ASSOCIATION OF ACIDOSIS WITH LOSS OF MUSCLE STRENGTH IN CHRONIC HEMODIALYSIS PATIENTS

https://doi.org/10.56238/sevened2024.039-036

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ABSTRACT

Objective: To analyze the effect of acidosis, by means of bicarbonate levels, on muscle strength (FM) in patients with renal failure undergoing hemodialysis (HD). **Methodology:** This is a cross-sectional study in patients undergoing chronic HD at a dialysis clinic in Joinville, Santa Catarina, between March and July 2023. All patients aged between 18 and 65 years and with a dialysis duration of more than 3 months were included in the study. The values of bicarbonate, a variable of main interest, were analyzed by means of blood gas analysis. FM, the outcome variable, was evaluated using the *Sit-to-Stand test* and upper limb dynamometry. Clinical and laboratory variables and dialysis adequacy were also considered. The effect of the variable of interest on the outcome was evaluated using multivariate logistic regression in an explanatory model. **Results:** Of the 90 patients, the mean age was 48.8 years, and 62.2% were male. Systemic arterial hypertension was found in 84.4% of the sample, followed by diabetes (24.4%) and stroke in 21.1%. The presence of loss of strength was found in 24 (26.7%) patients. There was no difference in the median bicarbonate values between patients with or without loss of strength. Bicarbonate values were not associated with a higher risk of strength loss (crude OR = 0.94; 95% CI 0.78-1.13; p= 0.505). Even after adjusting for other confounding variables, bicarbonate levels were not associated with the outcome studied (adjusted OR=0.83; 95% CI 0.66-1.04; p=0.0012). **Conclusion:** In the sample studied, acidosis, verified by bicarbonate values, was not associated with FM loss.

Keywords: Chronic kidney disease. Muscle Strength. Bicarbonate. Metabolic acidosis.

INTRODUCTION

Chronic kidney disease (CKD) has been consolidated as one of the main public health concerns in Brazil(1). According to the last census of the Brazilian Society of Nephrology (SBN) in 2021, about 153,831 patients were undergoing treatment, of which 95.3% are undergoing hemodialysis (HD)(1). Sarcopenia has been found in approximately 13 to 33% of this population, contributing to higher morbidity and mortality (3,4). Among the mechanisms associated with sarcopenia, acidosis has still been little studied in HD patients.

Sarcopenia is characterized by the progressive loss of muscle mass and strength, with direct implications for the functionality and quality of life of dialysis patients(3,4). Although sarcopenia is often found in patients undergoing chronic HD, it is not yet consistently evaluated in HD services. According to a study involving 62 dialysis centers in Brazil, only 23 (37%) routinely evaluated the presence of sarcopenia(2).

Several factors contribute to the development of sarcopenia in patients undergoing HD, including reduced physical activity, anorexia, loss of nutrients during HD, accumulation of uremic toxins, vitamin D deficiency and the use of multiple drugs, such as oral hypoglycemic agents and antihypertensive drugs(3).

In addition, chronic metabolic acidosis, a common complication among patients with renal failure undergoing hemodialysis, may also be related to the presence of sarcopenia in this population(4). Although acidosis is a common situation among patients with renal failure, and not always completely corrected in dialysis therapy(5), it is believed that its presence may favor the occurrence of sarcopenia due to increased muscle catabolism, reduced protein synthesis and activation of pro-inflammatory pathways(15,16). However, few studies have focused on the role of acidosis in the presence of sarcopenia among HD patients in Brazil. The objective of this article was to investigate the impact of metabolic acidosis, as assessed by bicarbonate levels, on FM in patients with chronic renal failure undergoing hemodialysis.

