Are PTH levels related to oxidative stress and inflammation in chronic kidney disease patients on hemodialysis?

Os níveis de PTH estão relacionados com estresse oxidativo e inflamação em pacientes renais crônicos em hemodiálise?

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ABSTRACT

Introduction: Patients at end stage renal disease have higher levels of inflammation and oxidative stress than the general population. Many factors contribute to these issues, and the parathyroid hormone (PTH) is also implicated. **Objective:** The study was conducted in order to assess the relationship between PTH levels and inflammation and oxidative stress in hemodialysis patients. **Methods:** Cross-sectional study with patients of two hemodialysis facilities in Londrina, Brazil. Patients with other conditions known to generate oxidative stress and inflammation were excluded. Blood levels of PTH and biochemical parameters of inflammation (interleukins 1 and 6, tumor necrosis factor-alpha) and oxidative stress (total plasma antioxidant capacity, malonic dialdehyde, lipid hydroperoxidation, advanced oxidation protein products, quantification of nitric oxide metabolites, and 8-isoprostane) were measured before a dialysis session. Then, we made correlation analyses between PTH levels - either as the continuous variable or categorized into tertiles-, and inflammatory and oxidative stress biomarkers. **Results:** PTH did not show any correlation with the tested inflammation and oxidative stress parameters, nor as continuous variable neither as categorical variable. **Conclusion:** In this descriptive study, the results suggest that the inflammation and oxidative stress of hemodialysis patients probably arise from mechanisms other than secondary hyperparathyroidism.

Keywords: hyperparathyroidism; inflammation; oxidative stress; renal insufficiency, chronic.

RESUMO

Introdução: Pacientes com doença renal em estágio terminal têm níveis de inflamação e estresse oxidativo maiores do que a população geral. Muitos fatores contribuem para isso, e o hormônio paratireoidiano (PTH) é um deles. **Objetivo:** Estudo foi realizado para avaliar a relação entre os níveis de PTH e níveis de inflamação e estresse oxidativo em pacientes em hemodiálise. **Métodos:** estudo transversal com pacientes de duas unidades de hemodiálise de Londrina, Brasil. Pacientes com condições causadoras de inflamação e estresse oxidativo foram exclusos. Níveis plasmáticos de PTH e parâmetros bioquímicos de inflamação (interleucina 1 e 6, fator de necrose tumoral alfa) e estresse oxidativo (capacidade antioxidante plasmática total, dialdeído malônico, hidroperoxidação lipídica, produtos avançados da degradação proteica, quantificação de metabólitos de óxido nítrico e 8-isoprostano) foram dosados antes da sessão de hemodiálise. Realizou-se análise de correlação entre os níveis de PTH - tanto como variável continua como variável categórica em tercis - e os parâmetros de inflamação e estresse oxidativo. **Resultados:** Não houve correlação do PTH com nenhum dos parâmetros testados, nem como variável contínua, nem como categórica. **Conclusão:** Neste estudo descritivo, os resultados sugerem que a inflamação e o estresse oxidativo em pacientes em hemodiálise provavelmente tem origem em mecanismos que não incluem o hiperparatireoidismo secundário.

Palavras-chave: hiperparatireoidismo; estresse oxidativo; inflamação; insuficiência renal crônica.

Introduction

Individuals with chronic kidney disease (CKD) undergoing dialysis have a mortality rate that is 20-100 times higher than that of the normal population, with cardiovascular disease being the major contributor to this excess mortality.[1] Traditional cardiovascular risk factors (e.g., hypertension, *diabetes mellitus*, smoking, dyslipidemia, and sedentary lifestyle, among others) are common in this population, but these factors do not fully explain this high mortality. Other nontraditional factors contribute to the increased risk of cardiovascular mortality in these patients, including disorders of bone and mineral metabolism in CKD (CKD-MBD), chronic inflammation, and oxidative stress.[2,3]

Secondary hyperparathyroidism (SHPT) is part of CKD-MBD and is characterized by high levels of parathyroid hormone (PTH) associated with high-turnover bone disease and vascular calcification. In high levels, PTH acts as an uremic toxin and contributes to bone loss, vascular and valvular calcification, anemia, cardiomyopathy, hypertension, and glucose intolerance.[4]

Regarding oxidative stress, it can be defined as tissue damage resulting from an imbalance between the generation of excessive oxidizing components and insufficient production of antioxidant defense mechanisms.[5] Although an essential mechanism in inflammation, tissue wound and repair and combat against microorganisms and cancer cells, the excess of oxidative substances is maladaptative.[6]

