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Correlation between functional capacity and oxidative stress and inflammation in hemodialysis patients

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ABSTRACT

Introduction: Patients with chronic kidney disease (CKD) may present impaired functional capacity due to peripheral muscle involvement. Oxidative stress and inflammation are probably involved in this pathophysiology. This study aimed to evaluate the association between functional capacity and biomarkers of oxidative stress as well as biomarkers of inflammation in patients under chronic hemodialysis therapy.
Method: Cross-sectional study including 41 patients from a single hemodialysis center. Functional capacity was assessed through the 6-min walk test (6MWT). The assessed blood biomarkers were: malondialdehyde (MDA) (oxidative stress, TBARS method) and angiopoietin-2 (Ang-2) (inflammation, ELISA). The influence of gender on impairment of functional capacity was further explored.
Results: There was an inversely proportional correlation between the 6MWD and MDA (r = -,322 and p = 0.040) and Ang-2 (r = -, 376 and p = 0.016) values. 6MWD was 370.9 ± 101.2 m and 391.4 ± 108.2 m in women and men, respectively (p < 0.001), which means 29.3% and 34.3% reduction of the expected values for healthy individuals from the same age range.
Conclusion: Patients with CKD under hemodialysis, regardless of gender, presented impaired performance in 6MWT and this impairment was associated with oxidative stress and inflammation.

1. Introduction

Chronic kidney disease (CKD) is defined as the presence of abnormalities in the kidney structure and/or function lasting longer than three months (KDIGO, 2013). It is a chronic disease that results in progressive and irreversible lost of kidney excretory and metabolic functions (Yilmaz et al., 2016; Zhenzhen et al., 2017).

Patients with advanced-stages CKD may have reduced functional capacity, defined as the ability to perform basic activities of daily living (ADL) (WHO, 2003). This results from peripheral muscle and pulmonary function impairment, which has multifactorial cause: uremic myopathy, chest deformities and bone demineralization due to renal osteodystrophy, anemia and malnutrition, endothelial injury, in addition to muscle disuse caused by physical inactivity (Sietsema et al., 2002; Painter, 2009). Oxidative stress and inflammatory injury to proteins and lipids also appears to contribute to the damage in the long term, resulting in decreased functional capacity of skeletal muscles, decreased muscle tone and trophism (Karacan et al., 2006; Ulubay et al., 2006). Functional capacity can be measured by the 6-min walking test (6MWT), a

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simple, low cost, and widely used tool (Solway et al., 2001; Rosa, 2003; Iwama et al., 2009; Cury et al., 2010).

There are no available robust data correlating functional capacity of CKD patients under chronic hemodialysis with blood biomarkers of oxidative stress and inflammation. Moreover, there is no robust evidence showing gender differences on the impairment of functional capacity in these patients. Men have physiological advantages in functional performance, justified by higher testosterone levels, higher number of red blood cells (greater effectiveness in transporting oxygen to the muscles), higher basal metabolism, lower body fat content and greater overall cross-sectional muscle area. This physiological advantage results in greater capacity to generate muscle strength and physical endurance (Monteiro, 1997; Leitão et al., 2000; Watkins, 2008; Thiago et al., 2016). Therefore, functional capacity impairment in men with CKD would be expected to be lower than in women There is only few studies addressing the functional capacity comparing genders in this context.

This study aimed to evaluate functional capacity and its association with blood biomarkers of oxidative stress and inflammation in patients with CKD under chronic hemodialysis therapy. Additionally, we explored the differences between genders in this context.

2. Methods

2.1. Study design and population

This was a cross-sectional pilot study including stage 5 CKD patients under chronic hemodialysis at a single center located in the Northeast region of Brazil, between 2015 and 2017.

We included CKD patients of both genders; aged between 30 and 70 years-old; with all CKD etiologies; with estimated glomerular filtration rate <15 mL/min/1.73 m^2 (Stage 5) under chronic hemodialysis (≥three months); and with sedentary behavior (according to the definition below). The exclusion criteria were as follows: cognitive and physical competence to perform the 6MWT (according to the judgment of the research team); chronic pulmonary diseases with known impaired pulmonary function; acute myocardial occurred in the last three months; decompensated cardiopathy (according to the judgment of the dialysis assistant physician); active infection under treatment with antibiotics or waiting treatment; patients participating or who participated in studies involving physical activity in the last six months.

