | 23.1% | |
| 1.5 - 2 | 22 | 30.6% | 15 | 45.5% | 7 | 17.9% | |
| 2 - 2.5 | 16 | 22.2% | 3 | 9.1% | 13 | 33.3% | |
| > 2.5 | 11 | 15.3% | 4 | 12.1% | 7 | 17.9% | |
| Serum uric acid [mg/dl] | | | | | | | |
| K: 2.4 - 5.7, M: 3.4 - 7.0 | 29 | 37.7% | 9 | 25.0% | 20 | 48.8% | **0.032** |
| K: >5.7, M: >7.0 | 48 | 62.3% | 27 | 75.0% | 21 | 51.2% | |
| OH [L] | | | | | | | |
| < -1.0 | 9 | 10.7% | 4 | 10.5% | 5 | 10.9% | **0.006** |
| -1.0 - 1.0 | 47 | 56.0% | 28 | 73.7% | 19 | 41.3% | |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| > 1.0 | 28 | 33.3% | 6 | 15.8% | 22 | 47.8% | |
| Rel OH [%] | | | | | | | |
| <-7.0 | 8 | 9.5% | 4 | 10.5% | 4 | 8.7% | **0.017** |
| -7.0-7.0 | 52 | 61.9% | 29 | 76.3% | 23 | 50.0% | |
| >7.0 | 24 | 28.6% | 5 | 13.2% | 19 | 41.3% | |
| Diabetes mellitus type 2 | | | | | | | |
| No | 63 | 75.0% | 28 | 73.7% | 35 | 76.1% | 0.800 |
| Yes | 21 | 25.0% | 10 | 26.3% | 11 | 23.9% | |

eGFR, estimated glomerular filtration rate; ULN, upper limit of normal; OH, overhydration; Rel OH, relative overhydration; p-values < 0.05 are marked in bold.

We found statistically significant strong or moderate correlations between ASM and almost all studied anthropometric variables in both sexes. ASM was strongly increasing with higher body mass, NH weight and BMI (p<0.001, p<0.001, p<0.001, respectively). Height was positively related with ASM: taller participants had elevated ASM (p<0.001 for women, p=0.004 for men). We observed significant positive correlations between ASM and LTM (p=0.001 for women, p<0.001 for men) but we found that LTI was positively associated with ASM in masculine population only (p<0.001). Moreover, ASM was increasing with the rise of fat mass and FTI in both sexes (p<0.001, p<0.001, respectively) but the correlations were stronger for women. ASM was associated significantly with Rel Fat only in the group of women (p=0.034) but moderately (Table 3).

We also found statistically significant moderate associations between HGS and anthropometric measurements in the studied population. HGS was positively related with body mass and NH weight in women (p=0.003, p=0.005, respectively). In the group of women those with increased BMI and fat mass had also higher HGS (p=0.003, p=0.015, respectively). There was a statistically significant relationship between HGS and height. Taller individuals had higher HGS in both sexes (p<0.001 for women, p=0.002 for men). Additionally, HGS was positively associated with LTM in men (p=0.018). The positive significant relationship was also observed between HGS and ASM in women (p=0.001) (Table 3).

Both ASM and HGS negatively correlated with age. Pearson correlation coefficient for association with ASM was r=-0.555 for men (p<0.001) and r=-0.288 for women (p=0.080) and for association with HGS was r= -0.459 for women (p=0.004) and r= -0.608 for men (p<0.001).

**Table 3.** The associations between appendicular skeletal muscle mass and hand grip strength, and the anthropometric variables of the studied population.

