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Intraoperative Arterial Biopsy in Incident Hemodialysis Patients: Differences Observed

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Keywords
Arterial biopsy · Chronic kidney disease · Vascular calcification

Abstract
Introduction: Arterial calcification (AC) is a common complication in chronic kidney disease (CKD) patients that starts to develop before these patients need renal replacement therapy. In these patients, calcification can involve tunica intima or tunica media. This study has looked for the prevalence, severity, and distribution of arterial wall calcification in incident hemodialysis patients through intraoperative arterial biopsy obtained during creation of arteriovenous vascular access for hemodialysis. ***Methodology:*** One hundred and seventy-two stage 5 CKD adults (98 male and 74 female) were included. Beside histopathology of the obtained arterial samples, all these cases were tested for serum calcium (Ca), phosphorus (P), alkaline phosphatase, uric acid, parathormone (PTH), fibroblast growth factor 23 (FGF23), and 25 hydroxy vitamin D. ***Results:*** Eighty six (50%) of the cases had AC (group I); 29 (17%) as intimal (subgroup Ii), 36 (21%) as medial (subgroup Im), while 21 (12%) had both intimal and medial calcification (subgroup Iim). Eighty-six patients (50%) were devoid of calcification (group II). Apart from the significantly higher serum level of PTH in group I, statistical analysis failed to disclose significant difference in any of the other studied parameters between the 2 groups. On the other hand, there were significant differences in serum P, Ca × P product, serum PTH, and FGF23 between patients according to intensity of calcification. ***Conclusion:*** Half of incident hemodialysis CKD patients have developed AC mainly in tunica media. Discrepancy in serum P can have an impact on calcification intensity.

Introduction

The high prevalence of arterial calcification (AC) is one of the outstanding consequences of chronic kidney disease (CKD) [1]. AC in CKD patients occurs in 2 dis-

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Table 1. Etiology of CKD

Etiology	*n* (%)
Diabetes mellitus	33 (19.2)
Ch. interstitial nephritis	15 (8.7)
Nephrolithiasis	12 (6.98)
Reflux nephropathy	4 (2.32)
Gouty nephritis	6 (3.49)
Obstructive uropathy	20 (11.6)
Systemic hypertension	15 (8.7)
Ch. glomerulonephritis	20 (11.6)
Polycystic kidney	1 (0.58)
Hereditary nephropathy	2 (1.16)
Urinary tract infection	7 (4.1)
Idiopathic	37 (21.5)

CKD, chronic kidney disease.

tinct sites, the tunica intima and tunica media layers of the arterial wall. Intimal calcification occurs on top of atherosclerotic plaques and medial calcification is a characteristic feature of arteriosclerosis [2, 3]. Medial calcification is more common in CKD patients [4]. It seems that AC occurs at earlier age in CKD patients, and as CKD progresses, the prevalence of this calcification increases [5].

There is no consensus on the most reliable tool to use in the diagnosis of AC in CKD patients [6]. Several imaging techniques have been evaluated for the existence and the severity of AC [7]. Computerized tomography (CT)-based techniques are more sensitive compared to plain X-rays at detection of AC. Moreover, CT scanning has the highest predictive value for cardiovascular events and mortality among CKD [6]. On the other hand, histopathologic examination of arterial samples obtained from animal models, human VSMCs explant cultures, and organ culture of vessel rings obtained during open surgery of abdomen and pelvis offers more comprehensive approach to study vascular calcification [8]. Intact arterial rings can be obtained from medium-sized abdominal or pelvic arteries during kidney transplantation or during insertion of peritoneal catheter for chronic peritoneal dialysis [8–10]. Vessel biopsy examination can detect spots of calcification that are very difficult to detect using different radiological techniques [1]. In addition, pathologic examination can confidently discriminate intimal from medial calcification [11, 12]. In adults suffering end-stage renal disease, the association between coronary artery calcium (Ca) scores and histological signs of AC was significant [13]. A more recent study has used samples of radial arteries obtained during arteriovenous fistula surgery as alternative approach [14].

