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Relationship Between Inflammatory Markers and Muscular Parameters Used in the Nutritional Evaluation of Renal Patients in Hemodialysis

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Abstract

Chronic Kidney Disease (CKD) is a manifestation that can lead to accumulation of toxins in the blood. Inflammation is a physiological process due to the different stimuli generated, as well as the dialysis process. The present research aims to associate these factors with the waist circumference (WC), the arm perimeter (AP), the Hand Grip Strength (HGS) and the adductor thumb muscle (ATM), used in the nutritional assessment of patients on hemodialysis treatment. Methods: 34 patients on dialysis with age ranging from 20 to 78 years were selected. The mean performance was calculated based on the mean and standard deviation, for all the variables, and for the degree of association between pairs of variables the Sperman correlation test was used. The significance level was set at 5% ($p < 0.05$). There was correlation between inflammatory markers and the WC. The BMI was used to classify the patients into the nutritional states of malnutrition and eutrophy. The AP was related to the HGS and ATM, and was associated with the imminence of inflammation for the patients. This study presents an evaluation on the WC and the HGS as contributing to the control of such inflammatory processes. What is laid bare herein is not only the issue of lean mass loss, but also one of the most frequent problems afflicting patients with CKD in HD, the increase of WP, a much discussed issue, which plays an important role in the pulmonary state, favoring complications in CKD patients.

Keywords

Renal Disease, Hemodialysis, Inflammation, Nutritional Evaluation

1. Introduction

Chronic kidney disease (CKD) is a clinical manifestation characterized by slow, progressive, and irreversible loss of kidney function, which can lead to an increase in toxin levels in the bloodstream. Moreover, other organs suffer physiological alterations derived from CKD, leading to inflammation and muscular mass loss, especially in patients submitted to hemodialysis (HD) [1].

The technology for dialysis treatment and the understanding of chronic renal failure (CRF) have risen significantly in the present days. However, there is still a noticeable increase in the mortality rate caused by associated morbidities. This inflammatory condition has contributed to the high mortality rate of these patients. Endothelial

dysfunction leads to the building up of adhesion molecules on the cell surface, which attract leukocytes. This event triggers and/or potentiates the inflammatory cascade [2].

Inflammation is a physiological process triggered by different stimuli generated by the CKD itself, further to the dialysis procedures. A change in body mass can also lead to dysregulated inflammatory cytokine production. Interleukin-2 (IL-2) is associated with immunological factors, whereas interleukin-6 (IL-6) and tumor necrosis factor (TNF-α) are related to malnutrition, body composition change, and increased oxidative stress levels [3].

High concentrations of IL-2, IL-6, and TNF-α can contribute to insulin resistance, increase lipolysis, promote atherogenesis, and elevate acute phase proteins, like the C-reactive protein (RPC) and fibrinogen, which are associated with hypercatabolism [3, 4].

Inflammation, however, can lead to protein-energy malnutrition (PEM), due to higher protein catabolism and a lower appetite, which are caused by cytokine activity [5]. Therefore, a change in body compositional mass is one of the consequences of CKD in patients subjected to hemodialysis. This is also associated with higher fat mass, especially in the abdominal region, and muscle mass loss with lower soluble protein levels, due to metabolic changes or protein loss during dialysis [6, 7]. Some indicators, such as hand grip strength (HGS) and adductor thumb muscle (ATM), are rapid, non-invasive and low-cost techniques which are very useful during nutritional evaluation to estimate muscle mass. Hand grip strength is associated with routine activities to analyze the functional integrity of upper limbs and is used to monitor motor function. Thus, HGS is established as a muscle strength and power indicator [8]. On the other hand, the ATM is a parameter that can indicate early malnutrition and can also be a marker of mortality risk, thus being a prognostic indicator for critical patients [9].

The relation between height and weight, added to the body perimeters are important indicators to be used during nutritional evaluation in CKD patients subjected to HD. This is due to the common findings observed regarding body compositional changes: reduction in lean mass percentage and fat buildup in the abdominal region [10]. The increase in fat mass, specifically that of visceral fat, promotes the production of IL-6, TNF-α, and other adipokines, which potentiate the catabolic effect in muscles. This generates a cycle, leading to additional fat accumulation and muscle loss [11].

