ORIGINAL ARTICLE

Serum Levels of Vitamin D and Parathyroid Hormone as Determinants of Sarcopenia in Patients with Chronic Renal Disease on Hemodialysis

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ABSTRACT

The development of sarcopenia is common in individuals with chronic kidney disease (CKD). Studies aim to evaluate the complex mechanisms that contribute to its development, including the correlation with serum hormone concentrations. The objective of this study was to measure the prevalence of palmar pinch strength (PPS) and muscle mass (MM) associated with serum concentrations of 25-hydroxyvitamin D (25-OHD) and parathyroid hormone (PTH) in individuals with CKD on hemodialysis. An observational, longitudinal, and prospective study was conducted. PPS and MM were monitored from a sample of 64 patients and data on anthropometry and serum concentrations of 25-OHD and PTH were collected. Low serum levels of 25-OHD and high blood concentrations of PTH were associated with an increased risk of developing sarcopenia because they contributed to the reduction of MM and PPS. For better comprehension of the mechanisms of this process, it is suggested the realization of new studies at the cellular, metabolic, and population level.

Key words: Chronic renal insufficiency, parathyroid hormone, sarcopenia, Vitamin D

INTRODUCTION

Chronic kidney disease (CKD) is a major global public health problem due to the progressive increase in incidence and prevalence rates, high cost, and high complexity, being considered a major cause of morbidity and mortality. At present, it is estimated the existence of more than 2 million individuals with this disease in Brazil, being equivalent to 1% of the Brazilian population.[1,2]

The term CKD comprises a set of heterogeneous changes, in which the excretory function is chronically compromised as a result of damage to the structure or function of the kidneys. Thus, its definition is based on three components: An anatomical or structural component, a functional component, or a temporal component.[3]

CKD patients are susceptible to changes in body composition, including reductions in muscle mass (MM) and, consequently, muscle strength (MS), which occur independently of age, and are mainly caused by increased protein catabolism. Thus, these individuals are more prone to the development of sarcopenia which, in addition to defining the presence of the decline in MM and strength, is also associated with worsening of physical performance.[4,5]

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The consequences of sarcopenia for these individuals are associated with increased morbidity and mortality and cardiovascular complications. Therefore, several studies in the area have been carried out, aiming to analyze the complex mechanisms that contribute to the loss of MM and MS, including the relationship of these variables with the serum concentrations of some hormones, such as parathyroid hormone (PTH) and Vitamin D.[6,7]

Vitamin D deficiency is commonly observed in individuals with CKD, since renal function is impaired, impairing the conversion of 25-hydroxyvitamin D (25-OHD) to its active form 1.25-dihydroxyvitamin D [1.25(OH)2D] that occurs at the renal level. In addition, the decrease in the serum level of 1.25(OH)2D contributes to the increase of PTH due to the reduction of intestinal calcium, resulting in problems such as secondary hyperparathyroidism and bone mineral disease.[8]

The relationship between Vitamin D and bone problems is widely available in the literature. However, this hormone has been associated with several non-bone manifestations, including its role in preventing the risk of falls and skeletal muscle.[9,10]

Some studies suggest that higher levels of Vitamin D are associated with higher MM, MS, and physical capacity. In addition, controlled double-blind clinical studies with several populations suggest an association between Vitamin D supplementation in MM and MS improvement. In contrast, other trials found opposite results, indicating Vitamin D supplementation as not effective in improving these variables.[11-13]

Although the molecular actions of Vitamin D in the skeletal muscle have already been widely mentioned in the literature, little is known about Vitamin D and PTH related to MM and MS in CKD, necessitating a higher level of evidence that may aid in the treatment of individuals affected by sarcopenia. Given this context, the aim of this study was to evaluate the prevalence of palmar pinch strength (PPS) and MM associated with serum concentrations of 25-OHD and PTH in patients with CKD on hemodialysis (HD).

METHODOLOGY

A prospective, longitudinal, observational, and quantitative approach study was conducted at a private clinic located in the city of Natal/RN, Brazil.

