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Original Article

Histopathological Changes of Radial Artery Wall in Patients of Chronic Kidney Disease Stage 5 Undergoing AV Fistula Formation and their Correlation with Serum iPTH Levels

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ABSTRACT. Vascular complications arise in uremic patients in the absence of clinically significant atherosclerotic disease. Elevated serum parathyroid hormone (PTH) and abnormal calcium (Ca) and phosphorus (P) balance have been implicated in vascular damage in chronic kidney disease (CKD) patients, but there is lack of histo-pathological studies. Patients with CKD stage 5 and 5D who underwent arterio-venous fistula were included in this study. Baseline and laboratory parameters including assessment of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, uric acid, albumin, calcium, phosphorus, intact PTH (iPTH) and vitamin D level were documented. The specimens of the arterial wall were obtained during the procedure and were analyzed. Patients were divided into two groups - iPTH <400 (Group A) and iPTH >400 (Group B). Mean intimal thickness (IT) was significantly high in patients of Group B (60.4 ± 24.1 µm) as compared with patients of Group A (37.8 ± 14.9 µm) (*P* = 0.003). Vascular calcification was comparable in both groups. The iPTH level was found to be an independent risk factor for high intima thickness (correlation coefficient 0.653) (*P*-value <0.01). Patients with high (≥400 pg/mL) iPTH have 8.93 times the risk of developing intimal thickness of ≥60 µm as compared with patients with low (<400 pg/mL) iPTH (*P*-value <0.05), with 95% confidence interval of 1.27, 62.61. The mean IT of the radial artery significantly correlated with the iPTH level, while vascular calcification was independent of the iPTH level. Hyperparathyroidism is an important cause of ongoing vascular damage and may contribute to higher vascular events in CKD patients.

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Introduction

Arterial disease is an important factor in uremic patients. Epidemiological studies have shown that damage of large arteries is a major contributing factor to morbidity and mortality in patients with chronic kidney disease (CKD)

and in those with end-stage renal disease (ESRD).[1] Atherosclerosis, a primary intimal disease characterized by the presence of plaques and occlusive lesions, is the most frequent underlying cause of these complications, but it is known that many vascular complications arise in uremic patients in the absence of clinically significant atherosclerotic disease.[2] Recently, attention has been focused on endocrine abnormalities in patients with CKD as a way to explain some of these associations.[3,4] Calcitriol deficiency leads to the development of secondary hyperparathyroidism (HPTH), as it promotes parathyroid gland growth (hyperplasia) and increased parathyroid hormone (PTH) synthesis through loss of the ability to upregulate vitamin D receptor expression within parathyroid cells.[5] The end result is elevated serum PTH and abnormal calcium (Ca) and phosphorus (P) balance. The degree of arterial wall changes in uremia may correlates with Ca, P and PTH levels.[6,7]

In a limited number of studies,[6,7] attempts have been made to correlate arterial pathological changes with several of the risk factors and laboratory parameters present in uremic patients. Hyperparathyroidism is one of the mechanisms of uremic toxicity.[8] In this trial, we studied the histopathological changes in the arterial wall of CKD stage 5 and 5D patients and correlated them with serum parathyroid levels.

Subjects and Methods

Patients with CKD stage 5 and 5D scheduled for creation of arterio-venous fistula were included in this cross-sectional study after obtaining proper consent. Detailed history was recorded for each patient to include gender, age, duration of disease and primary disease, co-morbidities and duration of hemodialysis (months). We reviewed the medical records for history of diabetes, hypertension, CKD and coronary artery disease (CAD). Hypertension was defined as a systolic blood pressure (SBP) >140 mm Hg or a diastolic blood pressure (DBP) >90 mm Hg on two repeated measurements, or the use of antihypertensive drugs. CAD included history of coronary events or coronary re-vascularization procedures. CKD was defined and classified as per the K/DOQI criteria. The estimated glomerular filtration rate was calculated from the serum creatinine level using the Cockcroft–Gault equation. The diagnosis of underlying basic renal disease was made on clinical evidences.

Laboratory measurements

Routine laboratory tests consisted of complete blood count, serum biochemistry including assessment of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, uric acid, albumin, calcium, phosphorus, intact PTH (iPTH) and vitamin D level. The serum iPTH level was performed by chemiluminescent microparticle immunoassay.

Surgical procedure

The surgeon obtained small specimens, a partial (elliptical) section of the arterial wall of the artery used to create the AVF before performing the anastomosis.