On the other hand, considering the inflammatory state plays a key role in triggering CKD complications in HD patients, it is not known whether HGS and ATM indicators, which estimate muscle mass, are related to inflammatory cytokine levels in the patients. It is well established that inflammation in CRF patients can lead to PEM, and these quick and simple techniques could predict the early risk of CRF. Moreover, the increase in waist perimeter (WP) is associated with elevated levels of inflammatory markers, since it is a metabolically active region, inducing cytokine production. The arm perimeter (AP) can also reflect subcutaneous adipocyte tissue buildup in the organism [12].

Nevertheless, it is not well established if the inflammation found in CKD in HD treatment patients is related to lean mass loss or adipocyte tissue buildup in the abdominal region. To this end, the present study aims to evaluate the nutritional status of patients and the relationship between inflammatory cytokines with WP, AP, HGS, and ATM, used during nutritional evaluation of CRF patients submitted to HD. This evaluation may even be used as a replacement for monitoring metabolic and body changes in patients under HD through more accessible and less expensive practices.

2. Methods

2.1. Patients

A transversal descriptive study was performed with available samples from CRF patients treated at a HD center over a period of 3 months. The criteria for selection were being a patient in dialytic treatment, and being over 18 years of age. The exclusion criteria were patients with diseases – other than malnutrition and/or changes relative to the underlying disease - that could exert a negative influence on localized or general muscle trophism, patients with altered level of consciousness, unaccompanied, and patients with any degree of edema, which may interfere in the measurements. Demographic data (age and gender) were collected from medical records. This research was approved by the ethical committee at University of Potiguar Research Center, under opinion number 063196/2014. Patients signed a free and informed consent form and could leave the study at any time they willed.

The anthropometric nutritional state indicators used were: height, weight, body mass index (BMI), WP, and AP. In addition, HGS and ATM depth were assessed. All the measurements were conducted by trained professionals to meet scientific criteria. The BMI, WP, AP, ATM and HGS were measured after each hemodialysis procedure.

The inflammatory markers collected and analyzed were the serum inflammatory cytokines IL-2, IL-6, and TNF-α.

2.2. Height and Weight

The first step was to confirm the correct template for the paper size. The template was tailored for output on the A4 paper size.

Weight and height were measured after the hemodialysis procedures. From patients' height and weight measurements, the BMI was calculated according to the World Health Organization (WHO) standards. Elderly patients' levels were assessed as proposed by Lipschitz [13].

2.3. Arm and Waist Perimeters

The sum of the areas from bone, muscle, and fat tissues of the arm represents the AP [14]. This measurement was performed as to Lohman et al. [15], comparing reference values from the NHANES (National Health and Nutrition Examination Survey) [16], demonstrated by the percentile table from Frisancho [17]. The WP was measured by

surrounding the patient with the flexible tape measure in the natural waist line (in the narrower region between the thorax and the hip, at the midpoint between the last rib and the iliac crest), at the time of expiration. It was measured and classified according to the WHO standards [18].

2.4. Muscle Mass

The measurement of ATM was obtained from patients in a seating position, with the arm contralateral to the vessel under assessment (arteriovenous fistulae) and the anterior dominant hand position supported by the patient's knee and elbow at a 90° angle.

A Sanny adipometer (clinical module, with a measurement range between 0 and 55 mm) with a continuous applied pressure of 10 g/mm^2 was used. The technique advocated by Lameu et al. [19] was used to pinch the adductor muscle on the imaginary triangle vertices formed by the thumb and index finger extensions. The results displayed were the mean for both sexes and were referenced according to Oliveira et al. [20]. The mean was calculated after three measures and the mean continuous pressure for each patient was obtained.

