

## Association of PTH and carotid thickness in patients with chronic kidney failure and secondary hyperparathyroidism

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### ABSTRACT

**Introduction:** Cardiovascular diseases (CVDs) are the leading cause of death in terminal patients with chronic kidney failure (CKF). Diverse risk factors are involved in the pathogenesis, and are classified as traditional, which affect the general population; and non-traditional, which are peculiar to patients with CKF. Secondary hyperparathyroidism, a non-traditional and common factor in CKF, can cause an increased rate of bone absorption with mobilization of calcium and phosphorus. If the product of calcium x phosphorus is increased, the solubility of this ionic pair may be exceeded and deposition of calcium phosphate in cardiac and vascular tissues occur (called metastatic calcification). **Objective:** To verify eventual relationship between the thickness of the common carotid artery and the levels of PTH in patients with CKF. **Methods:** Evaluations by Doppler ultrasonography were performed to measure the width of the carotid artery wall and to search for possible correlations between different values of PTH serum levels, mineral disturbances and traditional risk factors in the carotid changes found in individuals with dialytic CKF and secondary hyperparathyroidism. **Results:** Differences in the cholesterol level and age were observed in patients with signals of arterial calcification. A significant relationship was also observed between the PTH serum levels and the carotid artery wall thickness ( $r = 0.31$ ,  $p = 0.03$ ). **Conclusion:** Data from this study show the possible concomitance of traditional factors and factors related to CKF in the genesis of CVDs in uremia.

**Keywords:** carotid artery, common; heart diseases; hyperparathyroidism, secondary; kidney failure, chronic.

### INTRODUCTION

Cardiovascular disease is the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD). These patients are more susceptible to cardiovascular disease, as they present traditional (hypertension, *diabetes mellitus*, dyslipidemia, and smoking) and non-traditional risk factors arising from CKD (anemia, oxidative stress, microalbuminuria, and hyperparathyroidism).<sup>1</sup> Secondary hyperparathyroidism (SHPT) is a common complication in patients with CKD and a significant factor in the high rate of morbidity seen in this population.<sup>2</sup> Three interrelated factors - hypocalcemia, calcitriol deficiency (the active metabolite of vitamin D) and hyperphosphatemia - play a role in the pathogenesis of this condition. Increased phosphorus levels dramatically affect the development of SHPT in patients with advanced chronic kidney disease (CKD) by interfering directly with the physiology of the parathyroid glands.<sup>3</sup> Changes in vitamin D metabolism have been correlated with various organic alterations and are particularly prevalent in individuals with CKD.<sup>4</sup> Many patients present a combination of calcium overload (arising from hemodialysis or drug therapy) and hyperphosphatemia. In this situation, calcification may occur secondary to the deposition of calcium phosphate in cardiac and vascular tissues.<sup>5</sup>

Echocardiography and electrocardiography are useful in assessing

cardiovascular disease in uremic subjects.<sup>6</sup> Doppler ultrasonography allows the study of artery function and structure in humans. Increased common carotid intima-media thickness has been correlated with traditional cardiovascular risk factors, in addition to serving as a good predictor for cardiovascular and cerebrovascular events in certain populations and severity and extent of coronary disease.<sup>7</sup>

Recently, Duprez *et al.*<sup>8</sup> described a significant correlation between the levels of parathyroid hormone and the ability of the carotid artery to distend in patients with essential hypertension. However, few trials have looked into the impact of hyperparathyroidism on the function of the arterial system of subjects with chronic kidney disease.

This study aims to investigate possible correlations between high levels of PTH and other mineral metabolism disorders, traditional cardiovascular disease risk factors, and the properties of the common carotid artery walls of patients on hemodialysis.

## MATERIALS AND METHODS

This retrospective study was carried out at the Alagoas State University for Health Sciences with funding from the Alagoas State Research Support Foundation. The standards in effect for research protocols involving human beings (CEP 297/2005) were used to select patients of both genders with CKD on dialysis aged between 18 and 65 years. The subjects were divided into two groups. Group 1 included individuals with PTH levels lower or equal to 200 pg/ml, while Group 2 featured patients with PTH levels above 500 pg/ml. The subjects were divided by PTH levels below 200 pg/ml and above 500 pg/ml based on the study by Gu *et al.*,<sup>9</sup> in which the most significant alterations were seen in the subgroups of patients on hemodialysis with secondary hyperparathyroidism and PTH levels within these ranges.