Pathologic studies of vascular specimens

Cross-sections of the arterial sample were fixed in 10% neutral-buffered formalin for light microscopy. A pathologist unaware of clinical information and AVF outcomes performed all histologic evaluations. Specimens were cut into 5-µm sections and stained with hematoxylin-eosin and Masson's Trichrome. Images of the vascular cross-sections were captured at various magnifications and morphometric evaluation, including measurement of intimal thickness (IT), medial thickness (MT) and intimal–medial thickness (IMT), was performed using the Image J software (version 1.47 available at http://rsbweb.nih.gov/ij/). Von Kossa stain was used to highlight calcifications that were graded by the pathologist on a semiquantitative scale (0 none, 1 mild, 2 moderate and 3 severe).

Statistical analysis

Statistical analysis was performed using STATA 11.0 version. All the categorical va-

riables like sex, AVF, diabetes and hypertension have been compared using the chi square test or the Fisher exact test, depending on whichever was appropriate. Continuous variables have been compared between the two groups using the unpaired t-test. The effect of various given covariates on the dependant variables IT, MT and IMT has been evaluated using stepwise regression analysis.

Results

Thirty-three patients with distal AVF were enrolled in this study. One patient was excluded because of inadequate radial artery sample. A total of 32 radial artery specimens were assessed for IT, MT, IMT and calcification.

The cause of CKD in these patients was diabetic nephropathy in 17 patients (53.1%), chronic interstitial nephritis/unknown in 12 (37.5%) patients, chronic glomerulonephritis in two (6.2%) patients and autosomal dominant polycystic kidney disease in one (3.1%) patient.

Table 1 shows the baseline parameters of patients. The mean IT, MT and IMT were 49.9 ± 23.1 µm, 292.6 ± 102.3 µm and 342.3 ± 115.5 µm, respectively. Calcification was seen in nine (28.12%) patients in our study.

To see radial artery IT, MT, IMT and calcification according to the iPTH levels, patients were divided into two groups - iPTH <400 (Group A) and iPTH >400 (Group B). The results showed comparable baseline clinical and laboratory parameters, except for mean phosphorus level, which was significantly higher in Group B compared with Group A (P = 0.016). The mean IT was significantly high in patients of Group B (60.4 ± 24.1 µm) as compared with Group A (37.8 ± 14.9 µm) (P = 0.003) (Table 2). Vascular medial calcification was comparable in both groups.

The iPTH level was found to be an independent risk factor for high IT on regression analysis. The correlation between IT and iPTH is 0.653, which implies that there is a positive relationship between both the variables and also that it is highly significant, with P-value <0.01. Patients with high (≥400 pg/mL) iPTH have 8.93 times the risk of developing IT of ≥60 µm as compared with patients with low (<400 pg/mL) iPTH (P-value <0.05), with 95% confidence interval of 1.27, 62.61.

Table 1. Baseline parameters of patients included for histological evaluation (n = 32).

	Mean ± SD
Age (years)	49.9 ± 12.8
Male (%)	25 (71.4%)
Diabetes mellitus (%)	17 (48.5%)
Hypertension (%)	27 (84.3%)
Chronic kidney disease duration (years)	1.7 ± 1.2
Hemodialysis duration (months)	0.8 ± 0.3
Systolic blood pressure (mmHg)	142.5 ± 22.5
Diastolic blood pressure (mm Hg)	86.5 ± 12.2
HB (g/dL)	8.4 ± 1.3
Ca (mg/dL)	8.2 ± 0.9
Po_4 (mg/dL)	7.9 ± 2.2
$Ca*Po_4$	65.6 ± 20.5
Uric acid (mg/dL)	8.3 ± 2.6
iPTH (pg/mL)	432 ± 249.8
S. albumin (g/dL)	3.5 ± 0.6
Vitamin D (ng/mL)	28.1 ± 11.5
Triglyceride (mg/dL)	129.6 ± 65.1
T. cholesterol (mg/dL)	127.6 ± 41.2
LDL (mg/dL)	81.2 ± 30.7
Intima thickness (µm)	49.9 ± 23.1
Media thickness (µm)	292.6 ± 102.3
Intima–media thickness (µm)	342.3 ± 115.5
Calcification (%)	9 (28.12%)

Discussion

There are very few studies that have looked at the histopathological aspects of arterial wall changes primarily due to the fact that it is difficult to obtain the specimen of the arterial wall. The main pathologic derangement of the radial artery is intimal hyperplasia and role of atherosclerosis is unusual, in contrast to carotid and coronary arteries in which atherosclerosis occurs commonly.[9]

Clinical risk factors of increased intimal hyperplasia or IMT of the radial artery are known to be old age, diabetes mellitus, hyper-

Table 2. Clinical, laboratory and radial artery histopathological parameters according to serum iPTH levels.