METHOD

This is an observational, cross-sectional, descriptive and analytical study consisting of a non-probabilistic sample of 102 patients with renal failure on HD from a dialysis clinic in Joinville/Santa Catarina, Brazil. During March to July 2023, all patients on chronic hemodialysis therapy, aged between 18 and 65 years, HD therapy time equal to or greater than 3 months, and without hospital stay in the last 30 days were included in the study. Patients with residual diuresis >500ml/24 hours or with interdialytic weight gain (IPG) < 1% were excluded to allow the measurement of the simplified creatinine index (7). Patients who

changed their dialysis method during the study, those with physical limitations or those with limb amputation that made it impossible to perform the muscle assessment tests were also excluded. In addition, those with cognitive alterations or a previous diagnosis of dementia documented by the institution itself were excluded. All participants completed the informed consent form and the study was approved by the ethics committee of the University of the Joinville Region (CAAE nº 65523922.9.0000.5366).

VARIABLES COLLECTED

The variables considered were gender, age, comorbidities (hypertension, diabetes, stroke), type of vascular access, HD time, and body mass index (BMI). The mean of the last two values of dialysis adequacy (Kt/V), phosphorus, albumin, parathyroid hormone (PTH), hemoglobin, and interdialytic weight gain (IGG) for the current and previous month of the study was also considered. The simplified creatinine index (SCI) was evaluated as a marker of muscle mass, defined as a normalized rate of endogenous creatinine production, considering residual and dialyzed renal clearance, using the Canaud formula[a] ; (8). The lean tissue index (LTI) was estimated using the formula of Canaud et al[b]*;* (9). C-reactive protein (CRP) and blood gas analysis to assess bicarbonate levels were performed on blood samples collected at the beginning of the HD session, directly from the vascular access for the dialysis procedure, and were subsequently processed in a support laboratory in the same city. Regarding the evaluation of inflammatory markers, CRP measurement was conducted using the MULTIGENT PCR assay, a latex immunoassay designed for the accurate and reproducible measurement of CRP blood levels in serum and plasma. In addition, the bicarbonate dosage was performed using the GEM Premier 3000 system, which allows the measurement of blood bicarbonate by means of blood gas analysis. To assess the strength of the upper limbs, the Handgrip Strength (HGS), an analog Jamar hand-held dynamometer instrument was used. The evaluation was carried out through the measurement in kilogram (maximum of 100 kilos) force kgf, in a metallic structure and anatomical handle, easy to read with the pointer remaining at its maximum value during the test. The patient in a sitting position pulled the handle or lever of the dynamometer and kept it still for approximately two seconds, exerting only force. This process was carried out 3 times, with the highest result being recorded. The values considered as low FM were evaluated based on gender and age group, according to values obtained from a population without dialysis CKD in Brazil (12). To assess lower limb muscle strength (LLLL), the *Sit-to-stand test* (TSS) was used (10,11). To perform the TSS, the patient was initially seated in a chair without support arms, and for 30 seconds he had to sit and stand up without any

support of the arms, and the number of repetitions completed was considered. Both tests were performed before the HD session.

STATISTICAL ANALYSIS[1]

Categorical variables are presented by their frequency and percentage and numerical variables by their mean and standard deviation or median and interquartile variation. The chi-square test was used to compare categorical variables, and the *Student*'s *t-test* or *Mann-Whintey* test was used to compare the means of the quantitative variables, after verifying their normality using the Kolmogorov-Smirnov test. Altered dynamometry values were defined as those with measurements below the 50th percentile adjusted for age and sex, according to the reference population(10,12). The presence of altered strength was defined as all patients who had altered Dynamometry values and the sit-stand test in 30 seconds lower than the median found in the sample by sex (<10 for women or <11 for men). The means and frequencies of the variables analyzed between individuals were compared in relation to the presence or absence of strength loss using the *Student*'s t-test or Man-Whitney *test* to compare numerical variables and the chi-square test for categorical variables. We sought to analyze the association of bicarbonate values for the occurrence of altered force through an explanatory multivariate model. Thus, the crude odds ratio of bicarbonate values for the occurrence of force was reduced and adjusted for other potentially confounding variables was verified through Logistic Regression. All variables that modified the effect of the main variable of interest (bicarbonate) by 5% or more in the bivariate analysis were included in a final multivariate model, keeping sex and age fixed. A p< value of 0.05 was considered significant. The analyses were performed using the IBM SPSS statistical software, version 27.

