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NEPHROLOGY – ORIGINAL PAPER

Vascular calcifications and renal osteodystrophy in chronic hemodialysis patients: what is the relationship between them?

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Abstract
Introduction Vascular calcifications (VCs) and renal osteodystrophy (ROD) are frequently seen together and represent the major causes of morbidity and mortality in hemodialysis (HD) patients. Some studies suggest a pathogenic link between them, but there is no consensus as yet regarding this issue. The main objective of our study was to establish whether there is any relation between VCs and ROD in our HD patients. We evaluated the prevalence of VCs and ROD and the relationship between VCs and some clinical and biochemical characteristics of HD patients.
Methods We examined radiological signs of VCs and ROD on hands and pelvis bone radiographs in 81 chronic HD patients, and we calculated a VC score on this basis.
Results We found a significant relation between radiological signs of ROD and those of VC ($P = 0.019$). The patients with ROD had a higher mean VC score ($P = 0.02$). By linear regression, the VC score correlated directly with serum calcium (Ca), phosphorus (P), intact parathyroid hormone (iPTH) and CaxP product and inversely with serum albumin. The logistic regression model revealed that ROD, male gender and treatment with calcium salts were predictive of VCs development. There were no associations between VCs and age, HD vintage, diabetes, dialysate Ca concentration, vitamin D treatment, spKt/V, URR and C-reactive protein (CRP) levels.
Conclusion There seems to be a pathogenetic link between bone and artery diseases in chronic HD patients. Both VCs and ROD have a high prevalence. ROD, male gender and treatment with calcium salts are risk factors for VCs.

Keywords Hemodialysis · Vascular calcifications · Renal osteodystrophy

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Introduction

Chronic kidney disease (CKD), renal replacement therapies and various treatments induce complex

biochemical disturbances of the calcium–phosphate metabolism with a wide spectrum of bone, vascular and soft tissue abnormalities. Changes in mineral metabolism and bone structure are an almost universal finding in progressive chronic kidney disease [1–3].

The cardiovascular diseases are highly prevalent in hemodialysis (HD) patients. They are induced and favored greatly by vascular calcifications (VCs) [4, 5].

These cardiovascular and bone complications represent major causes for morbidity, impaired autonomy, decreased quality of life and eventually death in these patients [6, 7].

Renal osteodystrophy (ROD) represents a heterogeneous pattern of bone disturbances associated with CKD and concomitant diseases, including osteitis fibrosa cystica (OFC) induced by secondary hyperparathyroidism (SHPTH), osteomalacia (OM), adynamic bone disease (ABD), mixed uremic osteodystrophy, osteoporosis, aluminum bone disease, amyloid bone disease and metastatic calcifications [3]. Since 1943, when the term "ROD" was introduced [8], the diagnosis was based mostly on radiographic findings. Although numerous new diagnosis modalities such as PTH levels, bone mass density, and bone biopsy have been introduced in clinical practice [9–11], plain film radiography, especially fine quality hand radiography, still plays a role [12]. The main radiographic findings are induced by HPTH and are located especially in hands, clavicles, sacrum-iliac and pubic bones. OM and ABD are painful complications, and their main clinical and radiological manifestations are bone fractures [3, 12–15]. Recently, the "Kidney Disease: Improving Global Outcomes" (KDIGO) foundation recommended that the term "ROD" should be used exclusively for alterations in bone morphology assessed by biopsy associated with chronic kidney disease [2]. But bone biopsy is a laborious and painful procedure, it allows the analysis of a single bone site and it has limited indications in clinical practice. Therefore, bone radiographs remain a key method for the diagnosis of ROD.

Vascular calcifications can also be diagnosed by plain radiography, numerous studies demonstrating a good sensitivity and specificity compared with CT-techniques [16, 17]. Plain radiology is used in order to investigate various arterial sites situated in the pelvis, thigh [7, 18, 19], hands [4], abdominal aorta [17], feet [7] and even knee, arm and skull [5]. The KDIGO guideline for chronic kidney disease—mineral and bone disorders (CKD-MBD)—recommends only radiography for the detection of VCs as a screening tool [2, 20].

