Vascular Calcification in Dialysis Patients

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ABSTRACT

The risk factors for vascular calcification (VC) in dialysis patients include duration of dialysis, diabetes mellitus, aging, hyperphosphatemia, hyperparathyroidism, and calcium or vitamin D supplementation. This study was performed to evaluate the prevalence of and risk factors for VC in our dialysis population.

Methods. One hundred twenty-nine chronic dialysis patients underwent plain x-rays of the hands for VC. Patients were grouped as either positive (PVC) or negative (NVC) for VC. Age, gender, duration of dialysis, presence of non–insulin-dependent diabetes mellitus (NIDDM), oral calcium, and 1α-hydroxyvitamin D_3 supplement, serum levels of calcium (Ca), phosphorus (P), calcium phosphorus product (CaxP), alkaline phosphates (ALP) and intact parathyroid hormone (iPTH) were compared between the two groups.

Results. Thirty-four patients (26.35%) showed VC. There were no differences between PVC and NVC patients for duration of dialysis (38.4 $\pm$ 27.7 for PVC and 34.6 $\pm$ 31.2 months for NVC, $P = .80$), levels of serum Ca ($P = .26$), P ($P = .19$), CaxP ($P = .33$), ALP ($P = .89$), or iPTH ($P = .24$). Similarly, oral calcium and 1α-hydroxyvitamin D_3 intake were not different between the two groups ($P = .971$ and $P = .3710$ respectively). Compared to NVC patients, PVC patients were older (56.3 $\pm$ 10.4 versus 47.5 $\pm$ 16.1 years, $P = .008$) and had a greater incidence of NIDDM (17/34 PVC and diabetic versus 20/95 NVC, $P = .001$). In conclusion, for patients with a medium length of dialysis, the duration of dialysis as well as the doses of calcium salts and of 1α-hydroxyvitamin D_3 were not significantly associated with vascular calcifications, but it was not possible to exclude a role for these and other factors in patients with longer dialysis.

VASCULAR CALCIFICATION (VC) has been associated with increased morbidity and mortality in dialysis patients.[1] VC can be due either to calcification of atheromatous lesions,[2] or diffuse calcification of the arterial media layer, which is termed medial calcinosis.[3] The risks for the development of VC of medial calcinosis type include renal failure, diabetes, and old age.[4] VC of the medial calcinosis variety has been described in the aorta, coronary

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arteries, and inferior epigastric artery.[5] In chronic kidney disease patients, VC has been attributed to alterations in mineral metabolism and its treatment, as contributing factors to the development of vascular and soft tissue calcifications.[6] High serum phosphorus (P) and calcium phosphorus (CaxP) product were dependent factors for death in dialysis patients.[7] Even in children on dialysis, soft tissue and vascular calcifications have been noted.[8] Therefore we performed this study to assess the factors associated with the findings of medial calcinosis VC, in our dialysis population.

PATIENTS AND METHODS

Among all patients on chronic dialysis who were asked to undergo plain x-rays of their hands, 129 on dialysis for more than 3 months were included, excluding patients on dialysis for less than 3 months and transient patients. There were 87 patients on hemodialysis (HD) and 42 patients on peritoneal dialysis (PD). We recorded patient age, gender, time since starting dialysis in months, and presence or absence of non–insulin-dependent diabetes mellitus (NIDDM) as the cause of their underlying kidney failure. Patients were listed as taking oral calcium and oral 1α-hydroxyvitamin D_3 if they have been on these supplements since the start of their dialysis. Those who did not receive oral calcium or 1α-hydroxyvitamin D_3 supplements were classified as off treatment. Oral calcium was given in the form of calcium carbonate at a dose of 600mg twice daily as a phosphate binder: 1α-hydroxyvitamin D_3, orally in a dose of 0.5 mcg daily.

Serum levels of Ca, P, CaxP, alkaline phosphatase (ALP), and intact parathyroid hormone (iPTH) were taken as the average of the last three measurements. Laboratory investigations were performed monthly in the morning before the first weekly HD session for HD patients and at monthly intervals in PD patients. Ca was measured in mmol/L as total serum calcium and not the ionized form. P was measured in mmol/L and CaxP in $mmol^2/L^2$; ALP was measured in IU/L and iPTH as the intact hormone in pmol/L.