Study participants

The study was performed with individuals with CKD in the dialysis phase. Sampling was of the non-probabilistic type, being the sample performed by convenience and composed of 64 patients. Inclusion criteria were to have CKD and to undergo HD, to be 18 years of age or older, to have no clinical complications or interruption of the treatment, and to be able to communicate. Exclusion criteria consisted of individuals with cognitive deficits, wheelchair users, restricted to bed, and/or refusal by the interviewee to participate in the study.

Patients were initially approached during the dialysis procedure and participated in the main interview, being instructed on the methods used in the research and invited to participate in it. After the conclusion of the dialysis session, they were referred to the nutrition room to obtain the anthropometric and PPS data.

Patients who agreed to participate in the study signed the free and informed consent form – TCLE (Appendix A) and the study was approved by the local ethics committee.

Sarcopenia

PPS

As an indicator of MS, PPS was used, which is referred to as easy to implement, non-invasive, and low cost. The grip strength is not only seen as an intrinsic measure of hand or upper limbs strength but rather as an indicator of physical strength and general health since PPS is necessary for performing most daily tasks.[14]

Thus, PPS was measured using a Sanny® brand hand dynamometer grip strength. The maximum force (kilograms) was calculated based on three attempts of each hand and was performed twice, with a difference of 6 months between baseline and follow-up examination. The PPS change was calculated as the force difference between baseline and follow-up divided by baseline strength and multiplied by 100. This calculation was based on the methodology proposed by Visser *et al*.[7] as well as the definition of sarcopenia as a loss of PPS >40% during follow-up.

MM

The body composition was evaluated by means of the Sanny® four-pole bioimpedance (BIA1010) and was performed twice, with a difference of 6 months between baseline and follow-up examination. With the patient lying on a non-conductive surface, in the supine position, arms and legs abducted at 45° from the body, the electrodes were placed on the hands and feet, and the procedure was started as indicated by the bioimpedance protocol. The change relative to MM (kilograms) was calculated as the difference of MM between baseline and follow-up divided by baseline value and multiplied by 100. This calculation was based on the methodology proposed by Visser *et al*.[7] as well as sarcopenia, which was understood as a loss of MM >3% during follow-up.

Hormonal factors

The performance of biochemical exams is part of the clinical practice and the follow-up of patients with CKD in the dialysis phase. Therefore, serum levels of PTH and 25-OHD

were collected from the medical records of each patient.

Serum PTH levels were categorized into tertiles (<3 pg/dL, between 3 and 3.9 pg/dL and >4 pg/dL), and the group with the lowest PTH levels was used as the reference group. Serum levels of 25-OHD were categorized into three groups based on published cutoff points: <25, 25–49.9, and 50 ng/mL, the latter being considered as the reference group.

Both serum levels of PTH and 25-OHD, as well as the diagnosis of Vitamin D deficiency, were evaluated according to the criteria used in the study of Visser *et al*.[7] Vitamin D deficiency was defined as a serum concentration of <25 ng/mL.

Indicators of change of body composition

Potential confounding factors were initially measured in the study and included in the statistical analysis, being age in years, body weight, height, body mass index (BMI), and body weight change in percentage. A form (Appendix B) was used to fill in such data.

Body weight was measured with the patient barefoot and with the minimum of possible clothes, with the aid of a properly calibrated Toledo® digital scale, with a maximum capacity of 200 kg. The individual was asked to get on the equipment and was positioned centrally, upright, feet together, and arms extended along with the body and head positioned in the Frankfurt plane. The "dry weight," measured after the end of HD, was used. With the individual in the same position, the stature was measured with the aid of a stadiometer coupled to the scale.

The BMI was calculated based on weight and height measurements and the classification of the result was performed based on the BMI cutoffs recommended by the World Health Organization (1995), that is, low weight (IMC <18.5 kg/m²); eutrophy (IMC 18.5-24.99 kg/m²); overweight (IMC 25–29.99 kg/m²); and obesity (IMC ≥30.0 kg/m²).

