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Increased Levels of Serum Parathyroid Hormone and Fibroblast Growth Factor-23 Are the Main Factors Associated with the Progression of Vascular Calcification in Long-Hour Hemodialysis Patients

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Key Words
Vascular calcification · Parathyroid hormone · Long hemodialysis · Fibroblast growth factor-23 · Mineral metabolism

Abstract
The aim of the present study was to assess the frequency and factors associated with the progression of vascular calcifications (VCs) using a semiquantitative X-ray score. We included all prevalent hemodialysis patients with initial radiological scores ranging from 0 to 3 according to the severity of the VCs. Patients were classified as non-progressors or progressors after 3 years. Among the 85 patients, 44.7% were classified as progressors. Only exhibiting high levels of serum intact parathyroid hormone (PTH, >190 pg/ml) and fibroblast growth factor (FGF)-23 levels (>3,000 RU/ml) is associated with the risk of VC progression (OR 5.8, 95% CI 1.7–19.8, p = 0.004). Calcitriol analogs (38%), cinacalcet (15%), dialysate calcium (mean 1.48 mmol/l), dialysis session time (4–8 h) and calcium- (10%) and non-calcium-based phosphate binders (38%) were prescribed on an individual basis. Hyperphosphatemia (<10%) and, especially, hypercalcemia (1%) and hyperparathyroidism (>585 pg/ml = 0%) were infrequently observed. In conclusion, the main factor associated with VC progression was the association of higher serum PTH and FGF-23 levels. It remains to be seen whether patients should be treated to lower their PTH value, even within the target range, using calcitriol analogs, calcimimetics, parathyroidectomy, or by modifying the Klotho-FGF-23 axis.

Introduction

Vascular calcifications (VCs) have frequently been observed in chronic kidney disease (CKD), especially in hemodialysis (HD) patients [1, 2], and reflect more severe cardiovascular disease [3]. Coronary artery, thoracic and abdominal aorta, cardiac valvular, or peripheral artery calcifications have been studied and associated with mortality [4, 5]. Many factors have been associated with the risk of VC such as 'classical' cardiovascular and 'non-traditional' risk factors involving mainly mineral metabolism abnormalities and treatments. In our previous study, age, diabetes, and high serum fibroblast growth factor (FGF)-23 level were associated with the higher VC scores [4]. FGF-23 appears to be one of the strongest markers associated with the risk of both mortality [6] and VC in HD patients [7]. In another study, we showed that hyperphos-

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phatemia and hypercalcemia were not identified as risk factors because they were found to be uncommon when long-HD schedules and individualized therapies were used along with a homogeneous strategy [8]. However, we have reported that VCs are dramatically prevalent (83%), even in cases exhibiting few mineral metabolism abnormalities [4].

Coronary artery calcification (CAC) remains the gold standard in randomized controlled trials (RCTs) for VC assessment [9, 10], but is not recommended for routine diagnosis. Hence, by using a simple semiquantitative radiological score in long-hour hemodialysis patients, we have reported previously that aortic and peripheral VCs are associated with mortality [4]. The aim of the present study was to assess the frequency and factors associated with 3-year VC score progression in the same prevalent HD patients using the same radiological criteria.

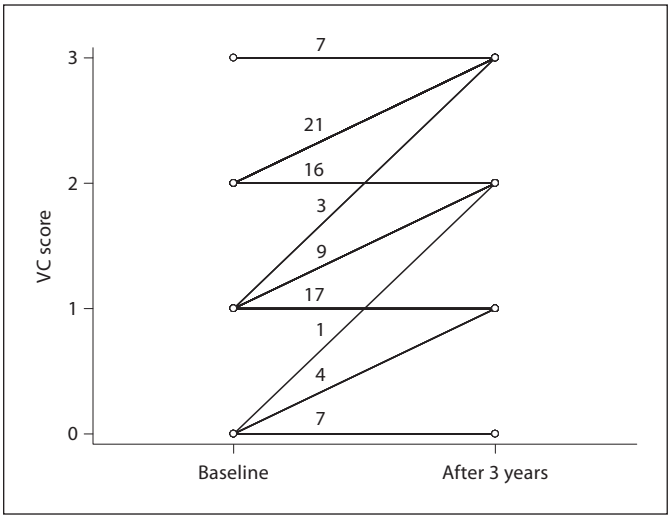

Fig. 1. VC scores between baseline and after 3 years.

