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Quality matters: chronic kidney disease progressively impacts muscle strength independently of changes in skeletal muscle mass

Supplementary materials, data and code sharing: https://osf.io/bm9zd/
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ABSTRACT

Background. Chronic kidney disease (CKD) is commonly associated with multifactorial neuromuscular impairment. Few studies have investigated CKD-induced changes in maximal voluntary force (MVF), and even fewer have longitudinal follow-up. The aim of this study is to investigate whether CKD progression modifies the relationship between skeletal muscle mass and force and the prevalence of sarcopenia and sarcopenic obesity.

Methods. The data used were prospectively gathered during routine check-ups in a network of nutritional centres in Mexico. From a dataset of 5430 patients, we selected 1098 patients with available anthropometric, kidney function, handgrip and bioimpedance data. The relationship between appendicular skeletal mass (ASM) and MVF was investigated in the different CKD stages using mixed models, while sarcopenia and sarcopenic obesity were compared using the Chi-2 test. Longitudinal analysis, considering individuals with at least two visits (n=516), was performed via regression models using the linear slopes with time of MVF, ASM and kidney function.

Results. After normalization with ASM, MVF was higher in CKD G1-G3 compared to G4 and G5 ($p \leq 0.001$, Cohen's d=0.270-0.576). Slopes between MVF and ASM were lower in CKD G3, G4 and G5 than in CKD G1-G2 (-1.131 [-2.067,-0.195], p=0.019; -1.728 [-2.809,-0.647], p=0.002; -1.744 [-2.876,-0.613], p=0.003, respectively). The prevalence of sarcopenia and sarcopenic obesity did not differ across CKD stages, but recovery was most commonly observed in CKD G1-G2. Longitudinal analysis showed an independent association between the slopes of MVF, kidney function and ASM.

Conclusions. CKD negatively, progressively and independently affects the neuromuscular system, and force production is reduced for any given muscle mass as CKD progresses. While no association was found between CKD stage and prevalence of sarcopenia, recovery was more frequent in the early CKD stages. These results suggest the importance of early rehabilitation programs to improve musculoskeletal health, quality of life and survival in CKD patients.

INTRODUCTION

The association between chronic kidney disease (CKD) and impairment of neuromuscular function is well acknowledged [1–4] as is the negative effect CKD has on exercise tolerance [5] and on survival [6]. Consequently, muscle strength is commonly assessed in both research and clinical practice on the basis of a finger flexion test, i.e., handgrip task [7–9].

Muscle strength is usually found to be lower in CKD patients than in age-matched non-CKD peers [10]. It has been known for decades that sensitive nerve conduction velocity is impaired in the advanced CKD stages [11]. Recently, Doshi et al. showed that during a 7-year follow-up, CKD patients had 2.3 times higher odds of having a reduction in motor nerve conduction velocity than controls [12]. Neurological complications impair functional capacity [13]. Skeletal muscle fat infiltration (i.e., myosteatosis), previously described in CKD patients [14], reduces physical performance [15] and limits muscle strength production. At the muscle fibre level, studies in CKD mice showed a -36% to -51% reduction in force production for a given cross-sectional area compared to control mice, which was thought to be caused mainly by a reduced number of myosin heads strongly bound to actin [16]. It is also acknowledged that other factors may be associated with lower force production, even when muscle mass is preserved. These include mitochondrial impairment [17], inflammation and hormonal disturbance [10]. These mechanisms may be the basis of the increased risk of sarcopenia and sarcopenic obesity in CKD [18], even though their relationship to CKD progression is not fully elucidated [19].

In the context of a multifactorial impairment, the relationship between impaired kidney function and muscle strength is unclear and few studies have addressed the relationship between muscle strength and kidney function [20,21]. The cross-sectional study design is the one most commonly used. In addition, despite an expected association between kidney function and muscle strength, information regarding muscle mass and its evolution over time is scarce. Evidence confirming that such a relationship exists is needed as in CKD patients force production does not rely only on muscle mass [1,3,4,16].

The primary aim of our study was to investigate whether the impairment in force associated with reduced kidney function can be attributed to a reduction in muscle mass. The secondary aim was to determine whether the prevalence of sarcopenia and sarcopenic obesity increases across CKD stages.

METHODS

Study design and setting of care

The study is retrospective and non-interventional. It employs anonymized data in the centre database that was gathered during routine clinical practice [22]

The overall cohort consists of patients receiving at least one consultation in one of the eight "Centros de attention nutritional" (CEAN, Centers of nutritional attention), in Mexico (one in Guadalajara, Monterrey, Pachuca, Puebla, Villahermosa and Tijuana, and two in Mexico City). The centres were founded by Fresenius Kabi to provide CKD patients with dietary consultations.

Glomerular filtration rate estimation

CKD was defined and staged in keeping with the KDIGO guidelines; estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation in removing body surface area (noBSA), as recommended [23]:

$$CKD\text{-}EPI\ noBSA\ =\ CKD\text{-}EPI\ \times \frac{individual\ BSA}{1.73m^2}$$

Body surface area was calculated in accordance with the Du Bois and Du Bois (1916) formula as follows [24]:

$$Body\ surface\ area\ =\ 0.007184 \times (height \times 100)^{0.725} \times weight^{0.425}$$

Bioimpedance protocol

Bioimpedance analysis [7] employed multifrequency bioimpedance devices, using the SECA mBCA 514 (SECA, Co., Hamburg, Germany) or the Avis 333 Plus Segmental Body Composition Analyzer (Jawon Medical, Seoul, South Korea) depending on centre.

