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Is the peripheral muscle weakness a limitation to exercise on chronic kidney disease?

A fraqueza muscular periférica é uma limitação ao exercício na doença renal crônica?

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Abstract

Introduction: Chronic kidney disease (CKD) is a global public health problem with systemic repercussions, compromising muscle function and making patients less exercise tolerant. **Objective:** To verify the contribution of peripheral muscle strength in the exercise capacity of patients in hemodialysis (HD), as well as to compare peripheral muscle strength and exercise capacity between renal patients and healthy individuals. **Method:** 50 patients with chronic kidney disease (CKD) who performed HD and 13 healthy subjects underwent anthropometric evaluation, evaluation of peripheral muscle strength, pulmonary function test and exercise capacity assessment. **Results:** Simple linear regression indicated that the peripheral muscle strength contributed 41.4% to the distance walked in the six-minute walk test (R2 0.414; $p < 0.001$), showing that for every 1 Kgf reduced in the right lower limb the patient it stops walking 0.5m while for every 1 Kgf reduced in the lower left limb the patient stops walking 0.8m. In addition, it was observed that patients with CKD had

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a reduction in right lower limb muscle strength (129.44 ± 48.05 vs. 169.36 ± 44.30, p = 0.002), left (136.12 ± 52, 08 vs 168.40 ± 43.35, p = 0.01) and exercise capacity (421.20 ± 98.07 vs. 611.28 ± 80.91, p < 0.001) when compared to healthy pairs. **Conclusion:** Peripheral muscle weakness is an important limiting factor for exercise in CKD and patients on HD experience a decline in peripheral muscle strength and exercise capacity when compared to healthy individuals.

Keywords*:* Chronic Kidney Disease. Renal Dialysis. Spirometry. Muscle Strength. Exercise Tolerance.

Resumo

Introdução: *A doença renal crônica (DRC) é um problema de saúde pública global com repercussões sistêmicas, comprometendo a função muscular e tornando os pacientes menos tolerantes ao exercício.* ***Objetivo:*** *Verificar a contribuição da força muscular periférica na capacidade de exercício de pacientes em hemodiálise (HD), bem como, comparar a força muscular periférica e a capacidade de exercício entre pacientes renais e indivíduos saudáveis.* ***Método:*** *50 pacientes com DRC que realizavam HD e 13 indivíduos saudáveis foram submetidos à avaliação antropométrica, avaliação da força muscular periférica, prova de função pulmonar e avaliação da capacidade de exercício.* ***Resultados:*** *A regressão linear simples indicou que a força muscular periférica contribuiu em 41,4% a distância percorrida no teste de caminhada de seis minutos (R2 0,414; p < 0,001), mostrando que para cada 1 Kgf reduzido no membro inferior direito o paciente deixa de caminhar 0,5m enquanto que para cada 1 Kgf reduzido no membro inferior esquerdo, o paciente deixa de caminhar 0,8m. Além disso, observou-se que pacientes com DRC apresentam redução da força muscular de membro inferior direito (129,44 ± 48,05 vs. 169,36 ± 44,30; p = 0,002), esquerdo (136,12 ± 52,08 vs. 168,40 ± 43,35; p = 0,01) e da capacidade de exercício (421,20 ± 98,07 vs. 611,28 ± 80,91; p < 0,001) quando comparados aos pares saudáveis.* ***Conclusão:*** *A fraqueza muscular periférica é um importante fator de limitação ao exercício na DRC. Além disso, pacientes em HD apresentam redução da força muscular periférica e da capacidade de exercício quando comparados a indivíduos saudáveis.*

Palavras-chave: *Doença Renal Crônica. Diálise Renal. Espirometria. Força Muscular. Tolerância ao Exercício.*

Introduction

Chronic kidney disease (CKD) is a global public health problem with systemic repercussions, compromising muscle function and making patients less exercise tolerant [1,2,3]. Although the onset of the disease is characterized by progressive loss of kidney function, its evolution is associated with physical inactivity, leading to muscle changes, reduced muscle mass and less peripheral muscle strength [3,4,5].

Previous studies have demonstrated that muscle dysfunction in this population is linked to factors resulting from progression of the disease, resulting in muscle protein catabolism and degradation [4,5]. Corroborating these findings, Lewis et al. [6] conducted muscle biopsies in patients with CKD and observed structural changes in peripheral muscles, which may compromise energy production, favoring reduced strength and exercise intolerance during hemodialysis (HD). Additionally, this population becomes sedentary as kidney replacement therapy begins, further exacerbating muscles already compromised by uremic sarcopenia [7].