Physical activity was considered as any movement of skeletal muscles resulting in energy expenditure greater than those produced during resting (Caspersen et al., 1985). Individuals who did not practice physical activities beyond those required in their work or those who practiced light physical activities during less than 150 min per week were considered sedentary (Haskell et al., 2007). As only sedentary individuals were included, physical activity levels were not recorded.

The study was performed in accordance with the Declaration of Helsinki, and was approved by the Local Ethics Committee (number 1,113,278).

2.2. Study procedures

Before dialysis session, patients were randomly selected and, provided they met the inclusion/exclusion criteria, they were invited to participate. After consent, blood samples were collected and patients underwent the 6MWT test.

Functional capacity was assessed by 6MWT (ENRIGHT, 2003). The 6MWT test was performed in accordance with American Thoracic Society recommendations (ATS, 2002), 1 h before the dialysis session. It was conducted on a 30-m flat track, and patients were instructed to walk from one end to the other as fast as possible. During the test, patients were encouraged with standardized sentences at every minute. Distance walked during 6 min (in meters, m) was defined as the 6-min walking distance (6MWD). The 6MWT work was defined as the body weight (in kg) × 6MWD (in m) (CARTER et al., 2003).

The distance predicted for each individual according to age and gender was calculated using the formula 622.461 - (1.846 x age) + (61.503 × 1/0), where 1 = male and 0 = female (Karacan et al., 2006).

Aiming to monitor the physical effort during the 6MWT, blood pressure, heart rate, respiratory rate, oxygen saturation, and Modified Borg scale (BORG, 1998) were assessed at baseline and at the sixth minute. The Modified Borg scale is numbered from zero to ten (0–10), where 0 is absence of symptoms of fatigue and 10 is the maximum symptom. The patients were advised to stop the test at any sign of discomfort. All evaluations were performed by previously trained professionals.

2.3. Blood biomarkers

Blood samples for biomarkers analysis were collected 10–30 min before the hemodialysis session. The samples were collected in adequate tubes for serum isolation and then serum samples were aliquoted and stored at −80 °C until the day of analyses.

Malondialdehyde (MDA) quantification was based on its reaction with thiobarbituric acid (TBARS). During this reaction, two TBARS molecules react stoichiometrically with one MDA molecule, forming a rose-colored chromophore that has maximum absorbance in an acidic solution at 535–560 nm (Draper; Hadley, 1990).

Serum angiopoietin-2 (Ang-2) was quantified through an enzyme-linked immunosorbent assay (ELISA), using commercial kits and according to the manufacturer's instructions (Duoset DY623, R&D Systems, Inc. MN, USA). The assay range of this kit was 93.8 to 6,000 pg/mL.

2.4. Statistical analysis

Normally distributed continuous variables were summarized as mean ± standard deviation and compared using Student's *t*-test. Non-normally distributed variables were expressed by median and interquartile range (IQR) and compared using Mann-Whitney test. Normal distribution was tested using Shapiro-Wilk test. Categorical variables were summarized as frequencies and proportions and compared by Fisher's exact or χ^2 tests. Pearson's Correlation Coefficient (r) was used to verify the correlations between the variables of parametric measurements.

Data were analyzed using the Statistical Package for the Social Sciences, version 20.0, and p values < 5% were considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics

Eighty-two patients were considered eligible. Of these, 38 refused to participate in the study and 3 were hospitalized at the time of evaluation. Thus, the analyzed sample consisted of 41 patients.

Except for higher percentage of prior smoking among men (50 vs. 23.5%, p = 0.005), there were no differences between groups (Table 1).

3.2. Functional capacity and its correlation with oxidative stress and Angiopoietin-2 levels

A statistically significant inverse correlation was observed between the distance walked and MDA (r = −0.322, p = 0.040) and Ang-2 blood biomarkers (r = −0.376, p = 0.016) (Figs. 1 and 2).