The HGS measures were collected through digital dynamometry (DAYHOME®, EH 101-37, with a maximum capacity of 90 kg and a scale of 1g). For the HGS evaluation, patients were guided to remain seated on an adjustable bench according to their height. The shoulder remained in a neutral position, with the elbows at a 90° angle and the wrist in a neutral position (intermediate between pronation and supination) while the evaluator sustained the dynamometer. Patients were also advised to perform the HGS test after the supervisor's command. Three repetitions were made for the dominant and non-dominant hands (5 seconds per measurement) with the mitt set on position two (according to the instrument), alternating the hand movement. The dominant hand was tested first, followed by the non-dominant hand, carefully following the instrumentation of the apparatus. The interval between one attempt and the next on the same hand was 1 minute, to avoid muscle fatigue during the test [21]. The results were displayed as mean and standard deviation from the two measurements, considering the Bonnahon [22] classification with reference values for men and women (dominant hand: men = 50.6 kg, women = 30.9 kg and non-dominant hand: men = 45.2 kg, women = 28.8 kg).

2.5. Inflamatory Markers

After enrollment and selection, patients had their venous blood drawn followed by IL-2, IL-6, and TNF-α measurements. All patients received standard treatment, no medication was added or withdrawn because of the study, and blood sampling was performed after the end of the study. Samples were centrifuged and stored at 80 °C for posterior analyses. Serum levels of IL-2, IL-6, and TNF-α were determined by the ELISA technique using a commercial kit from R&D Systems (Minneapolis, MN, EUA), following the manufacturer's instructions. The manufacturer's reference values for cytokines are the following: IL-2, <0.1 UI/mL; IL-6 <6.4 pg/mL; and TNF-α <8.1 pg/mL.

2.6. Statistical Analyses

All data were stored in a Microsoft Office Excel 2010® spreadsheet and analyzed using the GraphPad Prism 7.0 software. A descriptive analysis of the data was performed with mean and standard deviation. Variables were analyzed regarding normality through the Kolmogorov–Smirnov test and the degree of association between variables through the correlation coefficient r of the Spearman test. Significant levels of 5% ($p < 0.05$) were chosen for all the analyses.

3. Results and Discussion

In this study, a total of 34 patients were selected, being 14 female (41%) and 20 male (59%), and the mean age was 50.35 ± 11.29 years. Interestingly, the prevalence of the male gender in hemodialysis procedural studies has also been reported by Jaqueto et al [23].

Table 1 summarizes the descriptive statistical analysis, displaying the average values and standard deviations of the main analyzed variables regarding both of the genders.

Table 1. *Description of the profile for the 34CKD patients evaluated during the three months.*

Variable	Mean (± STDV)	Classification
Age	50.35 ± 11.29	Adults
Weight (kg)	60.8 ± 11	Eutrophy (109% the adequate)
MG (%)	59	-
FG (%)	41	-

MG – Male gender; FG – female gender.

The average weight from the 59 patients submitted to HD observed was 67.0 ± 14.7 kg. This result is very similar to the findings of Barros et al. [24]. Although malnutrition is a critical issue in CKD patients under HD, overweight/obesity is also observed.

The patients in this study presented malnutrition and eutrophy, according to their BMI. This index is considered an important marker for the nutritional state in patients submitted to HD. Patients presenting malnutrition and inflammatory conditions have a higher risk for death due to cardiovascular diseases, due to their greater susceptibility to inflammation. Furthermore, when there is an association between BMI and other nutritional parameters (WP and AP), a body compositional change, such as adipose tissue buildup and muscle loss, can be inferred. These changes are common in HD patients and can estimate further risks [10]. Other studies demonstrate a relation between visceral fat and atherosclerosis, insulin resistance [25], and inflammatory processes [26]. Although HD patients usually present subcutaneous fat loss, they also present an increase in visceral adipocyte tissue, as observed by their elevated WP [27]. The data regarding AP and WP for the evaluated patients corroborates previous findings reported in the literature, since they presented visceral fat accumulation and subcutaneous fat decrease. Visceral fat releases 2–3-fold more IL-6 than subcutaneous fat [26], which

implies that these tissues are biologically different [28].

The research showed (Table 2) an increase in inflammatory markers, as indicated by the IL-2 (0.14 ± 0.08), which did not present detectable physiological levels. Moreover, average IL-6 (19.73 ± 4.67 pg/mL) and TNF-α (9.79 ± 5.21 pg/mL) levels were higher than the reference values described by Saldanha et al. (IL-6 = 2.7 ± 0.3 pg/mL and TNF-α = 2.3 ± 1.2 pg/ml, respectively) [29].