Aim of the Study

In this study, we tried to look for the prevalence, severity and distribution of arterial wall calcification in incident hemodialysis patients (patients that were prescribed hemodialysis and those that started hemodialysis for <2-week duration) using arterial biopsy samples obtained during creation of an arteriovenous fistula as a vascular access for regular hemodialysis.

Patient and Methods

One hundred and seventy-two incident hemodialysis end-stage renal disease patients (98 male and 74 female) were included. The age of this group ranged between 24 and 62 years. The underlying causes of their CKD are summarized in Table 1. After discussing the procedure with each patient separately, a written consent was obtained. Prior to performing the anastomosis between the arterial and venous walls, an arterial tissue biopsy including all layers of the artery wall was selected carefully and thoroughly excised from both arterial walls dedicated for the anastomosis with an approximate length equal to the planned anastomotic suture line and a width of 1 mm. The arterial biopsy specimens were formalin-fixed, processed in alcohol, cleared in xylene, and incubated in paraffin blocks. Four sets of slides were prepared from serial cuts (5 μ thick); stained with hematoxylin/eosin, Masson's trichrome, Alizarin red, and Verhoeff-van Gieson stains. All stained slides were examined under light microscope to evaluate the presence of arterial wall calcification, atheromatous lesions, intimal fibroelastosis, disruption of elastic lamina, and fibrosing lesions. Calcific deposits were tabulated according to their location (intimal or medial) and the extent of the deposits in the arterial wall if discrete intimal spots of calcification, single segment of calcification involving one 10× field, more than one 10× field of calcification, or diffuse arterial wall calcification.

A blood sample was obtained from every patient to test for serum Ca, P, alkaline phosphatase, uric acid, parathormone (PTH), fibroblast growth factor 23 (FGF23), IL6, and 25 (OH) vitamin D. Samples were collected after 6 h fasting and then centrifuged to separate plasma that was either immediately assayed or stored below –70 °C. Serum level of Intact PTH was determined by enzyme-amplified sensitivity immunoassay (Roche Diagnostics, IN, USA). Intact FGF23 was measured by using a 2-site (NH2-terminal/C-terminal) enzyme-linked immunosorbent assay (Immutopics, CA, USA). Serum IL6 was measured using ELISA (e Bioscience, ESP) immediately after blood collection. Assays were performed according to the manufacturer's guidelines. The sensitivity of the kit was 2 pg/mL, and inter- and intra-assay assessments of reliability of the kits were conducted. Serum 25 (OH) vitamin D was assessed using HPLC.

Table 2. Group I vs. II

Parameter	Group I (86)		Group II (86)		*p* value
	median (IQR)	mean ± SD	median (IQR)	mean ± SD	
Age, years	41 (15)	42.1±9.29	41 (16.25)	41.2±9.9	ns
BMI, kg/m^2	22 (4.5)	22.1±2.94	22.6 (4.75)	22.35±3.1	ns
Serum albumin, g/dL	3.6 (0.4)	3.6±0.26	3.6 (0.2)	3.66±0.23	ns
SerumAP, IU/L	160 (16)	160.3±12.5	160 (20.5)	162.3±15.9	ns
Serum Ca, mg/dL	8 (0.8)	8±0.62	8 (1.03)	8.1±0.79	ns
Serum P, mg/dL	5.2 (1.53)	5.2±0.95	5 (1.15)	5±0.8	ns
Serum Ca × P	41.97 (12.07)	42.6±8.86	40.6 (12.2)	40.8±8.7	ns
Serum PTH, pg/mL	415 (173)	420.2±93.1	355 (100.6)	380.3±64.2	<0.002
Serum FGF23, pg/mL	256 (45)	253.5±25.7	261 (34.5)	259.2±22.5	ns
Serum IL6, pg/mL	24.5 (10)	27.15±5.6	25 (5.7)	26.7±5.08	ns
Serum 25 (OH) vitamin D, ng/mL	16.8 (11.03)	16.7±6.1	16 (10.1)	16.1±5.76	ns
Serum UA, mg/dL	5.6 (2.8)	5.6±1.92	5 (2)	5.48±1.98	ns

Group I, patients with arterial calcification; group II, patients devoid of calcification; BMI, body mass index; AP, alkaline phosphatase; Ca, calcium; P, phosphorus; UA, uric acid; PTH, parathyroid hormone; FGF23, fibroblast growth factor 23; IL6, interleukin 6; ns, non significant >0.05.

