Associação dos marcadores do estado oxidativo e inflamatório com a desnutrição em pacientes hemodialisados com ferritina menor do que 500 ng/mL

The association of markers of oxidative-inflammatory status with malnutrition in hemodialysis patients with serum ferritin lower than 500 ng/mL

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Data de submissão: 24/10/2011.
Data de aprovação: 17/12/2012.

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DOI: 10.5935/01012800.20130002

Abstract

Introduction: Enhanced inflammatory-oxidative status is well established in chronic kidney disease. **Objective:** The objective of this study was to evaluate the oxidative- inflammatory status and iron indices in patients undergoing maintenance hemodialysis (HD) with serum ferritin lower than 500ng/mL, and to correlate them with nutritional status. **Method:** In a cross-sectional survey 35 HD patients (23 with normal nutritional status, 12 with Protein-Energy-Wasting syndrome, PEW), and healthy volunteers (n = 35) were studied. Serum concentration of iron, ferritin, transferrin saturation, malondialdehyde (MDA), protein carbonyl (PC), high-sensitive serum C - reactive protein (hs-CRP) and blood counts were determined. The nutritional status was determined by anthropometric and biochemical criteria. **Results:** HD patients showed low values of hemoglobin and higher values of ferritin, MDA and PC when compared with healthy volunteers. HD subjects with PEW had higher values of PC and hs-PCR as compared to HD patients with normal nutritional status. A multiple logistic regression analysis showed that the independent variables PC (Wald Statistic 4.25, p = 0.039) and hs-CRP (Wald Statistic 4.83, p = 0.028) where related with the patients' nutritional condition. **Conclusion:** In HD patients with serum ferritin below 500 ng/mL was observed one association of the markers of oxidative stress and inflammation with poor nutritional status independently of serum ferritin, gender and age.

Keywords: inflammation, iron, dietary, nutritional status, oxidative stress, renal dialysis.

Resumo

Introdução: Na doença renal crônica, a presença de um estado inflamatório-oxidativo aumentado está bem estabelecida. **Objetivo:** O objetivo do presente estudo foi avaliar o estado oxidativo e inflamatório e o perfil do ferro em pacientes submetidos à hemodiálise crônica de manutenção, com ferritina menor do que 500 ng/mL, e correlacioná-los com o estado nutricional. **Método:** Em estudo transversal, em 35 pacientes sob hemodiálise (23 com estado nutricional normal, 12 com desnutrição energético-proteica (DEP) e 35 voluntários sadios foram determinados os índices hematimétricos e as concentrações séricas do ferro, da ferritina e avaliada a saturação de transferrina. O estado oxidativo foi determinado por meio das concentrações séricas do malondialdeído (MDA) e da proteína carbonil (PC). Nos indivíduos sob hemodiálise o estado inflamatório foi avaliado por meio da proteína C reativa ultrassensível determinada no soro (hs-PCR). O estado nutricional foi determinado por critérios antropométricos e bioquímicos. **Resultados:** Os pacientes da hemodiálise mostraram anemia e um estado oxidativo mais elevado do que os voluntários sadios. Os pacientes hemodialisados com DPE mostraram ferritina e um estado inflamatório-oxidativo mais elevado se comparados aos com boa condição nutricional. Em análise de regressão logística múltipla, os níveis séricos de PC e hs-CRP foram correlacionados com o estado nutricional. PC (Estatística Wald 4.25, p = 0,039), CRP (Estatística Wald 4.83, p = 0,028). **Conclusão:** Em indivíduos submetidos à hemodiálise, com ferritina menor do que 500 ng/mL. Observou-se uma associação entre os marcadores de estresse oxidativo e inflamatório com o estado nutricional, independentemente da idade, gênero e dos índices do ferro.

Palavras-chave: diálise renal, estado nutricional, estresse oxidativo, ferro na dieta, inflamação.