| | **Appendicular skeletal muscle mass** | | | | | | | | | **Hand grip strength** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Total** | | | **Women** | | | **Men** | | | **Total** | | | **Women** | | | **Men** | | |
| | **n** | **r** | **p-value** | **n** | **r** | **p-value** | **n** | **r** | **p-value** | **n** | **r** | **p-value** | **n** | **r** | **p-value** | **n** | **r** | **p-value** |
| Body mass [kg] | 84 | 0.903 | **<0.001** | 38 | 0.949 | **<0.001** | 46 | 0.922 | **<0.001** | 84 | 0.319 | **0.003** | 38 | 0.468 | **0.003** | 46 | 0.109 | 0.472 |
| NH Weight | 84 | 0.882 | **<0.001** | 38 | 0.950 | **<0.001** | 46 | 0.897 | **<0.001** | 84 | 0.315 | **0.004** | 38 | 0.449 | **0.005** | 46 | 0.147 | 0.330 |
| Height [cm] | 84 | 0.694 | **<0.001** | 38 | 0.640 | **<0.001** | 46 | 0.421 | **0.004** | 84 | 0.666 | **<0.001** | 38 | 0.548 | **<0.001** | 46 | 0.452 | **0.002** |
| BMI [kg/m²] | 84 | 0.701 | **<0.001** | 38 | 0.879 | **<0.001** | 46 | 0.826 | **<0.001** | 84 | 0.048 | 0.666 | 38 | 0.352 | **0.030** | 46 | -0.036 | 0.814 |
| LTM [kg] | 84 | 0.664 | **<0.001** | 38 | 0.505 | **0.001** | 46 | 0.594 | **<0.001** | 84 | 0.490 | **<0.001** | 38 | 0.212 | 0.200 | 46 | 0.348 | **0.018** |
| LTI | 84 | 0.433 | **<0.001** | 38 | 0.273 | 0.097 | 46 | 0.500 | **<0.001** | 84 | 0.238 | **0.029** | 38 | 0.007 | 0.968 | 46 | 0.221 | 0.141 |
| Fat [kg] | 84 | 0.614 | **<0.001** | 38 | 0.799 | **<0.001** | 46 | 0.653 | **<0.001** | 84 | 0.103 | 0.350 | 38 | 0.392 | **0.015** | 46 | 0.013 | 0.932 |
| Rel Fat | 84 | 0.090 | 0.415 | 38 | 0.344 | **0.034** | 46 | 0.227 | 0.129 | 84 | -0.146 | 0.185 | 38 | 0.196 | 0.238 | 46 | -0.080 | 0.596 |
| FTI | 84 | 0.449 | **<0.001** | 38 | 0.723 | **<0.001** | 46 | 0.593 | **<0.001** | 84 | -0.058 | 0.599 | 38 | 0.319 | 0.051 | 46 | -0.063 | 0.677 |
| ASM (BIS) [kg] | | | | | | | | | | 84 | 0.501 | **<0.001** | 38 | 0.531 | **0.001** | 46 | 0.188 | 0.210 |

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BMI, body mass index; LTM, lean tissue mass; LTI, lean tissue index; Rel Fat, relative fat; FTI, fat tissue index; ASM (BIS), appendicular skeletal muscle mass measured by bioimpedance spectroscopy; p-values < 0.05 are marked in bold; r, Pearson correlation coefficient.

Table 4 presents the associations between ASM, HGS and clinical variables. There was a statistically significant relationship between ASM and certain clinical parameters. Women with higher serum albumin showed lower ASM (p=0.011). We also found that participants with increased OH had lower ASM in both sexes (p=0.006 in women, p=0.026 in men). Men with diabetes had higher ASM comparing to those without diabetes (p=0.014).

Additionally, we observed a statistically significant relationship between HGS and clinical variables in the studied population. HGS was much lower in male participants with serum urea above normal values (p<0.003), however all females presented concentrations of serum urea above ULN. Additionally, individuals with serum uric acid above normal range had also lower HGS (p<0.039 for both sexes together) (Table 4).

**Table 4.** The associations between appendicular skeletal muscle mass and hand grip strength, and the clinical variables of the studied population.

