Association between body fat, inflammation and oxidative stress in hemodialysis

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Abstract

Introduction: The presence of malnutrition has been associated with inflammation and oxidative stress (OS) in patients on chronic hemodialysis (HD). **Objective:** To assess the association between nutritional status markers, such as body fat (BF), markers of inflammation and of OS in patients on HD. **Methods:** Cross-sectional study performed with 40 patients on HD. The nutritional status was evaluated by use of the modified subjective global assessment (SGAm), normalized total protein equivalent of nitrogen appearance (PNAn), serum albumin (Alb-s), body mass index (BMI), BF, and lean body mass (LBM). Inflammation and OS were assessed by use of high-sensitivity protein C-reactive (HS-PCR), interleukin-6 (IL-6), advanced oxidation protein products (AOPP), 8-hydroxydeoxyguanosine (8OHdG), and pentosidine. **Results:** Some degree of malnutrition was observed in 37% of the patients assessed through SGAm. Median and variation of BF (kg) were 16.2 and 5.3-36.7, respectively. Regarding the markers of inflammation and of OS, a positive and significant correlation was observed between BMI and HS-PCR ($R = 0.37$; $p = 0.02$), BF and HS-PCR ($R = 0.32$; $p = 0.04$), and between HS-PCR and IL-6 ($R = 0.51$; $p = 0.0007$). A negative correlation was found between Alb-s and HS-PCR ($R = -0.31$; $p = 0.05$). Only in males HS-PCR related to BMI ($R = 0.54$; $p = 0.01$) and to BF ($R = 0.52$; $p = 0.01$). No association was found between markers of inflammation and of OS. **Conclusion:** Markers of malnutrition and of overweight did not correlate with OS. The association of HS-PCR with BMI and BF only in the male sex may suggest differences in the inflammatory response between the sexes.

Keywords: inflammation, oxidative stress, nutritional status, hemodialysis.

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Introduction

Protein-energy malnutrition (PEM) is a consistent finding in a large proportion of patients with chronic kidney disease (CKD). In those patients, PEM has been suggested to result from a chronic inflammatory process.[1,2] The combination of factors, such as uremic syndrome per se, heart failure, persistent infections, bioincompatibility of the dialyzer membrane, and the build-up of advanced glycation end-products, may contribute to the development of inflammation in that clinical condition.[3,4]

Associations between malnutrition, high levels of C-reactive protein protein C-reactive (PCR), and the presence of atherosclerosis in patients with CKD have been reported.[5,6] In those patients, high levels of PCR seem to affect the generation of pro-inflammatory cytokines [interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor α (TNF-α)].[7,8] In fact, high levels of those cytokines may induce muscle mass loss, reducing albumin synthesis, inhibiting appetite, and contributing to the development of malnutrition.[9] In addition, the association of inflammation and oxidative stress (OS) has been reported in patients with CKD. Oxidative stress occurs in inflammation sites, during small injuries, and as part of the reaction to invasive microorganisms.[10] That reaction causes the production of several reactive oxygen species (ROS), generating modified macromolecules, which then could be involved in the atherogenic process.[5]

In addition, the association between body fat (BF), inflammatory markers, and OS has been investigated.[3,11] The adipose tissue is a complex organ with functions

other than energy storage, and secretes several adipokines, such as TNF-α, IL-6, type 1 plasminogen activator inhibitor (PAI-1), PCR, resistin, and acylation stimulationstimulating protein. [12-15] In the general population, mortality rate is known to decrease when body mass index (BMI) is low. [16] On the other hand, in patients on hemodialysis (HD), a direct relation between obesity and survival persists with a wide variation in body weight. [13] In view of that, the present study investigated the associations between nutritional status markers, such as BF, inflammatory markers, and OS markers in stable patients on chronic HD.

Pacients and Methods

At the beginning, 150 patients of three dialysis centers in the city of Curitiba, Paraná sState, Brazil, were assessed. The inclusion criteria were as follows: age greater thanover 18 years and minimum dialysis time in the program of three months. Patients with acute inflammatory disease (systemic lupus erythematosus and rheumatoid arthritis), infections, malignanciesneoplasia, alcohol abuse, and liver diseases were excluded from the study. Considering the criteria, 40 stable patients on HD were qualified to take part in the study, which was approved by the Committee on Ethics of the Hospital Universitário Evangélico de Curitiba. Written informed consent was provided by all patients.