Individuals were asked to stand in the orthostatic position during the whole-body analysis. Appendicular skeletal mass (ASM) and fat mass (FM) were estimated both in absolute terms (kg) and in relation to body mass (%) [7].

Handgrip strength protocol

The Takei T.K.K.5401 GRIP-D handgrip dynamometer (Takei Scientific Instruments Co., Tokyo, Japan) was used to assess handgrip force. Patients were asked to stand in an upright position with the dynamometer in their dominant hand (the one used for writing) and their arm in a vertical position. Patients were then told to squeeze the dynamometer as hard as possible and maintain their grip for 5 seconds. Three measures were recorded and the maximal voluntary force (MVF) obtained for analysis was the average of the three. MVF was analysed in Newton (N) units and normalized to ASM (kg of MVF/kg of ASM; MVF_{ASM}) to better reflect the force produced in relation to muscle mass.

Definitions

Both sarcopenia [25] and sarcopenic obesity [26] were defined as recommended by the European Working Group on Sarcopenia in Older People (EWGSOP-2) [25]. Probable sarcopenia was defined as low handgrip strength (i.e., <26 kg in males and <16 kg in females) [27] and in these patients, confirmed sarcopenia was defined as low ASM (i.e., <20 kg in males and <15 kg in females) [27].

Sarcopenic obesity was defined using the two-step algorithm of the European Society for Clinical Nutrition and Metabolism (ESPEN) and European Association for the Study of Obesity (EASO) [26]. The screening cut-off was set at ≥30 $kg \cdot m^{-2}$ of BMI. In screened patients, confirmed sarcopenia considered both low handgrip strength (i.e., <26 kg in males and <16 kg in females) [27] and high relative FM (i.e., >27% FM in males and >38% FM in females) [28].

Selection of the study population

The selection of the study population is described in Figure 1. After eliminating from the original dataset (i.e., 24,767 observations and 5,430 adult patients) cases that lacked essential data (age, date of first consultation, kidney function), the initial dataset included 23,927 observations (5,162 patients), for a total follow-up of 3,906 patient years.

Based on this initial dataset, a first selection (i.e., determining the final dataset) was performed to answer to the working hypothesis, and a subsequent selection was made to perform the longitudinal analysis, as follows (Figure 1):

- Exclusion of observations of patients missing height, weight, handgrip or bioimpedance assessment; this produced a final dataset of 2,490 observations (1,098 patients, 435 patient years).
- In order to perform the longitudinal analysis, the requisite was for the patient to have had at least two visits and that information on eGFR, MVF and ASM had been recorded. This selection consists of 516 patients with 1,908 observations.

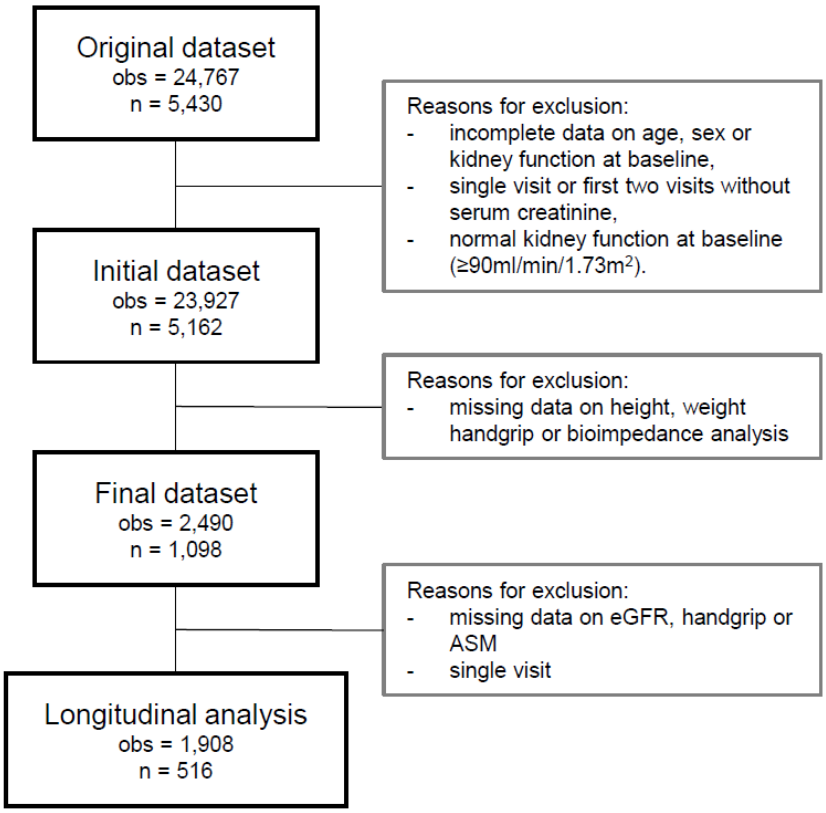

Figure 1 Selection of the study group population. obs: observations; n: number of patients; eGFR: estimated glomerular filtration rate; ASM: appendicular skeletal mass

Statistical analysis

Descriptive analysis

Statistical analysis was performed using R programming language v.4.3.1 (R core Team, Vienna, Austria) with RStudio v.2023.06.2 (Posit Software©, Boston, MA, USA) interface. Given the

size of the cohort, the distribution shapes of continuous variables were assessed using histograms and Q-Q plots. Variables were presented using mean and standard deviation (SD) or median and quartiles [Q1-Q3] accordingly. Qualitative variables were presented using count and percentage.