Patients and Methods

All prevalent HD patients from the initial study, between January 2006 and January 2007, were included and observed over a period of 3 years. Patients had an initial radiological semiquantitative score ranging from 0 to 3, according to the severity and extent of the VC from 8 fine-detail plain radiological films (front pelvis, profile lumbar and knee, right hand and arm, chest, skull, and orthopantomogram). The VC scores were as follows: 0 = absence of VC; 1 = light aortic or iliac VC; 2 = major aortic + iliac + femoral VCs, and 3 = severe diffuse VCs with aortic, iliac, femoral, popliteal, and arm artery VCs. Concurrently, bone mineral density (BMD) was measured using a Hologic® QDR-1000 (Hologic Inc., Waltham, Mass., USA) DXA densitometer. The right femoral neck and ultra-distal wrist BMDs were recorded.

Three years later, between January 2009 and January 2010, the initial patients still presenting to the center underwent a new radiographic VC score determination under the same conditions as used previously. Patients were classified into 2 groups, i.e., nonprogressors and progressors, according to their VC score change by the same radiologist who assessed the radiographic films. We recorded the medical history, cardiovascular events, risk factors, treatments (statins, warfarin, vitamin D, cinacalcet, and phosphate binders), and standard laboratory values. The following parameters were also evaluated: annual serum FGF-23 values (FGF-23, ELISA c-term; Immutopics Inc., San Clemente, Calif., USA); biannual 25-hydroxyvitamin $D_2 + D_3$ (25-OH-D, Liaison; DiaSorin Inc., Stillwater, Minn., USA), bone alkaline phosphatases (b-ALP, chemiluminescence; Beckmann Inc., Urbana, Ill., USA), and β-Crosslaps (CTX, Chemiluminescence; Roche Diagnostic, Basel, Switzerland). Monthly testing of parathyroid hormone (PTH) using a second-generation assay (PTH, Roche Elecsys) was also conducted.

All samples were taken before a midweek session. Kt/V was calculated using Daugirdas' second-generation single-pool formula. Patients were hemodialyzed 3 times/week with a 4- to 8-hour schedule using polysulfone high-flux filter (FX80 and FX100, Fresenius S.E., Bad-Homburg, Germany) and a dialysate calcium concentration varying from 1.25 to 1.75 mmol/l, according to PTH, calcium, and bone marker serum levels. This therapeutic strategy has been reported previously with a systematic vitamin D supplementation using monthly cholecalciferol, a phosphate-binder prescription using calcium carbonate, or sevelamer according to calcemia, serum PTH, and bone marker levels with a target of <1.7 mmol/l of phosphatemia; and using alfacalcidol and cinacalcet for the treatment of hyperparathyroidism (HPT) and a few cases of parathyroidectomy (PTX) [8].

Statistical Analysis

For each patient, for further analysis, we retained the mean of all the available values and mean treatment doses during the observational period. The Student t test or the Mann-Whitney test was used to compare the 2 groups according to the variable distribution. Fisher's exact test was applied for proportion comparison. Logistic regression was applied to determine the factors significantly associated with the 2 groups (VC progression). A receiver operator curve (ROC) was generated for the main continuous data associated with VC progression. The odds ratio (OR) associated with the group of VC progressors was calculated for the groups of patients with different associations of the 2 main factors according to their median distribution. The results are reported as mean ± standard deviation. Differences with p values of ≤0.05 were considered statistically significant. Statistical analyses were performed using MedCalc© software 11.5.1.0 (MedCalc Software, Mariakerke, Belgium).