Introduction

Anemia is a very common condition in advanced renal disease and contributes to a higher morbi-mortality in this group of patients.[1,2] Intravenous iron is widely used to maintain adequate iron stores and prevent iron deficiency anemia. The long-term safety of intravenous iron has raised concerns with respect to oxidative stress, cellular injury, and accelerated atherosclerosis.[3] Previous data suggest that iv iron could increase oxidative stress and induce endothelial-cell injury in chronic kidney disease patients.[4-6]

Moreover, uremic patients have an increased formation of reactive oxygen species. In addition to iron administration, other factors such as uremic toxins and hemodialysis, due to aspects related to membrane and dialysis-water biocompatibility and a chronic inflammatory state, contribute to intensify this oxidative stress leading to greater cardiovascular risk.[7,8] Furthermore, patients undergoing maintenance hemodialysis have a high prevalence of protein-energy wasting, inflammation, and enhanced oxidative stress, the so-called "malnutrition-inflammation complex syndrome".[9,10]

It was previously shown that inflammation was the possible cause of increased serum ferritin level in 34% of hemodialysis patients.[11] Serum ferritin values in the range of 200-2000 ng/mL may be increased due to non-iron-related factors, and PEWhemodialysis patients with ferritin greater than 800 ng/mL have higher serum hs-CRP than those with a serum ferritin value inferior to 800 ng/mL.[12]

Currently, there is insufficient evidence to recommended IV iron if ferritin > 500 ng/mL, although the upper limit of serum ferritin of 800 ng/mL may be considered for some patients with poor responsiveness to erythropoietin.[13]

Common tests such as serum ferritin and transferrin saturation lack precision to be a good marker of iron status in hemodialysis patients,[14,15] and the ferritin level threshold below which iron depletion can be considered is probably higher than that observed in healthy individuals. The objective of this study was to evaluate the oxidative- inflammatory status and iron indices in patients undergoing maintenance hemodialysis (HD) with serum ferritin lower than 500 ng/mL, and to correlate them with nutritional status.

Materials and Methods

Fifty-four patients with chronic renal disease submitted to chronic hemodialysis were recruited from one outpatient center of dialysis at the University Hospital of Brasília. Eligibility criteria included the following: 18 years old or older, male or female, six or more months on dialysis treatment, absence of malignancy, acute inflammatory diseases, vasculitis, and haemoglobinopathies. Also, eligible subjects needed to have good adherence and stability to dialysis treatment, vascular access to hemodialysis by means of artery-venous shunt and ferritin levels lower than 500 ng/mL. Thirty-five patients met the criteria (19 female and 16 male). The causes of chronic kidney disease were hypertensive nephrosclerosis (13), chronic glomerulonephritis (10), polycystic disease (4), diabetic nephropathy (6), and undetermined (2). Eligible HD patients represent an ethnically heterogeneous group of Brazilian individuals. A written consent was obtained from the participants according to a protocol approved by the Faculty of Health Sciences, University of Brasilia Ethics Committee. Each patient had been undergoing standard bicarbonate HD session three times a week, 4 hours per session, using polysulfone membrane with blood flow of 300-350 ml/min and dialysis flow of 500 ml/min. Prescribed medications included angiotensin-converting enzyme inhibitors, calcium channel blockers, angiotensin II receptors blockers, phosphate binders and vitamin D analogues. None of the patients received hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins), antioxidants agents (vitamin C or E) or anti-inflammatory drugs. HD subjects were receiving regular doses of parenteral iron (IV) to maintain their body iron stores and erythropoietin (rHuEPO) to stimulate erythropoiesis, according to guidelines for the treatment of anemia in hemodialysis subjects.[16,17] Data for the total dose of iron supplement and erythropoietin administered were obtained from the medical records of each patient.