Comparison of clinical data across CKD stages

Comparison of clinical data (i.e., handgrip and bioimpedance) between CKD stages was performed using one-way ANOVA with Holm post hoc when normality and homoscedasticity assumptions (tested using Levene's test) were met. Otherwise, a Kruskal-Wallis test with a Wilcoxon rank sum post hoc test with a Holm correction was used. Effect size, calculated using {effectsize} package v.0.8.6, was reported using partial eta squared (η_p^2) or Cohen's d with pooled standard deviation in multiple or binary comparisons, respectively. Effect sizes were considered as small ($\eta_p^2 \geq 0.01$, Cohen's $d \geq 0.2$), medium ($\eta_p^2 \geq 0.06$, Cohen's $d \geq 0.5$) or large ($\eta_p^2 \geq 0.14$, Cohen's $d \geq 0.8$). Prevalence of sarcopenia was tested across period of follow-up using the Cochran-Mantel-Haenzen for repeated measures and across CKD stages using the Chi-2 test (χ^2).

Mixed models

The effect of eGFR on the relationship between ASM and MVF was investigated using linear mixed models with {nlme} package v.3.1-162. MVF was considered as an outcome and ASM and eGFR as independent variables of interest. All the models were adjusted for age, sex and BMI, and took into account patient's follow-up as a time effect (i.e., defined as a random slope) and individual baseline characteristics (i.e., defined as random intercept). A stepwise approach was used in order to: assess the effect of independent variables only (Model 1); consider a contrast approach within CKD stages so that any progressive impairment could be detected (Model 2); consider the interaction term between CKD stages and ASM (Model 3). Marginal (i.e., only fixed effects) and conditional (i.e., fixed and random effects) coefficients of determination for mixed models were calculated using {MuMIn} package v.1.47.5.

In keeping with common clinical practice, in mixed models n°1, eGFR was reversed in order to consider reduction in kidney function rather than an improvement (i.e., -1 × eGFR), stratified by intervals of 10 ml/min of eGFR.

Longitudinal analysis

The longitudinal analysis takes into account the slopes of MVF, ASM and eGFR over time (obtained from linear regressions), for each individual. Outlier slopes (defined as variations >100

ml/min/year for eGFR or >1000 N/year for MVF) were deleted (38 individuals), leading to a final sample of 478 individuals. The tripartite association was tested using regression models, considering MVF slope as a dependent variable, adjusted for sex and age and BMI at first visit. A first model was performed to test eGFR and ASM slope independently and the interaction term was tested using another model. Statistical significance was considered when p-values were < 5%.

Results

Baseline data

The initial dataset of 5,162 patients (Supplementary Table 1) had similar anthropometric characteristics compared to those of the final dataset (n= 1,098; Table 1). Characteristics of patients across CKD stages are presented in Table 1. Overall, the majority of patients were over 55; nearly all of them were overweight; and the prevalence of males and females was balanced.

Table 1. Characteristics of patients across CKD stages

		CKD Groups			
	All	G1-G2	G3	G4	G5
Anthropometric data					
N patients, n (% of total)	1,098	67 (6.1 %)	314 (28.6 %)	390 (35.5 %)	327 (29.8)
Age (years), median [Q1-Q3]	65 [56-73]	61 [51-68]	66 [58-73]	66 [58-75]	63 [54-70]
Weight (kg), median [Q1-Q3]	69.1 [59.5-78.5]	65.0 [56.2-69.9]	68.3 [59.3-79.2]	69.3 [58.8-77.7]	71.0 [61.4-81.2]
Height (m), mean (SD)	1.59 (0.10)	1.56 (0.08)	1.58 (0.10)	1.58 (0.09)	1.60 (0.10)
BMI ($kg.m^{-2}$), median [Q1-Q3]	27.3 [24.4-30.5]	26.1 [22.8-28.2]	27.6 [24.3-30.5]	27.3 [24.3-30.6]	27.3 [24.6-30.5]
Sex (females), n (%)	565 (51.5 %)	37 (55.2 %)	176 (56.1 %)	204 (52.3 %)	148 (45.3 %)
Education, n (%)					
Illiterate	22 (2.7 %)	1 (2.2 %)	13 (5.5 %)	5 (1.7 %)	3 (1.3 %)
Elementary school	228 (28.3 %)	5 (10.9 %)	52 (21.8 %)	102 (35.1 %)	69 (29.7 %)
Middle school	123 (15.2 %)	9 (19.6 %)	33 (13.9 %)	45 (15.5 %)	36 (15.5 %)
High school	395 (48.9 %)	29 (63.0 %)	125 (52.5 %)	126 (43.3 %)	115 (49.6 %)
University	39 (4.8 %)	2 (4.3 %)	15 (6.3 %)	13 (4.5 %)	9 (3.9 %)
CKD aetiology, n (%)					
Diabetes	320 (46.1 %)	16 (34.8 %)	78 (37.0 %)	117 (49.2 %)	109 (54.8 %)
Vascular	139 (20.0 %)	12 (26.1 %)	45 (21.3 %)	49 (20.6 %)	33 (16.6 %)
Glomerular	6 (0.9 %)	2 (4.3 %)	2 (0.9 %)	1 (0.4 %)	1 (0.5 %)
Immunologic	8 (1.2 %)	0	3 (1.4 %)	4 (1.7 %)	1 (0.5 %)
Other	60 (8.6 %)	1 (2.2 %)	25 (11.8 %)	21 (8.8 %)	13 (6.5 %)
Unknown	161 (23.2 %)	15 (32.6 %)	58 (27.5 %)	46 (19.3 %)	42 (21.1 %)