Results

Among the 161 initial patients, 45 died, 12 underwent successful kidney transplantation, 19 were lost to follow-up due to center change, and 85 were still present after 3

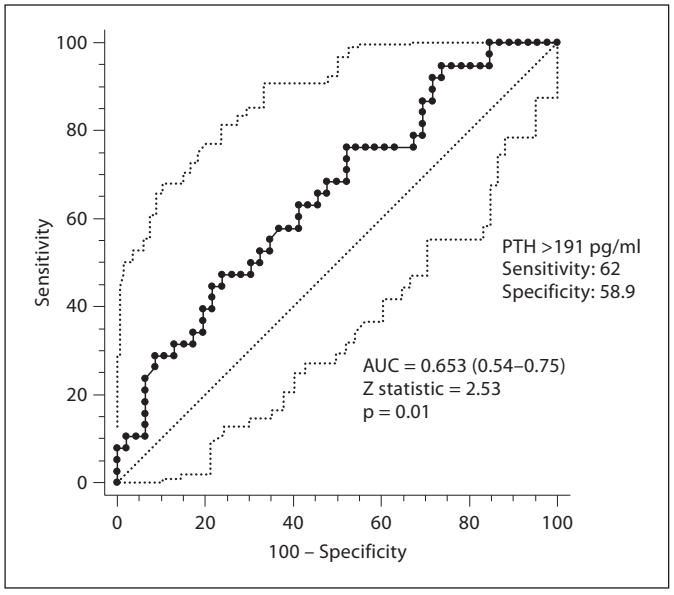

Fig. 2. ROC analysis of serum PTH levels for predicting VC outcome. AUC = Area under the curve.

years and were the subjects of the present investigation. Figure 1 displays the VC score change after 3 years. Among the 85 patients, 47 were classified as non-progressors and 38 as progressors (44.7%). The proportion of progressors increased with increasing initial score as follows: 41.6% = 0; 41.3% = 1, and 56.7% = 2. The VC score did not decrease, and after 3 years 92% of the remaining patients displayed significant VC versus 86% of all patients with baseline values.

The characteristics of the 2 groups are summarized in table 1. The dialysis session time remained stable with only 9% of patients dialyzed 3 × 4 h/week. Only serum PTH and FGF-23 levels were higher in the progressor group. It is important to note that very few hyperphosphatemia cases were observed (≤10%), only 1 case of hypercalcemia and no severe HPT cases (>585 pg/ml) were observed. Figure 2 presents the ROC analysis of serum PTH values for association with VC progression. The best cut-off value was >191 pg/ml, corresponding to the median PTH value, with a specificity of 58.9% and a sensitivity of 62% (AUC 62.5%, p = 0.01). The same ROC analysis for FGF-23 shows an optimal cutoff of 3,025 RU/ml with a specificity of 59% and a sensitivity of 61% (AUC 62.5%, p = 0.04).

The logistic regression of factors associated with progressors is reported in table 2, confirming that serum PTH and FGF-23 levels were the most significant factors,

Table 1. Comparison of patients' characteristics, biological and treatment data between progressors and non-progressors