Although the literature confirms that peripheral muscle weakness is associated with poor physical fitness and mortality in this population [3,8,9], its influence on exercise intolerance in these patients remains unknown. As such, this study aimed to assess the contribution of peripheral muscle strength to the exercise capacity of patients on HD and compare peripheral muscle strength and exercise capacity between patients with CKD and healthy individuals.

Method

The study was approved by the Research Ethics Committee of the Santa Catarina State University (CAAE: 45904615.7.0000.0118) and used a descriptive, observational cross-sectional design. The sample consisted of 50 patients with CKD who were undergoing HD at the APAR VIDA Kidney Clinic, in São José, Santa Catarina state (SC), Brazil, and 13 healthy individuals recruited from the community. All participants gave written informed consent. Assessments were carried out at the UDESC Health Sciences and Sports Center. All the participants were submitted to anthropometric evaluation, peripheral muscle strength assessment, pulmonary function testing and exercise capacity analysis patients with CKD were assessed on the same day they underwent HD.

The following inclusion criteria were used: (1) diagnosed with CKD and undergoing regular HD for at least 6 months; (2) stable and under medical supervision; (3) no uncontrolled hypertension, unstable angina, severe heart arrhythmia or recent coronary artery disease (3 months or less); (4) no respiratory, orthopedic and/or neurological diseases that might compromise assessment; and (5) no physical exercise for at least 6 months. Patients were excluded from the study when they were (1) unable to perform any of the assessments (inability to understand or cooperate); and (2) exhibited cardiorespiratory and/or musculoskeletal complications during evaluation.

Inclusion criteria for healthy subjects were (1) no neurological, cardiac, systemic or osteoarticular diseases; (2) normal lung function; (3) nonsmoker; and (4) body mass index (BMI) < 30 Kg/m^2, and the exclusion criterion was being unable to perform any of the assessment tasks due to lack of understanding or cooperation.

Matching

Healthy individuals were matched to patients with CKD by sex, age (±3 years) and BMI classification. For intergroup comparison of the variables, the values of patients with BMI < 30Kg/m^2 were considered.

Anthropometric assessment

For anthropometric assessment, body weight and height were measured on a calibrated balance and stadiometer, respectively. Next, participants were classified based on their BMI as underweight (<18.5 Kg/m^2), normal weight (18.5-24.9 Kg/m^2), overweight (25-29.9 Kg/m^2) and obese (≥30 Kg/m^2) [10].

Evaluation of peripheral muscle strength

Peripheral muscle strength was assessed using the Biodex System 4 Pro in isometric mode. Participants were seated on the device with their hips flexed (85°) and lateral condyle of the femur aligned with the axis of rotation. Straps were also used to prevent compensatory movement and keep the trunk, hips and lower limb assessed stable. Five maximum voluntary isometric contractions were performed at 60° knee flexion [11,12] and held for 5 seconds, with a 90-second rest interval between contractions. The highest peak value for the knee extensor muscles of each lower limb was recorded for analysis.

Pulmonary function test

Lung function was evaluated using a previously calibrated portable digital spirometer (EasyOne®; NDD), in accordance with the recommendations of the American Thoracic Society and European Respiratory Society [13]. The variables analyzed were forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and the FEV1/FVC ratio. The results were expressed as absolute values and percentages of predicted normal values [14]. Patients with CKD who exhibited below normal values were submitted to spirometry again after inhaling a bronchodilator. Ventilatory disorders were classified based on normal pulmonary function scores of FVC and FEV1 ≥ 80% of the predicted value and FEV1/FVC ≥ 0.7.

Exercise capacity assessment

Submaximal exercise capacity was evaluated by the six-minute walk test (6MWT), in line with American Thoracic Society recommendations [15]. Participants were instructed to walk as far as possible along a 30-meter corridor for 6 minutes. Blood pressure, heart rate, oxygen saturation, sensation of dyspnea and lower limb fatigue (modified Borg scale) were measured at the beginning and end of the test. The test with the longest distance was used for analysis and results were expressed as absolute values and percentages of predicted normal values, in accordance with Britto et al. [16].

Statistical analysis

Statistical Package for the Social Sciences software (SPSS version 20.0) was used for all analyses. Data normality was evaluated using the Shapiro-Wilk test. The relationship between peripheral muscle strength and exercise capacity in patients with CKD was analyzed with Pearson's correlation coefficient. Next, two simple linear regressions were performed to determine the contribution of the muscle strength of the right and left lower limb to exercise capacity. Intergroup comparison of peripheral muscle strength and exercise capacity was carried out with the independent sample t-test, applying the Mann Whitney U test and independent t-test for the remaining intergroup comparisons, according to data normality. Significance was set at 5% ($p<0.05$).