RESULTS

From the initial total sample of 102 patients, 8 patients with residual diuresis >500ml or with RGI < 1% and 4 patients who changed dialysis methods before complying with the

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[1] Calculation of SCI

[a] SCI was calculated using the Canaud formula

SCI (mg/kg/day) = 16:21 + 1:12 * [1 if male; 0 if female] – 0:06 *age (years) – 0:08 * spKt/V urea + 0:009 * pre – dialysis SCr (lmol/L)

[b] LTI was estimated using the formula by Canaud et al.

Estimated LTI (mg/m²) = (SCI + Post HD weight (kg) * 0:029 +7:38)/(Body height (m)) ²

protocol were excluded from the study. The final sample of 90 patients had a mean age of 48.8 years, with 56 (62.2%) males, with systemic arterial hypertension (84.4%) and diabetes (24.4%) being the most prevalent comorbidities. The main vascular access for HD was the arteriovenous fistula in 78.9% of the sample. The median time on HD was 63.1 months, with an interquartile range (IQR) of 25.0/113.7 months. The presence of altered strength of both upper limb and lower limb was observed in 26.7% of the total sample. Other characteristics of the total sample are described in Table 1.

Table 1 - General Characteristics of the Sample

	Total Sample n=90	
Age, years; mean (SD)	48,8	11,5
Gender, male; total (%)	56	62,2
Comorbidities, yes; total (%)		
Diabetes	22	24,4
Hypertension	76	84,4
STROKE	19	21,1
Type of Vascular Access; Total (%)		
Fistula	71	78,9
Catheter	19	21,1
Time in HD, months; median (VIQ)	63,1	25,0/113,7
KT/V; Mean (SD)	1,4	0,3
Creatinine mg/dL; mean (SD)	10,7	2,9
Phosphorus, mg/dL; median (VIQ)	5,5	4,3/6,6
Albumin, mg/dL; mean (SD)	4,1	0,4
PTH, pg/ml; median (VIQ)	403,2	199,7/836,0
Hemoglobin, g/dL, mean (SD)	11,2	1,6
CRP-US, mg/L; median (VIQ)	0,46	0,2/1,4
Bicarbonate, mEq/L; Average (SD)	21,0	2,5
Dynamometry < 50th percentile, yes	63	70,0
30s SST, median (VIQ)	11	8,2/14,0
Men	11	10/14
Women	10	6,2/13
Changed strength, yes; total (%)	24	26,7
GPI, %; median (VIQ)	3,8	1,2
SCI, mg/kg/day; unit; mean (SD)	14,0	0,8
LTI, mg/m2; mean (SD)	16,2	2,6
BMI, kg/m2; median (VIQ)	23,6	21,6/28,4

SD=standard deviation; VIQ= interquartile variation (25/75th percentile); HD=hemodialysis; PTH=parathyroid hormone; hs-CRP = ultrasensitive C-reactive protein; 30s SST = sit-to-stand test; RG=interdialytic weight gain; SCI=simplified creatinine *index*; LTI= lean *tissue index;* BMI = body mass index.

The characteristics of the sample of patients without loss of strength (PFS) and with loss of strength (PFC) are shown in Table 2. PFS patients were younger (median age 48 years, IQR 41.8/55.0) compared to PFC patients (median 55.5 years, IQR 44.7/63.7; p=0.012). A higher prevalence of SAH was observed in SPF patients compared to PFC patients (89.4% versus 70.8%; p=0.047). In addition, patients with a lower Kt/v index ((Kt/v < 1.31, SD 0.27) showed a higher propensity for PF compared to those with a higher index (Kt/v≥ 1.48, SD 1.29), with a statistically significant difference (p=0.006).