Table 2. *Inflammatory cytokines serum levels from 34 patients with CKD evaluated during three months.*

Variables	Mean (± STDV)	Classification
IL-2 (UI/ml)	0.14 ± 0.08	Over the adequate
IL-6 (pg/ml)	19.73 ± 4.67	Over the adequate
TNF-α (pg/ml)	9.79 ± 5.21	Over the adequate

IL – Interleukin; TNF-α– Tumor necrosis factor.

This increase in inflammatory markers is expected for HD patients with chronic kidney failure. This condition increases oxidative stress, and due to body exposure to the HD procedure, the immunological response is more active, releasing even more cytokines [30, 31]. These cytokines promote protein catabolism and muscle mass loss, further to being proatherogenic, which contributes to cardiovascular diseases in CKD patients [32, 33]. Thus, these higher levels of cytokines may lead to CKD and potentiate metabolic changes, leading to a body compositional change. This condition results in lean mass loss and increased visceral fat (Table 3), which can predict mortality in HD patients.

Figure 1 shows the correlation between WP (female and male 88 ± 6.78 and 95 ± 8.34, respectively) and inflammatory cytokines (IL-2, IL-6, and TNF-α). There is a noticeable association between these results: the higher the WP, the stronger the inflammatory response. These data are in accordance with the findings of Kershaw and Flier [34], who reported that the increase in body fat in CKD patients induces metabolic changes, including an increase in the inflammatory state.