Microsoft computer statistics package was used for data analysis. Data were summarized as mean and SD. Comparison between groups was evaluated using Student *t* test. Comparison between more than 2 independent groups was evaluated using ANOVA test.

Results

Results are summarized in Tables 1–5 and Figures 1–4.

Eighty-six samples (50%) were devoid of calcification. Calcification was detected within the tunica intima (29 cases, 17% of the samples, designated as subgroup Ii), the tunica media (36 cases, 21% of the samples, designated as subgroup Im), or both intimal and medial in 21 cases (12%, designated as subgroup Iim). Calcification varied in severity from discrete spots to diffuse calcification. Discrete spots were restricted to tunica intima in seven cases (4% of cases, designated as Ia), a solitary calcific segment was detected in 24 cases (14% of cases, designated Ib), 35 cases had multiple calcific segments (20% of cases, designated as Ic), while 20 cases have shown diffuse AC (12% of cases, designated as Id).

Among the different studied parameters, there was no significant difference in any of these parameters between cases having AC (group I) and those devoid of calcification (group II), except in serum PTH that was higher in group I (420.2 ± 93.1 vs. 380.3 ± 64.2 pg/mL in group I vs. II, respectively, $p < 0.002$; Table 2).

Statistics did not disclose significant differences in any of the studied parameters between subgroup Im versus subgroup Iim. These 2 subgroups were thus considered as one subgroup in further statistical analysis and were renamed as Imed subgroup. There is no significant difference in BMI, serum albumin, serum alkaline phosphatase, serum Ca, serum IL6, serum 25 (OH) vitamin D, or serum uric acid between subgroup Ii, subgroup Imed, and group II. On the other hand, patients in subgroup Ii are significantly older and had significantly lower serum FGF23 compared to subgroup Imed and group II, while patients in subgroup Imed had significantly higher serum phosphrous (P) compared to either subgroup Ii and group II. The significantly higher serum PTH observed in group I compared to group II was still observed in the 2 subgroups Ii and Imed (Table 3).

When group I was categorized according to the intensity of calcification, ANOVA test showed significant difference between group II and the 4 subgroups of group I in serum P, Ca × P product, serum PTH, and serum FGF23 (Table 4). It is worth mentioning that serum P tended to be lower in subgroups Ia and Ib compared to group II. On the other hand, serum P was higher in subgroups Ic and Id. This increase was of borderline significance in subgroup Ic and highly significant in Id. In comparison to group II only subgroup Id has shown a significant increase in Ca × P product. The only subgroup that had significant difference in serum PTH compared to group II was subgroup Ib that showed highly significant increase. The significant difference in se-

Table 3. Comparison of cases with intimal or medial versus cases devoid of calcification