The percentage of loss or weight gain was calculated based on the data of usual weight and the current weight. The calculation was performed by dividing the usual weight by the current weight and multiplying by 100.[15]

Statistical analysis

Statistical analysis was performed using PRISMA 2017 software version 7.0 for Macbook. The distributions of PTH and 25-OHD concentrations were standardized by transformation into their normal logarithm and were used as continuous variables, as well as categorized variables, since the aim was to evaluate potentially non-linear relationships with sarcopenia.

Significant differences between groups were tested using one-way ANOVA. *P* values were considered statistically significant at $P < 0.05$.

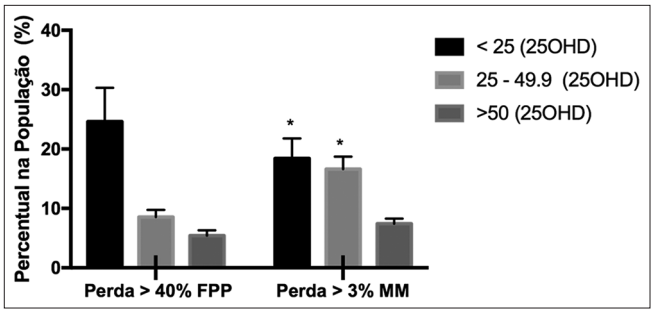

Figure 1: Prevalence of loss of palmar grip strength (> 40% PPS) and muscle mass (> 3% MM) for 6 months according to serum 25-OHD concentrations. *There was no significant difference between them.
Source: Own study (2018)
Note: Palmar Pinch Strength (PPS), Muscle Mass (MM).

RESULTS

In Figure 1, the loss of PPS and MM during a 6-month period was measured, according to blood concentrations of 25-OHD. The results indicate that individuals with serum level of 25-OHD lower than 25 ng/mL tended to have higher PPS losses and those with blood concentrations between 25–49.9 ng/mL and greater than 50 ng/mL of 25-OHD were likely to show lower losses of the same variable.

Regarding MM, individuals with serum concentrations lower than 25 ng/mL or 25–49.9 ng/mL of 25-OHD were more likely to present higher MM (>3%) losses in comparison with those with concentrations of >50 ng/mL. That is, individuals with lower levels of 25-OHD were more likely to have loss of grip strength (>40%) and MM (>3%).

Table 1 shows the characteristics of the 64 study participants. Regarding the mean, it was observed that participants who lost PPS (>40%) were older had lower weight, BMI, and grip strength compared to those who had adequate parameters. In addition, they had 1.3% (5.4) reduction in body weight.

Regarding the mean of the participants who lost MM (>3%), it could be observed that they were older, presented lower weight, BMI, and MM compared to those who had adequate parameters. There was also 13.2% loss of body weight in the same group.

There was a significant difference only regarding PPS between the group with adequate parameters and the group with PPS losses ($P < 0.001$) and regarding the change in body weight between the group with adequate parameters and the group with MM loss ($P < 0.05$).

In Figure 2, the loss prevalence of PPS (>40%) and MM (>3%) was measured over a period of 6 months, according to parathyroid blood levels (PTH). The results demonstrated that

Table 1: Distribution of the anthropometric variables of palmar pinch strength and muscle mass of patients with CKD undergoing HD

Variable	Palmar pinch strength			Muscle mass		
	Adequate	Loss >40%	*P*	Adequate	Loss >3%	*P*
Age (years)	49.5 (6.4)	53.3 (7.2)	0.134	48.7 (5.2)	51 (5.9)	0.097
Weight (kg)	72.4 (8.6)	67.6 (9.2)	0.367	73.4 (10.3)	68.9 (9.4)	0.567
BMI (kg/m^2)	25.4 (6.4)	22.4 (3.9)	0.198	25.1 (7.4)	23.9 (4.2)	0.678
Pinch strength (kg)	48 (17.8)	19 (10.5)	0.001	-	-	-
Muscle mass (kg)	-	-	-	20.2 (4.7)	18.4 (4.9)	0.079
Weight change (%)	+0.7 (3.8)	−1.3 (5.4)	0.321	−0.3 (2.9)	−13.2 (3.5)	0.05