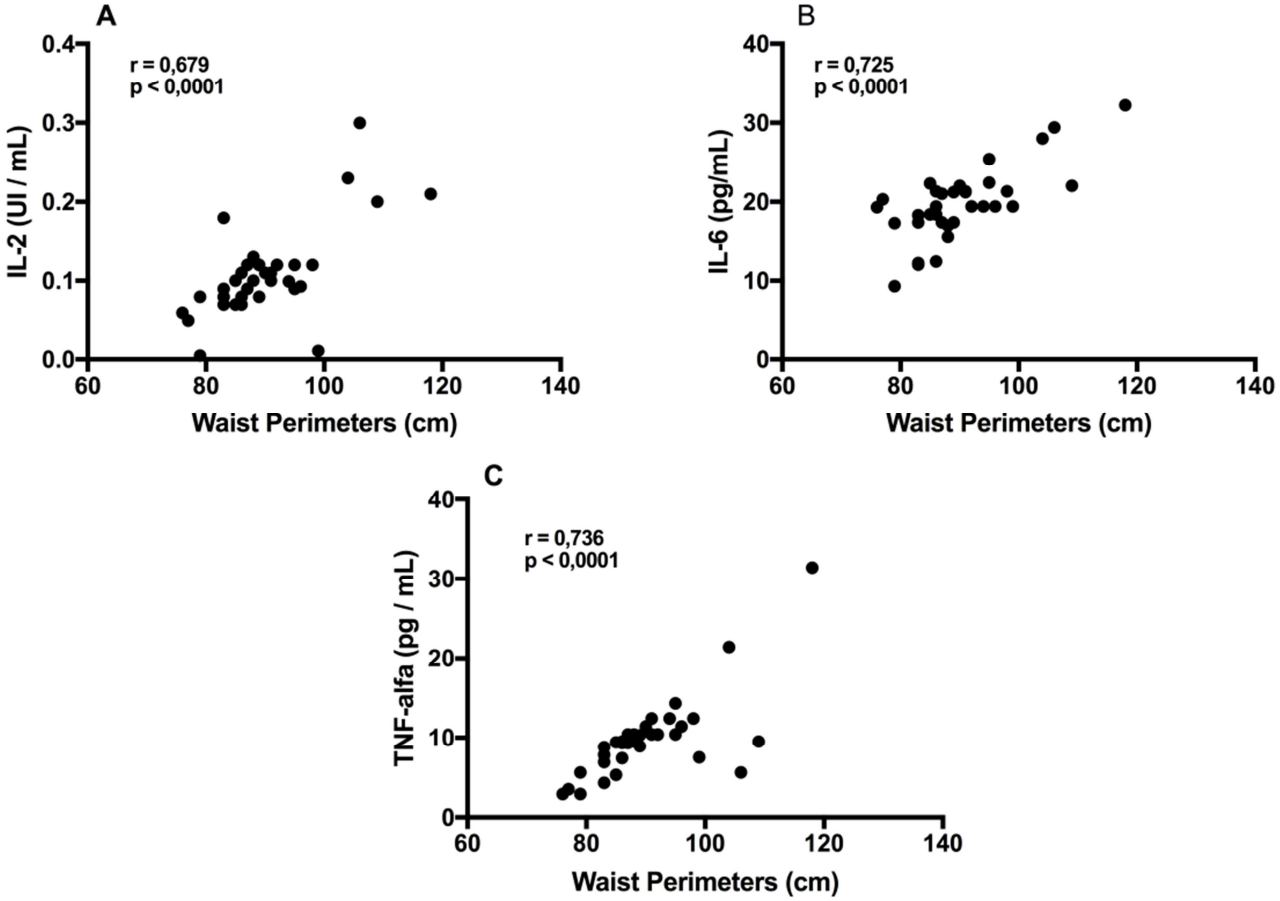

Figure 1. *Relation between waist circumference and digital cytokines (IL-6, IL-2 and TNF-alpha).*

The IL-6 cytokine has a powerful influence on the HD patients' mortality. It is estimated that approximately 20% of the total serum concentration originates from adipose tissue [35]. Moreover, studies suggest that the IL-6 is a proatherogenic cytokine that stimulates the soluble intercellular adhesion molecule-1 (Sicam-1). This component mediates leukocyte migration and adhesion on the endothelial surface [36], thus being able to trigger atherosclerosis through metabolic, endothelial, and clotting mechanisms [31].

A functional impairment was also observed by means of the HGS (17.03 ± 14.24 kg), evaluated according as to Bonnahon [22]. This evaluation considered the age of the population studied.

Some studies show that the HGS is the best morbidity

marker for HD patients due to the influence of this procedure on functional capability [37]. During treatment, patients present a variety of restrictions to physical activities. This condition can, thus, lead to a sedentary lifestyle, which may reduce the ability to perform activities with minimal effort requirements. This also leads to functional capability impairment, which represents a higher mortality risk due to the low HGS for both genders [38].

Sarcopenia, caused by lean mass loss associated with muscle strength reduction, has a strong relation with low HGS. This condition is common in CKD patients submitted to HD, and some studies report a high prevalence of sarcopenia in this population [39].

When correlating HGS and cytokines, the only association observed was that of HGS with IL-6 and TNF-α (Figure 2 A-B). These findings are in line with the data analyzed (Table 3). These cytokines may be involved in the inflammatory responses for those patients, especially when due to visceral fat buildup, observable by an increase in WP measurements and a decrease in HGS. Adipocyte tissue localized at the waistline is considered an endocrine organ and is related to inflammatory cytokine release, mainly that of IL-6 and TNF-α [40]. A correlation with AP was not observed.

Table 3. *Nutritional evaluation for the 34 patients with CKD evaluated during three months.*

Variables	Mean (± STDV)	Classification
Nutritional state evaluation		
BMI 18.5-24.9	22.6± 2.12	Eutrophic
BMI < 18.5	14.7± 1.23	Malnourished
AP Men	28.1± 3.12	Below average
AP women	25.49± 2.89	Below average
WP men	95 ± 8.34	High risk of metabolic complications
AP women	88 ± 6.78	High risk of metabolic complications
Lean mass estimate		
HGS (kg)	17.03 ± 14.24	Below average
ATM (mm)	15.97 ± 7.53	Eutrophic

ATM – Adductor thumb muscle; HGS – Hand grip strength.