A detailed history of all the patients was taken and they underwent clinical examination. Anthropometric data includes dry weight (weight after dialysis session), body mass index, and assessment of subcutaneous fat and muscle mass stores, which were determined using a body fat caliper (Cescorf-Brazil). All measurements were taken by the same observer on the opposite side of the artery-venous shunt. Percentiles of triceps skinfold thickness (TSF), mid-arm- circumference (MAC), and mid-arm-muscle circumference (MAMC) were calculated according to Frisancho.[18] The following formula was employed to calculate MAMC: MAMC (cm) = MAC (cm) - (TSF (mm) x 0.314).[19]

The patients' dietary intake of energy, protein, carbohydrate, lipids, and iron was calculated based on the averages of three 24-hour dietary intake recalls, comprising one day of the weekend and two non- consecutive week days. Nutrients, calories and protein intake were calculated using data of food composition.[20] The values obtained were compared with those specifically recommended for dialysis subjects according to NKF/DOQI.[21]

Blood samples were drawn immediately before the hemodialysis session to determine hemoglobin(Hb), hematocrit(Hct), iron, ferritin, and transferrin saturation. After the dialysis session, more blood was taken to determine post-dialysis urea to calculate eKtv of urea. Mean values of the three measurements were used given the high intraindividual variability for ferritin. Albumin, intact paratohormony (iPTH), highly sensitive C reactive protein (hsCRP), protein carbonyl (PC), and malondialdehyde (MDA) were determined in the last month of the study. The nutritional condition of HD patients was classified according to Blackburn.[22] To compare oxidative stress (OS) in hemodialysis patients and healthy subjects, 35 healthy volunteers pared to age, gender and social status were included. They were volunteers of the pilot project "Prevalence of risk factors to non-communicable chronic diseases on the Federal District -Brasilia, Brazil", which was a cooperative study developed by the University of Brasília and the Health Secretary of the Federal District. Participants of this study represented a random sample of the population of the city of São Sebastião, DF. They were submitted to an interview and samples of blood for Hb, iron status andOS determinations were drawn the morning after the interview, as described in Yokota.[23]

Laboratory analysis

A complete blood count including Hb, mean corpuscular hemoglobin concentration (MCHC), and Hct was done using an automatized cell count (Abbott Cell-Dyn 3700SL, Abbott Laboratories, Diagnostic Division, Illinois, USA); serum iron, iron binding capacity, albumin and urea were measured using an autoanalyser (Mega, Bayer, Germany); serum ferritin was measured by Enzyme Linked Immuno Sorbent Assay (Katal biotechnology- Brazil); iPTH was measured employing chemiluminescent method; hsCRP was measured by nephelometric method (Cardiophase hsCRP, Dade Behring, Germany). Transferrin saturation percentage was calculated by means of the formula TSAT (%) = Iron/IBC x 100.

Adequacy of dialysis (ekT/v for urea) was calculated according to the single-compartment model of Daurgidas.[24]

Serum malondialdehyde (MDA) was measured by a fluorimetric method based on the reaction between MDA and thiobarbituric acid (TBA). 50 µL of serum, 1 mL of deionized water and 1 mL of TBA 29 mmol/L in acetic acid were added to each tube, agitated and heated in a water bath at 100ºC for 1 hour. After cooling, 25 µL of HCl 5 mol/L and 3.5 mL of n-butanol were added, and the tubes were agitated for 5 seconds. The alcoholic phase was separated by centrifugation at 900 x g for 10 minutes. The sample fluorescence was determined at 547 nm with excitation at 525 nm, in spectrofluorometer (FP-777 JAS.CO). The standard curve was prepared using 1,1,3,3-tretraethoxypropane standard solutions (Sigma, Germany) in the concentration range of 0 - 0.150 µmol/L, linearity of 0.9816.[25]