All patients were on HD for 3-4 hours/day, three times a week, using an arteriovenous fistula with modified cellulose membranes (cellulose acetate or cellulose derivatives). The medications used were as follows: human recombinant erythropoietin; iron saccharate; phosphorus chelating agents with calcium; oral active vitamin D; and antihypertensive agents (beta-blockers, calcium channel blockers, furosemide, angiotensin-converting enzyme inhibitors).

Nutritional Assessment

The patients underwent a nutritional assessment 15 to 30 minutes after HD session. The nutritional assessment was performed by a trained nutritionist and comprised the following: dry weight (kg) (scale Filizola S/A, São Paulo, Brazil); height (cm); BMI (kg/m^2); arm circumference (AC) (cm); skinfolds (mm); modified subjective global assessment (SGAm); and protein equivalent of nitrogen appearance (PNA).

The SGAm aimed at assessing the presence of malnutrition. The method consists in collecting historical data from the patient, such as weight loss, food intake, gastrointestinal symptoms, functional status, comorbidities, and period of time on dialysis time. Then, a nutritional physical examination is performed to assess the reserves of muscle mass and body fat, in addition to the presence of edema and ascites. According to the final result, the patients are classified into well nourished or malnourished.[17] Current protein intake was estimated by calculating the PNA, as previously described.[18] The result in grams was normalized to body weight (PNAn).

The BMI was calculated by dividing the dry weight by the square of the height. According to the WHO guidelines[19], the cutoff point ≥ 25.0 kg/m^2 was used to classify overweight. Four skinfolds (triceps, biceps, subscapular, and suprailiac) were measured on the side without the arteriovenous fistula, with a calibrated plicometer (Sanny American Medical, São Bernardo do Campo, Brazil). Each skinfold was measured three times, and the final result for each was the arithmetic mean. The percent body fat (%F) was estimated by the sum of the four skinfolds and application of the Durnin & Womersley table.[20] The BF in kilograms (kg) was calculated considering the result of %F and total body weight. The reserve of lean body mass (LBM) was calculated by subtracting BF in kilograms from body weight. The nutritional status was correlated with markers of inflammation and of OS.

Laboratory Analysis

Venous blood samples were collected in a midweek morning before a dialysis session. Blood was centrifuged at 3000 G for ten minutes. The supernatant was transferred to a new tube stored at -80º C until analysis. Serum albumin (Alb-s) was determined through the bromocresol purple method. High sensitivity PCR (HS-PCR) was performed with nephelometry. Plasma IL-6 was analyzed by using enzyme-linked immunosorbent assay (ELISA, Ortho, Raritan, USA).

To assess OS, advanced oxidation protein products (AOPP) and pentosidine were analyzed as previously described.[21,22] Because plasma pentosidine is highly bound to albumin,[23] its concentrations (pmol/l) were corrected by Alb-s. That marker was expressed as plasma pentosidine content (pmol) per mg of albumin.[24] Serum 8-hydroxydeoxyguanosine (8-OHdG) was measured by use of competitive ELISA (Japan Institute for the Control of Aging, Fukuroi, Shizuoka, Japan). The test uses the monoclonal antibody, and its normal level ranges from 0.12 to 10.0 ng/mL.[25]

Statistical Analysis

Data are shown as mean ± standard deviation (SD) or median. Values of $p < 0.05$ indicated statistical significance. The statistical analysis was performed

using NCSS 2001 and PASS 2002 (Hintze J. NCSS & PASS Statistical System Kaysville, Utah). The two groups were compared by using the Student t test for normally distributed variables, or the Mann-Whitney U test or Kruskal-Wallis test for non-normally distributed variables. The study of categorical variables was performed by analyzing contingency tables. Non-normally distributed variables were correlated by using the Spearman test. For assessing the influence of explicative variables in the markers, the Fisher exact test was adopted.