Numerous studies have demonstrated associations between atherosclerosis and osteoporosis in the general population [21–23]. This association between bone and vascular disorders was also observed in patients with CKD, concerning the two main types of CKD-MBD, high bone turnover (SHPTH) and low bone turnover (ABD) diseases [24, 25], but this association is not consistent in all studies. The coexistence of abnormal bone and VCs represents a double threat for dialysis patients. Today experts use the terms "kidney—bone—vascular axis" or "bone—arteries cross-talk in CKD" [26]. The KDIGO proposed this new term, CKD-MBD, in the attempt to bring together alterations in mineral metabolism, bone changes and vascular or other soft tissue calcifications [2, 20].

The main objective of our study was to see whether there is a link between VCs and ROD in a cohort of HD patients, using radiography for diagnosis. Secondary objectives were to evaluate the prevalences of ROD and VCs, as well as the relationship between VCs and several clinical and biochemical characteristics of HD patients, especially mineral metabolism markers.

Patients and methods

This cross-sectional study has been carried out in a cohort of randomly selected HD patients treated in Nefromed Dialysis Center, Cluj-Napoca, Romania. Eligibility criteria were dialysis duration $\geq$6 months, age >18 years, and patients' agreement to undergo radiological examination. Exclusion criteria were previous parathyroidectomy, previous renal transplant, and other known bone disease. The scoring ranged from 0 (meaning no calcification) to 8 (meaning bilateral calcification of all the arteries).

The data regarding demographical and clinical characteristics (age, gender, HD vintage, presence of diabetes, dialysate Ca concentration, and treatments with calcium-based phosphates binders and vitamin D) were recorded. The patients were treated with conventional HD, 12 h a week, with polysulphone dialyzer membranes. They received calcium carbonate or calcium acetate as phosphate binders and vitamin D

(calcitriol). Blood samples for the biochemical evaluation were drawn prior to the HD session.

The plain radiographic films of hands and pelvis evaluated all bone abnormalities (Figs. 1, 2). ROD was defined based on the following diagnostic criteria: subperiosteal bone erosions located on the radial border of the middle phalanges of the index and long fingers and on the femoral neck; resorbtion of the terminal phalanges tuft (acroosteolysis); juxta-articular bone erosions around the metacarpo-phalangeal joints, appearing as small lucent defects (cysts); subchondral bone resorption of the sacrum-iliac and the pubic joints with a widened and irregular joint space and sometimes vertical joint subluxation; erosive enthesopathy, and brown tumors. We considered all the above as typical features of SHPTH-associated bone disease. Looser zones on pubic branches, iliac bones, femoral neck and long bones are rare, but suggestive for osteomalacia. Osteoporosis and fractures were considered also to be signs of ROD.

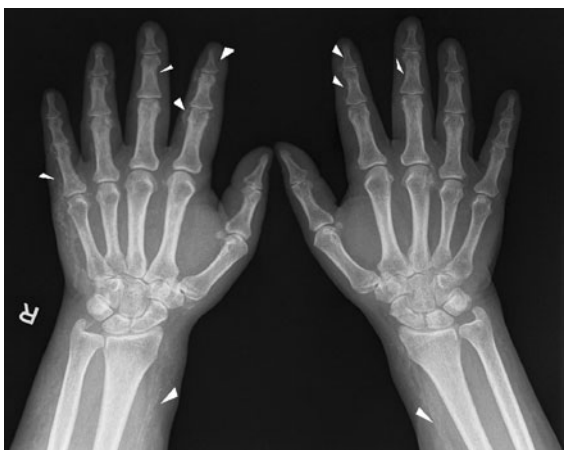

Fig. 1 Hands radiograph. Subperiosteal bone resorbtion on the radial border of the middle phalanges of the index and medius; acroosteolysis in the distal phalanges. Radial and digital arteries calcifications