Source: Own study (2018). CKD: Chronic kidney disease, HD: Hemodialysis, BMI: Body mass index

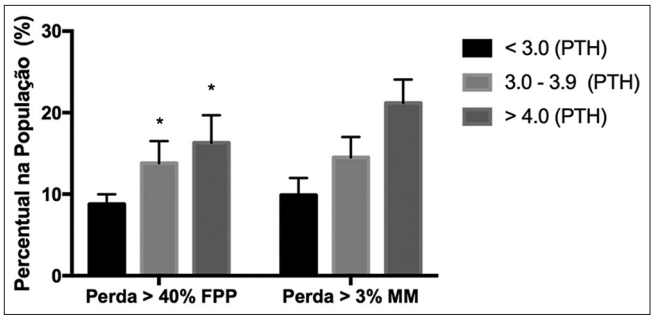

Figure 2: Prevalence of loss of palmar pinch strength (>40% PPS) and muscle mass (>3% MM) for 6 months according to serum concentrations of parathyroid hormone. *There was no significant difference between them. Source: Own study (2018). PPS: Palmar pinch strength, MM: Muscle Mass

individuals with PTH blood concentrations of >4 pg/dL and between 3 and 3.9 pg/dL tended to show greater loss of PPS compared to those with blood concentrations below 3 pg/dL.

Regarding MM, individuals with PTH blood concentrations higher than 4 pg/dL tended to present higher losses of this variable in comparison with those with concentrations lower than 3 pg/dL and between 3 and 3.9 pg/dL. Thus, the results suggest that individuals with elevated serum PTH levels are more likely to exhibit reductions in grip strength and MM.

DISCUSSION

Vitamin D has been extensively associated with several non-bone manifestations, including its effects on the risk of falls and skeletal muscle related to reduced MS and MM, which are common in sarcopenia (Bischoff-Ferrari *et al*., 2009[3]; de Flávia *et al*.[9,16])

The occurrence of sarcopenia in individuals with CKD is common and may occur at any stage of the disease. It is associated with several factors and, more recently, several studies have begun to evaluate the effect of Vitamin D on the parameters of sarcopenia (Souza *et al*., 2014).[6]

Thus, the present study tested the relationship of PPS and MM with serum concentrations of 25-OHD and PTH since these variables are directly related to sarcopenia. Analyzing Figures 1 and 2, they suggest that low serum concentrations of 25-OHD and elevated serum levels of PTH contribute to the increased risk of developing sarcopenia.

The results found corroborate with the study carried out by Visser *et al*.,[7] which propose that a lower concentration of 25-OHD and a higher concentration of PTH increase the risk of developing sarcopenia in old age, associated with loss of PPS and appendicular muscle mass. This study was conducted with a large cohort and was the first population-based study carried out to investigate the prognostic value of serum levels of 25-OHD in sarcopenia in elderly individuals, using a longitudinal design.

Another study, conducted by Janssen *et al*.,[12] in which they sought to determine the association between serum concentrations of 25-OHD with muscle mass, strength, and performance, showed that higher serum levels of 25-OHD were significantly associated with higher MM, PPS, and physical performance in middle-aged men and women.

Regarding the research done with individuals with CKD, a study carried out by Gordon *et al*.,[17] which aimed to evaluate the association of Vitamin D with physical performance and MM, found that 1.25(OH)2D is a determinant of physical performance and MM in patients with CKD in Stages 3 and 4.