3.3. Gender performance on 6MWT and correlation with biomarkers

There were no differences between groups in Borg scale at baseline (median 1, IQR 0–2.5, p = 0.134), and at the sixth minute (median 2, IQR 0.25–4.5, p = 0.584).

The mean 6MWD in women and men groups were 370.9 ± 101.2 m and 391.4 ± 108.2 m, respectively (p = 0.543). The 6MWT work was higher in men (30,916.4 ± 9,483.7 kg m, vs. 23,635.7 ± 6,763.1 kg m, p = 0.001). Both groups presented lower performance than expected for age: 29.3% of predicted for women (p < 0.001) and 34.3% for men (p < 0.001) (Fig. 3), but the performance loss was similar between groups (p = 0.380) (Fig. 3).

In women group, 6MWD was inversely correlated with Ang-2 (r = −0.550, p = 0.022), but not with MDA (r = −0.419, p = 0.094). In men group, no correlation was observed between 6MWD and Ang-2 (r = −0.177, p = 0.407) or MDA (r = −0.292, p = 0.166), but outliers were detected, which may have interfered in the analysis. After excluding outliers, 6MWD was also negatively correlated with Ang-2 in men group (1 patient excluded, r = −0.610, p = 0.002) and no significant correlation was observed with MDA (2 patients excluded, r = 0.379, p = 0.082).

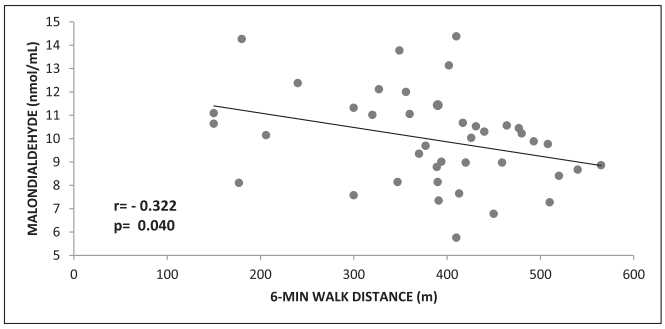

Fig. 1. Correlation between Malondialdehyde levels and 6-min walk distance. Pearson's correlation coefficient (r).

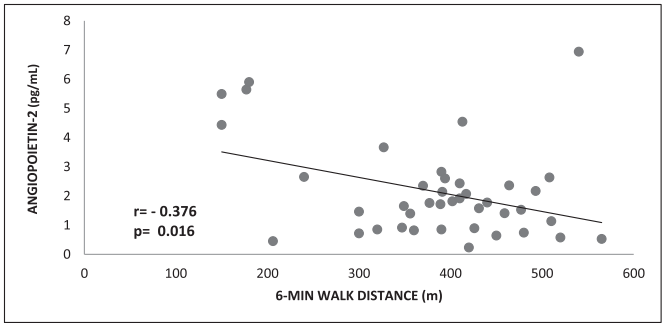

Fig. 2. Correlation between Angiopoietin-2 and 6-min walk distance. Pearson's correlation coefficient (r).

4. Discussion

This study demonstrated that patients with stage 5 CKD under hemodialysis present lower functional capacity than that predicted for healthy individuals. The observed inverse correlation between 6MWD and MDA and Ang-2 might suggest that oxidative stress and inflammation are possibly involved in the pathogenesis of muscular and pulmonary damage. However, our study was not designed to access causality. Also, non-tested variables can affect these results. Both genders presented inferior functional capacity performance, without differences in the magnitude of the impairment.

There are consistent evidence showing that patients with CKD have weakness of peripheral and respiratory muscles and low cardiopulmonary fitness. These disorders result in negative impact on functional capacity, limitation of daily life activities and reduced quality of life (GESUALDO et al., 2017; IWAMA et al., 2009; ULUBAY et al., 2006). The impairment in functional capacity is multifactorial. Volume overload, anemia, sarcopenia, extraosseous calcification, and metabolic disorders are some of the factors involved (Karacan et al., 2006; Tavana; Mirzaei, 2016).