| | **Appendicular skeletal muscle mass** | | | | | | | | **Hand grip strength** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Total** | | | **Women** | | | **Men** | | | **Total** | | | **Women** | | | **Men** | |
| | **n** | **mean±SD** | **p-value** | **n** | **mean±SD** | **p-value** | **n** | **mean±SD** | **p-value** | **n** | **mean±SD** | **p-value** | **n** | **mean±SD** | **p-value** | **n** | **mean±SD** | **p-value** |
| Serum albumin [g/dL] | | | | | | | | | | | | | | | | | | |
| < 3.9 | 9 | 22.56±5.36 | 0.073 | 3 | 23.16±6.82 | **0.011** | 6 | 22.26±5.20 | 0.896 | 9 | 23.61±5.54 | 0.603 | 3 | 20.33±1.15 | 0.642 | 6 | 25.25±6.23 | 0.185 |
| 3.9 - 4.9 | 72 | 19.44±4.81 | | 33 | 16.38±3.95 | | 39 | 22.02±3.89 | | 72 | 25.49±10.55 | | 33 | 18.77±5.69 | | 39 | 31.17±10.42 | |
| Hemoglobin [g/dL] | | | | | | | | | | | | | | | | | | |
| < 11.0 | 16 | 18.99±5.79 | 0.580 | 8 | 17.63±6.07 | 0.605 | 8 | 20.35±5.55 | 0.221 | 16 | 23.34±7.19 | 0.413 | 8 | 21.00±6.28 | 0.209 | 8 | 25.69±7.66 | 0.125 |
| 11.0 - 18.0 | 66 | 19.75±4.68 | | 30 | 16.7±3.98 | | 36 | 22.29±3.61 | | 66 | 25.67±10.74 | | 30 | 18.32±4.99 | | 36 | 31.81±10.41 | |
| eGFR [mL/min/1.73 m2] | | | | | | | | | | | | | | | | | | |
| ≤ 29 | 62 | 19.39±4.78 | 0.304 | 28 | 16.73±4.45 | 0.694 | 34 | 21.58±3.89 | 0.185 | 62 | 24.28±9.49 | 0.131 | 28 | 18.23±5.35 | 0.212 | 34 | 29.26±9.30 | 0.146 |
| 30 -4 4 | 22 | 20.64±5.17 | | 10 | 17.38±4.53 | | 12 | 23.36±4.06 | | 22 | 28.07±11.38 | | 10 | 20.70±5.02 | | 12 | 34.21±11.66 | |
| Serum creatinine [ULN] | | | | | | | | | | | | | | | | | | |
| < 1.5 | 18 | 17.90±4.55 | 0.138 | 15 | 17.03±3.81 | 0.971 | 3 | 22.27±6.34 | 0.191 | 18 | 21.28±6.31 | 0.105 | 15 | 19.47±4.93 | 0.786 | 3 | 30.33±4.51 | 0.741 |
| 1.5 - 2.0 | 31 | 19.40±5.14 | | 14 | 17.15±5.64 | | 17 | 21.26±3.95 | | 31 | 24.40±11.48 | | 14 | 17.75±4.63 | | 17 | 29.88±12.62 | |
| 2.0 - 3.0 | 27 | 20.53±4.04 | | 6 | 16.11±1.71 | | 21 | 21.80±3.610 | | 27 | 27.59±9.28 | | 6 | 19.25±6.01 | | 21 | 29.98±8.72 | |
| > 3.0 | 8 | 22.24±6.35 | | 3 | 16.64±6.54 | | 5 | 25.60±3.40 | | 8 | 29.81±11.70 | | 3 | 20.50±10.33 | | 5 | 35.40±9.05 | |
| Serum urea [ULN] | | | | | | | | | | | | | | | | | | |
| ≤ 1 | 3 | 23.97±2.83 | 0.408 | 0 | - | 0.706 | 3 | 23.97±2.83 | 0.833 | 3 | 50.33±8.08 | **<0.001** | 0 | - | 0.937 | 3 | 50.33±8.08 | **0.003** |