Results

The study comprised 40 patients (mean age, 52 ± 11 years; 21 males). The causes of CKRD were as follows: chronic glomerulonephritis (n = 18; 45%); hypertensive nephrosclerosis (n = 13; 32.5%); diabetic nephropathy (n = 7; 17.5%); and others (n = 2; 5%). The clinical and biochemical characteristics of the patients on HD are shown in Table 1. Approximately 63% of the patients were considered well nourished by the SGAm, and 50% had BMI ≥ 25.0 kg/m², indicating overweight. The

Table 1 Clinical and biochemical characteristics of patients on chronic hemodialysis

Parameters	Total (n = 40)	Male (n = 21)	Female (n = 19)
Age (years)†	52 ± 11	50 ± 10	54 ± 12
Time on dialysis (months)‡	17.95 (3.20 - 73.70)	16,70 (3,50 - 73.70)	19.50 (3,20 - 52.10)
Kt/V†	1.31 ± 0.15	1.26 ± 0.13	1.35 ± 0.16
SGAm (well nourished %)	63%	62%	63%
PNAn (g/kg/d)†	1.00 ± 0.24	0.91 ± 0.24	0.88 ± 0.18
Albumin (mg/dL)†	3.65 ± 0.35	3.70 ± 0.39	3.60 ± 0.31
IMC (kg/m²)†	25.24 ± 4.67	24.37 ± 3.01	26.20 ± 5.94
MCM (kg)†	48.67 ± 9.50	54.69 ± 7.58	42.01 ± 6.53*
GC (kg)‡	16.20 (5.30 - 36.70)	13.10 (5.30 - 23.20)	20.80 (6.40 - 36.70)*
PCRas (mg/L)‡	3.40 (0.10 - 97.80)	2.80 (0.10 - 31.60)	3.70 (0.10 - 97.80)
IL-6 (pmol/L)‡	2.65 (0.40 - 10.80)	2,50 (0,40 - 6,30)	3.20 (1.50 - 10.80)
PPOA (µmol/L)‡	145.26 (87.01 - 368.38)	144.47 (87.01 - 368.38)	151.18 (100.91 - 256.09)
8OHdG (pmol/L)‡	0.44 (0.13 - 0.75)	0.45 (0.22 - 0.75)	0.43 (0.13 - 0.65)
Pentosidine/Albumin (pmol/mg)†	541.16 ± 248.18	561.82 ± 246.59	518.33 ± 254.64

† Values expressed as mean ± SD; parametric Student t test
‡ Values expressed as median and variation; nonparametric Mann-Whitney test
* p < 0,05; Kt/V: calculation of urea kinetics; SGAm: modified subjective global assessment; PNAn: normalized protein equivalent of nitrogen appearance; BMI: body mass index; LBM: lean body mass; BF: body fat; HS-PCR: high-sensitivity protein C-reactive; IL-6: interleukine-6; AOPP: advanced oxidation protein products; 8OHdG: 8-hydroxydeoxyguanosine.

patients classified as malnourished by SGAm had a mean BMI and median BF significantly lower than those in the well-nourished group (Table 2). The group of patients with BMI ≥ 25.0 kg/m² had a median BF significantly higher than that with BMI < 25.0 kg/m² (Table 3).

No correlation was found between the nutritional markers of malnutrition. However, a positive and significant correlation was found between BMI and BF (R = 0.78; p = 0.001), BMI and HS-PCR (R = 0.37; p = 0.02), and between BF and HS-PCR (R = 0.32; p = 0.04) (Figure 1). Male patients had a positive and significant correlation between BMI and HS-PCR (R = 0.54; p = 0.01), and between BF and HS-PCR (R = 0.52; p = 0.01) (Figure 1). Those associations were not found in the female group.

A negative and significant correlation was observed between Alb-s and HS-PCR (R = -0.31; p = 0.05), and a positive correlation was observed between HS-PCR and IL-6 (R = 0.51; p = 0.0007). No correlation was observed between the nutritional markers (SGAm, PNAn, and LBM) and the inflammatory markers (HS-PCR and IL-6). Finally, no significant correlation was found between the nutritional parameters and the OS markers (Tables 2 and 3).