Recently, research has verified the effects of Vitamin D on muscle. There are several lines of evidence that support the role of this vitamin in muscle health. Among them, there are observational studies that suggest a positive association between 25-OHD and MS or function and that Vitamin D supplementation works by increasing MS and balance. In addition, several studies point to the existence of specific nuclear receptors (Vitamin D receptor [VDR]) of Vitamin D in human skeletal muscle and its activation, which is related

to the promotion of muscle protein synthesis.[18]

The active form of Vitamin D [1.25(OH)2D] exerts a large part of its actions through the link with the VDR. This intracellular hormone receptor binds specifically to 1.25(OH)2D, mediating its effects. The molecular mechanisms of this action involve genomic and non-genomic effects. As for the genomic effects, it is suggested that they are mediated by the genetic transcription of messenger RNA and subsequently the production of new proteins that affect the contractility, proliferation, and differentiation of muscle cells, resulting in muscle growth. The probable metabolism of Vitamin D in the control of sarcopenia is present in Figure 3.[19,20]

Vitamin D deficiency is generally associated with increased serum PTH levels. It can be explained because the deficiency leads to a reduction in calcium absorption and, consequently, an exacerbated increase in PTH secretion by the parathyroid glands. In addition, the synthesis of 1.25(OH)2D is stimulated by PTH, thus, a drop of 25-OHD also ends up stimulating PTH production.[21]

Treating CKD, as the kidneys lose their ability to excrete toxic substances accumulated in the body, this problem consequently leads to the occurrence of hyperphosphatemia, which ends up generating a greater stimulation of the production of PTH and triggering secondary hyperparathyroidism.[22]

Thus, in addition to the relationship between Vitamin D and MS and mass, research has also been done on the association of these variables with serum PTH levels. According to Haroon and FitzGerald,[20] studies have shown that PTH impairs skeletal muscle function in animal models through muscle proteolysis and the intracellular reduction of inorganic phosphate, creatine phosphate, and Ca-ATPase in muscle cells.

It is possible that PTH exerts a direct effect on skeletal muscle since its administration has demonstrated effects related to the production, transport, and energy use, besides its influence on the metabolism of amino acids and proteins in the skeletal muscle of rats, contributing to weight loss, muscle weakness, and atrophy. In addition, this hormone is also known to induce the production of interleukins in the liver of rats with consequent increase in circulating levels of these *in vivo* cytokines. Studies performed with elderly individuals have associated high levels of interleukin-6 with lower MM and muscular strength.[23]