Parameter	Ii (29) median (IQR) mean ± SD	Imed (57) median (IQR) mean ± SD	Group II (86) median (IQR) mean ± SD	*p*1	*p*2	*p*3
Gender, male/female	11/18	37/20	50/36			
Age, years	45 (12) 45.5±8.05	36.5 (16) 40.4±9.48	41 (16.25) 41.2±9.9	<0.02	<0.03	ns
BMI, kg/m^2	22.6 (5.5) 22.7±3.18	21.35 (3.8) 21.9±2.79	22.6 (4.75) 22.4±3.12	ns	ns	ns
Serum albumin, g/dL	3.6 (0.45) 3.6±0.28	3.6 (0.3) 3.6±0.25	3.6 (0.2) 3.66±0.23	ns	ns	ns
Serum AP, IU/L	160 (16) 157±13.2	163 (14) 162±11.8	160 (20.5) 162.3±15.9	ns	ns	ns
Serum Ca, mg/dL	8 (0.8) 7.8±0.66	8.15 (0.7) 8.1±0.59	8 (1.03) 8.1±0.79	ns	ns	ns
Serum P, mg/dL	4.7 (1.45) 4.7±0.79	5.3 (1.65) 5.5±0.92	5 (1.15) 5±0. 8	<0.001	ns	<0.002
Serum Ca × P	36.6 (11.95) 37.03±7.6	42.6 (10.5) 44.6±8.39	40.6 (12.2) 40.8±8.7	<0.001	<0.04	<0.01
Serum PTH, pg/mL	428 (161) 428±82.1	420 (193) 416±98.66	355 (100.6) 380±64	ns	<0.01	<0.02
Serum FGF23, pg/mL	238 (38.5) 245.6±26.3	256.5 (40.8) 257.5±24.6	261 (34.5) 259±22.5	<0.05	<0.02	ns
Serum IL6, pg/mL	23.4 (5.6) 26±4.42	24.5 (9.15) 27.7±5.69	25 (5.7) 26.7±5.08	ns	ns	ns
Serum 25 (OH) vitamin D, ng/mL	16 (10.7) 16.7±6.1	16.8 (11.08) 16.1±5.8	16 (10.1) 16.1±5.76	ns	ns	ns
Serum UA, mg/dL	5 (2.95) 5.5±1.99	6 (2.08) 5.9±1.9	5 (2) 5.48±1.98	ns	ns	ns

Ii, subgroup showing calcification restricted to tunica intima; Imed, subgroup having medial calcification, II, group devoid of calcification; BMI, body mass index; AP, alkaline phosphatase; Ca, calcium; P, phosphrous; UA, uric acid; PTH, parathyroid hormone; FGF23, fibroblast growth factor 23; IL6, interleukin 6; *p*1, significance level between subgroup Ii and subgroup Imed; *p*2, significance level between subgroup Ii and group II; *p*3, significance level between subgroup Imed and group II; ns, non significant >0.05.

rum FGF23 is attributed to the significantly lower levels in subgroups Ia and Ib compared to the other 2 subgroups and group II (Table 5).

Discussion

The first difference observed in this study is that pathologic examination is not superior to CT-based diagnostic techniques that are keeping as the most sensitive for the evaluation of existence of AC. In previous studies, AC was encountered in at least 79% of incident hemodialysis patients [15–17]. The present study demonstrated AC in 50% of cases. Pathologic examination can detect tiny calcification spots not readily detected by radiologic diagnosis. However, pathologic examination is limited to the site of sampling contrary to radiologic examination.

The second difference observed is concerned with the site of calcification within the arterial wall. One-third of the calcifications are restricted to the tunica intima. This intimal calcification was not limited to atheromatous lesions in examined patients.