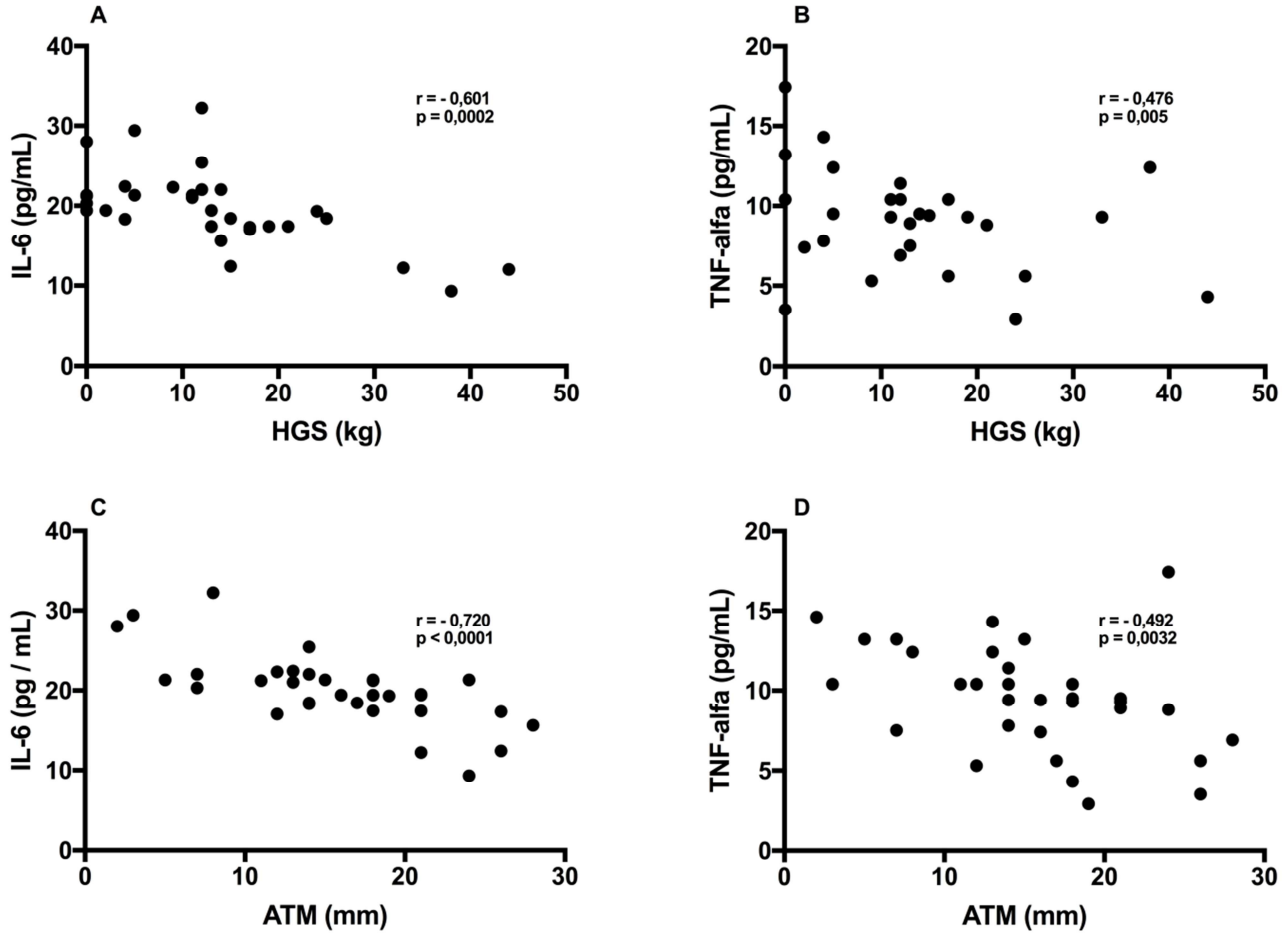

Figure 2. *Thumb peristalter index and inflammatory cytokines (IL-6, IL-2 and TNF-alpha).*

On the other hand, correlations between HGS and the IL-6 cytokines ($r = 0.601$; $p = 0.0002$) and TNF-α ($r = 0.476$; $p = 0.005$) were negative. This may indicate that the lower the HGS, the higher the inflammatory response. These data corroborate previous studies which show correlation between increased proteolysis and an elevated inflammatory response [41, 42]. Studies on the involvement of proteolytic pathways in muscles demonstrate that these routes in HD patients are neither upregulated nor overly active [43, 44]. Therefore, HGS can be a simple, affordable, and practical tool for muscle mass loss assessment. In this study, there was a huge proportion of patients evaluated through the HGS with functional capability impairment, possibly derived from functional losses as described above.