The concentration of serum protein carbonyls groups was determined by the spectrophotometric method based on the reaction of 2.4-dinitrophenylhydrazine with protein carbonyls. Serum samples containing 500 µg of protein were homogenized in 25 mmols/L Tris, pH 9.0, 6 mols/L urea to a final volume of 200 µL. Next, an equal volume of 20% trichloroacetic acid was added and centrifuged at 9,000 x g for 1 minute to precipitate proteins. The pellet was re-suspended in 200 µL 25 mmol/L Tris, pH 9.0, 6 mols/L urea. 700 µL 0.2% 2.4-dinitrophenylhydrazine (2,4-DNPH) in 2 mols/L HCl were added to the sample and 700 µL 2 mols/L HCl to a blank tube, respectively. Samples were agitated at 4ºC for 15 minutes on a shaker (TE-420, Tecnal) at maximum speed. 700 µL 20% trichloroacetic acid (TCA) were added to precipitate the proteins. The pellet was washed three times at room temperature with 1 mL ethyl acetate:ethanol, 1:1, air dried and re-suspended in 500 µL 500 mols/L potassium phosphate, pH 2.5, containing 6 mols/L guanidine HCl. The mixture was agitated at 4ºC for 30 minutes on a shaker. The absorbance was measured at 376 nm.[26]

Statistical analysis

All Continuous variables were analyzed for normal distribution using the Kolmogorov-Smirnov test. According the distribution of data the *t* test or Mann Whitney U tests were employed to compare continuous variables. The Chi-square test and the Fisher Exact Test were employed for categorical variables. Spearmen correlation test was employed to verify the association among ferritin levels and CRP, Tbars and PC. Multiple logistic regression analysis was used to evaluate which clinical and laboratory independent variables where associated with nutritional status. The nutritional condition was the dependent outcome and age, gender, time on dialysis, ferritin, albumin, Tbars, PC, CRP, and Ktv, were included as either continuous or dichotomous data. SigmaStat® 3.11/ SigmaPlot 9.01 for windows (Systat Software, Inc, USA, 2004) and Prism 4 for Windows® (Graphpad Software, Inc., USA, 2005) software packages were employed for analysis and graphic design of the data.

A p value of less than 0.05 was considered significant.

Results

In this study, and according to the NKF-K/DOQI,[22] the dietary intake was suitable for all nutrients except forcalories and proteins in 57% of HD patients.

Using the anthropometric and biochemical criteria the hemodialysis patients showed a prevalence of 34.3% of mild to moderate PEW syndrome according to the criteria of Blackburn[22] as demonstrated in Table 1.

Table 1 Used criteria for the clinical diagnosis of PEW in hemodialysis patients

Body mass
Triceps skinfold thickness (≤ percentile 5 of the standard reference, according to Blackburn[22])
Muscle mass
Reduced mid-arm-muscle circumference (MAMC) (≤ percentile 5 of the standard reference, according to Blackburn[22])

Comparisons of the levels of Hb, ferritin, and the serum markers of oxidative stress between the 35 healthy volunteers and HD subjects are shown in Table 2. Results show that renal subjects have higher levels of ferritin, MDA and PC, and lower levels of Hb in relation to healthy individuals. Hemodialysis subjects received maintenance doses of iron and human erythropoietin(HrEPo) throughout the study, and the doses of both drugs were not statistically different between those patients with good nutritional condition and those with PEW:Iron (mg/Kg/week, 1.73(2.2-1.6) *vs*. 2.1(2.4-1.7); HrEPo(ui/Kg/week): 138.8(199.2-69.9) *vs*. 94.3(174.0-86.9) $p > 0.05$ Mann-Whitney.

PC, Tbars, and hs-CRP levels in HD subjects were not correlate with the ferritin levels. ($p > 0.05$, Spearman Correlation Test).