	Non-progressors (n = 47)	Progressors (n = 38)
Age, years	67.4 ± 8	66.6 ± 9
Female gender, %	52	44
Dialysis vintage, months	82 ± 95	76.8 ± 78
Body mass index	25.2 ± 5.5	26.5 ± 6
Diabetes, %	28.3	44.7
Stroke, %	17.4	5.2
Peripheral vascular disease, %	19.6	23.7
Cardiac disease, %	13	18.4
Liver disease, %	13	10.5
Cancer, %	8.8	13.2
Tobacco use, n	22	32
Parathyroidectomy, %	15.6	9.5
Warfarin, %	15.2	21.1
Statins, %	37	44.7
Native vitamin D, %	89	92
Alfacalcidol, %	39	36.8
Weekly dose, μg	3.4 ± 2	3 ± 1.6
$CaCO_3$, %	10	9.2
Daily dose mg	833 ± 450	777 ± 390
Sevelamer, %	32.6	38.2
Daily dose, mg	3,680 ± 1,440	4,160 ± 2,240
Cinacalcet, %	9.7	23.7
Daily dose, mg	52.5 ± 10.6	53.5 ± 8
25-Hydroxyvitamine D, nmol/l	105 ± 35.6	108.7 ± 36.5
Calcemia, mmol/l	2.22 ± 0.09	2.23 ± 0.1
Hypercalcemia episodes, n (%)	0	1 (2.6)
Phosphatemia, mmol/l	1.33 ± 0.2	1.41 ± 0.2
Phosphatemia >1.7 mmol/l, n (%)	3 (6.3)	4 (10.5)
PTH, pg/ml	179.6 ± 103	244.3 ± 114*
PTH >585 pg/ml, %	0	0
b-ALP, μg/l	22.3 ± 15	21 ± 11.5
t-ALP, U/l	279 ± 180	279.6 ± 151
CTX, μg/l	2 ± 0.9	2.1 ± 0.8
FGF-23, log RU/ml	2,640 ± 2,810	4,204 ± 4,110*
Albumin, g/l	36.1 ± 2.6	35.5 ± 3.7
CRP, mg/l	12 ± 10	14.1 ± 11.8
Hb, g/l	11.6 ± 0.9	11.7 ± 0.9
Dialysate calcium, mmol/l	1.48 ± 0.1	1.48 ± 0.1
Dialysis session time, min	390 ± 70	380 ± 70
Kt/V	2.5 ± 0.5	2.4 ± 0.4
nPCR, g/kg/day	1.32 ± 0.3	1.27 ± 0.2
Hip BMD, g/m^2	0.7 ± 0.14	0.72 ± 0.17
Wrist BMB, g/m^2	0.47 ± 0.1	0.5 ± 0.1

* $p < 0.05$.

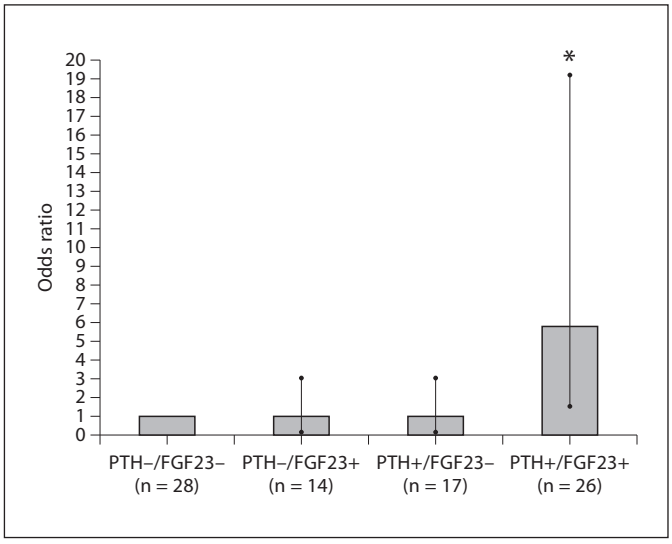

Fig. 3. OR for being a VC progressor. Patients' clinical values were as follows: serum PTH ≥190 pg/ml (PTH+) or <190 pg/ml (PTH–), and FGF-23 ≥3,300 RU/ml (FGF23+) or <3,300 RU/ml (FGF23–). The reference group was PTH–/FGF23–. * p = 0.004.

whereas diabetes, older age, dialysis duration, and phosphatemia were not significantly predictive. In figure 3, the ORs for becoming a progressor are compared between 4 groups according to the association of serum PTH < or ≥190 pg/ml with serum FGF-23 < or ≥3,000 RU/ml (data are expressed as the log of the median value). High serum PTH and FGF-23 were the only variables significantly and strongly associated with VC progression (OR 5.8).

Discussion

Our one-center study showed that, after 3 years, HD patients with long dialysis schedules displayed VC progression in less than half of the cases. Our individualized strategy allowed controlling some likely risk factors such as hypercalcemia, hyperphosphatemia, and severe HPT. In these conditions, the main factor associated with VC progression was the association of higher serum PTH, even in the recommended range, and FGF-23 levels. VC refers to the deposition of calcium phosphate, most often as hydroxyapatite, in the arteries. Extensive calcification of the vascular system is a key characteristic of aging. A passive deposition of calcium and phosphate may be necessary to trigger an active cellular process in the smooth muscle cells of the arterial wall [11]. Cardiac calcifications