Table 4. Subgroup Ia, Ib, Ic, and Id versus group II

Parameter	Ia (7) median (IQR) mean ± SD	Ib (24) median (IQR) mean ± SD	Ic (35) median (IQR) mean ± SD	Id (20) median (IQR) mean ± SD	Group II (86) median (IQR) mean ± SD	F value	*p* value
Age, years	47 (14) 47.9±5.98	45 (14) 44±8.5	40 (18) 39.7±10.1	41 (14) 42±8.8	41 (16.25) 41.2±9.9	1.53	ns
BMI, kg/m^2	22.6 (7.1) 22.5±3.7	23.5 (4.33) 23±3	21.2 (3.6) 21.1±2.7	22.6 (2.75) 22.8±2.6	22.6 (4.75) 22.4±3.12	1.84	ns
Serum albumin, g/dL	3.5 (0.6) 3.6±0.3	3.6 (0.3) 3.6±0.3	3.7 (0.2) 3.7±0.3	3.6 (0.38) 3.5±0.25	3.6 (0.2) 3.66±0.23	1.6	ns
Serum AP, IU/L	154 (24) 151±15.6	160 (9.5) 160±12.9	164 (18) 162±11.2	160 (18.5) 161±12.3	160 (20.5) 162.3±15.9	1.17	ns
Serum Ca, mg/dL	7.7 (1.2) 7.5±0.8	8 (0.48) 8±0.64	8.2 (0.9) 8.1±0.6	8 (0.9) 8±0.6	8 (1.03) 8.1±0.79	1.17	ns
Serum P, mg/dL	4.8 (1.4) 4.6±0.9	4.75 (1.5) 4.8±0.8	5.3 (1.5) 5.4±0.96	6 (1.2) 5.75±0.8	5 (1.15) 5±0.8	5.52	<0.001
Serum Ca × P	36.6 (12.2) 34.7±7.4	36.4 (12.4) 38.5±8.4	42.3 (10.3) 43.6±8.6	47.6 (9.1) 46.2±7.6	40.6 (12.2) 40.8±8.7	4.07	<0.004
Serum PTH, pg/mL	334.7 (121) 357±55.5	473 (135) 458±77.2	420 (197.6) 421±108	376 (88.75) 395±75.7	355 (100.6) 380±64	5.9	<0.001
Serum FGF23, pg/mL	221 (39) 234±23.5	237 (36) 246 ±26.7	257 (35) 258±24.4	268 (33) 262±22.6	261 (34.5) 259±22.5	3.49	<0.01
Serum IL6, pg/mL	24 (10.4) 25.8±5.02	23.6 (4) 26±5.4	25 (10.2) 26.8±5.6	28.5 (8.75) 29.6±5.8	25 (5.7) 26.7±5.08	1.44	ns
Serum 25 (OH) vitamin D, ng/mL	16.8 (9.5) 17.4±6.07	17.3 (11.7) 16.1±6.8	15.4 (11.1) 16.1±5.8	17.2 (11.45) 17.3±6.1	16 (10.1) 16.1±5.76	0.29	ns
Serum UA, mg/dL	4.5 (2.5) 4.5±1.9	5.5 (2.98) 5.5±2.1	5.9 (2.1) 6±2	5.25 (2.1) 5.3±1.5	5 (2) 5.48±1.98	1.01	ns

Subgroup Ia, patients with spots of arterial calcification; subgroup Ib, patients with single segment of arterial calcification; subgroup Ic, patients with multiple segments of arterial calcification; subgroup Id, patients with diffuse arterial calcification; group II, patients devoid of calcification.

BMI, body mass index; AP, alkaline phosphatase; Ca, calcium; P, phosphorus; UA, uric acid; PTH, parathyroid hormone; FGF23, fibroblast growth factor 23; IL6, interleukin 6; ns, non significant >0.05.

Table 5. Detailed analysis of the significant parameters

Parameter	Ia (7) range mean ± SD	Ib (24) range mean ± SD	Ic (35) range mean ± SD	Id (20) range mean ± SD	II (86) range mean ± SD	*p*1	*p*2	*p*3	*p*4	*p*5	*p*6	*p*7	*p*8	*p*9	*p*10
Serum P, mg/dL	3–5.6 4.6±0.9	3.4–6.1 4.8±0.8	3.6–7.5 5.4±0.96	4–7 5.75±0.8	3–6.8 5±0.8	ns	ns	S	ns	S	H.S.	ns	ns	ns	H.S.
Serum Ca × P	23.1–43.5 34.7±7.4	25.5–56.7 38.5±8.4	27–63.8 43.6±8.6	28–58.1 46.2±7.6	24.48–64 40.8±8.7	ns	S	S	ns	S	S	ns	ns	ns	S
Serum PTH, pg/mL	307–439 357±55.5	307–577 458±77.2	307–613 421±108	307–591 395±75.7	307–536 380±64	S	S	ns	ns	ns	S	H.S.	ns	S	ns
Serum FGF23, pg/mL	211–274 234±23.5	218–312 246±26.7	205–316 258±24.4	219–294 262±22.6	209–310 259±22.5	ns	S	S	S	ns	S	S	ns	ns	ns

*p*1, significance level between subgroup Ia and subgroup Ib; *p*2, significance level between subgroup Ia and subgroup Ic; *p*3, significance level between subgroup Ia and subgroup Id; *p*4, significance level between subgroup Ia and group II; *p*5, significance level between subgroup Ib and subgroup Ic; *p*6, significance level between subgroup Ib and subgroup Id; *p*7, significance level between subgroup Ib and group II; *p*8, significance level between subgroup Ic and subgroup Id; *p*9, significance level between subgroup Ic and group II; *p*10, significance level between subgroup Id and group II.