The different characteristics of HD subjects and of those with normal and poor nutritional status are shown in Table 3. Gender and diabetic ratios, months on dialysis, e kT/v, iron, transferrin saturation, ferritin, albumin, iPTH, Hb, and MDA were not different for the subjects with PEW and those with normal nutrition. However, PEW patients showed higher levels of PC and hs-CRP in relation to those with normal nutritional status. A multiple logistic regression analysis showed that the independent variables PC, Odds ratio (95% IC) = 5.2 (24.0-1.1), $p = 0.039$ and CRP Odds ratio (95% IC) = 62.1 x 10^3 (192467.7 x 10^3 - 20.0), $p = 0.028$) where related with the patients' nutritional condition independently of age, gender, and iron status. Figures 1 and 2 shows respectively that the medians (range) of PC and hs-CRP were statistically higher in HD patients with PEW as compared with those with good nutritional condition.

Discussion

The relationship among haematimetrics and iron indices, OS, and nutritional status in 35 HD patients was analyzed in this study. Hb, serum ferritin and OS, evaluated by the serum concentration of MDA and PC, were also evaluated in 35 healthy volunteers.

Anemia was present in all renal subjects (Hb concentration < 14 and < 12 mg/dL for men and women, respectively), despite levels of serum ferritin between 100 to 500 ng/mL, and the use of parenteral iron and erythropoietin. Dialysis patients also exhibited higher levels of serum MDA and PC in relation to healthy volunteers, a factcompatible with the higher oxidative stress previously observed in renal patients.[8,27,28] A chronic Inflammatory status described in hemodialysis patients[29-31] may contribute to iron functional deficiency by making it difficult to attain the target hematocrit, increasing these individuals' risk of infections and cardiovascular diseases. In addition, an association among biomarkers of inflammation, oxidative stress, and PEWin HD patients, called the "oxidative

Table 2 Levels of hemoglobin (HB), ferritin, lipid peroxidation (MDA) and protein carbonyl (PC) in health volunteers and in hemodialysis patients

Variables	Health volunteers N = 35	Renal patients N = 35	*p* value
Hb (g/dL)	14.0 (14.9-13.0)	10.5 (11.4-10.2)	< 0.001*
Ferritin (ng/mL)	35.1 (122.8-21.8)	195.9 (268.4-148.0)	< 0.001#
MDA (µmol/L)	0.2 (0.2-0.1)	2.1 (3.2-1.6)	< 0.001*
PC (nmol/mg total protein)	0.9 (1.5-0.7)	1.9 (2.6-1.3)	0.001*

Abbreviations: N: number of subjects; Hb: hemoglobin; MDA: malonaldehyde; PC: Protein Carbonyl. Data are expressed as median (interquartile range). * *t* test; # Mann-Whitney Rank Sum Test.

Table 3 Characteristics of hemodialysis patients with normal nutritional status and protein-energy-wasting (PEW)

Characteristics	Overall (N = 35)	Normal Nutritional Status (N = 23)	PEW (N = 12)	*p* value
Age (y)	41.0 (47.0-41.0)	36.0 (48.5-30.7)	45.5 (46.5-38.0)	.38*
Male:female	16:19	10:13	6:6	.99#
Diabetic:nondiabetic	6:29	4:19	2:10	1.00##
Months on dialysis	26.0 (35.0-13.0)	26.0 (39.5-12.2)	27.0 (34.2-15.2)	.50*
Weight (kg)	57.9 (60.8-49.0)	59.1 (61.7-56.7)	53.0 (57.3-44.1)	.013**
BMI (kg/m^2)	21.4 (23.8-19.8)	23.4 (24.5-21.1)	19.8 (20.7-18.6)	< .001*
ekT/v for urea	1.4 (1.5-1.2)	1.4 (1.7-1.2)	1.4 (1.4-1.3)	.67*
TSF (mm)	12.8 (18.0-8.7)	15.0 (19.0-11.0)	9.1 (12.4-8.5)	.025*
MAMC (cm)	23.2 (25.2-21.3)	23.7 (26.4-22.5)	21.5 (23.1-19.8)	.006**
MAC (cm)	27.0 (30.0-24.8)	29.5 (30.8-27.0)	24.5 (26.5-23.5)	< .001*
Ferritin (ng/mL)	195.9 (268.4-148.0)	190.3 (259.4-148.0)	201.7 (292.9-154.5)	.701**
Iron (mg/mL)	65.3 (89.6-55.7)	70.6 (90.1-55.0)	64.6 (81.0-57.8)	.35**
TS (%)	37.8 (48.5-29.2)	38.7 (48.5-32.4)	31.3.7 (45.2-27.7)	.25*
Albumin (g/dL)	4.4 (4.6-4.2)	4.4 (4.7-4.3)	4.2 (4.5-4.0)	.19*
iPTH (pg/mL)	170.0 (446.0-84.8)	180.0 (499.7-88.1)	140.0 (327-72)	.54*
Hb (g/dL)	10.5 (11.4-10.2)	10.6 (11.4-10.2)	10.4 (11.1-9.7)	.26**
MDA (µmol/L)	2.1 (3.2-1.6)	2.1 (3.1-1.6)	2.2 (3.2-1.8)	.39**
PC (nmol/mg protein)	1.9 (2.6-1.3)	1.7 (2.0-1.1)	2.3 (3.3-1.3)	.04**
CRP (mg/dL)	0.3 (0.6-0.3)	0.3 (0.5-0.2)	0.7 (0.9-0.4)	.003*