Table 2. Logistic regression of factors associated with progressors

	Odds ratio	95% CI	p
Age, years	1.039	0.9772–1.106	0.2
Dialysis vintage, months	1.003	0.998–1.009	0.3
Female gender	0.51	0.185–1.426	0.2
Diabetes	3.13	0.979–9.43	0.052
FGF-23, log RU/ml	1.0001	1.0000–1.0002	0.049
PTH, pg/ml	1.006	1.0017–1.012	0.009
Phosphorus, mmol/l	2.3	0.358–15.399	0.4

in dialysis patients were first reported in the 1980s [1]. Coronary calcification scores are 2 to 5 times higher in HD patients than in cardiac patients without renal disease and 10 times higher than in the general population [12]. Cardiac valve calcifications are 5 to 10 times more frequent in dialysis patients than in the normal population [13].

VC can have severe clinical consequences and is considered an accurate predictor of future adverse cardiovascular events. VC has been associated with atherosclerosis [3], increased arterial stiffness [14], and mortality [15] in dialysis patients. Using a semiquantitative score of the aorta and iliofemoral arteries, we have reported that VC is observed in 83% of prevalent HD patients, and that higher VC scores are associated with mortality [4]. Our VC progression rate is close to that reported using an aortic arch calcification score: 30% of cases after a mean 2.3 years [16]. These findings provide important clues that may aid in identifying modifiable VC risk factors in order to decrease the risk of associated morbidity and mortality.

The main factors associated with VC were age, dialysis duration, inflammation, diabetes, tobacco use, as well as hypercalcemia and lower PTH related to higher $CaCO_3$ doses [2, 14]. We failed to find a significant association between VC progression and diabetes probably due to the small size of our cohort.

Subsequently, London et al. [17] reported that low bone turnover disease is associated with VC either in PTX or in cases of excessive aluminum and calcium load. It is not known if PTX patients are at higher risk for VC resulting from actual adynamic bone disease or, more likely, from previous severe HPT that was treated with high calcitriol analogs and calcium salt doses. Hence, both factors seem to be associated with an increased risk of VC.

These data have been taken into account by the National Kidney Foundation's Kidney Disease Outcomes

Quality Improvement (KDOQI) Guidelines, which recommends restricting calcium salt intake, targeting low-level albumin-corrected calcemia, and maintaining a PTH range between 150 and 300 pg/ml in order to prevent adynamic bone disease and severe HPT [18]. The Treat-to-Goal study demonstrated that sevelamer attenuated the progression of cardiac calcification as compared with calcium salts [9]. Even with similar hyperphosphatemia control, patients treated with calcium salts displayed higher mean calcemia, more frequent hypercalcemia episodes, and a tendency to lower PTH levels (mean PTH value <150 pg/ml). Subsequently, Chertow et al. [19] reported that CAC progression was associated with low PTH levels in patients treated with $CaCO_3$ and with high PTH levels in patients treated with sevelamer.

In 2008, the CARE-2 study reported that calcium acetate and sevelamer did not prevent the progression of cardiac calcification when statins were used in order to optimize low-density lipoprotein [10]. One of the main differences between the Treat-to-Goal and Care-2 studies was that the mean serum PTH levels were higher in the latter (approx. 400 pg/ml). Another study by London et al. [20] reported that adynamic bone disease is more frequently associated with the aortic calcification score in patients receiving high $CaCO_3$ doses, whereas Noordjizj et al. [16] and Coen et al. [21] reported that VC progression was associated with higher PTH (>300 pg/ml) in HD patients. In 2007, Neves et al. [22] reported that nephrectomized rats infused with PTH developed intense medial calcification. Moreover, high PTH levels were associated with aortic calcific stenosis in cardiac patients [23].