Oxidative stress and inflammation also probably have a significant role in the impairment of functional capacity among CKD patients. Damage to muscle cells is a result of proteolysis and apoptosis (Cavalcante et al., 2008; Cunha et al., 2009; Medeiros et al., 2002). We explore this hypothesis using MDA e Ang-2 as biomarkers.

Table 1
Clinical and demographic characteristics.

	Total N = 41	Men N = 24	Women N = 17	*p* value
Age (years)	50.0 ± 13.4	47.8 ± 12.5	53.0 ± 14.4	0.219
BMI (kg/m^2)	28.2 ± 6.1	28.5 ± 6.3	27.7 ± 6.1	0.681
Time on HD (months)	24 (36–14)	27 (36–16)	14 (28–7)	0.126
Diabetes, n (%)	11 (26.8)	06 (25)	05 (29.4)	0.235
SAH, n (%)	41 (100)	24 (100)	17 (100)	0.130
Smoking, n (%)				
Current	0 (0)	0 (0)	0 (0)	NA
Past	16 (39)	12 (50)	04 (23.5)	0.005
Causes of CKD, n (%)				0.889
Glomerulonephritis	24 (58.6)	14 (58.3)	10 (58.8)	
Diabetes	11 (26.8)	06 (25)	05 (29.4)	
SAH	06 (14.6)	04 (16.7)	02 (11.8)	
MDA at baseline (ng/ml)	10.0 (8.5 −11.1)	9.8 ± 1.8	10.2 ± 2.2	0.761
Ang-2 at baseline (ng/ml)	2.2 ± 1.6	2.0 ± 1.6	2.4 ± 1.7	0.412

BMI = body mass index; HD = Hemodialysis; CKD = chronic kidney disease; SAH = systemic arterial hypertension; NA: not applicable; MDA = Malondialdehyde; Ang-2 = Angiopoietin-2.

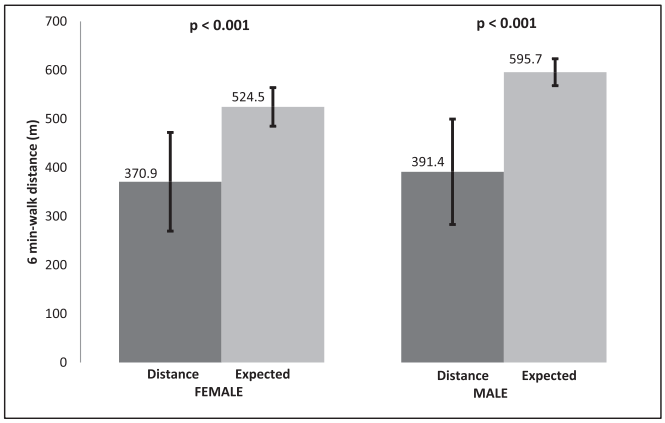

Fig. 3. Predicted and executed 6-min walk distance in patients with Stage % CKD under hemodialysis, comparing the performance of genders.

Ang-2 is a glycoprotein with approximately 70 kDa, expressed in endothelial cells, vascular smooth muscle cells, and pulmonary epithelial cells. It is secreted in blood during angiogenesis, inflammation and cell stress processes. It is a natural angiopoietin-1 (Ang-1) antagonist, causing cell death, aberrant neovascularization and endothelial abnormalities (FAGIANI & CHRISTOFORI, 2012). Ang-2 production results in pathological angiogenic activity through competition for the same Ang-1 receptor (Tie2), expressed at vascular remodeling sites. The inhibition of Ang-1 results in the minimization of its anti-inflammatory effect, causing a decrease in vascular stability and maturation. The chronic inflammation resulting from this dispute results in pathological vascular angiogenesis (Cavalcante et al., 2008). Moreover, Ang-2 has recently been identified as a prognostic biomarker of cardiovascular events and mortality in patients with CKD and in those with subclinical cardiovascular disease (Monteiro, 1997; Thiago et al., 2016; WATKINS, 2008).