Abbreviations: N: number of subjects; BMI: Body mass index; eKtv for urea, adequacy of dialysis; TSF: Triceps skinfold thickness; MAMC: Mid-arm-muscle circumference; MAC: Mid-arm circumference; TS: transferrin saturation; iPTH: Parathyroid hormone; Hb: hemoglobin; MDA: malonaldehyde; PC: Protein Carbonyl; CRP: C-reactive protein. Data are expressed as median (interquartile range).* Mann-Whitney Test; ** *t* test; # Fisher Exact Test; ## Chi-square test.

stress complex syndrome", may play a major role in long-term complications affecting morbidity and mortality in HD patients.[9,32]

Serum ferritin is an indicator of iron storage but its concentration may be affected by inflammation. The influence of the inflammatory status on serum ferritin was well demonstrated, mainly in HD patients with higher ferritin levels, that is, above 500 ng/mL. Our results showed that in HD patients with serum ferritin below 500 ng/mL, PC, Tbars, and hs-CRP were not correlate with the ferritin levels ($p > 0.05$, Spearman Correlation Test).

In this study, mild to moderate PEW and inadequate calorie and protein intake were observed in 34.3% of the dialysis patients. This group of HD patients exhibited, in relation to dialysis patients with good nutritional status, higher levels of hsCRP and higher PC levels compatible with the presence of protein energy malnutrition, inflammation, and enhanced oxidative stress. Inflammation and oxidative stress may act synergistically and tend to be involved in the development of long-term complications, including PEW, atherosclerotic cardiovascular and bone vascular diseases.[9] HD patients also showed higher

Figure 1. Values of plasma protein carbonyl in hemodialysis patients with normal nutritional status (NNS) and with Protein-Energy-Wasting syndrome (PEW).