| 1 - 1.5 | 20 | 19.42±5.06 | | 11 | 16.49±3.07 | | 9 | 23.00±4.77 | | 20 | 23.18±7.43 | | 11 | 20.00±4.88 | | 9 | 27.06±8.39 | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1.5 - 2 | 22 | 19.06±5.46 | | 15 | 17.76±5.30 | | 7 | 21.85±5.06 | | 22 | 23.84±10.85 | | 15 | 18.80±6.46 | | 7 | 34.64±10.71 | |
| 2 - 2.5 | 16 | 21.16±3.68 | | 3 | 19.67±5.65 | | 13 | 21.51±3.31 | | 16 | 25.88±8.93 | | 3 | 18.00±1.00 | | 13 | 27.69±8.96 | |
| > 2.5 | 11 | 20.59±5.46 | | 4 | 16.38±5.03 | | 7 | 22.99±4.29 | | 11 | 24.73±8.02 | | 4 | 19.00±6.98 | | 7 | 28.00±6.97 | |
| Serum uric acid [mg/dL] | | | | | | | | | | | | | | | | | | |
| K: 2.4 - 5.7; M: 3.4 - 7.0 | 29 | 19.72±5.15 | 0.965 | 9 | 15.79±5.66 | 0.395 | 20 | 21.48±3.88 | 0.263 | 29 | 28.24±11.15 | **0.039** | 9 | 18.94±5.70 | 0.937 | 20 | 32.43±10.49 | 0.266 |
| K: > 5.7; M: > 7.0 | 48 | 19.77±5.06 | | 27 | 17.30±4.14 | | 21 | 22.95±4.35 | | 48 | 23.34±9.11 | | 27 | 19.11±5.32 | | 21 | 28.79±10.14 | |
| OH [L] | | | | | | | | | | | | | | | | | | |
| < -1.0 | 9 | 25.00±3.71 | **<0.001** | 4 | 23.27±4.87 | **0.006** | 5 | 26.38±2.07 | **0.026** | 9 | 29.61±11.37 | 0.121 | 4 | 20.50±7.94 | 0.715 | 5 | 36.90±7.86 | 0.298 |
| -1.0 - 1.0 | 47 | 18.13±4.61 | | 28 | 16.09±3.77 | | 19 | 21.14±4.12 | | 47 | 23.37±10.12 | | 28 | 18.46±4.75 | | 19 | 30.61±11.62 | |
| > 1.0 | 28 | 20.67±4.30 | | 6 | 16.41±4.10 | | 22 | 21.83±3.63 | | 28 | 27.07±9.19 | | 6 | 19.75±6.74 | | 22 | 29.07±8.84 | |
| Rel OH [%] | | | | | | | | | | | | | | | | | | |
| < -7.0 | 8 | 24.74±3.88 | **0.003** | 4 | 23.27±4.87 | **0.005** | 4 | 26.22±2.36 | 0.086 | 8 | 28.19±11.26 | 0.536 | 4 | 20.50±7.94 | 0.695 | 4 | 35.88±8.68 | 0.374 |
| -7.0 - 7.0 | 52 | 18.69±4.73 | | 29 | 16.36±3.99 | | 23 | 21.61±3.95 | | 52 | 24.39±10.19 | | 29 | 18.91±5.26 | | 23 | 31.30±10.78 | |
| > 7.0 | 24 | 20.26±4.52 | | 5 | 14.90±1.96 | | 19 | 21.68±3.89 | | 24 | 26.21±9.63 | | 5 | 17.40±3.91 | | 19 | 28.53±9.38 | |
| Diabetes mellitus type 2 | | | | | | | | | | | | | | | | | | |
| No | 63 | 19.23±4.37 | 0.118 | 28 | 16.71±4.12 | 0.674 | 35 | 21.25±3.46 | **0.014** | 63 | 25.95±10.51 | 0.288 | 28 | 19.43±5.63 | 0.295 | 35 | 31.17±10.65 | 0.465 |
| Yes | 21 | 21.16±6.08 | | 10 | 17.41±5.37 | | 11 | 24.57±4.59 | | 21 | 23.24±8.60 | | 10 | 17.35±4.18 | | 11 | 28.59±8.12 | |