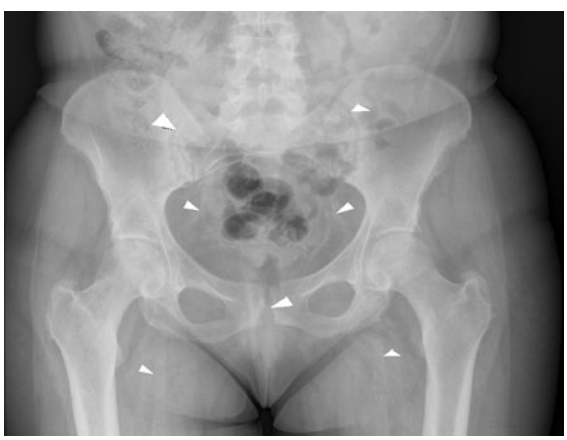

Fig. 2 Pelvis radiograph. Subcondral resorbtion in the sacro-iliac and public joints. Iliac and femoral arteries calcifications

Peripheral VCs were evaluated on the same radiographic films. The hands films were used to evaluate digital and radial arteries (Fig. 1), and pelvic films to evaluate iliac and femoral vessels (Fig. 2). We used the Adragao score for VCs [4], whose methodology is described in detail elsewhere [27]. The study protocol was approved by the institutional ethics committee.

The radiological findings were analyzed by two physicians, a radiologist and a nephrologist, both blinded to the clinical and laboratory data.

We measured serum calcium (Ca), inorganic phosphorus (P), alkaline phosphatase (ALP), intact parathormone (iPTH), urea, albumin and C-reactive protein (CRP). Calcium–phosphate product (CaxP), spKt/V $= 2.4 \times (1 -$ urea postHD/urea preHD) $- 0.276$ and URR $= (1 -$ urea postHD/urea preHD) $\times 100$ were calculated.

Statistics

Data were expressed as mean $\pm$ standard deviation (SD) for continuous factors, as frequencies for qualitative variables. For continuous variables, the statistical comparison was made using *t*-test or Mann–Whitney rank sum test. Chi-square or Fisher exact test was used to evaluate the relation between qualitative variables. We compared groups with and without VCs and constructed regression models (logistic for VC as binary variable and linear for VC as continuous variable) with VC as dependent variable to assess the association with ROD and other markers of CKD-MBD. When building a multivariable regression model, the enter method was used. A $P < 0.05$ was taken as significant. All statistical analyses were performed using Sigma Stat and SPSS 13.0 statistic packages.

Results

The study cohort consisted of 81 hemodialysis (HD) patients, 35 women and 46 men, among which 10

patients had diabetes mellitus (DM). Seventy-two patients (88.9%) were treated with calcium salts and 43 patients (53%) with vitamin D compounds. No patient received aluminum-containing phosphate binders. The descriptive statistics results are presented in Table 1.

Subperiosteal bone erosions was the main radiographic finding, located on the radial border of the middle phalanges of the index and medius, in 22 patients. Acroosteolysis was found in 10 patients. Erosions were located also on other fingers and metacarpal bones. There was a wide range of bone and joint changes, such as carpal, metacarpal, cubital and radial styloid cysts, recent and old bone fractures in 3 patients, hip prostheses in 2 patients, pelvis subchondral cysts, subchondral sclerosis in 7 patients, chronic osteoporosis in 31 patients, erosions and widening of sacrum-iliac joints in 35 patients and of pubic joints in 16 patients, juxta-articular soft tissue calcifications in 16 patients and pelvic calcified enthesopathy in 5 patients. No Looser zones or brown tumors were observed.

Vascular calcifications were found in the following locations: radial artery in 42 patients (31 bilateral), digital arteries in 19 patients (19 bilateral), iliac artery in 44 patients (38 bilateral), and femoral artery in 41 patients (38 bilateral).

The VC score distribution was as follows: score 0 in 24 patients; score 1 in 6 patients; score 2 in 12 patients; score 3 in 3 patients; score 4 in 7 patients; score 5 in 3 patients; score 6 in 9 patients; score 7 in 1 patient; and score 8 in 16 patients.