Lipid peroxidation is a reaction resulting in the production of free radicals and harmful aldehydes, such as MDA, propanodial, and 4-hydroxynonenal (4-HNE). MDA is a useful biomarker reflecting lipid and protein peroxidation mediated by free radicals. It is an important indicator of tissue damage induced by oxidative stress (Grotta et al., 2008; Marakala et al., 2012).

Almost one third of patients in our study were diabetic and hyperglycemia is associated with high oxidative stress level, result of protein glycosylation, glucose auto-oxidation and also through by polyol pathway (Dogra et al., 2001; Brownlee, 2001; Thomas et al., 2002). A study comparing functional capacity and oxidative stress biomarkers in diabetic versus non-diabetic stage 5 CKD patients is being conducted by our group. Other factors that can contribute to oxidative stress and influence functional capacity are advanced age and sedentary behavior, as previously demonstrated by other studies (Trentini et al., 2004; Hung et al., 2009; Cury et al., 2010). However, testing the effect of these variables was beyond the objectives of this study.

The consequences of reduced functional capacity can be noticed in studies evaluating the quality of life in CKD patients, affecting work, social and leisure activities. Physical inactivity feeds back the impairment of functional capacity (Trentini et al., 2004). Training programs for peripheral and/or respiratory muscle strengthening and intradialytic physical exercises in patients with CKD are capable of improving the oxidative capacity of muscles and decrease endothelial dysfunction, resulting in functional capacity improvement, suggesting a important role of Physical Therapist professionals in the care of CKD patients (Cheema & Singh, 2005; B et al., 2007, Campos et al., 2018).

We observed reduction of 6MWD in both genders. Despite the biological advantages of men, the performance reduction was similar between groups. Importantly, the study was not designed to primarily evaluate this endpoint and sample size was limited. The limited sample size also precluded any conclusion on the correlation between 6MWT and the tested biomarkers in gender groups subanalysis.

Although we excluded patients with some conditions that could interfere on the 6MWT (cardiovascular, pulmonary and cognitive impairment), other factors might influence 6MWT results, such as muscle weakness and power. However, as submaximal exercise test, 6MWT is a good option for patients with comorbidities limiting their performance to reach their maximal exercise capacity, as patients with stage 5 CKD. In addition, it is a simple, safe, inexpensive, reproducible test and reproduce the activity of daily life (Rasebaka et al., 2009; Du et al., 2017).

As another limitations, this was a single center study; and we could not evaluate other inflammation and endothelial function-related biomarkers, such as VCAM-1 and ICAM-1, interleukins, parathyroid hormone and albumin. As strengths, as far as we know, this is the first study evaluating the involvement of oxidative and inflammatory stress in the impairment of functional capacity in CKD patients under chronic hemodialysis therapy.

5. Conclusion

In conclusion, patients with stage 5 CKD under chronic hemodialysis presented impaired performance in 6MWT, regardless of gender, and this impairment was associated with oxidative stress and inflammation.

CRediT authorship contribution statement

Ítalo Caldas Silva: Data collection and analysis, Writing - original draft. **Débora Fortes Marizeiro:** : Data collection and analysis. **Elizabeth De Francesco Daher:** Review of data and writing analysis. **Tainá Veras de Sandes-Freitas:** Formal analysis, Review of data and writing analysis. **Gdayllon Cavalcante Meneses:** Analysis of biomarkers. **Gabriela Freire Bezerra:** Analysis of biomarkers. **Alexandre Braga Libório:** Review of data analysis and writing. **Alice Maria Costa Martins:** Analysis of biomarkers. **Nataly Gurgel Campos:** Data collection; Review of data analysis and writing.

Declaration of competing interest

The authors declare that they participated in the conception, analysis of results and effectively contributed to the realization of the article: " Correlation between functional capacity and biomarkers of oxidative stress and inflammation in stage 5 patients with chronic kidney disease under hemodialysis therapy". They disclose the responsibility for its content, which has not omitted any links or financing agreements between the authors and companies that may have an interest in the publication of this article. We declare that the article cited above is original and that it has no conflict of interest with the topic addressed in the article.

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