	iPTH <400 pg/mL (Group A) (n = 15)	**iPTH >400 pg/mL (Group B) (n = 17)**	***P*-value**
Age (years)	50.7 ± 12.7	49.3 ± 13.3	0.778
Antihypertensive drugs	2.1 ± 1.30	2.1 ± 1.7	0.937
Hypertension (%)	12 (80%)	18 (88.24%)	0.522
Diabetes mellitus (%)	8 (53.30%)	9 (52.94%)	0.982
Hemodialysis duration (months)	0.8 ± 0.35	0.8 ± 0.3	0.747
Systolic blood pressure (mm Hg)	137.6 ± 17.7	146.8 ± 25.8	0.254
Diastolic blood pressure (mm Hg)	84.2 ± 12.7	88.5 ± 11.8	0.329
HB (g/dL)	8.2 ± 1.42	8.5 ± 1.3	0.608
Ca (mg/dL)	8.4 ± 1.0	8.1 ± 0.9	0.314
Po_4 (mg/dL)	6.9 ± 1.87	8.8 ± 2.2	0.016
Ca*Po_4	58.4 ± 16.1	72.0 ± 22.2	0.060
Uric acid (mg/dL)	7.9 ± 2.3	8.6 ± 2.8	0.471
S. albumin (g/dL)	3.4 ± 0.62	3.5 ± 0.5	0.768
Vitamin D (ng/mL)	30.7 ± 12.6	25.8 ± 10.2	0.235
Triglyceride (mg/dL)	147.8 ± 86.3	113.5 ± 33.3	0.140
T. cholesterol (mg/dL)	132.8 ± 50.3	123.1 ± 32.1	0.513
LDL (mg/dL)	87.4 ± 28.7	75.76 ± 32.1	0.289
Intima thickness (µm)	37.8 ± 14.9	60.4 ± 24.1	0.003
Media thickness (µm)	262.7 ± 54.2	318.7 ± 127.1	0.124
Intima–media thickness (µm)	300.5 ± 61.5	379.1 ± 139.5	0.053
Calcification (%)	4/15 (26.67%)	5/17 (29.41%)	0.868

tension and atherosclerosis.[9,10] Because of the high incidence of diabetes mellitus, hypertension and atherosclerosis in uremic patients, it is suggested that radial arterial IMT in uremic patients may be thicker than that of age-matched healthy populations. Ejerblad et al[11] first reported that the radial arterial wall in hemodialysis patients measured by histological examination was significantly thicker than that of control subjects. The mean IMT of the radial artery in our study (n = 32) was 342.3 ± 115.5 µm, which is higher than the radial artery IMT in the control groups reported in earlier studies.[12] The mean IT (49.9 ± 23.1 µm) and MT (292.6 ± 102.3 µm) were also high in our study as compare with the thickness reported in healthy patients.[12,13]

Between the two groups studied, the baseline parameters were comparable, except for high phosphorus levels seen in Group B. Because of decreased glomerular filtration rate and altered endocrine function of the kidneys, the parathyroid–vitamin D–renal axis gets deranged, which results in phosphate retention and secondary hyperparathyroidism in majority of the patients.[14,15] Studies have shown that serum phosphate excess is associated with higher iPTH levels among CKD patients.[16]

In our study, the mean IT was high in Group B patients (60.4 ± 24.1 µm) as compared with that in Group A patients (37.8 ± 14.9 µm) (P = 0.003). A study carried out in 85 children on dialysis by Shroff et al[17] showed that patients with mean iPTH levels less than twice the upper limit of normal had vascular measures that were comparable to age-matched controls, but those with iPTH levels greater than twice the upper limit of normal had greater carotid IMT, stiffer vessels and increased cardiac calcification evaluated by ultrasound. This may signify that PTH itself contributes to vascular injury via mechanisms other than its effect on Ca–PO_4 homeostasis. It would be impossible to extricate the individual effects of Ca–PO_4 and PTH. PTH may mediate vascular damage by playing a permissive role in arteriolar wall thickening,[18] increasing triglycerides and LDL cholesterol and contributing to chronic hypertension. Progression of these vascular changes is reduced after parathyroidectomy.[19]

In our patients, although phosphorus was high in the iPTH >400 group, on regression analysis, the IT was independently associated with a high iPTH value. The vascular calcification score was not correlated with iPTH levels in our study. This has already been demonstrated in other studies as well.[20-22]

In conclusion, secondary hyperparathyroidism and hyperphosphatemia are quite prevalent in CKD stage 5 and in incident-dialysis patients. The mean IT of the radial artery significantly correlated with the iPTH level, while vascular calcification was independent of the iPTH level. Thus, hyperparathyroidism is an important cause of ongoing vascular damage and may contribute to higher vascular events in CKD patients. Thus, iPTH is an important therapeutic target in CKD patients.

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Conflict of Interest

There is no conflict of interest in the publication of this article. We have not submitted any data of this study as an article in any other journals.

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