Albumin levels were significantly different between the groups, with lower albumin values in the PFC group compared to the SPF group (4.00 g/dL versus 4.20 g/dL; p = 0.006). The RGI index was also higher in the PFS group, compared to the PFC group (median of 3.94 versus 3.46; p = 0.040). Other comparative characteristics between the SPF and CPF groups are summarized in Table 2.

Table 2 - Characteristics of the sample by loss of strength (30s SST < median by sex [10 women and 11 men] and dynamometry below the median by sex and age)

	No loss of strength n=66 (73.3%)		With loss of strength n=24 (26.7%)		p-value
Age, years; median(VIQ)	48,00	41,75/55,00	55,50	44,75/63,75	0,012
Gender, male; total (%)	38	57,6	18	75,0	0,207
Comorbidities, yes; total (%)					
Diabetes	15	22,7	7	29,2	0,725
Hypertension	59	89,4	17	70,8	0,047
STROKE	15	22,7	4	16,7	0,771
Type of Vascular Access; Total (%)					0,771
Fistula	51	77,3	20	83,3	
Catheter	15	22,7	4	16,7	
Time in HD, months; median (VIQ)	57,38	24,12/112,67	66,42	31,22/125,55	0,625
KT/V; Mean (SD)	1,48	0,29	1,31	0,27	0,006
Creatinine mg/dL; mean (SD)	10,88	2,88	10,37	2,92	0,235
Phosphorus, mg/dL; median (VIQ)	5,30	4,30/6,42	5,90	4,60/7,12	0,262
Albumin, mg/dL; mean (SD)	4,20	4,00/4,40	4,00	3,70/4,10	0,006
PTH, pg/ml; median (VIQ)	403,25	198,32/804,05	359,00	196,80/1353,02	0,629
Hemoglobin, g/dL, mean (SD)	11,33	1,49	10,85	1,82	0,125
CRP-US, mg/L; median (VIQ)	0,42	0,19/1,14	0,57	0,25/2,00	0,290
Bicarbonate, mEq/L; Average (SD)	21,11	2,53	20,71	2,51	0,255
GPI, %; median (VIQ)	3,94	1,20	3,46	1,09	0,040
SCI, mg/kg/day; unit; mean (SD)	14,00	0,86	13,87	0,77	0,254
LTI, mg/m2; mean (SD)	15,45	14,21/17,87	16,35	14,56/17,90	0,584
BMI, kg/m2; median (VIQ)	23,59	21,56/28,22	24,14	21,35/29,36	0,722

30s SST = sit-to-stand test; SD=standard deviation; VIQ= interquartile variation (25/75th percentile); HD=hemodialysis; PTH=parathyroid hormone; hs-CRP = ultrasensitive C-reactive protein; RG=interdialytic weight gain; SCI=simplified creatinine *index*; LTI= lean *tissue index;* BMI = body mass index.

Table 3 shows the crude and bivariately adjusted odds ratio between bicarbonate levels for the occurrence of strength loss. Bicarbonate values were not associated with a higher chance of brute strength loss (OR=0.94; 95% CI 0.79-1.13) or after bivariate adjustment for other variables.

Table 3 - Crude and adjusted odds ratio between bicarbonate levels for the occurrence of strength loss

	OR	95% CI	p-value
Bicarbonate, mEq/L, per unit of increase	0,94	0,78-1,13	0,505
Tuned for:			
Age, years, per unit increase	0,91	0,74-1,12	0,367
Gender, male vs. female	0,92	0,75-1,11	0,379
Time in HD, months, per unit of increase	0,94	0,78-1,14	0,520
Access, arteriovenous fistula vs. catheter	0,93	0,76-1,12	0,443
Kt/V, per unit of increase	0,89	0,73-1,09	0,891