Ca, calcium; P, phosphorus; PTH, parathormone; FGF23, fibroblast growth factor 23; ns, non significant; HS, highly significant; S, significant.

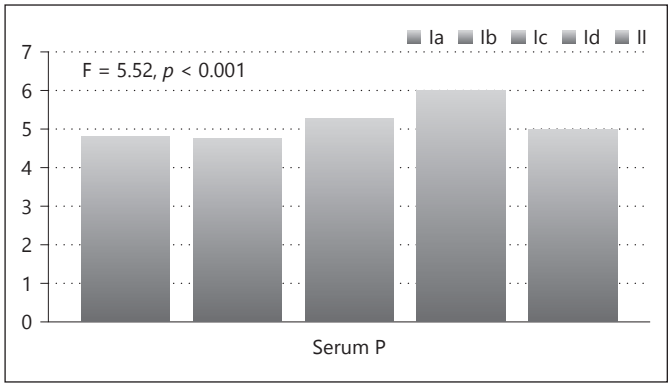

Fig. 1. Serum P in patients with different grades of AC versus those devoid of calcification. P, phosphorus.

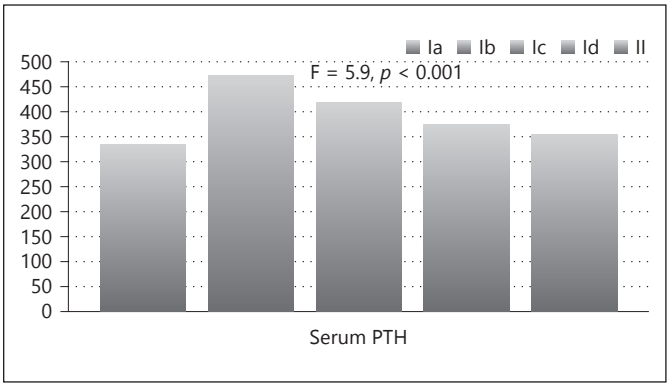

Fig. 3. Serum PTH in patients with different grades of AC versus those devoid of calcification. PTH, parathormone.

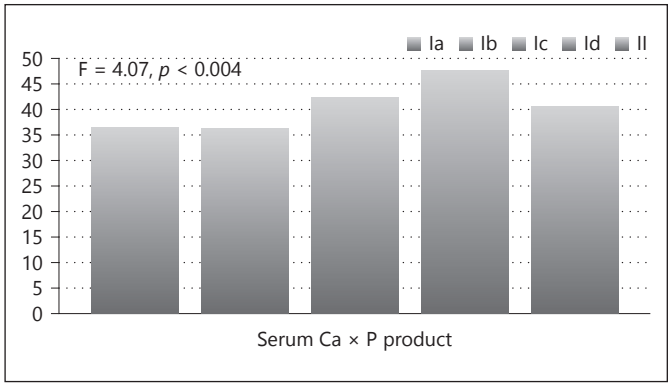

Fig. 2. Serum Ca × P product in patients with different grades of AC versus those devoid of calcification. Ca, calcium; P, phosphorus.