eGFR, estimated glomerular filtration rate; ULN, upper limit of normal; OH, overhydration; Rel OH, relative overhydration; p-values < 0.05 are marked in bold.

Finally, to investigate the relationship of HGS with clinical variables in multivariate analysis, the stepwise forward multiple linear regression was applied. Clinical variables significantly associated with HGS or ASM in univariate analysis (uric acid, OH, urea) were considered for estimation of the final model together with non-modifiable variables such as gender, age and height. In the estimated model height, gender, age, serum concentration of uric acid and absolute overhydration remained statistically significant (Table 5). These variables accounted for 62.1% of statistical variability in HGS.

**Table 5.** Stepwise forward multiple linear regression of hand grip strength in the studied population.

| | **Coefficient** | **95%CI** | **p-value** |
|---|---|---|---|
| Height [cm] | 0.405 | 0.122;0.688 | **0.006** |
| Age [years] | -0.231 | -0.353;-0.109 | **<0.001** |
| Gender [men] | 8.981 | 3.960;14.002 | **0.001** |
| Uric acid [mg/dL] | -1.078 | -2.110;-0.045 | **0.041** |
| OH [L] | -0.805 | -1.579;-0.032 | **0.042** |

OH, overhydration; p-values < 0.05 are marked in bold.

## Discussion

In our study we evaluated whether the chosen anthropometric and clinical variables are related to the same extent with the components of sarcopenia – skeletal muscle mass and muscle strength in the population of patients with eGFR < 45 ml/min/1.73m² not treated with dialysis. We confirmed

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that ASM, LTM, LTI, height, body mass and NH weight were significantly higher in men than in women. On the contrary, women had higher Rel Fat compared to men (p=0.010), and also increased FTI, but at the border of significance (p=0.075). However, we did not observe the diversity in BMI according to gender (Table 1). Men had higher HGS comparing to women (p<0.001).

Regarding clinical variables our sample presents typical features of advanced CKD population: the majority of patients showed increased serum urea concentrations, 62.3% participants had plasma uric acid above ULN, and above 30% of the sample presented fluid overload (Table 2).

*Appendicular Skeletal Muscle Mass and Anthropometric Variables*

We found that ASM was significantly associated with anthropometric variables. ASM was positively related with total body mass (p<0.001), NH weight (p<0.001), height (p<0.001), BMI (p<0.001), LTM (p<0.001) and fat (p<0.001) in both sexes. However, LTI was related with ASM only in the group of men (p<0.001) and Rel fat - only in the feminine population (p=0.034) (Table 3). In our study height was strongly associated with ASM, what may depend on the greater total mass of skeletal muscles in taller patients. However, total body mass, BMI and total fat mass were also positively associated with ASM. Increased ASM in individuals with higher total body mass or BMI may be due to higher absolute muscle mass as neither total body mass, nor BMI allow to differentiate muscle or fat mass. Regardless of the associations between anthropometric variables and ASM, we need to be aware that all these variables are correlated. This means that each single studied anthropometric parameter includes information about every other one. Therefore, it is difficult if not impossible to distinguish – especially in cross-sectional designs – which anthropometric parameters are crucial for ASM.

According to the reverse epidemiology phenomenon in CKD which states that obese patients have lower morbidity and higher survival rate compared to malnurished individuals, also knowing that higher skeletal muscle mass is related with decreased mortality, and based on our findings, the obesity paradox in CKD may be the result of higher ASM in obese subjects [11]. Tomborelli Bellafronte also presumed that the obesity paradox in CKD population may be the result of the protective effect of lean mass even in patients with the presence of greater adiposity [12]. We may conclude that taller and heavier patients with CKD not treated with dialysis have higher ASM.

*Hand Grip Strength and Anthropometric Variables*

In our study we found that HGS was associated with anthropometric parameters such as total body mass (p=0.003), NH weight (p=0.004), height (p<0.001), LTM (p<0.001), LTI (p=0.029) and ASM (p<0.001). However the statistical significance in the group of women was observed between HGS and body mass (p=0.003), NH weight (p=0.005), height (p<0.001), BMI (p=0.030), fat (p=0.015) and ASM (p=0.001). In the group of men only the relationship between HGS and height (p=0.002), and between HGS and LTM (p=0.018) remained statistically significant (Table 3). There are numerous studies which confirmed the relationship between HGS and certain anthropometric variables. The study of Cheng which included 10407 participants reported that patients with higher BMI had also increased HGS [13]. Very interesting are also the results of Curtis who stated that lower BMI is related with higher likelihood of probable sarcopenia (defined as decreased muscle strength), whereas overweight and obesity seemed to play a protective role [14]. Although we do not know the exact impact of BMI on HGS, it is more likely that patients with higher BMI tend to have higher HGS due to greater muscle mass. HGS was also observed to be associated with fat mass. There are studies which found negative relationship between HGS and total fat mass and between HGS and relative fat [15,16]. Jiang, who examined 161 CKD patients also observed that individuals with increased total body fat had lower HGS [15]. We obtained opposite results but only in the group of women – participants with elevated total fat mass showed higher HGS (p=0.015). Regarding height, it was the only anthropometric parameter which was significantly related with HGS both when data were mixed and when data were separated in our study. In multivariate analysis we also observed that height remained a significant determinant of HGS in the group of CKD patients (p<0.001) (Table 3, Table 5). There are many studies which evaluated the association between HGS and height or weight.