Diabetes, yes	0,93	0,77-1,13	0,468
Systemic Arterial Hypertension, yes	0,95	0,78-1,16	0,645
Stroke, yes	0,95	0,78-1,15	0,573
Phosphorus, per unit of magnification	0,94	0,78-1.13	0,507
PTH, per unit of augmentation	0,95	0,78-1,15	0,581
Albumin, per unit of increase	0,96	0,78-1,17	0,672
Hemoglobin, per unit increase	0,93	0,76-1,12	0,926
PCR-US, per unit of magnification	0,94	0,77-1,13	0,495
GPI (%), per unit of increase	0,89	0,73-1,09	0,276
SCI, per unit of increase	0,94	0,78-1,13	0,514
LTI, per unit of increase	0,93	0,77-1,13	0,475
BMI, per unit of magnification	0,93	0,77-1.13	0,485

HD=hemodialysis; PTH=parathyroid hormone; hs-CRP = ultrasensitive C-reactive protein; RG=interdialytic weight gain; SCI=simplified creatinine *index*; LTI= lean *tissue index;* BMI = body mass index

Table 4 presents the final multivariate model, including the values of Kt/v and GPI, which modified the effect of the main variable by 5% or more, in addition to sex and age. After adjusting for the other variables, bicarbonate values were not associated with FM loss (OR=1.05; 95% CI 0.99-1.11).

Table 4 - Multivariate analysis of the association between bicarbonate levels for the occurrence of strength loss by Logistic Regression

	OR	95% CI	p-value
Age, years, per unit increase	1,05	0,99-1,11	0,680
Gender, male vs. female	1,81	0,57-5,75	0,317
Kt/V, per unit of increase	0,16	0,02-1,21	0,076
GPI (%), per unit of increase	0,74	0,46-1,22	0,239
Bicarbonate, mEq/L, per unit of increase	0,83	0,66-1,04	0,112

RG=interdialytic weight gain

DISCUSSION

This study sought to evaluate the effect of acidosis, through bicarbonate levels, in patients with renal failure undergoing HD on FM. However, in the sample tested, the levels of acidosis did not demonstrate any significant association with the loss of FM(13).

About a quarter of the patients had loss of strength, and these patients were older and had lower albumin values. It was also observed that the PFS group was larger when compared to the PFC, when associated with SAH as a pathology. Strategies such as preserving or minimizing protein loss, adequate management of fluid intake, and dietary counseling are essential to mitigate these risks and improve clinical outcomes(14).

Although the correction of acidosis is associated with benefits, such as the reduction of protein catabolism and the improvement of nutritional status, with the potential to minimize muscle loss, our study did not identify this significant association(15). Some experimental studies carried out in developed animals show that metabolic acidosis plays a

significant role in the progression of CKD, contributing to metabolic and structural alterations that aggravate functional impairment(16,17).

This study is in agreement with other studies that also did not observe significant differences (15,18). These findings suggest that, in patients with CKD undergoing adequate hemodialysis, the correction of metabolic acidosis, reflected by normal bicarbonate values, can contribute to reduce muscle mass loss, but without a statistically evident relationship(19,20). These positive effects, by preserving kidney function and improving nutritional and metabolic parameters, help protect against muscle atrophy. In addition, other studies indicate that FM loss or sarcopenia are directly related to metabolic acidosis, which is aggravated in patients with CKD(21,22).

Some limitations and weaknesses of this study may be related to the method used to assess FM in patients, such as the handgrip test and the TSS, which could be specifically targeted to sarcopenia, also limiting an age range. This could be associated with other outcomes. Although the main hypothesis of this study has not been confirmed, our study found a relevant prevalence of patients with PFC verified by simple tests and with association with nutritional markers and adequacy of dialysis therapy. Thus, further studies are needed to deepen the findings found and their association with acidosis in these patients.

CONCLUSION

Although bicarbonate values did not show an association with loss of strength, a relevant prevalence of FBC patients was found in the sample studied. In addition, our findings suggest that factors related to dialysis adequacy may have some influence on this association between acidosis and loss of FM. Considering that the control of acidosis has been pointed out as one of the important factors in reducing the risk of muscle mass loss in patients with renal failure on HD, further studies are needed to deepen our findings.

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