Table 2 Clinical and biochemical characteristics according to the Subjective Global Assessment

	Well nourished (n = 25)	Malnourished (n = 15)	p
Female sex (%)	30.00	17.50	NS
Male sex (%)	32.50	20.00	NS
Age (years)†	51 ± 12	53 ± 10	NS
Dialysis time (months)‡	19.50 (3.20 – 71.90)	16.30 (3.80 – 73.70)	NS
Kt/V†	1.30 ± 0.14	1.31 ± 0.19	NS
PNAn (g/kg/d)†	1.07 ± 0.22	0.93 ± 0.14	< 0.05
Albumin (mg/dL)†	3.60 ± 0.32	3.73 ± 0.40	NS
BMI (kg/m2)†	26.62 ± 4.18	22.96 ± 4.66	< 0.05
LBM (kg)†	50.30 ± 9.70	45.96 ± 8.82	NS
BF (kg)‡	18.40 (8.70 – 36.70)	13.30 (5.30 – 31.00)	< 0.05
HS-PCR (mg/L)‡	3.40 (0.10 – 97.80)	2.80 (0.10 – 33.20)	NS
IL-6 (pmol/L)‡	2.50 (0.40 – 8.90)	3.20 (1.10 – 10.80)	NS
AOPP (µmol/L)‡	148.87 (105.76 – 281.69)	143.75 (87.01 – 368.38)	NS
8OHdG (pmol/L)‡	0.44 (0.22 – 0.65)	0.40 (0.13 – 0.75)	NS
Pentosidine/Albumin (pmol/mg)†	521.20 ± 250.44	574.43 ± 249.33	NS

† Values expressed as mean ± SD; parametric Student t test
‡ Values expressed as median and variation; nonparametric Mann-Whitney test
Kt/V: calculation of urea kinetics; PNAn: normalized protein equivalent of nitrogen appearance; BMI: body mass index; LBM: lean body mass; BF: body fat; HS-PCR: high-sensitivity protein C-reactive; IL-6: interleukine-6; AOPP: advanced oxidation protein products; 8OHdG: 8-hydroxydeoxyguanosine.

Table 3 Clinical and biochemical characteristics according to body mass index.

	IMC < 25,00 kg/m² (n = 20)	IMC ≥ 25,00 kg/m² (n = 20)	p
Age (years)†	51 ± 12	52 ± 10	NS
Dialysis time (months)‡	14.15 (3.20 – 73.70)	19.50 (3.20 – 71.90)	NS
Kt/V†	1.35 ± 0.17	1.26 ± 0.12	NS
PNAn (g/kg/d)†	1.04 ± 0.22	0.99 ± 0.19	NS
Albumin (mg/dL)†	3.65 ± 0.39	3.64 ± 0.31	NS
LBM (kg)†	45.74 ± 9.66	51.60 ± 8.61	NS
BF (kg)‡	12.85 (5.30 – 20.80)	25.55 (9.80 – 36.7)	< 0.05
HS-PCR (mg/L)‡	2.25 (0.10 – 33.20)	4.80 (0.20 – 97.80)	NS
IL-6 (pmol/L)‡	2.50 (0.40 – 10.80)	2.80 (1.10 – 8.90)	NS
AOPP (µmol/L)‡	150.03 (87.01 – 368.38)	142.46 (100.91 – 281.69)	NS
8OHdG (pmol/L)‡	0.48 (0.28 – 0.75)	0.42 (0.13 – 0.62)	NS
Pentosidine/Albumin (pmol/mg)†	604.30 ± 268.02	478.03 ± 214.95	NS

† Values expressed as mean ± SD; parametric Student t test
‡ Values expressed as median and variation; nonparametric Mann-Whitney test
Kt/V: calculation of urea kinetics; PNAn: normalized protein equivalent of nitrogen appearance; LBM: lean body mass; BF: body fat; HS-PCR: high-sensitivity protein C-reactive; IL-6: interleukine-6; AOPP: advanced oxidation protein products; 8OHdG: 8-hydroxydeoxyguanosine.