The patients were divided into two groups: with and without VCs. We compared these two groups regarding the presence of ROD, clinical characteristics and biochemical parameters. The group with VCs consisted of 45 patients with ROD and 12 patients without ROD. In the group without VCs, there were 12 patients with ROD and 12 patients without ROD. We found a significant relation between the presence of radiological signs of ROD and VCs ($P = 0.019$).

We also divided the population in groups with and without ROD, comparing the mean VC scores. The patients with ROD had a higher mean VC score ($P = 0.02$) (Fig. 3); The serum iPTH levels in various groups are shown in Table 2.

In univariate analysis, the presence of VCs was associated with higher serum Ca, P, ALP levels (Table 3) and higher CaxP product. There were no correlations between VCs and age, gender, HD vintage, presence of diabetes, dialysate Ca concentration, vitamin D treatment, spKt/V, URR, and CRP (Table 3).

Table 1 Characteristics of the cohort

Feature	
Number of patients	81
ROD prevalence (%)	70.37
VCs prevalence (%)	70.37
Male gender (%)	56.8
Diabetes mellitus (%)	12.34
Mean age (years)	56.67 ± 12.03
Age range (years)	28–82
Mean HD vintage (months)	52.11 ± 49.58
HD time range (months)	7–231
Ca (mg/dl)	8.16 ± 1.06
P(mg/dl)	6.06 ± 1.76
CaXP (mg^2/dl^2.)	49.21 ± 18.35
ALP (U/l)	290.18 ± 180.75
iPTH (pg/ml)	610.69 ± 649.6
spKt/V	1.32 ± 0.22
URR	66.86 ± 9.56
Albumin (g/dl)	4.09 ± 0.45
CRP (mg/dl)	1.27 ± 1.36

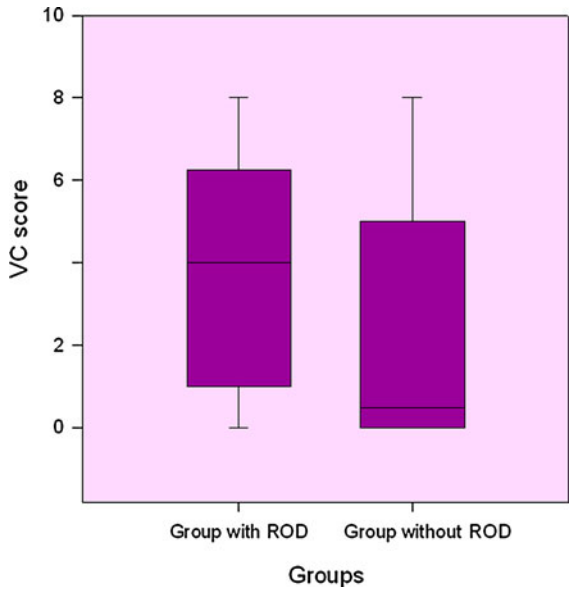

Fig. 3 The mean VC score in the groups with and without ROD ($P = 0.02$)

Table 2 The serum iPTH levels in the studied population

	iPTH(pg/ml)			Total patients
	<150	150–300	>300	
Group with ROD	10	12	35	57
Group without ROD	9	3	12	24
Group with VC	12	11	34	57
Group without VC	7	4	13	24
Total HD patients	19	15	47	81

By linear regression, the VC score as a continuous variable correlated directly with serum Ca, P, iPTH and CaxP and inversely with serum albumin (Table 4).

In order to assess the influence of the studied variables on the presence of VCs, we introduced the data in logistic regression. The independent variables were age, gender, diabetes, dialysate Ca, Ca and vitamin D treatments, serum Ca, P, CaxP, iPTH, ALP, spKt/V, URR, serum albumin and CRP. The created model revealed that ROD ($P = 0.029$; OR = 7.704; 95% CI = 1.239–47.916), gender ($P = 0.036$; OR = 7.226; 95% CI = 1.138–45.882) and oral treatment with calcium salts ($P = 0.04$; OR = 1.006; 95% CI = 1–1.011) are predictive for VCs presence (Table 5).