In this way, states of increased generation of reactive oxygen species (ROS) lead to inflammatory states, since ROS are released from monocytes and polymorphonuclear cells with pro-inflammatory cytokines, which amplify, in turn, the generation of oxidants.[7] Chronic kidney patients represent a population highly subjected to inflammation states and increased oxidative stress, either by its own characteristics (high prevalence of *diabetes mellitus* and advanced age, either by characteristics related to uremia and therapy dialysis, such as time on dialysis,[8,9] compatibility of dialysis membranes, exposure to endotoxins and parenteral administration of iron.[10]

A potential role of hyperparathyroidism in the genesis of inflammation/oxidative stress is suggested by the demonstration of direct relationship between PTH levels and inflammatory markers in general population and in patients with primary hyperparathyroidism.[11-14] Furthermore, other authors demonstrated, in cases of secondary aldosteronism found in patients with congestive heart failure, a development of secondary hyperparathyroidism state, which leads to a rise in intracellular calcium concentration and consequently increased production of reactive oxygen species.[15,16] Additionally, parathyroidectomy reduced oxidative stress in rats with secondary hyperparathyroidism induced by aldosterone-NaCl treatment,[15] and in a patient with primary hyperparathyroidism.[17]

However, other conflicting data exist regarding the correlation between inflammation and PTH levels, at least in non dialysis patients.[18,19] In CKD patients, low PTH levels are associated with inflammation and oxidative stress, possible as a result of Malnutrition Inflammation Atherosclerosis (MIA) syndrome.[20] To the best of our knowledge, there is only small studies that looked upon the severity of secondary hyperparathyroidism and oxidative stress in hemodialysis patients.[21-23]

Therefore, the purpose of this study was to evaluate possible correlations between PTH levels and inflammation and oxidative stress biomarkers, and PTH levels and some routine laboratory tests in hemodialysis patients.

Materials and methods

Design and population

We performed a cross-sectional study in two hemodialysis units. Patients were recruited between May and July 2012. Inclusion criteria were as follows: age 18 years or older and on hemodialysis with arteriovenous fistula (native or graft) for at least 3 months. Exclusion criteria were previous parathyroidectomy and conditions known to generate oxidative stress and inflammation, as follows: hemodialysis with temporary central venous catheter, neoplasm, active infection that caused hospitalization in the 15 days before blood collection, hepatitis B or C and human immunodeficiency virus.

Of the 155 selected patients who met the inclusion criteria, 23 patients were withdrawn from the final analysis, due to lack of material to complete analysis (11), death (4), active infection during blood collection (4), inadequate blood collection (2), introduction of a venous catheter for hemodialysis (1), and partial recovery of renal function leading to discharge from the dialysis center (1).

Dialysis sessions took between 210 to 240 minutes, with a blood flow of 300 to 450 ml/min and dialysate at 500 ml/min, three times per week. The dialyzers were hollow fiber cellulose triacetate (surface area depended on the patient's body surface), with pure water in the dialysate. The dialysis target was an unbalanced Kt/V of 1.2. Participants provided written informed consent prior to participation. The study was approved and registered (No. 07791) by the local Ethics Committee.

Data collection

Through chart review and interviews, we collected demographic data and information regarding time on dialysis, underlying disease, comorbidities, current smoking status (yes or no) and medication use. The mean dose of EPO (in U/kg/week) was based on the last 30 days before blood sample collection.

Biochemical analyses

We obtained blood samples of patients (~20 mL) at the time of puncture for initiation of the first hemodialysis session in the week, after 8 hours of fasting. Samples were collected in vacuum tubes (Vacutainer®, Franklin Lakes, NJ, USA) without anticoagulant, centrifuged at 830 g for 15 minutes and the resulting serum stored at -70 °C until analysis. All patients with regular parenteral iron use during hemodialysis had suspended use of this medication for at least 1 week before the collection procedure.

Laboratory parameters

We measured serum creatinine, urea before and after the session (for calculation of efficiency of dialysis or Kt/V), ferritin, hemoglobin, calcium, phosphorus, alkaline phosphatase, uric acid, and albumin according to standard techniques. Intact parathyroid hormone (iPTH) was measured by electrochemiluminescence (Modular Analytics E170, Roche, Mannheim, Germany). To avoid variation in nomenclature throughout this paper, we have chosen the use of the acronym PTH, even though the performed dosage was of the intact molecule. We measured levels of vitamin D (25-hydroxyvitamin D) by chemiluminescence (Architect i2000, Abbott, IL, USA).