HD patients were dialyzed using synthetic membranes (Hemophan or polysulfone) and a bicarbonate dialysate solution. Dialysis was performed using Fresenius 4008H dialysis machines. The dialysate solution contained a fixed concentration of Ca at 1.75 mmol/L. The duration of dialysis was individually tailored to control body fluids and blood chemistries (4–5 hours thrice weekly). PD solution had a fixed concentration of Ca at 1.75mmol/L as well.

Hand x-rays were taken annually in our dialysis patients as part of their medical management for the presence of renal osteodystrophy. VC was classified as present if the plain x-ray showed any calcification of any vessel in the hands, which may include radial, palmar arterial arch, or palmar digital arteries. All x-ray films were read by a consultant radiologist without prior knowledge of our intention to conduct this study. Patients were grouped as either with VC (positive VC [PVC]) or lacking VC (negative VC [NVC]) based on the x-ray findings.

Statistical Analysis

Data were expressed as mean values ± SD. Patients were classified as those with or without VC (PVC versus NVC). Student's *t*-test was used to compare the differences between PVC and NVC patients for age, time since starting dialysis, and levels of Ca, P, CaxP, ALP, and iPTH. χ^2 tests were used to compare the statistical differences for the presence of NIDDM and the intake of calcium or 1α-hydroxyvitamin D_3 between PVC and NVC patients.

RESULTS

Among 129 dialysis patients were studied for the presence of VC, 34 had evidence of VC (26.35% PVC) and 95 patients, no signs of VC (73.64% NVC). The duration of dialysis for PVC patients was 36.4 ± 27.7 months compared to 34.6 ± 31.2 months for NVC group, a difference that was not significant ($P = .80$). Levels of Ca and P were similar between PVC and NVC patients (2.165 ± 0.216 versus 2.231 ± 0.283 mmol/L [$P = .26$] and 1.888 ± 0.646 versus 1.690 ± 0.69 mmol/L, [$P = .19$]). CaxP showed no differences between the two groups (4.06 ± 1.43 versus 3.74 ± 1.58, $P = .33$). ALP showed no differences between the two groups (103 ± 46.6 versus 101.1 ± 58.9, $P = .89$), nor did iPTH levels (38.9 ± 42 versus 39.7 ± 28.5, $P = .24$).

Oral calcium intake was present in 23 PVC and 65 NVC patients. χ^2 analysis showed no statistically significant differences between the two groups with a P value of .971. Similarly, oral intake of 1α-hydroxyvitamin D_3 was present in 14 PVC and 54 NVC patients, a difference that was not different between the two groups (χ^2, $P = .370$).

Age, however, was significantly different between PVC and NVC patients. For PVC patients, the mean age ± SD

Table 1. Characteristics of the 129 Chronic Dialysis Patients According to the Presence or Absence of Vascular Calcification

Characteristics	Vascular Calcification ($n = 34$, 26.35%)	No Vascular Calcification ($n = 95$)	*P*-Value
Age (y)¶	56.3 ± 10.4	47.5 ± 16.1	.008*
Gender (M/F)	20/14	43/52	.175**
Duration of dialysis (mo)¶	38.4 ± 27.7	34.6 ± 31.2	.80*
Diabetes mellitus	17	20	.001**
Serum calcium (mmol/L)¶	2.165 ± 0.216	2.231 ± 0.283	.26*
Serum phosphorus (mmol/L)¶	1.880 ± 0.646	1.690 ± 0.690	.19*
Serum calcium × phosphorus product ($mmol^2/L^2$)¶	4.07 ± 1.43	3.74 ± 1.58	.33*
Serum alkaline phosphatase (IU/L)¶	103 ± 46.6	101.1 ± 58.9	.89*
Serum parathyroid hormone (pmol/L)¶	38.9 ± 42	27.4 ± 28.5	.24*
Oral calcium supplement	23	65	.971**
Oral 1α-hydroxyvitamin D_3 supplement	14	54	.370**

*P-values determined with use of t-test.
**P-values determined with use of χ^2 test.
¶Values are means ± SD.

was 56.3 ± 10.4 years compared to NVC patients whose age distribution was 47.5 ± 16.1 years ($P = .0083$). NIDDM was present in 37 (28.6%) among all dialysis patients. The combination of NIDDM and VC was present in 17 (13%) of all dialysis patients compared with 63 nondiabetic NVC patients ($P = .001$; Table 1).