Discussion

The prevalence of mineral and skeletal complications in long-term HD patients increases as the life expectancy of these patients improves [2, 3, 28]. Most of the patients treated for more than 10 years experience skeletal complications that may impair their autonomy. On the other hand, cardiovascular disease represents the most important cause of death in these patients, vascular calcifications playing an important role [4, 5, 29].

Our study demonstrated there is a link between bone and vascular disease in HD patients. The presence and the severity of VCs were significantly related to ROD occurrence. We also found a high prevalence of these two complications in our HD patients.

The association between radiographic ROD and VCs could shed a light on the pathophysiologic links between bone and vascular disease. The osteoporosis–VC association can be observed in the general population in the absence of overt mineral

Table 3 Comparison between the two groups of patients: with and without VCs

Feature	Patients without VC	Patients with VC	*P*
Number of patients	24	57	
ROD (%)	50	78.94	**0.019**
Age (years)	57.4 ± 12.3	56.4 ± 11.9	0.72
HD vintage (months)	26.5 (15.5–43.5)	37 (19.5–94.3)	0.12
Male gender (%)	10 pts (41.66%)	36 pts (63.15%)	0.44
Diabetes (%)	2 pts (8.33%)	8 pts (14.03%)	0.71
Dialysate Ca (mmol/l)	1.5 (1.5–1.63)	1.5 (1.25–1.5)	0.048
Calcium salts treatment (g/year)	317.9 ± 196.1	307.9 ± 167.6	0.81
Vitamin D treatment (mcg/year)	22.5 (0–67.5)	5.75 (0–37.5)	0.10
Serum Ca (mg/dl)	7.77 ± 1.17	8.33 ± 0.98	**0.029**
Serum P (mg/dl)	5.47 ± 1.34	6.31 ± 1.88	0.05
CaxP (mg^2/dl^2)	40.4 ± 14.2	52.9 ± 18.7	**0.004**
ALP (U/l)	188 (160.5–246)	258 (183–349.5)	**0.009**
iPTH (pg/ml)	305.5 (139.2–535.8)	392 (198.2–1091.2)	0.12
Spkt/V	1.4 (1.25–1.5)	1.3 (1.2–1.4)	0.17
URR	70.2 (63.5–74.3)	66.6 (61.2–71.5)	0.17
Albumin (g/dl)	4.24 (3.91–4.49)	4.16 (3.9–4.3)	0.17
CRP (mg/dl)	0.56 (0.26–1.33)	0.95 (0.5–1.59)	0.13

Note: Bold values indicate statistically significant

Table 4 Linear regression for VC as a continuous dependent variable

Independent variable	*P*
Age (years)	0.34
HD vintage (months)	0.86
Dialysate Ca (mmol/l)	0.10
Treatment Ca (g/year)	0.42
Treat vit D (mcg/year)	0.15
Serum Ca (mg/dl)	**0.02**; $R = 0.25$ (direct)
Serum P (mg/dl)	**0.03**; $R = 0.23$ (direct)
CaxP (mg^2/dl^2)	**0.002**; $R = 0.32$ (direct)
iPTH (pg/ml)	**0.05**; $R = 0.21$ (direct)
ALP (U/l)	0.08; $R = 0.19$
Spkt/V	0.13
URR	0.12
Albumin (g/dl)	**0.019**; $R = -0.26$ (inverse)
CRP (mg/dl)	0.42

Note: Bold values indicate statistically significant

metabolism disorders. In CKD or ESRD patients, the relationship between VCs and bone disorders is associated with deterioration of mineral and bone metabolism caused by changes in serum phosphate and calcium and disruption of endocrine pathways, which intervene in osteoblast-like transformation of vascular smooth muscle cells [30].