Inflammatory parameters

Levels of interleukin (IL)-1, IL-6, and tumor necrosis factor alpha (TNF-α) were measured by ELISA.

Oxidative stress parameters

Oxidative stress was analyzed through the levels of the total plasma antioxidant capacity (TRAP), lipid hydroperoxidation (FOX), nitric oxide metabolites (NOx), malonic dialdehyde (MDA), advanced oxidation protein products (AOPPs) and 8-isoprostane. The FOX level was quantified using the spectrophotometric technique described by Jiang *et al.*,[24] based on the oxidation of ferrous to ferric ions under acidic conditions by peroxides. Peroxide reacts with the indicator dye (xylenol orange) to produce a colored complex that is read by spectrophotometry (Helios α ThermoSpectronic®, Waltham, MA, USA) at 560 nm.

NOx levels were assessed indirectly by determining the concentration of plasma nitrites, using an adaptation of the method described by Navarro-Gonzálvez *et al.*[25] The method is based on the reduction of nitrate to nitrite, mediated by redox reactions between nitrate in the sample and system with copper-cadmium reagents, resulting in diazotization. The compound formed by complexation with Griess reagent is detected colorimetrically at 550 nm.

TRAP was measured by chemiluminescence based on an adaptation of the method described by Repetto *et al.*[26] The 2,2' azo-bis rapidly generates peroxyl radicals via interaction with carbon-centered radicals and molecular oxygen. These free radicals react with luminol (which acts as an amplifier), producing chemiluminescence. The addition of plasma reduces the baseline levels of chemiluminescence for a period of time (induction time) proportional to the concentration of plasma antioxidants. Once the free radicals regenerate, chemiluminescence returns to its initial levels. The system was calibrated with a vitamin E analogue (Trolox). A comparison of the induction time after the additions of Trolox and plasma gives TRAP values of Trolox equivalents. The obtained values were corrected for serum uric acid levels.

To quantify AOPPs, we used the method described by Witko-Sarsat *et al.*,[27] based on the reaction of oxidized proteins with potassium iodide under acidic conditions. We read the absorbance of the reaction immediately in a spectrophotometer (Helios α ThermoSpectronic®) at 340 nm. To assess levels of serum MDA, we modified the method described by Bastos *et al.*[28] The formation of MDA occurs by decomposition of lipid hydroperoxides. Its concentration has been used to estimate the intensity of lipid peroxidation in cells and tissues. This method consists of measuring a pink chromogen

formed by the reaction of MDA with two molecules of thiobarbituric acid under acidic conditions and at high temperatures, with quantification by high performance liquid chromatography (HPLC). Finally, we measured 8-isoprostane by enzyme immunoassay using commercial kits from Cayman Chemical Company (Ann Arbor, Michigan, USA). For all the parameters of inflammation an oxidative stress measured, we did not insert a normality range due to the lack of validation regarding normal values in CKD population.

Statistical analysis

Quantitative variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR), depending on the normality of the data. Spearman correlation coefficient analysis was used to test the possible relations between PTH levels and other continuous variables. Comparison between inflammatory and oxidative stress biomarkers between groups classified according to tertiles of PTH levels was tested using Kruskal-Wallis test. The level of significance was 5% ($p < 0.05$). Statistical analysis was performed using SPSS version 19 (SPSS, Chicago, IL, USA).

Results

Of the 155 patients selected for the study, 132 were included in the statistical analysis. All patients had their parameters of oxidative stress measured. General patient characteristics are shown in Tables 1 and 2. The patient population contained a high prevalence of male, caucasian patients, with a mean age of 55 years. The median dialysis vintage was 34.5 months. The prevalence of *diabetes mellitus* was 31.8%. The most common baseline renal disease was hypertensive nephrosclerosis, followed by chronic glomerulonephritis and diabetic nephropathy. The median of PTH was 326 pg/mL. About other relevant laboratorial data, we found a high prevalence of vitamin D insufficiency/deficiency - almost 90% - with a median of 24.5 ng/mL.

Correlation analysis between PTH levels and inflammatory markers (IL-1, IL-6 and TNF-α) or oxidative stress (8-isoprostane, NOx, MDA, FOX, AOPP and TRAP) did not show any statistically significant correlation (Table 3). Due to different definitions of abnormal high levels in clinical practice supported by KDIGO and KDOQI, we performed an additional analysis categorizing PTH in tertiles, which also showed no significant statistical association with the biomarkers assessed (Table 4).