DISCUSSION

Arterial stiffening is a major predictor of all causes and of cardiovascular mortality among HD patients.[9,10] This increased arterial stiffening is multifactorial as seen in experimental uremia and in uremic patients, namely fibroelastic intimal thickening, calcification of elastic lamellae, increased extracellular matrix with more collagen, relatively less elastic fiber content, and deposition of bone matrix proteins.[11,12] Arterial calcium content is increased and arterial calcifications are frequently observed in dialysis patients.[13] Multiple factors have been implicated in the development of arterial calcifications.[14] The prevalence of arterial calcification increases with age both in the general population and dialysis patients.[15] Our results agree with the published data on the presence of vascular calcification with aging. In our patients, PVC individuals had a mean age of 56.3 years compared to NVC patients with a mean age of 47.5 years values, which are comparable to those in the published literature.

In dialysis patients, arterial calcification increases with longer duration of dialysis.[16] The issue of the effect of dialysis duration on PVC was not evident in our study, however. The lack of effect of duration of dialysis may lay in the possibility that our patients had not been on dialysis long enough. Studies that showed positive effects of time since starting dialysis on VC have had patients on dialysis for at least 81 months, a time period that is at least twice as long as that in our patients.[17]

The radial artery has been cited as one of the vessels affected by medial calcinosis,[18] a site that is easy to evaluate radiologicaly. This simple method of obtaining a plain x-ray to look for radial artery calcification or calcification of any of the vessels in the hands makes it an easy screening test for VC which is why we chose it. Secondary hyperparathyroidism, hyperphosphatemia, elevated CaxP, and increased vitamin D concentrations are frequently shown as the principal causes associated with arterial calcifications.[19,20] Arad et al[20] did not find the serum concentrations of Ca, 1,25-vitamin D_3, or PTH to be associated with the presence of arterial calcifications. Our results agree with those of Arad; Ca and iPTH levels were not associated with VC even though our patients had elevated levels of iPTH. Although Ca levels were in the normal range among our patients, the calcium content of these patients can still be elevated. This is perhaps a limiting point in this study; we looked at Ca concentration in plasma rather than tissue content. In a study by Guerin et al,[21] the CaxP was lower than the critical value for calcium precipitation (ie, 5.65 $mmol^2/L^2$) and serum calcium was not increased in dialysis patients with arterial stiffening and vascular calcification.[17] Our results showed a CaxP that was lower than the critical value for Ca precipitation as well. This observation may be due to the fact that the Ca level was in the normal range with mild elevation in P level, findings that are in agreement with those by Guerin. Moreover in Guerin study, patients with greater vascular calcifications showed lower PTH levels and the only variable that was independently associated with vascular calcification was the amount of calcium carbonate intake. Our results showed that levels of iPTH for PVC patients were higher than those levels for NVC patients, however, even though they were not statistically significant. Although Guerin and others have found calcium intake to be associated with the presence of VC in dialysis patients, we did not find such an association, neither did we observe one for 1α-hydroxyvitamin D_3 intake.[14,17] The reasons for this lack of association could lay in the methods of prescribing calcium and 1α-hydroxyvitamin D_3 supplements to these patients. Other studies have tailored calcium and 1α-hydroxyvitamin D_3 supplement intakes to the level of P, while we supplemented our patients with a fixed regimen. The P level in our patients was similar to the published studies, which brings the point that increasing the dosage of calcium or 1α-hydroxyvitamin D_3 does not add further benefits but rather leads to increasing the possibility of VC.

Diabetes mellitus is another risk factor associated with the presence of vascular calcification.[22] A history of coronary artery disease and diabetes correlated with VC by both histology and spiral computed tomography in a study that looked for bone matrix protein deposition in dialysis patients.[12] Our results showed a strong association between diabetes and VC in dialysis patients.

In conclusion, this study showed that vascular calcification is common among dialysis patients and that aging and diabetes are strongly associated with its presence. Other factors such as Ca, P, CaxP, ALP, and iPTH were not associated with the presence of VC, neither the intake of calcium carbonate or 1α-hydroxyvitamin D_3 at least in patients with medium length of dialysis. However, it is not possible to rule out a role for these and other factors in patients with longer durations of dialysis.

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