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Byambaa found that HGS was significantly related with height, not weight [17]. The report of Ong also confirmed that HGS was significantly positively associated with height [18]. The study of Xu which included more than 1500 healthy young participants found that HGS was associated with weight, not height. However, the report of Angst showed that both weight and height are significant determinants of HGS [19]. Very similar results were presented by Günther who also observed that, apart from gender and age, height and weight were the highest predicive variables of HGS [20]. The number of studies which evaluated the anthropometric determinants of HGS in CKD population is small. The study of Corona which included hemodialysis patients found that HGS was associated both with height and weight [21]. Hasheminejad also found the significant positive relationship between HGS and height, and also between HGS and weight in end-stage kidney disease [22]. In our study we included patients with advanced CKD not treated with dialysis and found that taller participants had higher HGS, hence we may conclude that height should be taken into consideration when assessing HGS in CKD patients. However, we should realise that because ASM is related to other anthropometric variables and ASM is related to HGS, the association of HGS with these anthropometric variables may be a spurious effect of their intermediate position within the causal chain.

*Appendicular Skeletal Muscle Mass and Clinical Variables*

We found that ASM was significantly negatively associated with serum albumin in women, those with correct plasma albumin presented lower ASM compared to participants with decreased albumin, who had higher ASM (p=0.011). Serum albumin is known to play a role as a nutritional marker. Decreased serum albumin is one of the diagnostic criteria of protein-energy wasting (PEW) in CKD, which includes also the degree of the muscle mass loss [23]. The probable reason of our results is confunding by age. The mean age of women with correct serum albumin in our study was 68 years and in women with decreased serum albumin it was significantly lower – 45 years. Since age negatively correlates with ASM, this was the most likely reason why women with higher serum albumin had lower ASM in our study. Additionally, there are studies which reported that serum albumin is a poor nutritional marker in patients with advanced CKD [24]. The study of Chen also reported the similar results regarding albumin and muscle mass in the group of women as they found negative association between muscle mass and albumin in feminine population [25]. Further studies are needed to explain these inconsistent findings according to gender, but the possible cause is the different hormonal or inflammatory impact on serum albumin concentrations in men and women.

We also found that ASM was associated with OH and Rel OH. Participants with higher absolute OH and Rel OH had lower ASM when the data of men and women were mixed (p<0.001, p=0.003, respectively). Absolute OH was also higher in patients with lower ASM when the data were separated (p=0.006 for women, and p=0.026 for men). According to Rel OH, when the data were separated we observed such association in feminine population only (p=0.005) (Table 4). Our results are in opposite to the results of other studies where skeletal muscle mass was positively associated with hydration status [26]. A possible reason for the positive association between fluid overload and ASM may be that overhydration overestimates the mass of skeletal muscle [26]. In our study the negative effect of excessive fluid load on ASM may be caused by the fact that patients with overhydration had on average much lower BMI than other participants (Table 4).

We also observed that men with diabetes had higher ASM (p=0.014) which is the opposite of some other studies (Table 4). The report of Hong which included over 200000 participants in a cohort study demonstrated in multivariate analysis that skeletal muscle mass was negatively associated with the development of diabetes [27]. However, our study was cross-sectional and the relatively small sample size precluded from performing in-depth analyses.

*HGS and Clinical Variables*

In our study we found a negative association between HGS and serum UA, also in multivariate analysis after adjusting for age, gender and height (p=0.041) (Table 5). Participants with lower plasma UA had higher HGS. The relationship between UA and HGS was the subject of observation in several

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studies and the conclusions are not clear. Yi reported an inverse correlation between uric acid and relative HGS in women with the average age of 47 years [28]. García-Esquines also found a negative association between serum UA and HGS, however only in participants aged 20-40 years. This relationship was positive in population above 60 years. They suggested that the association between HGS and UA may depend on age [29]. Results similar to ours were revealed by the study of Huang who found that HGS was much lower in individuals with hyperuricemia compared to those with correct serum UA [30]. The association between UA and muscle strength may be due to the role of UA in oxidative balance. Increased subclinical inflammatory state in CKD is known to be a significant factor contributing to protein-energy wasting (PEW) and sarcopenia. UA may have both pro-oxidative and anti-oxidative properties depending on its extracellular or intracellular actions [31]. In our study, higher serum UA was associated with lower HGS in CKD patients which may be associated with increased pro-inflammatory properties of UA in the studied population.