Table 1 General patients characteristics

Variable results	
Male (%)	92 (69.7%)
Age (years)	55.1 ± 14.8
Dialysis vintage (months)	34.5 (18-74.7)
Race (%)	
White	97 (73.5%)
Afroamericans	19 (14.4%)
Others	16 (12.1%)
CKD etiology (%)	
HN	45 (34.1%)
CGN	35 (26.5%)
DN	34 (25.8%)
ADPKD	4 (3.0%)
Others	14 (10.6%)
MBP (mmHg)	97.3 ± 9.1
BMI	23.4 (20.8-27.7)
Current smoking (%)	19 (14.4%)
Diabetic patients (%)	42 (31.8%)
Patients on statins (%)	33 (25.0%)
ACEI/ARB (%)	69 (52.3%)
Calcitriol (%)	50 (37.9%)
EPO dose (U/kg/sem)	115.7 (0-178.7)

Results expressed as mean ± SD or median and interquartile range. CKD: Chronic Kidney Disease; HN: Hypertensive Nephrosclerosis; DN: Diabetic Nephropaty; CGN: Chronic Glomerulonephritis; ADPKD: Autossomic Dominant Polycistic Kidney Disease; MBP: Mean Blood Pressure; BMI: Body Mass Index; ACEI: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; EPO: Erythropoietin.

Correlation between PTH levels (as the continuous variable) and hemoglobin, ferritin, EPO dose, calcium, phosphorus, vitamin D, serum albumin, or alkaline phosphatase showed a weak positive correlation with PTH levels and phosphorus (Spearman, $\rho = 0.219$, $p = 0.01$) and a moderate positive correlation with PTH and alkaline phosphatase (Spearman, $\rho = 0.455$, $p < 0.001$) (Table 5).

Discussion

The present study aimed at correlating PTH levels with some parameters of inflammation and oxidative stress in chronic renal failure patients on hemodialysis. Surprisingly, PTH as a continuous variable showed no correlation with the analyzed parameters. Likewise, levels of inflammation and oxidative stress markers

Table 2 Patients laboratorial data

Variable results	
Hemoglobin (12-15 g/dL)	11.5 (10-12.5)
Creatinine (0,7-1,3 mg/dL)	9.1 ± 3.0
PTH (15-65 pg/mL)	326 (136-661.3)
Kt/V (> 1,2)	1.3 ± 0.3
Calcium (8,4-9,5 mg/dL)	8.8 (8.5-9.3)
Phosphorus (3,5-5,5 mg/dL)	5.6 (4.3-7.0)
Alkaline Phosphatase (40-130 U/L)	129 (95.3-180.5)
Ferritin (200-500 ng/mL)	772.4 (475.1-1041.5)
25(OH)D (> 30 ng/mL)	24.5 (19.5-28.4)
Albumin (3,5-5,2 g/dL)	4.2 (3.9-4.4)
IL-1 (pg/mL)	2 (2-2)
IL-6 (pg/mL)	3.8 (1.7-7.7)
TNF-α (pg/mL)	2 (2-49.8)
MDA (nM/mg protein)	78.8 (64.2-96.8)
TRAP/URCA (trolox)	171.3 ± 30.9
NOx (μM)	11.3 (8.9-15.9)
AOPP (μmol/L)	154.3 (123.7-202.6)
FOX (mM)	0.82 (0.65-0.97)
8-isoprostane (pg/mL)	74.6 (25.6-193.0)

Results expressed as mean ± SD or median and interquartile range. Kt/V: Dialytic adequacy; 25(OH)D: Vitamin D; IL-1 and 6: Interleukin 1 and 6; TNF-α: Tumor Necrosis Factor alpha; MDA: Malonic Dialdehyde; TRAP: Total Plasma Antioxidant Capacity; URCA: Uric Acid; NOx: Nitric Oxide metabolites; AOPP: Advanced Oxidation Protein Products; FOX: Lipid Hydroperoxidation.

were similar between PTH levels tertiles. Noyan *et al.*[21], in a trial with 50 hemodialysis patients and 20 control subjects, found similar results. In their study, dialysis patients were categorized into two groups according to PTH levels (> 300 pg/mL and < 300 pg/mL). Oxidative stress was evaluated with two biomarkers (AOPP and MDA), plus myeloperoxidase activity (pro-oxidant) and catalase activity and ascorbic acid (antioxidants).