The chemiluminescent IMMULITE® 2000 Intact PTH, DPC® kit (normal: 7-53 pg/ml) was used to measure intact PTH. Diabetic patients, individuals with liver disease, active infection,

subjects on drugs or compounds that may alter bone metabolism (aluminum, GnRH analogues, anticonvulsants, cadmium, cyclosporin A, cholestyramine, steroids, statins, heparin, thyroid hormone, methotrexate, opioids and their derivatives, or oral retinoids), persons under 18 and over 65 years of age, and pregnant women were excluded.

The Kolmogorov-Smirnov test, Student's *t*-test, the Mann-Whitney U test, and Pearson's correlation coefficient were used in statistical analysis. The *p*-value was set at 0.05 to reject the null hypothesis. Statistical analysis included clinical variables such as age, gender, time on dialysis, and workup variables such as PTH (normal: 11 to 54 pg/ml), calcium (normal: 8.5 to 10.5 mg/dl), UV phosphorus (normal: 2.5 to 5.0 mg/dl), calcium-phosphorus product (normal: 55 mg<sup>2</sup>/dl<sup>2</sup>), hemoglobin (normal: 11.5 to 16.0 g/dl), hematocrit (normal: 36% to 47%), and LDL cholesterol (ideal value < 100 mg/dl) levels.

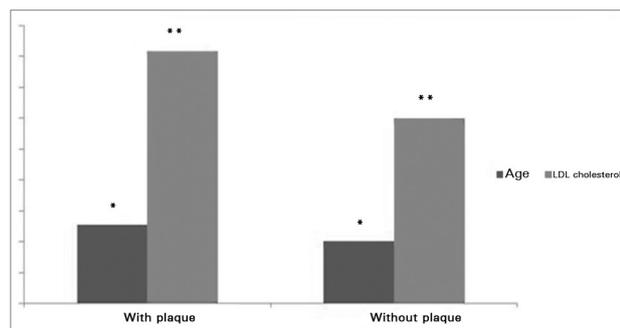
Doppler ultrasonography was performed by the same examiner on a General Electric LOGIQ 7 device with linear transducers on the frequency range of 8 to 12 MHz. The middle third of the right common carotid artery was chosen as the site of reference to analyze the intima-media thickness (IMT). Normal values were 0.9 mm for women aged 49 years and under and up to 1.0 mm for women aged 50 and over. For male subjects, the normal value was up to 1.0 mm, regardless of age. Patients underwent examination of other segments of both carotid arteries for highly echogenic plaques suggesting calcification.

## RESULTS

When traditional factors were considered, no difference was seen in age or cholesterol levels between the two groups of individuals. However, presence of plaque in ultrasound examination yielded differences between patients. Patients without plaque were aged 41 ± 4 years, whereas patients with plaque were aged 49 ± 6 years (*p* = 0.04). The cholesterol levels of individuals with

carotid plaque were higher ( $p = 0.03$ ) than the levels observed in subjects without plaque ( $196 \pm 36$  and  $103 \pm 25$  mg/dl, respectively). Figure 1 shows the differences in age and LDL cholesterol in patients with and without carotid artery plaque.

**Figure 1.** Age (years) and levels of LDL cholesterol (mg/dl) of dialysis patients with chronic kidney disease and secondary hyperparathyroidism, with and without atheromatous plaques in their carotid arteries. \* $p = 0.04$ ; \*\* $p = 0.03$ .



Seven patients (four females and three males) were included in Group 1. Mean age was  $46 \pm 5$  years and mean IMT was  $0.79 \pm 0.15$  mm. In this group, the highest IMT value was 1.0 mm. Three of the seven patients (42.86%) had highly echogenic atheromatous plaques suggestive of carotid artery calcification.