BMI: body mass index; CKD: Chronic kidney disease

Muscle force across CKD stages

Muscle force and body composition were different in the early and late stages of CKD (Table 2). Absolute ASM (in kg) was higher in the G5 group compared to the G4, G3 and G1-G2 groups ($p< 0.001$, Cohen's $d= 0.331$; $p< 0.001$, Cohen's $d= 0.329$ and $p= 0.007$, Cohen's $d= 0.445$, respectively). Relative ASM (in %) was higher in G5 compared to the G3 and G4 groups ($p< 0.001$, Cohen's $d= 0.287$ and $p< 0.001$, Cohen's $d= 0.307$, respectively). Absolute FM (in kg) was higher in the G3 group compared to the G1-G2 and G5 groups ($p= 0.018$, Cohen's $d= 0.375$ and $p= 0.003$, Cohen's $d= 0.226$, respectively). Relative FM (in %) was lower in the G5 group compared to the G4 and G3 groups ($p< 0.001$, Cohen's $d= 0.305$ and $p< 0.001$, Cohen's $d= 0.440$). Absolute MVF in Newtons (N) was lower in G4 compared to G5 ($p= 0.034$, Cohen's $d= 0.210$), while relative MVF_{ASM} was higher in G1-G2 compared to G4 and G5 ($p= 0.003$, Cohen's $d= 0.411$ and $p< 0.001$, Cohen's $d= 0.576$, respectively) and MVF_{ASM} in G3 was also higher compared to G4 and G5 ($p= 0.002$, Cohen's $d= 0.270$ and $p< 0.001$, Cohen's $d= 0.408$, respectively).

Table 2 Body composition and handgrip results

		CKD Groups						
	All	G1-G2	G3	G4	G5	Test statistics	p-values	ES
ASM (kg), median [Q1-Q3]	17.8 [13.5-23.1]	16.2 [14.1-20.5]	17.1 [13.1-22.1]	16.7 [13.1-22.3]	19.5 [14.6-24.6]	$\chi^2(3)= 24.051$	**<0.001**	0.022
ASM (%), median [Q1-Q3]	25.6 [20.9-31.0]	26.1 [21.6-31.4]	24.7 [20.5-30.3]	24.6 [20.2-30.1]	27.3 [22.5-32.1]	$\chi^2(3)= 21.255$	**<0.001**	0.019
FM (kg), median [Q1-Q3]	24.2 [17.8-31.1]	21.3 [16.2-29.1]	25.7 [19.3-31.8]	25.0 [17.9-31.7]	22.6 [16.8-29.3]	$\chi^2(3)= 16.725$	**0.001**	0.015
FM (%), median [Q1-Q3]	35.9 [27.8-44.2]	37.0 [26.4-43.9]	38.6 [30.4-46.5]	36.4 [28.7-44.7]	31.9 [25.6-40.9]	$\chi^2(3)= 33.697$	**<0.001**	0.030
MVF (N), median [Q1-Q3]	206 [157-272]	220 [165-267]	206 [161-273]	196 [149-257]	220 [163-283]	$\chi^2(3)= 8.966$	**0.030**	0.008
MVF_{ASM} (a.u.), mean (SD)	1.24 (0.34)	1.36 (0.30)	1.31 (0.34)	1.22 (0.34)	1.18 (0.31)	F(3,1094)= 12.050	**<0.001**	0.032

BMI: body mass index; CKD: chronic kidney disease; ASM; appendicular skeletal muscle mass; FM: fat mass; MVF: maximal voluntary force; MVF_{ASM}: MVF normalized for ASM; ES: effect size; a.u.: arbitrary unit. Statistics comprise F statistics in ANOVA or Kruskal Wallis Chi-2 test (χ^2).

As highlighted in Figure 2, plotting all the observations of the final dataset, a reduction in MVF_{ASM} was first evident in CKD stage G3b and became more severe as CKD increased in severity.