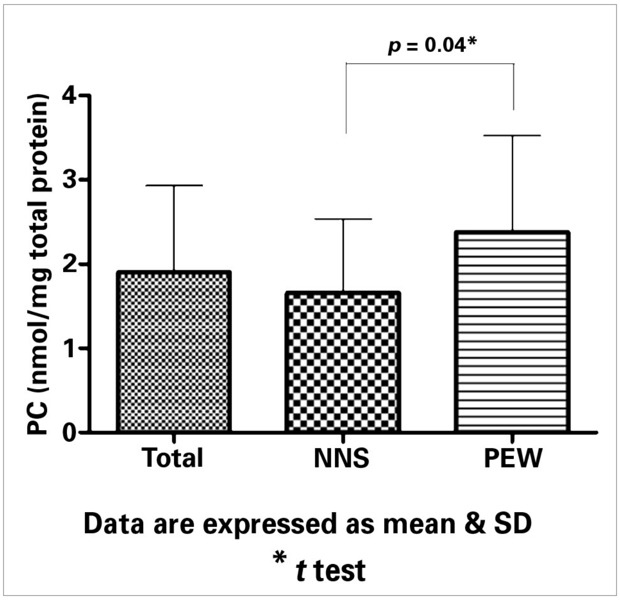
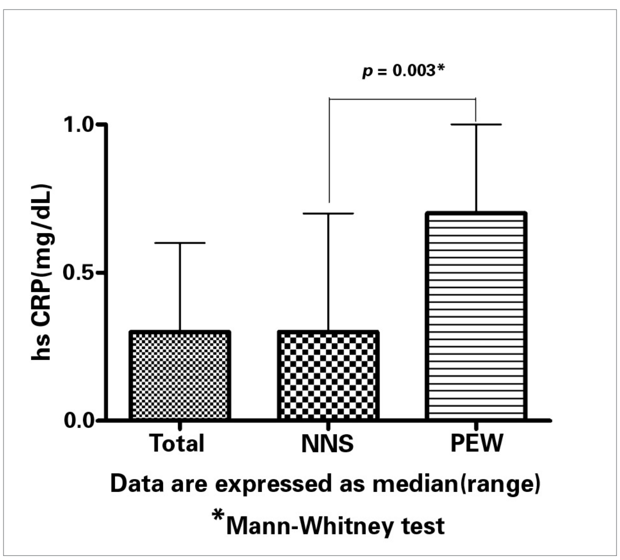


Figure 2. Values of highly-sensitive serum C reactive protein (hs-CRP) in hemodialysis patients with normal nutritional status (NNS) and with Protein-Energy-Wasting syndrome (PEW).



ferritin levels and the association between oxidative stress and iron status was investigated as well. Iron supplements could potentially result in the release of free iron and induce production of free radicals by means of Fenton reaction.[33]

Previous evidence has shown that in renal patients on hemodialysis treatment enhanced oxidative- inflammatory stress may be associated with iron load and this may contribute to iron functional deficiency by making it difficult to attain the target hematocrit.[4-6,34-38] However, the lowest level of ferritin to maintain control of anemia without inducing oxidative tissue damage and increasing the risk of infections and cardiovascular diseases is still unknown.[38]

Senol *et al.*[39] found that 34 well-nourished HD patients had higher hsCRP and lipid peroxidation products (red blood cell malondialdehyde) when compared with 22 healthy controls. They did not observe a significant relationship between ferritin and RBC-MDA when they compared HD patients with normal (< 800 ng/ml) and high (> 800 ng/ml) ferritin levels. The authors concluded that HD patients have higher oxidative and inflammation status, but they could not find a relationship between ferritin level and OS markers in HD patients receiving erythropoietin.

In the present study, HD patients had lower ferritin cut-off values and approximately 34% showed mild calorie-protein wasting. Also, we could not find a relationship between ferritin levels and markers of oxidative stress and inflammation. Moreover, the malnourished HD patients showed higher values of PC and hsCRP as compared with HD patients with good nutritional condition. This data confirm the association between PEW and higher inflammatory-oxidative status, independent of iron status. Furthermore, a logistic regression analysis showed that the independent variables PC and hsCRP were related with the nutritional condition independently of age, gender, and iron status.

The limitations of this study are its relatively small sample size and its cross-sectional nature. The distinctive lipid and protein oxidation pathways or products stability may be responsible for the differences in the oxidative status observed in our patients.

In conclusion, in this ethnically heterogeneous group of Brazilian HD patients, the subjects with PEW showed higher oxidative and inflammatory status as compared with subjects with normal nutritional condition.

Furthermore, in HD patients with serum ferritin below 500 ng/mL, one association of carbonyl stresses and inflammation with poor nutritional condition was showed to be independent of ferritin levels. However, prospective and long-term follow-up studies are needed to confirm this data.

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