They found just a decrease in catalase activity in patients with PTH > 300 pg/mL, without any additional effect of PTH levels in ROS generation. Yet, adding more controversies to the issue, there are reports of improvement,[17] deterioration,[29] or unchanged[19] inflammatory markers after parathyroidectomy in patients with primary HPT. Almqvist *et al.*[29] analyzed 45 patients with primary hyperparathyroidism and normal renal function. Serum concentrations of IL-6, C-reactive protein (CRP) and erythrocyte sedimentation rate were measured at baseline and one year after parathyroidectomy. They found an increase in serum concentrations of these biomarkers of inflammation after the surgery.

Ogard *et al.*,[19] in a similar population, did not find any correlation between serum levels of PTH after parathyroidectomy and markers of inflammation (IL-6, CRP, TNF-alpha). Finally, Navarro-González *et al.*[18] did not find this direct relationship in non-dialysis patients (stages 3 and 4 of chronic kidney disease).

Conversely, two longitudinal studies brought different data about the relationship among PTH, inflammation and oxidative stress. Wu *et al* showed in a study with 25 hemodialysis patients on high levels of PTH compared with 20 controls that the treatment with calcitriol for 16 weeks reduced not only the levels of PTH, but also decreased inflammatory (CRP and IL-6, CD4+ cytokines) and oxidative stress markers (TRAP) with statistical significance.[22]

Lu *et al.*,[23] in a trial with a similar study design with 24 hemodialysis patients searching for levels of IL-6 and markers of bone remodeling, found lower levels of IL-6 compared to the baseline after 16 weeks of intravenous calcitriol treatment, in parallel with PTH reduction. The authors suggested that the calcitriol reducing effect over the inflammatory markers is a result of the decrease in PTH levels and the pleiotropic effects of calcitriol.

In the same way, patients with primary HPT and HPT secondary to states of aldosteronism (found, for instance, in patients with congestive heart failure) also present exacerbated inflammatory state. The explanation for this exacerbated inflammatory

Table 3 Spearman coefficient correlation between parathyroid hormone and oxidative stress/inflammation biomarkers

PTH	IL-1	IL-6	TNF-α	MDA	TRAP	NOx	AOPP	FOX	8-Iso
Correlation coeficiente	0.047	-0.126	0.076	0.072	-0.112	0.060	0.118	0.079	0.043
Significancy	0.591	0.148	0.389	0.412	0.202	0.492	0.179	0.369	0.622

PTH: Parathyroid Hormone; IL-1 and 6: Interleukin 1 and 6; TNF-α: Tumor Necrosis Factor alpha; MDA: Malonic Dialdehyde; TRAP: Total Plasma Antioxidant Capacity (corrected for serum uric acid); NOx: Nitric Oxide metabolites; AOPP: Advanced Oxidation Protein Products; FOX: Lipid Hydroperoxidation; 8-Iso: 8-Isoprostane.

Table 4 Relationship between parathyroid hormone tertiles and parameters of inflammation and oxidative stress

	PTH < 198	198 ≤ PTH ≤ 517	PTH > 517	Test	
Variables	Median	Median	Median	Kruskal-Wallis	*p*-Value
IL-1	2.00	2.00	2.00	0.072	0.965
IL-6	3.74	4.72	3.44	2.274	0.321
TNF-α	2.00	2.00	2.00	0.595	0.743
MDA	75.60	81.60	75.77	1.913	0.384
TRAP	174.95	162.85	166.23	1.015	0.602
NOx	10.44	11.30	12.77	2.015	0.365
AOPP	150.72	135.45	157.46	2.654	0.265
FOX	0.83	0.80	0.88	4.063	0.131
8-Iso	69.20	82.20	76.10	0.051	0.975

PTH: Parathyroid Hormone; IL-1 and 6: Interleukin 1 and 6; TNF-α: Tumor Necrosis Factor alpha; MDA: Malonic Dialdehyde; TRAP: Total Plasma Antioxidant Capacity (corrected for serum uric acid); NOx: Nitric Oxide metabolites; AOPP: Advanced Oxidation Protein Products; FOX: Lipid Hydroperoxidation; 8-Iso: 8-Isoprostane.