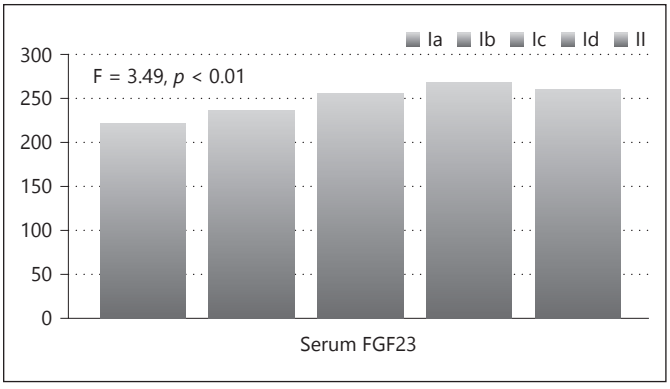

Fig. 4. Serum FGF23 in patients with different grades of AC versus those devoid of calcification. FGF23, fibroblast growth factor 23.

The third difference observed was extracted from the observation of insignificant difference in serum P, Ca × P product, or FGF23 between patients having and those devoid of calcification. Patients devoid of calcification in the examined samples could have lesions in other sites. In addition, meticulous analysis of the different subgroups showed marked discrepancy in the values of these parameters. While serum PTH was significantly higher, serum P tended to be lower, and Ca × P product and FGF23 were significantly lower in intimal calcification subgroup compared to group II. On the other hand, medial calcification subgroup had significantly higher serum P, PTH, and Ca × P product compared to group II. These discrepancies would criticize the different studies that looked for the different abnormalities in bone mineral metabolism in relation to AC in CKD patients. Most of these studies did not have the proper tools that discriminate intimal from medial calcification [11, 12]. The discrepancy in serum P was also dependent on the severity of calcification. While this level tended to be lower in subgroups Ia and Ib, it tended to be higher in subgroup Ic and was significantly higher in subgroup Id. These findings might criticize the role of P in mild and moderate calcification.

The striking results of FGF23 represent the fourth difference observed in this study. In the last 8 years, tens of articles have disclosed a strong association between AC and FGF23 [17–19]. The insignificant difference in serum FGF23 between the 2 groups together with the significantly lower serum level in intimal calcification subgroup, the insignificant difference in medial calcification group, the significantly lower level in subgroup Ia and Ib, and the insignificant difference in subgroups Ic and Id compared to group II cast doubts about this association. Contrary to the prevailing impression, the current study might add further support to the conclusion of

Scialla et al. [20], that FGF23 is not associated with and does not promote AC.

The fifth difference observed is the lack of association between interleukin 6 as a marker of inflammation and AC. This association was suggested in many animal studies and in chronic hemodialysis patients [21, 22]. Similar findings are not reported in predialysis CKD patients.

The sixth difference observed is the lack of any significant difference in serum 25 (OH) vitamin D in between the different studied groups and subgroups. A significant negative association between serum 25 (OH) vitamin D and AC was reported in 210 predialysis CKD patients [23]. However, earlier studies failed to find any significant association among hemodialysis patients [24].

The seventh difference observed is concerned with the role of serum P, Ca × P product, and FGF23 as causes of early appearance of AC. In the present study, patients in subgroups Ia and Ib serum P and Ca × P product have a tendency of lower level compared to group II patient. Serum FGF23 was significantly lower in these subgroups compared to group II. If these findings will be confirmed in future studies, the accusation of P as initiator of vascular calcification might be erroneous. This result has also alerted the authors to the early study of the effect of different phosphate binders in moderate CKD patients having normal or near normal pretreatment serum P level. Although the phosphate binders significantly lowered serum and urinary P and attenuated secondary hyperparathyroidism among these patients, they also promoted the progression of vascular calcification [24].

Finally, it seems that our knowledge about the etiopathogenesis of vascular calcification in CKD patients is still very insufficient. We still need a more comprehensive tool that can assess noninvasively the site of calcification within the arterial wall, can detect early calcification lesions with high sensitivity, can properly assess the severity of calcification, and can screen the whole arterial tree.

Conclusion

Half of incident hemodialysis CKD patients have developed AC mainly in tunica media. Discrepancy in serum P can have an impact on calcification intensity.

Statement of Ethics

The local Ethical Committee of the Internal Medicine department, School of Medicine, Cairo University, approved this work. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Disclosure Statement

The authors have declared that no conflict of interest exists.

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