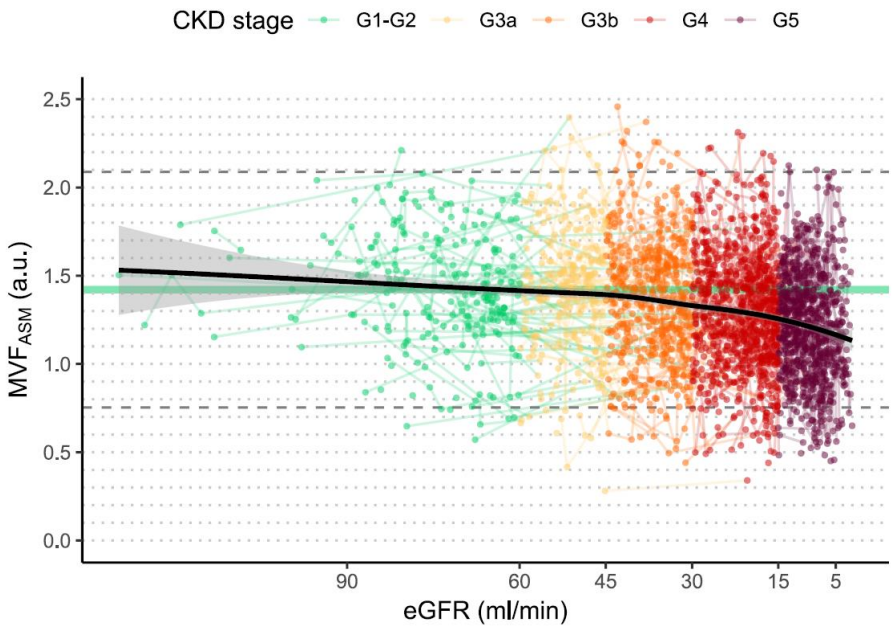

Figure 2 Relation between eGFR and maximal voluntary force normalized for appendicular skeletal muscle mass (MVF_{ASM}), with longitudinal observations connected by lines. The green horizontal line and the grey dashed lines respectively represent the mean MVF_{ASM} of the G1-G2 group with the limits of agreement (±1.96 * standard deviation); the solid black line represents the locally estimated scatterplot smoothing with the 95% confidence interval shown as the shaded grey area. a.u.: arbitrary unit; eGFR: estimated glomerular filtration rate

Effect of CKD stage on the relationship between ASM and MVF

Independently of age, sex, BMI and ASM, each reduction of 10 ml/min in eGFR was associated with a statistically significant reduction in MVF (-1.911 [95%CI: -2.962, -0.860] N, p< 0.001; Model 1, Table 3).

MVF was significantly reduced in the G5 group compared to the G1-G2 group (-8.415 [95%CI: -15.246, -1.584] N, p= 0.016, respectively; Model 2, Table 3). Compared to the CKD G1-G2 group, neither G3 nor G4 was different.

The relationship between MVF and ASM changes across CKD stages, as shown in the significant interactions highlighted in Model 3 (Table 3, Figure 3A). The slopes of this relationship were reduced in CKD G3, G4 and G5 compared to CKD G1-G2 (-1.131 [95%CI: -2.067, -0.195],

p= 0.019; -1.728 [95%CI: -2.809, -0.647], p= 0.002 and -1.744 [95%CI: -2.876, -0.613], p= 0.003, respectively). For the sake of clarity, the predicted values of MVF according to observed ASM and the interaction terms shown in Model 3 were represented in Figure 3B.

Table 3. Handgrip prediction using a linear mixed model

Unit: N		CI 95%		
Fixed effect	Estimate	Lower	Higher	p-value
Model 1				
ASM (kg)	3.830	3.179	4.481	**<0.001**
eGFR (per loss of 10 ml/min)	-1.911	-2.962	-0.860	**<0.001**
Model 2				
ASM (kg)	3.802	3.152	4.452	**<0.001**
CKD stages (G1-G2)	Ref.			
G3	1.764	-3.551	7.139	0.511
G4	-5.509	-11.678	0.660	0.081
G5	-8.415	-15.246	-1.584	**0.016**
Model 3				
ASM (kg) × CKD stage G1-G2	Ref.			
ASM (kg) × CKD stage G3	-1.131	-2.067	-0.195	**0.019**
ASM (kg) × CKD stage G4	-1.728	-2.809	-0.647	**0.002**
ASM (kg) × CKD stage G5	-1.744	-2.876	-0.613	**0.003**

All models were adjusted for age, sex and BMI. Random slopes and intercepts were defined for time and individuals, respectively. Full models can be found in the Supplementary Table 2. Model 1: R^2 for fixed effects only (0.588) and with random effects (0.920); Model 2: R^2 for fixed effects only (0.588) and with random effects (0.921); Model 3: R^2 for fixed effects only (0.593) and with random effects (0.920).

Visually, differences in slope lead to differences in MVF starting from ~20 kg ASM, and are more evident in patients with higher ASM.