Table 5 Spearman coefficent correlation between parathyroid hormone levels and laboratorial data assessed in the study population

PTH	IL-1	IL-6	TNF-α	MDA	TRAP	NOx	AOPP	FOX	8-Iso
Correlation coeficiente	0.047	-0.126	0.076	0.072	-0.112	0.060	0.118	0.079	0.043
Significancy	0.591	0.148	0.389	0.412	0.202	0.492	0.179	0.369	0.622

PTH: Parathyroid Hormone; IL-1 and 6: Interleukin 1 and 6; TNF-α: Tumor Necrosis Factor alpha; MDA: Malonic Dialdehyde; TRAP: Total Plasma Antioxidant Capacity (corrected for serum uric acid); NOx: Nitric Oxide metabolites; AOPP: Advanced Oxidation Protein Products; FOX: Lipid Hydroperoxidation; 8-Iso: 8-Isoprostane.

state is based on the increase in intracellular and mitochondrial free calcium - the calcium paradox -, which favors the production and release of ROS. In subjects undergoing states of aldosteronism (found, for example, in patients with congestive heart failure), excessive urinary loss of divalent cations such as calcium and magnesium occurs. These losses lead to the development of SHPT in an attempt to correct these losses. The high levels of PTH in this situation promote, despite normal or low serum calcium, large increase in intracellular calcium and increased ROS levels.[15,16] Increased intracellular calcium and ROS open mitochondrial channels, causing swelling and mitochondrial dysfunction, with subsequent evolution to cellular necrosis. The repair process of this cardiomyocyte necrosis evolves with areas of myocardial fibrosis, thus increasing the risk of heart disease in this population (left ventricular hypertrophy, arrhythmias, and heart failure). Vidal *et al.*[15] demonstrated that aldosterone infusion in rats previously submitted to parathyroidectomy prevented aldosterone induced increase in oxidative (H_2O_2 production by monocytes) and nitrosative (α1-antiproteinase activity in plasma) stress.

In the present study, PTH levels did not correlate with EPO dosage and some laboratory tests routinely performed in hemodialysis patients, such as hemoglobin, ferritin, calcium, vitamin D, or albumin, but did positively correlate with phosphorus and alkaline phosphatase, this one a known marker of bone remodeling related to SHPT severity.[30] Di Marco *et al.*[31] showed that endothelial cell lines exposed to high phosphate concentrations, similar to phosphate levels found in uremic patients, have generated reactive oxygen species *in vitro*. The lack of correlation between PTH levels and hemoglobin or EPO dose is somewhat surprising, because primary[32,33] and secondary[34,35] HPT are classically associated with anemia, as PTH may directly inhibit erythropoiesis and induce bone marrow fibrosis.[36]

PTH levels were not associated with albumin, an indicator of nutritional status and a negative marker of inflammation, neither with vitamin D. Regarding PTH and vitamin D, two other studies have shown no or only weak correlations between these biomarkers in CKD patients and the general population.[37,38] In the same line, some clinical trials showed only a slight reduction in PTH levels with replacement therapy with ergocalciferol in CKD.[39,40]

In contrast, Gracia-Iguacel *et al.*,[41] in a population of dialysis patients (hemodialysis, hemodiafiltration, and peritoneal dialysis) f ound, in univariate analysis, a negative correlation between PTH and vitamin D.

The relationship between inflammation, oxidative stress, and the SHPT of hemodialysis patients is of great scientific interest. Although the present study was not the first to examine this relationship in these patients, it is the largest reported*. For evaluation of ROS, we used, as recommended, a panel of biomarkers rather than a specific marker, using well-established measurement techniques and seeking to exclude from the analysis patients or conditions that could interfere with ROS generation or the inflammatory state. It is known that parenteral iron and EPO agents, as well as temporary vascular access and infections, may exacerbate the inflammatory state.[34]

One important limitation of the study is its cross-sectional nature, which prevents the determination of the relationship between cause and effect. Other limitation is the rather limited breadth of the panel of oxidative stress biomarkers used in the study. Finally, we did not put in our trial a control group for comparison of values of inflammation and oxidative stress in non-CKD population because, in our understanding, many other trials have shown the relationship between kidney disease and increased levels of these biomarkers.[42-44]

Conclusion

Despite the evidences of a relationship between hyperparathyroidism, the calcium paradox, and ROS/inflammation, this study was not able to identify a significant correlation among PTH levels and biomarkers of inflammation and oxidative stress in chronic hemodialysis patients. It is well known that CKD patients present a state of increased inflammation and ROS that have multifactorial genesis. This could explain, in part, the findings of this study. In other words, our results may suggest that the inflammation and oxidative stress of hemodialysis patients probably arise from other mechanisms than secondary hyperparathyroidism, or that it contributes very little to the genesis of these phenomena.

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