Results

The sample consisted of 50 patients on HD, 28 of whom were male (56%) and 17 classified as obese based on their BMI (34%). With respect to pulmonary function, 19 patients had normal function (38%), 25 some form of restrictive ventilatory defect (48%), 5 some degree of obstruction (10%) and 2 exhibited mixed ventilatory defects (4%). The characteristics and variables of patients with CKD are described in Table 1.

Table 1 - Characteristics and variables of patients with CKD

Anthropometric data	**Mean ± SD**
Sex (M/F)	28/22
Age (years)	56.86 ± 12.41
Body weight (Kg)	76.81 ± 14.67
Height (m)	1.63 ± 0.09
BMI (Kg/m^2)	28.88 ± 5.59
Pulmonary function test	**Mean ± SD**
FEV_1/FVC	0.79 ± 0.07
Pulmonary function test	**Mean ± SD**
FVC (%)	78.88 ± 17.54
FEV_1 (%)	78.06 ± 18.25
Peripheral muscle strength	**Mean ± SD**
RLL (Kgf)	124.34 ± 49.62
LLL (Kgf)	128.68 ± 52.52
Exercise capacity	**Mean ± SD**
6MWT (m)	407.00 ± 101.33
Predicted (%)	66.80± 15.10

(to be continued)

(conclusion)

Note: SD: standard deviation; M: male; F: female; BMI: body mass index; FEV_1/FVC: ratio between forced expiratory volume in 1 second and forced vital capacity; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; RLL: right lower limb; LLL: left lower limb; 6MWT: distance walked in the 6-minute walk test.

There was a moderate correlation between muscle strength in the right ($r=0.64$; $p<0.001$) and left lower limb ($r=0.65$; $p<0.001$) and exercise capacity in patients with CKD (Figure 1).

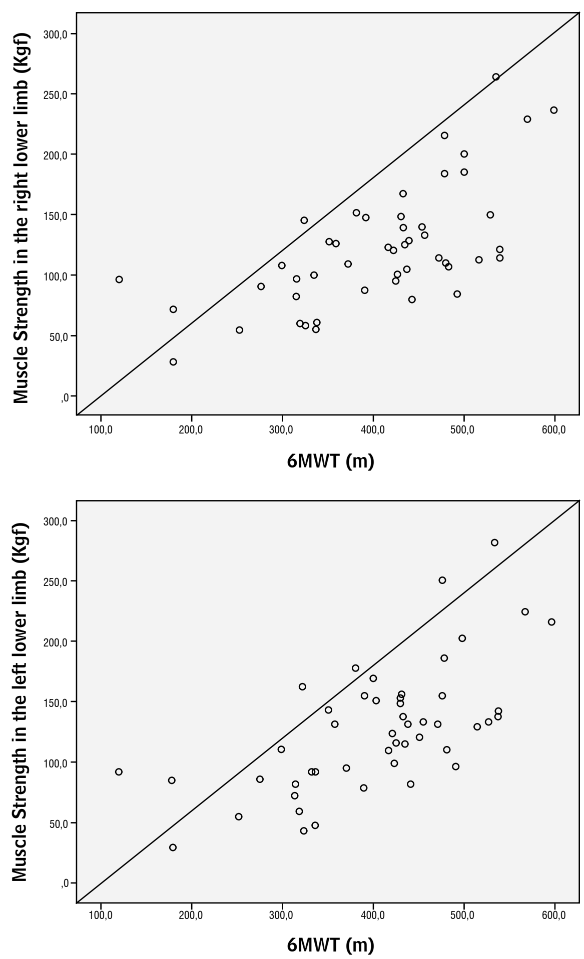

Figure 1 – Relationship between muscle strength in the left and right lower limb and distance walked in the 6MWT among patients on HD.

Thus, simple linear regression demonstrated that muscle strength in the lower limbs increases the distance walked in the 6MWT by 41.4% (R2 0.414; $p < 0.001$), indicating that for every 1 Kgf decline in strength in the right and left lower limb, patients walked 0.5 and 0.8 m less, respectively.

Patients classified as obese were excluded from the intergroup comparison of anthropometric variables, peripheral muscle strength and exercise capacity. There was no statistical intergroup difference in anthropometric variables, confirming that the groups were homogeneous in these aspects. However, patients on HD exhibited a significant reduction in peripheral muscle strength and exercise capacity when compared to their healthy counterparts (Table 2).