Furthermore, some studies presented a relation between inflammation and malnutrition, which derives from protein catabolism, lower albumin synthesis, and appetite inhibition [45]. Interestingly, inflammatory cytokines can reduce appetite, increase leptin levels [46], reduce motility, and modify gastric secretion [47].

Regarding the ATM, mean levels obtained from these patients (15.97 ± 7.53) were increased in comparison with those reported by Oliveira et al. (11.85 ± 1.63) [20]. It is of great matter that these patients maintain their muscle mass. Recent studies reported that ATM depth is an important muscle mass marker in some clinical cases. Oliveira et al. [48] and Bragagnolo et al. [49] showed there is a good correlation between ATM thickness and anthropometric parameters, which evaluate the percentage of fat and lean mass in HD patients. However, not all studies reported the use of this marker for nutritional state evaluation.

There is also a negative correlation between ATM and the inflammatory cytokines IL-6 and TNF-α ($r = 0.720$; $p < 0.0001$) (Figure 2 C-D). Interestingly, the same condition was observed when compared to the HGS, another lean mass estimative tool. It is well established that a cytokine increase can influence the patient's metabolic rate, leading to fat and muscle mass loss [11]. The majority of the patients evaluated in this study, as to their BMI, presented eutrophy. However, lean mass and subcutaneous fat loss were also detected by the HGS and AP, respectively. Additionally, fat buildup in the visceral region was detected.

Altogether, the data obtained from these evaluations show that patients suffer not only a body compositional change, represented by lean mass loss, but also a body fat redistribution (visceral and subcutaneous). Therefore, the ATM evaluation of all the patients at this stage of the disease was not very efficient to detect lean mass loss, even though it was still present. Moreover, Agarwal et al. [50] showed that an increase in vascular permeability, stasis, or vasodilatation can lead to edema. This is usually common in HD patients and can be an interference factor for the correct ATM assessment. However, the ATM and HGS presented a negative correlation with the evaluated cytokines (IL-6 and TNF-α) in this study. Thus, they represent markers related to imminent inflammatory risks in these patients.

Among the inflammatory markers, it is known that TNF-α can lead to anorexia (common in CKD) [51], lipolysis, and oxidation [52]. This, in turn, triggers the ATP-dependent ubiquitin-proteasome pathway, which can worsen protein ingestion, resulting in proteolysis and insulin resistance and complicating muscle mass gain [53].

For these reasons, the inflammatory contribution to the PEM has been studied in HD patients, due to its anorectic and catabolic effects. Ikizler et al. [54] observed that during HD there was an increase in total body (10%) and muscle (133%) proteolysis. A variety of factors is associated with muscle mass loss in CKD, such as appetite and hormone alterations and physical inactivity. The latter is a common factor which induces not only malnutrition but also muscle atrophy in HD patients. Hence, patients present a significant decrease in ATM and HGS levels [55].

Cytokine levels detected in patients included in this study, during the evaluation and analysis periods, seem to be related to adipocyte tissue accumulation in the abdominal region rather than lean mass loss, even though it is still present as demonstrated above.

4. Conclusions

Chronic kidney disease is associated with elevated inflammatory cytokines and PEM, due to body compositional changes in HD patients. Furthermore, in this study HD patients presented an increase in WP, which contributed to elevated inflammatory cytokines levels. In those patients, lean mass loss was detected by HGS reduction, even when the majority of them presented a eutrophic nutritional state. Thus, this study is regarded as relevant and brings up a clinical aspect common in CKD patients submitted to HD. Increased WP, which is not well discussed in the literature, and plays a key role in the inflammatory state that can lead to CKD complications. Therefore, this subject must receive more attention from health professionals, especially regarding the nutritional state of CKD patients submitted to HD. Further research is needed in order to confirm the alternative of replacing the inflammatory markers with the anthropometric measures in the hospital for dialysis patients.

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