The present study did not confirm that VC progression was associated with low PTH levels and $CaCO_3$ use. Hence, our strategy is quite different from that used in the 1990s with sevelamer primarily used as a first-line phosphate binder, individualized dialysate calcium and alfacalcidol prescribed according to serum PTH, bone marker levels, and calcemia. Long dialysis allows control of hyperphosphatemia with a lower phosphate binder. Moreover, long daily nocturnal HD has been reported to be associated with low CAC progression rates [24]. This strategy prevented hypercalcemia, iatrogenic adynamic bone disease, and severe HPT [8]. It was proposed, therefore, that once these conditions disappeared, slightly high PTH levels associated with high FGF-23 concentrations remain the main mineral metabolism disorder associated with VC evolution.

At the time of this writing, the most recent RCT dealing with VC progression was the ADVANCE study [25]. This study failed to demonstrate any advantage from preventing or delaying CAC progression by using cinacalcet plus low-dose calcitriol analogs (CAs) versus higher CA doses in conjunction with only calcium-based phosphate binders in the 2 arms. In contrast, the main factors associated with VC progression were higher calcemia and phosphatemia, lower PTH levels, and no cinacalcet use. These findings led the authors to hypothesize that, in these cases, high CA doses may accelerate VC. However, Ogawa et al. [26] reported that VC patients using higher CA doses progressed less frequently. In our present study, the progressors were more frequently treated with cinacalcet (23.7 vs. 9.7%), when relative PTH levels were higher, but not with alfacalcidol or $CaCO_3$. Cinacalcet and alfacalcidol were prescribed, not only based on PTH levels, but also according to phosphatemia and primarily according to calcemia. Finally, non-progressors displayed a tendency to have undergone previous PTX (15.6 vs. 9.5%). The patients studied here with PTH <50 pg/ml were all totally parathyroidectomized and were in the non-progressor group. Furthermore, regression of VCs has been reported in HD patients after PTX [27]. Finally, the USRDS reported a long-term survival advantage for PTX patients [28].

So what is the best way to decrease the excessive PTH serum level? Using cinacalcet, CA, or PTX? We reported that higher serum FGF-23 levels were associated with the more severe VC scores [4] and these results have been confirmed in other studies [29]. We also reported that serum FGF-23 values correlate with phosphatemia, calcemia, and PTH levels in the same HD population [30]. Normally, FGF-23 regulates PTH synthesis, but in kidney disease, associated parathyroid resistance is likely caused by decreased expression of the Klotho-FGFR1 complex [31]. This led to the hypothesis that refractory HPT is, at least in part, due to lack of Klotho and FGFR1 expression [32] leading to higher FGF-23 levels. In our study, FGF-23 levels were higher in the progressor group, especially in cases when PTH was >190 pg/ml.

This association could reflect a more resistant HPT [33], and the association of cinacalcet and low CA dose could be advocated for lowering PTH and FGF-23 [34]. Measuring FGF-23 and Klotho proteins levels will likely help to explain these observations. Whether therapeutic intervention into the Klotho/FGF-23 axis will be promising remains to be determined. In 2000, Block and Port [35] asked for a revaluation of PTH target levels between 100 and 200 pg/ml in order to prevent VC and mortality in HD patients. It is assumed that they were correct.

Our study has some limitations. This is only an observational study and the hypothesis generated by our results needs to be confirmed.

The gold standard for VCs remains the coronary score of Agatston or the abdominal aortic Framingham score, and our radiological scores have not been validated in RCTs. However, others have reported VC scores using plain X-ray imaging of aortic, pelvic, and hand arteries [36–38]. Furthermore, we have reported a clear relationship between our radiological score and mortality [4]. Our specific strategy reported here, using longer dialysis sessions and individualized treatment, cannot be generalized worldwide. However, we are able to conclude that successfully addressing primary mineral metabolism disorders did not prevent VC progression.

Conclusion

VC progression during this 3-year study was observed in 44.7% of prevalent HD patients who underwent long-dialysis sessions and were provided with an individualized therapy. This led to suppression of expected factors such as hypercalcemia, hyperphosphatemia, and severe HPT. The main VC progression-associated factors were higher serum PTH, even in the target range, and FGF-23 levels. Whether this will lead to greater decreases in PTH levels, as judged by routinely measured serum FGF-23 values, remains to be assessed.

Disclosure Statement

G.J., C.L., B.M., J.-M.H., P.D., and C.C. are consultants for Fresenius Medical Care.

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