Group 2 had seven patients, five males and two females. Patient mean age was  $48 \pm 5$  years. The mean IMT was  $0.89 \pm 0.1$  mm and the highest IMT value was 1.1 mm. Five of the seven patients (71.43%) had highly echogenic atheromatous plaques. Not even multivariate analysis could establish an unequivocal correlation between PTH levels and presence of arterial plaque. Table 1 shows the characteristics of the two groups. Nonetheless, a correlation was observed between PTH levels and carotid artery wall thickness ( $r = 0.31$ ,  $p = 0.03$ ), as seen in Figure 2.

## DISCUSSION

In general, clinical variables did not differ between the two groups tested for PTH levels. Workup variables were used to divide the patients into groups, and consequently patients in Group 1 had higher PTH levels.

Cardiovascular disease is the leading cause of morbidity and mortality in patients with any

stage CKD, a finding justified in part by the high prevalence of traditional risk factors in this population. Recently, however, the administration of vitamin D derivatives was described to have a positive impact on the mortality rate of these patients, stressing the role of non-traditional risk factors in the pathogenesis of cardiovascular disease in patients on dialysis.<sup>10</sup>

In uremic patients, SHPT is characterized by parathyroid hyperplasia and increased production and secretion of PTH, a phenomenon resulting from hypocalcemia, hyperphosphatemia, and other factors.<sup>2,3,5</sup> Rats with CKD were protected from hyperplasia by hyperphosphatemia.<sup>3</sup> Portale *et al.*<sup>10</sup> studied eight children with CKD and reduced levels of calcitriol on dialysis and found that 80% of them had calcifications. The presence of calcifications was also correlated with parathyroid hormone levels, revealing the role of PTH on cardiovascular alterations regardless of other factors. SHPT is a very common condition in CKD patients and has been associated with metastatic artery calcification, a finding independently associated with increased morbidity and mortality of individuals on dialysis.<sup>2,5,11</sup> Carotid calcifications affect half of the individuals on dialysis and have been correlated with left ventricular hypertrophy, myocardial infarction, and cardiac arrest.<sup>2</sup> Prognosis has been associated primarily with calcifications located in the tunica media of arteries.<sup>2</sup> Although parathyroidectomy may reduce the calcium-phosphorus product and decrease the occurrence of metastatic calcifications, preexisting alterations are irreversible.<sup>2</sup> These findings suggest that SHPT therapy should be introduced in the early stages of the disease to prevent cardiovascular events.<sup>5</sup> Additionally, effective management of SHPT may prevent other complications such as fractures.<sup>12</sup>

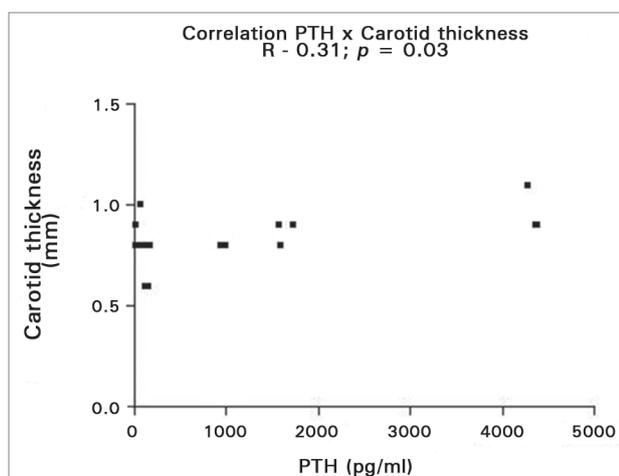
The effects of PTH upon the structure and function of the arterial walls have been studied, but a lot remains to be clarified, such as the impact of the hormone on other variables such as blood pressure. PTH causes acute transient renal vasodilation in the renal and coronary

**TABLE 1** DATA FROM PATIENTS OF BOTH GENDERS WITH CHRONIC KIDNEY DISEASE ON DIALYSIS AGED BETWEEN 18 AND 65 YEARS. GROUP 1: PTH LEVEL OF 200 PG/ML OR LOWER; GROUP 2: PTH LEVEL ABOVE 500 PG/MLPG/ML