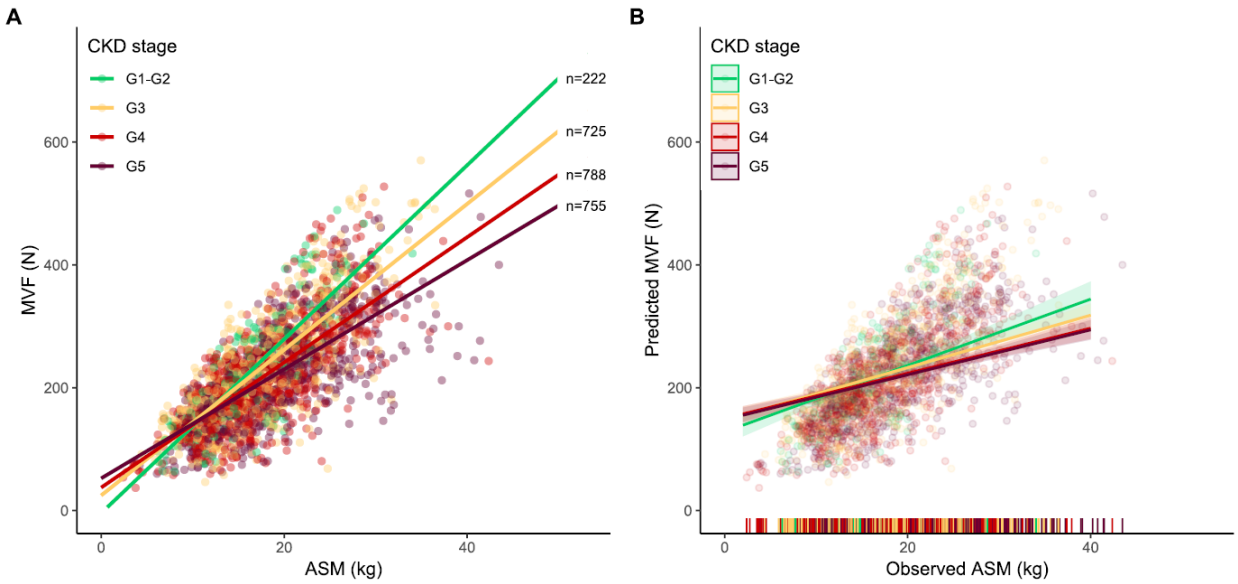

Figure 3 Relationship between (A) maximal voluntary force (MVF) and appendicular skeletal muscle mass (ASM) with the linear fitting with respect to CKD group; and between (B) the predicted MVF derived from a mixed effects model (Model 3) and the observed ASM with solid lines representing the statistical interaction terms according to CKD stage (Table 3).

Prevalence and evolution of sarcopenia in CKD stages

Considering all CKD patients, the prevalence of confirmed sarcopenia was quantified at 27.4% at their first consultation. Furthermore, 16.9% of patients were identified as with probable sarcopenia (i.e., low muscle force only). Consequently, 44.3% of the CKD patients studied had suffered from low muscle force. The prevalence of confirmed sarcopenia was balanced across follow-up ($\chi^2(7)= 1.345$, $p= 0.987$). Finally, no difference in the prevalence of sarcopenia at baseline was noted across CKD stages ($\chi^2(3)= 4.595$, $p= 0.204$).

As visualized in Figure 4A, the incidence of a new diagnosis of sarcopenia during follow-up was similar in all CKD stages (Figure 4B). Conversely, a shift from confirmed sarcopenia to no sarcopenia was observed in the early CKD stages, but was minimal in G4 and G5.7

Prevalence of sarcopenic obesity in CKD stages

Of the 28.7% obese CKD patients at baseline, 10.5% were identified as having had confirmed sarcopenic obesity (Figure 4C). No difference in confirmed sarcopenic obesity was noted during follow-up ($\chi^2(7)= 1.508$, p= 0.982), or across CKD stages at baseline ($\chi^2(3)= 2.631$, p= 0.452).

The prevalence of sarcopenic obesity remained stable during follow-up (Figure 4C). This stability was noted in all CKD stages (Figure 4D). In this context, considering only obese patients (i.e., screened sarcopenic obesity), the incidence of confirmed sarcopenic obesity did not increase in patients in our cohort as CKD became more severe. On the contrary, recovery from sarcopenic obesity (i.e., from confirmed sarcopenic obesity to no sarcopenic obesity) was noted in the G1-G2 group while we observed that only a small number of patients in G4 and G5 went from confirmed sarcopenic obesity to screened sarcopenia (i.e., obesity alone).

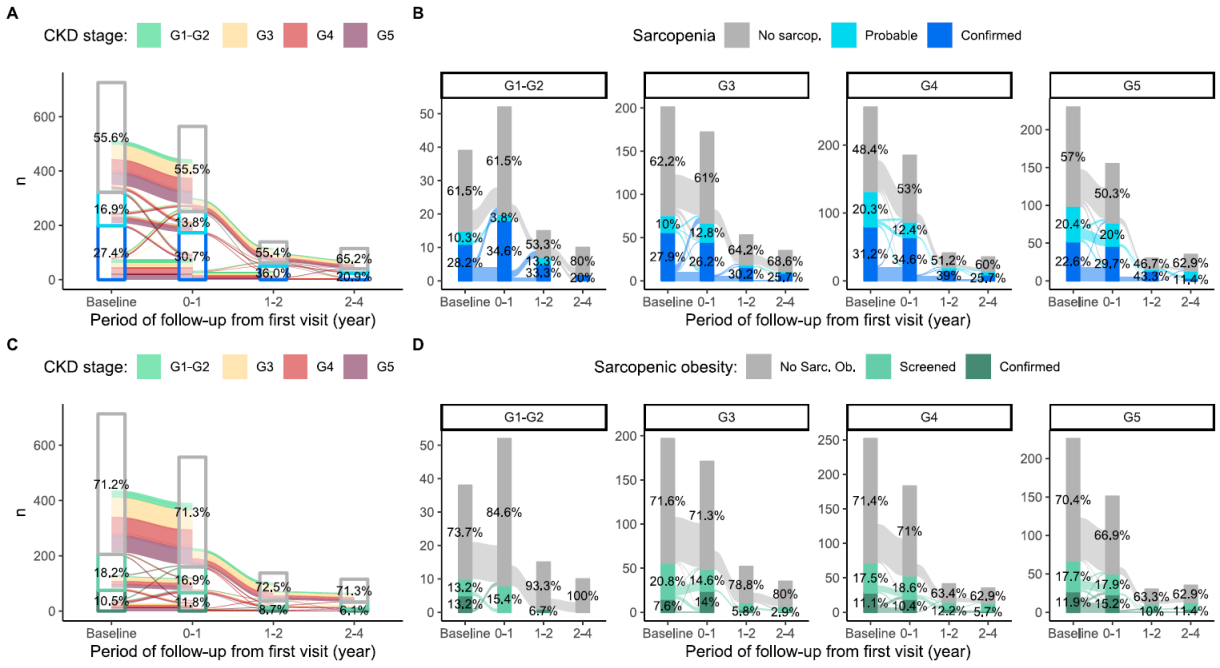

Figure 4 Prevalence of sarcopenia as defined by EWGSOP-2 (A, B) and sarcopenic obesity as defined by ESPEN and EASO (C, D) during different periods of follow-up from baseline (connecting curves, called alluviums, represent individual evolutions in sarcopenic status over time).