Vitamin D supplementation in patients with CKD in HD

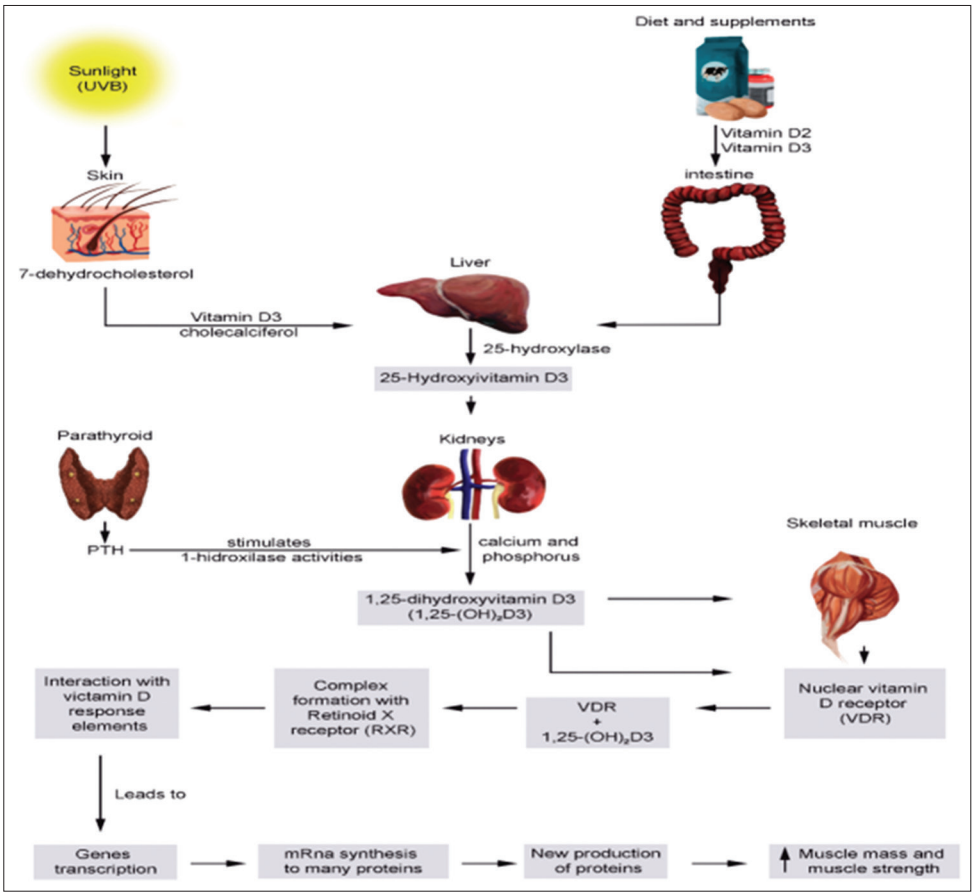

Figure 3: Proposed metabolic mechanism of Vitamin D in the control of sarcopenia. Source: Own study (2018)

seems to have conflicting results regarding strength and MM gain. In the study carried out by Gordon *et al*.,[24] with individuals with CKD who were in the dialysis phase, it was found that individuals receiving calcitriol or paricalcitol supplementation had better results in physical performance tests, greater strength, and MM when compared to those who did not receive them.

Similar results were observed in the study carried out by Cangussu *et al*.,[11] which sought to investigate the effects of Vitamin D isolated on the muscular function of 160 Brazilian women shortly after menopause. It has also shown that supplementation in individuals with Vitamin D deficiency provides a significant protective effect against sarcopenia by increasing MS and controlling for the progressive loss of MM.

However, the same results were not observed in the randomized clinical trial conducted by Hewitt *et al*.[25] with patients who were in HD. After 6 months of study, there were no significant differences in MS and functional capacity between the group receiving placebo and the group receiving cholecalciferol supplementation.

Some of the limitations of the present study consisted in the evaluation of only two parameters and could interfere in the final result since the existence of other variables and the evaluation of the activity of genes and cellular mechanisms may allow the discovery of new forms of treatment. However, the two variables evaluated can be used in clinical practice, contributing to the analysis, prognosis, or evolution of several cases of renal patients on HD.

In addition, the type of sampling was non-probabilistic, so it was not possible to generalize the results for the entire population. Therefore, it is suggested to carry out new studies with probabilistic sampling, larger sample, and longer follow-up time and with other populations and ethnic groups.

FINAL CONSIDERATIONS

According to the results, it is suggested that lower serum 25-OHD concentrations and higher PTH levels contribute to the increased risk of developing sarcopenia in individuals with CKD on HD. Therefore, they should be submitted to preventive measures and continuously observed for the presence of sarcopenia from the early stages of the disease, to reverse or reduce the process of muscle loss and, consequently, reduce the complications generated by sarcopenia in renal patients.

Due to the diverse associations found, a greater level of evidence is needed regarding the effects of Vitamin D and PTH on skeletal muscle cell metabolism in renal patients. Therefore, further longitudinal studies are necessary, as well as randomized controlled trials, that verify the effects of Vitamin D supplementation in individuals with CKD on HD, to contribute to the implementation of preventive measures for the development of sarcopenia.

CONCLUSION

It then concludes that it suggests which are the lowest 25-OHD levels and highest levels of PTH contribution to increase the risk of developing sarcopenia in individuals with CKD on hemodialysis.

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How to cite this article: Santos L, de Lima TL, da Costa KC, Caetano AL, de Farias EHC, da Silva DCP, Fayh APT, Serquiz AC. Serum Levels of Vitamin D and Parathyroid Hormone as Determinants of Sarcopenia in Patients with Chronic Renal Disease on Hemodialysis. Clin J Nutr Diet 2020;3(1):1-7.