Since OH was related to ASM in bivariate analysis, we decided to include OH in the multivariate model for HGS and obtained a significant negative association with HGS ($p=0.042$) after adjusting for age, gender and height (Table 5). Patients with fluid overload showed lower HGS, therefore it may be concluded that OH can contribute to the development of sarcopenia in CKD. There are not many reports on relationship between OH and HGS. Garagarza conducted the study with 155 ESRD patients treated with hemodialysis and observed a negative relationship between HGS and OH [32]. Future studies on the impact of fluid overload on muscle strength in CKD patients are needed.

We observed the significant bivariate relationship between HGS and serum urea. Patients with correct plasma urea concentrations had significantly higher HGS compared to individuals with elevated serum urea levels ($p<0.001$). Urea belongs to uremic toxins increasing with deteriorating kidney function. In our study, only 3 participants had correct serum urea concentrations which is an expected result for the population with an advanced kidney function decrease. The small number of participants with correct serum urea concentrations caused the exclusion of urea from the final regression model after implementation of stepwise procedure (Table 5). It is worth mentioning that in our study a negative relationship between HGS and urea was found regardless of the degree of kidney function decrease.

We did not observe association between HGS and hemoglobin. Anemia is known to be associated with weaker muscle strength. It is probably caused by impaired muscular oxygen transport and consumption which leads to chronic tissue hypoxia and worsens muscular function. The results of numerous studies which examined the relationship between hemoglobin and HGS are not consistent [33-35]. Despite the fact that patients with CKD are prone to develop anemia the relationship between hemoglobin and HGS was not present in our study, neither in men nor in feminine population.

HGS may also depend on diabetic status. The mechanisms of muscle strength decrease by hyperglycemia are multifactorial, including insulin resistance, increased secretion of inflammatory cytokines and oxidative stress. There are numerous studies which evaluated the association between HGS and hypergycemia. The study of Lee which included above 8000 participants showed that HGS was significantly inversely associated with type 2 diabetes mellitus and insulin resistance regardless of gender [36]. Mainous found that individuals with prediabetes had also lower HGS compared to patients with normoglycemia [37]. In our study with the CKD patients, we found no relationship between diabetes and HGS.

We also did not observe a significant relationship between HGS and serum albumin. We observed that in the group of men higher albumin concentrations were accompanied by higher HGS, contrary to women – those with correct serum albumin levels had lower HGS. Since serum albumin as a marker of nutritional status was found to be positively associated with HGS, our contradictory findings seemed confusing [38]. The probable reason of our results was confounding by age as it was explained above in the paragraph on the relationship between ASM and serum albumin.

The limitation of our study is its relatively small sample size. A larger number of participants would enable a more detailed and more comprehensive analysis. Additionally, the cohort design would be more appropppriate than a cross-sectional study and would allow to establish initial

conditions. Probably another limitation of our study is that HGS was measured as arithmetic mean of two arms what is not the most common approach but seemed to be more repeatable.

In summary, although sarcopenia is defined as low HGS and decreased ASM, there are still patients with low muscle strength and normal muscle quantity and conversely, with correct muscle strength and decreased muscle mass who cannot be diagnosed as sarcopenic but should be treated as pre-sarcopenic individuals. Therefore, it is crucial to look for significant determinants of HGS and ASM separately in order to prevent the muscle strength and ASM deterioration. Not many studies evaluate separately two compartments of sarcopenia in CKD population such as ASM and HGS, and frequently give inconsistent results. According to the findings of our study, which evaluated separately the determinants of ASM and HGS in non-dialysis dependent CKD patients, we may conclude that - apart from the negative correlation with age - ASM is associated mainly with anthropometric parameters but HGS is related both with antropometric and clinical variables which are specific for CKD advancement. Future, well-designed studies on ASM and HGS determinants in CKD are needed in order to prevent the deterioration of ASM and HGS and thus to minimize the likelihood of developing sarcopenia and its consequences such as high morbidity and mortality.

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**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.
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