Longitudinal analysis

Mean follow-up was 8.3 months (Min: 0.3; Max: 57.0 months) for 332 patient years of follow-up. Regression analysis using individual slopes showed an association between MVF and both eGFR slopes (0.616 [95%CI: 0.095, 1.137] N/year, p= 0.021, Figure 5) and ASM slopes (1.485 [95%CI: 0.310, 2.660] N/year, p= 0.013), adjusted for age, sex and BMI.

Finally, no interaction between eGFR and ASM slopes was noted (p= 0.081). As shown in Figure 5, the relationship between eGFR, MVF and ASM slopes over time remained highly heterogeneous.

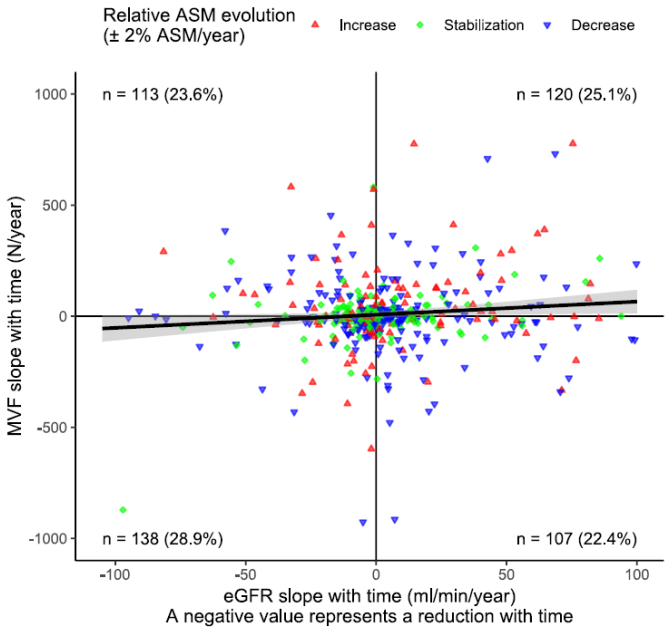

Figure 5 Association between the evolution over time of eGFR and MVF based on ASM evolution categories (increase: >2% ASM/y; decrease: <2% ASM/y, stabilization: patients remaining). The solid black line represents a linear regression (with the 95% confidence interval shown as the shaded grey area). Numbers and percentages in each extremity represent the proportion of individuals in each part of the graphic. MVF: maximal voluntary force; eGFR: estimated glomerular filtration rate; ASM: appendicular skeletal mass

Discussion

The present study, performed using data from a large cohort of CKD patients, was undertaken to shed light on the relationship between muscle mass and muscle force production across CKD stages. The main result is to have demonstrated for the first time that in humans the relationship between muscle mass and muscle force production changes across CKD stages (Figure 3, Table 3). The lower the eGFR, the lower the slope of the relation between MVF and ASM, i.e., for any given muscle mass, muscle force production decreases as CKD progresses.

The second important result, derived from the longitudinal analysis, is that there is a negative independent association between MVF evolution over time and both eGFR and ASM evolution over time, further suggesting that CKD-related progressive impairment in muscle strength is related not just to changes in ASM. However, slopes of eGFR decline and force decrease over time and their relationships are highly heterogeneous, underlining the importance of individualized therapeutic and rehabilitation programs.

The third important result was to describe, in the context of a high prevalence of sarcopenia and sarcopenic obesity in this CKD cohort, that recovery from sarcopenia or sarcopenic obesity is possible. Recovery was most often observed in the early CKD stages, clearly demonstrating that the earlier treatment begins, the more likely it is to be effective.

It is well acknowledged that CKD patients have lower muscle force compared to matched peer controls [4]. A recent study showed an impairment in exercise capacity and a reduction in systemic muscle force production (i.e., upper and lower extremity and respiratory muscles) [29]. The odds of having low muscle force (defined as <30 kg in males and <20 kg in females) increases starting in CKD stage 2 compared to controls and stage 1 patients [21]. However, given the relatively low sample size of our G1-G2 group, we were not able to distinguish between these stages. In a multiple regression model adjusted for several cofounding factors, Lin et al. (2019) found a significant association between eGFR and MVF [20]. Our results are in accordance, confirming this negative association (Table 3) but also identifying a precocious impairment in MVF_{ASM} associated with eGFR decline (Figure 2, Table 3).

Of note, very few previous studies have reported longitudinal data on muscle mass and muscle force in CKD patients. In a 2-year longitudinal follow-up study, Leikis et al. (2006) found a stable thigh muscle cross-sectional area with a reduction of 10 ml/min/1.73m^2 in eGFR (i.e., 35 to 25 ml/min/1.73m^2), but a statistically significant reduction in leg MVF at most of the angular

velocities tested [30]. A similar discrepancy between MVF and ASM in CKD was recently described in a murine model in which the authors identified lower force production (matched in cross-sectional area) in isolated muscle fibres of CKD mice compared to healthy control mice. This impairment was associated with a reduction in myosin heads bound to actin [16]. In humans, the factors that have been considered to explain the loss of muscle force and mass include neurologic impairment [11–13], myosteatosis [14,15], mitochondrial dysfunction [17], inflammation and hormonal imbalance [10]. Further testing is needed to determine whether the results for CKD mice are confirmed in CKD patients.