Parameters	Group 1 (n = 7)	Group 2 (n = 7)	p
Age (years)	48.6 ± 10.2	47.8 ± 3.9	ns
Hematocrit (%)	33.5 ± 4.1	28.4 ± 4.1	ns
Hemoglobin (g/dl)	11.6 ± 2.1	9.3 ± 1.5	ns
Calcium (mg/dl)	9.2 ± 0.8	9.2 ± 0.5	ns
UV phosphorus (mg/dl)	5.9 ± 1.1	6.6 ± 0.9	ns
Calcium-phosphorus product	46.4 ± 61.4	61.3 ± 10.8	ns
PTH (pg/ml)	102.8 ± 60.4	2210 ± 1473	< 0.0001
Carotid thickness (mm)	0.8 ± 0.2	0.9 ± 0.1	ns

PTH: Parathyroid hormone; ns: Not significant.

**Figure 2.** Correlation between PTH levels (pg/ml) and carotid wall thickness (mm) of dialysis patients with chronic kidney disease and secondary hyperparathyroidism.



territories, mediated by the sodium-potassium pump and prostaglandins. Moreover, calcium is known to produce alterations in the vascular walls and blood pressure levels of patients with primary hyperparathyroidism. Parathyroidectomy has been reported to reduce blood pressure levels and bone loss in experimental models of hypertension.<sup>13,14</sup> Ultrasound images of the arterial walls of 30 patients with untreated essential hypertension showed a significant correlation between PTH level and carotid diameter and distensibility.<sup>8</sup> It has been experimentally shown that the endothelium also expresses the PTH-related protein receptor (PTH/PTHrP).<sup>15</sup>

Ultrasound examination of patients with primary hyperparathyroidism has revealed significant increases in stiffness, mean and maximum IMT, in addition to substantial reductions in carotid diameter.<sup>7,16</sup> However,

some authors have claimed that the increased cardiovascular morbidity and mortality in subjects with primary hyperparathyroidism correlates not only with high levels of calcium and PTH, but also with coexisting traditional risk factors.<sup>7</sup> Gheissari *et al.*<sup>17</sup> found a significant correlation between the IMT and PTH levels of 16 subjects ( $12.76 \pm 4.5$  years) with end-stage renal disease and, similarly to the present study, failed to observe differences between the IMT of patients and controls.

Anemia and changes in phosphorus and calcium levels have been correlated with cardiovascular anomalies in uremic patients. However, they are expected to produce a disordered state when present continuously. As these variables were not analyzed longitudinally, they could not be correlated to anomalies in ultrasound examination.

In this study, significant differences in some traditional factors were found in patients with carotid alterations. A discrete correlation between carotid wall thickness and PTH levels was also observed. These findings are not unprecedented, but they support the conclusions of authors such as Nishizawa *et al.*<sup>18</sup> on the role of dialysis, and normal levels of PTH, calcium, and phosphate in the prevention of atherosclerosis in patients on hemodialysis. Our study had two important limitations. First, the small number of enrolled patients, a fact that hindered the verification of statistical differences between groups; anemia, for one, could elicit significant differences if a larger group of subjects had been studied. And second - a limitation inherent to retrospective

studies - we were unable to use ABPM data to compare between the blood pressure levels of subjects in both groups, as most of the records referred to isolated BP measurements. The BP data obtained from different measurement methods indicated homogeneous levels of hypertension, but they were not listed on a table. Interestingly, no significant difference was found between the groups with respect to time on dialysis, a factor that may affect carotid artery thickness.

## CONCLUSION

Traditional and non-traditional cardiovascular risk factors are both present in patients on dialysis with cardiovascular disease. This study revealed a significant correlation between the carotid intima-media thickness and PTH levels. However, the sample of the population analyzed in this preliminary study is not large enough to validate its findings. A prospective study with a greater number of patients paired against a control group and a more comprehensive array of data (time on dialysis, drug therapies in use, BMI, electrocardiograms and echocardiograms, blood pressure levels, renal function, liver function, PTH, TSH, free T4, electrolytes, lipid profile, blood glucose, uric acid, CBC, and others) is thus needed.

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