Discussion

In the present study, the most significant finding was the correlation of BMI and BF with HS-PCR, especially in male patients on HD. Thus, inflammation seems to be more correlated with excessive fat and body weight than their deficiency, and differences in the inflammatory response between the sexes seem to coexist. On the other hand, oxidative stress apparently has no close relation to the routine markers of malnutrition or overweight. Recent studies have shown an association of BMI and BF with inflammatory markers.[26,27] High BF apparently activates the inflammatory cascade. In fact, the adipose tissue is complex, with functions that go beyond the simple storage of energy. It is an active system that secretes several adipokines (TNF-α, IL-6, IPA-1, PCR, resistin, and PEA) that contribute to systemic inflammation.[14,15,28] In a cross-sectional analysis of the MDRD (Modification of Diet in Renal Disease) study, a positive correlation was found between PCR and BMI[28] in patients in the pre-dialysis phase. In that study, patients with high BMI and PCR had a higher prevalence of cardiovascular disease (CVD). Additionally, Beddhu *et al.* [29], analyzing 70,028 patients on dialysis, have shown that a BMI elevated due to an increase in BF was correlated with an increase in the prevalence of atherosclerosis, and, subsequently, with an increase in mortality. This shows that traditional risk factors for CVD, such as overweight, are relevant in the population with CKRD.[29]

More recently, the distribution of BF has been suggested as another important aspect. In the present study, the positive correlation of BF and BMI with HS-PCR has been found only in men. The reasons for that are not clear, but, depending on the location of the adipose tissue, distinctions in the endocrine and metabolic functions may be found. Visceral fat has already been known to be more common in male patients.[30] Metabolic disorders and CVD are associated with visceral fat, but not with subcutaneous deposits.[30] In patients with CKRD, Axelsson *et al.* [14] have shown that the visceral fat in the trunk is a metabolically active deposit and may be the key-factor for developing resistance to insulin and premature atherosclerosis. According to Fried *et al.* [31], the omental adipose tissue produces three times more IL-6 than the subcutaneous adipose tissue. It has been proposed that adipose cells of several regions have different origins, and, thus, express different genes, such as leptin, TNF-α, angiotensinogen, and IPA-1.[32] The mechanisms responsible for the differences in storage in the adipose tissue are still unknown, and further studies are required to investigate those findings.

Modified global subjective assessment is a reliable tool for assessing early malnutrition.[33] In our study, patients classified as malnourished according to SGAm had significantly lower values of BMI and BF, which would be expected. However, analyzing the results that reflect the PNAn of the patients, associations of that marker of malnutrition with markers of inflammation and of OS could not be found. As previously shown in Brazilian patients on HD [34], associations between markers of malnutrition and of inflammation coexist, but are not necessarily interrelated in patients with CKRD. Pupim *et al.*[35] have reported that nutritional markers were independently associated with mortality despite the presence of inflammation. Thus, malnutrition, inflammation, and OS have been suggested to be independent risk factors for mortality, but they frequently coincide.

The lack of correlation between the markers of nutrition, inflammation, and OS could be partially explained by the susceptibility of OS markers to other variables, such as antioxidant food intake.[36] The reduction in vitamin levels, mainly the hydrosoluble ones, may occur due to restrictive diets in an attempt to avoid hyperkalemia. Another explanation is that the majority of our patients had normal levels of albumin and were not malnourished. Danielski *et al.*[37] have shown that the levels of markers of inflammation and of OS were increased in patients with hypoalbuminemia as compared with those of normoalbuminemic patients. Similarly, Stenvinkel *et al.*[38], using plasmalogen as a marker of OS, have shown that malnourished patients on HD had an increase in OS as compared with the properly nourished group. Therefore, the lack of association between inflammation and OS may be influenced by the low prevalence of malnutrition, as well as by the antioxidant effect of albumin.

Although several other studies have shown an association between inflammatory markers and OS in patients with CKRD [10,39,40], the present study has not found the same correlations. Some limitations of the present study should be stressed. First, the lack of association between the markers of nutrition, inflammation, and OS may have been due to the small size of the sample. Second, the assessment of BF distribution could have been relevant to explain the fact that HS-PCR correlated with BF only in the male group. Finally, assessing the serum levels of antioxidants in the population studied could help to determine the actual OS status of that population.

Conclusion

In conclusion, the present study suggests that malnutrition is not necessarily associated with inflammation and with OS in patients on HD. However, the association between BF and inflammation in the male population may indicate a difference in the inflammatory response between sexes, which should be confirmed with controlled studies involving a larger number of patients

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