With regard to the longitudinal effect of CKD on MVF and ASM, our analysis showed a statistically significant association between eGFR evolution and MVF evolution, independently from ASM evolution over time. Despite this finding, as shown in Figure 5, the dispersion of individual slopes suggests that several factors modulate this outcome at the individual level. Overall, the dissociation between the evolution of ASM and MVF in CKD patients points to the need to develop integrative therapeutics, i.e., considering as many neuromuscular function determinants as possible, rather than focusing on muscle mass only. Multifactorial pathogenesis appears to be the basis of high inter-individual heterogeneity (Figure 5), requiring personalized interventions to preserve musculoskeletal health.

To contextualize the third relevant point, the worldwide prevalence of sarcopenia in CKD patients was recently estimated at 20.4% (95% CI: 14.9-26.5%) using the EWGSOP-2 definition [31]. In Mexico, the prevalence of sarcopenia is estimated at 33.3% in CKD patients (95 % CI: 19.7-50.4%), which is in keeping with our results [31]. An increase in the prevalence of sarcopenia across CKD stages is a matter of debate [32]. Previous studies did not find statistically significant differences between CKD stages [31,33,34] or display conflicting results [35]. However, a recent study showed an association between sarcopenia and rapid decline in kidney function [36]. Sarcopenic obesity is associated with poorer health outcomes compared to sarcopenia or obesity alone [37], but this is debated in CKD patients [38]. The prevalence of sarcopenic obesity is estimated at 10-12% in CKD patients [31], and varies widely depending on definition criteria. The prevalence of sarcopenic obesity in our study is in line with the state of the art, ranging from 7.6% to 13.2%, and sarcopenia and sarcopenic obesity do not differ across CKD stages at baseline, as has been shown in other reports [31,33,34].

In our study the differences in slopes leading to different MVF were more marked in patients with higher ASM (evident starting at ~20 kg ASM); this suggests that results may be offset in patients with severe sarcopenia, but also indicates that interventions to preserve force should

be extended to include CKD patients with preserved muscle mass. Our study is one of the few to add information obtained during follow-up; interestingly the incidence of new cases of confirmed sarcopenia or sarcopenic obesity was not different in CKD stages (Figure 4) and recovery from both conditions was observed mainly in the early CKD stages.

Our study has strengths and limits. The large sample size is the most important strength, together with the fact that data were gathered "blindly", i.e. before this study was planned, in the context of routine care. The cohort was almost exclusively composed of Hispanic individuals and our findings require confirmation in ethnically diverse populations. It is to be expected that patients followed up at CEAN centres have better nutritional status and therefore may not be fully representative of the Mexican CKD population. In the context of fragmented and insufficient CKD and nutritional CKD care in Mexico, this is however the largest available cohort in this setting and one of the largest worldwide, and can be taken as an example of a sample of CKD patients on regular renal and diet care.

The handgrip task has limits, since it employs solicitation of the upper limbs only [39]. However, it allows rapid muscle function assessment in daily clinical practice and is less sensitive to the cofounding effect of peripheral neuropathy, which commonly affects the lower limbs of CKD patients with or without diabetes [13]. Furthermore, the test is feasible in the presence of lower-limb amputations, is reproducible and can be considered representative of lower-limb strength, reflecting fatigability and functional capacities. Furthermore, ASM was estimated using bioimpedance. This evaluation can be affected by hydration status [39], which carries the risk of overestimating ASM in the late CKD stages [19], but remains reliable in CKD patients with normal hydration [40].

The effect size of CKD on different markers (e.g., ASM, MVF) may have been underestimated because the control group was composed of CKD G1-G2 patients and they cannot be assimilated to non-CKD controls. However, this may even reinforce interest in the differences between CKD stages.

Lack of biochemical data other than data on kidney function is another limit of the study; in the context of the fragmented Mexican health care system, however, most patients pay for their laboratory tests, and this limits routine controls, while potentially adding a bias if only cases with larger sets of data are selected (patients with altered values are more likely to have had frequent check-ups). Finally, groups were defined using a creatinine-based equation, which may predispose to misclassification. However, quantification of serum cystatin C is expensive, limiting

its use especially in low- and middle-income countries. Once more these limitations could be tested in future research.

Conclusion

In summary, eGFR decrease negatively affects the musculoskeletal system, leading to lower muscle force production for any given level of muscle mass. This reduction is more evident in patients with preserved muscle mass. Over time, a reduction in muscular force is independently associated with a reduction in eGFR and ASM. While the prevalence of sarcopenia and sarcopenic obesity at baseline did not differ across CKD stages, recovery seems to be more frequent in the early CKD stages.

Our results highlight the importance of focusing on force determinants (e.g., myofibrillar protein function, neural activation, metabolic balance) in rehabilitation programs, ideally starting in the early CKD stages, and of including also patients with preserved muscle mass in these programs, in order to improve or preserve musculoskeletal health, and consequently quality of life and survival in CKD patients.

Contributions

Substantial contributions to conception and design: AC and GBP

Acquisition of data: JNH, RUA and AGE

Analysis and interpretation of data: AC, PydM, MT and GBP

Drafting the article or revising it critically for important intellectual content: AC and GBP

Final approval of the version to be published: AC, PydM and GBP

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Data and Supplementary Material Accessibility

The dataset employed and the R-script for statistical analysis can be found in the following repository (https://doi.org/10.17605/OSF.IO/BM9ZD).

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