In our study, most of the bone X-ray changes belonged to OFC, secondary to HPTH. Osteoporosis and fractures could be due to any kind of disease included in the concept of ROD, but the exact subtype of ROD could not be specified in this study. Regarding osteoporosis, KDIGO recommends that the term should not be used to describe bone fragility in CKD patients, since bone is likely to be more severely affected by CKD than might be expected from normal aging, because of the extreme turnover and remodeling that occur in CKD [20].

The increased bone resorbtion seen in HPTH is frequently associated with VCs [31, 32]. A high frequency and extent of VCs are also observed in patients with bone demineralization and low bone turnover [18, 24, 25].

Some authors demonstrated an association between high serum iPTH levels and the severity of coronary calcifications in HD patients [33]. We previously described a positive relationship between peripheral VCs and mineral metabolism markers, with serum iPTH being predictive for VC severity [27].

Some studies suggest that serum Ca, P and CaxP are responsible for cardiovascular calcifications or for the link between bone and VCs [34–36]. We observed in our study that high serum Ca, P, CaxP and ALP were associated with VCs in univariable analysis; Ca, P, CaxP and iPTH correlated directly

Table 5 Logistic regression with VC as binary dependent variable

	P	OR	95.0% C.I.	
			Lower	Upper
Age (years)	0.878	1.005	0.940	1.075
Gender (%)	**0.036**	7.226	1.138	45.882
DM (%)	0.466	2.344	0.237	23.188
ROD	**0.029**	7.704	1.239	47.916
CaxP (mg^2/dl^2)	0.561	1.217	0.627	2.362
Ca (mg/dl)	0.977	0.945	0.021	42.421
P (mg/dl)	0.560	0.213	0.001	38.791
iPTH (pg/ml)	0.490	1.001	0.999	1.003
ALP (U/l)	0.130	1.007	0.998	1.015
URR	0.803	1.088	0.559	2.118
Ktv	0.882	0.120	0.000	177848456954.560
Albumin(mg/dl)	0.986	0.983	0.143	6.744
CRP(mg/dl)	0.730	00.921	0.575	1.474
Oral Ca salts (g/year)	**0.040**	1.006	1.000	1.011
Vit D treat (mcg/year)	0.289	0.991	0.975	1.008
Ca dialysate (mmol/l)	0.273	0.040	0.000	12.717

Note: Bold values indicate statistically significant

with VCs in linear regression analysis. The multivariable analysis revealed that beside ROD, oral treatment with calcium salts is a risk factor for VCs, which is in accordance with other studies [37, 38].

Low levels of serum albumin were correlated with the VC score, and male gender was a risk factor for VCs, similar to other studies [5], both being recognized as cardiovascular risk factors.

We cannot distinguish whether the ROD radiological findings belong to high or low turnover bone disease, but their presence means that the bone is damaged because of the CKD. The particularity of our study is that we used the old radiography as a tool with two edges: one is considered sharp for diagnosing VCs and the other is maybe unfairly considered blunt, for evaluating ROD. Since both ROD and VCs are chronic conditions, we used ROD to assess the pathogenetic link between bone and vasculature, as single serum markers like P, Ca and PTH may not be representative of abnormalities that develop over a longer period of time.

Possible limitations

The accuracy of radiography for classifying ROD findings as high or low bone turnover disease may not be satisfactory. It can only indicate that there is a bone problem. There are concerns about radiation exposure. With renal failure, some possible preexistent bone diseases (like senile osteoporosis) might be considered as ROD. This could be a misleading approach. This semiquantitative VC score may not be suited for assessing progression.

Conclusion

Our study demonstrated that ROD and VCs do not develop independently, but they seem to be linked with each other. The VC score correlates with high Ca, P, iPTH and CaxP and low albumin serum levels. ROD, male gender and oral treatment with calcium salts are risk factors for VCs. Without underestimating the value of new diagnostic tests, we suggest that, even if considered obsolete, radiography should not be abandoned, as it can provide valuable information about both of these important complications of CKD: bone and vascular disease. Along with biochemical markers, radiography can help nephrologists to get a better picture of this new nosologic entity: CKD-MBD.

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