Table 2 – Comparison of anthropometric variables, peripheral muscle strength and exercise capacity in patients on HD (excluding obese patients) and healthy controls

Variable	HD Patients (Mean ± SD)	Healthy Controls (Mean ± SD)	p
Sex (M/F)	15/10	9/4	-
Age (years)	53.76 ± 15.03	52.96 ± 14.63	0.86
Body weight (Kg)	71.07 ± 8.01	71.31 ± 7.88	0.94
Height (m)	1.64 ± 0.08	1.65 ± 0.05	0.57
BMI (Kg/m²)	26.32 ± 2.52	25.96 ± 2.14	0.59
Muscle strength RLL (Kgf)	129.44 ± 48.05	169.36 ± 44.30	0.002*
Muscle strength LLL (Kgf)	136.12 ± 52.08	168.40 ± 43.35	0.01*
6MWT (m)	421.20 ± 98.07	611.28 ± 80.91	<0.001*
Predicted (%)	66.05 ± 14.62	93.29 ± 5.50	<0.001*

Note: HD: hemodialysis; SD: standard deviation; M: male; F: female; BMI: body mass index; RLL: right lower limb; LLL: left lower limb; 6MWT: distance walked in the 6-minute walk test; *: p<0.05.

Discussion

Given that it assesses an everyday activity, the 6MWT is widely used in clinical practice to analyze functional and exercise capacity in healthy individuals and patients with different diseases [15,16,17]. Britto et al. [17] reported that nonmodifiable variables such as sex and anthropometric are responsible for 46% of the performance variability in this test. As such, modifiable outcomes that seem to contribute to exercise tolerance should be investigated for different diseases. In the present study, muscle strength in the lower limbs was responsible for more than 40% of performance variability in the 6MWT among patients on HD.

Our results demonstrated that patients on HD exhibited less right (p = 0.002) and left lower limb muscle strength (p = 0.01) and reduced exercise capacity (p < 0.001) when compared to healthy controls, corroborating the findings reported in the literature [1,17,18]. Musso, Jauregui and Núñez [5] recently published a literature review that addresses factors related to the development of uremic sarcopenia in CKD. Hormonal changes, systemic inflammation, insulin resistance, metabolic acidosis and nutrient deficiencies are repercussions of the progression of the disease and, via different pathways, lead to the breakdown of muscle proteins in this population. Muscle function may also be further compromised, since patients tend to be more sedentary [7]. Additionally, muscle biopsies revealed poor oxidative capacity and reduced capillary density in the muscle tissue of these individuals [6]. These alterations highlight the fact that the muscular system of these patients produces less energy and is more prone to fatigue. These findings and the results obtained here confirm that decreased muscle function is an important limiting factor for exercise during HD.

In other chronic diseases, weak peripheral muscles were also reported in conjunction with poor exercise capacity [19-22]. These results corroborate those recorded here, since patients on HD walked almost a meter less when their strength declined by one unit. Additionally, the average 6MWT value observed in our patients confirms this exercise intolerance, since it was statistically lower than that recorded for controls. This emphasizes the need for physical therapists to be aware of peripheral muscle weakness in CKD, since systemic repercussions of the disease affect not only the muscular system, but patient functionality.

Previous studies demonstrated that uremic sarcopenia is associated with a decline in physical function in this population [3,8,9]. Thus, reduced muscle mass and strength may negatively affect performance in activities of daily living and physical exercise, forcing patients into a vicious cycle of sarcopenia-sedentarism-sarcopenia and making them increasingly exercise intolerant. Uremic sarcopenia has also been described as a factor related to mortality in this population [3,8,9,23], signaling the importance of early diagnosis of the condition by health care teams as well as possible treatment options.

Our findings also indicated altered pulmonary function in patients with CKD, with almost half the sample (48%) exhibiting some type of restrictive ventilatory defect. This corroborates the results of Schardong, Lukrafka and Garcia [24], who observed worse spirometric variables in patients on HD, with 45% of their sample displaying a decline in the predicted value for FVC%. Because they generate systemic repercussions, respiratory disorders are frequent complications in this population [25-27]. Reduced lung function may be the result of uremic toxins that alter the permeability of the blood-air barrier, associated with fluid buildup, leading to pulmonary edema and restrictive ventilatory defects [28,29]. Uremic sarcopenia also generates respiratory muscle dysfunction, further compromising pulmonary function [1,30].

Thus, peripheral muscle strength is a significant factor in exercise limitation for patients on HD. As a result, physical therapists should aim to minimize the effects of sarcopenia in CKD, in order to improve the functionality and quality of life of this population.

Conclusion

Peripheral muscle weakness is an important limiting factor for exercise in CKD and patients on HD experience a decline in peripheral muscle strength and exercise capacity when compared to healthy individuals.

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