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RESEARCH ARTICLE

PREVALENCE AND SEVERITY OF ABDOMINAL AORTIC CALCIFICATION IN INCIDENT NON-DIABETIC HEMODIALYSIS PATIENTS

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ABSTRACT

Background: Vascular calcification (VC) is the most common complication in patients with chronic kidney disease (CKD). In order to evaluate the real burden of mineral bone disorders in the etio-pathogenesis of arterial calcification during the pre-dialysis course of CKD, we evaluated the prevalence and severity of abdominal aortic calcification (AAC) in non-diabetic CKD patients newly admitted to hemodialysis (HD).
Methods: 81 end stage renal disease (ESRD) Patients starting HD within one month were recruited. They underwent thorough clinical examination, laboratory assessment for serum calcium, phosphorus, intact parathyroid hormone (PTH), fibroblast growth factor (FGF23) and alkaline phosphatase and spiral computed tomography (CT) to assess AAC score.
Results: AAC was present in 64 patients (79%). There was a significant correlation between AAC score and age ($r = 0.609$, $p < 0.001$), and FGF23($r = 0.800$, p-value < 0.001).
Conclusion: This study has confirmed that the frequency and severity of AAC are significant in incident hemodialysis patients. Serum FGF-23 level is the only biochemical parameter with a statistically significant correlation with AAC in incident hemodialysis patients.

INTRODUCTION

Cardiovascular disease (CVD) is the major cause of mortality among CKD patients [1]**.** 40% of deaths among CKD patients during the first 3 years of dialysis are due to CVD [2]. Vascular calcification has drawn much attention as an index of cardiovascular disease and as a predictor of mortality among HD patients**.** Beside traditional risk factors for CVD, mineral bone disorders associated with CKD have been identified as disease-specific risk factors for CVD in HD patients [3].In clinical observations, a strong relationship between coronary artery calcification and cardiovascular mortality has been reported in HD patients [4].

Electron beam computed tomography (CT) and multi-detector CT remain the gold-standard imaging techniques for diagnosis of VC as they provide a quantitative calcification score. Calcification scores strongly predict cardiovascular events in the general population and in dialysis population [5]. The Kidney Disease: Improving Global Outcomes (KDIGO) has recommended that a lateral abdominal radiograph and echocardiography should be used as appropriate alternatives to cardiac CT to detect vascular calcification [6]. While plain X-rays may be good initial investigations, they lack sensitivity and do not allow for a quantitative assessment of calcification load. Therefore, electron beam CT or multi-detector spiral CT should be used to quantify and assess time-related alterations in VC score [7].

In order to evaluate the real burden of mineral bone disorders as major risk factor predisposing to arterial calcification during the pre-dialysis course of CKD, we planned this cross sectional study to look for the prevalence and severity of AAC in CKD patients that do not have diabetes mellitus and are newly admitted to HD.

MATERIALS AND METHODS

This cross sectional cohort study was conducted on 81 CKD stage 5D that started regular HD 30 days or less. Diabetic patients, Patients on oral anticoagulation, those with history of parathyroidectomy and pregnant patients were excluded.

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All patients were first interviewed for signing a consent and Clinical examination.

A pre-dialysis blood sample was then obtained to assess serum corrected calcium, phosphorus, alkaline phosphatase, intact PTH and FGF23. Assay of FGF23 using enzyme-linked immunosorbent assay (ELISA) was done according to manufacturers' instructions. CT scans were performed using GE medical systems Light speed 16 multislice spiral CT scanner (120kVp, 75mAs, 1.375 pitch and 10 mm slice thickness). Images were acquired in a spiral mode while the patient is lying supine with free breathing. The count of calcification score was done [8].

RESULTS

The study included 81incident HD patients (47 males and 34 females, 58% and 42% respectively). 18 patients (22.2%) had history of coronary heart disease, 4 (5%) had peripheral arterial disease and 28 (34.6%) were smokers. 54 (66.7%) had systemic hypertension, 3 (3.7%) had glomerulonephritis, 2 (2.5%) had autosomal dominant polycystic kidney disease, and the remaining 27.1% of patients had CKD of undefined etiology. Table1 summarizes the results of different clinical and laboratory parameters.

Table 1 Clinical and laboratory characteristics among the studied group.

Parameter	Range	Mean ± SD
Age (years)	19 -71	43.68±13.66
Duration on HD (days)	3 - 30	16.37±7.04
FGF23 (Pg/mL)	2.4 - 184.6	81.7±34.86
iPTH (Pg/mL)	14.6 - 420	92.04±88.11
Corrected Ca (mg/dL)	7.1 - 10.2	8.51±0.7
PO4 (mg/dL)	2.4 - 7.3	4.24±1.2
ALP (U/L)	55 - 365	156.95±79.66

FGF23 (fibroblast growth factor 23), iPTH(intactparathormone hormone), Ca (Calcium), PO4 (Phosphorous), ALP (Alkaline phosphatase).

There was no noticed calcification within the abdominal aorta in 17 patients (21%), while the remaining patients showed variable calcification score (Fig.1).

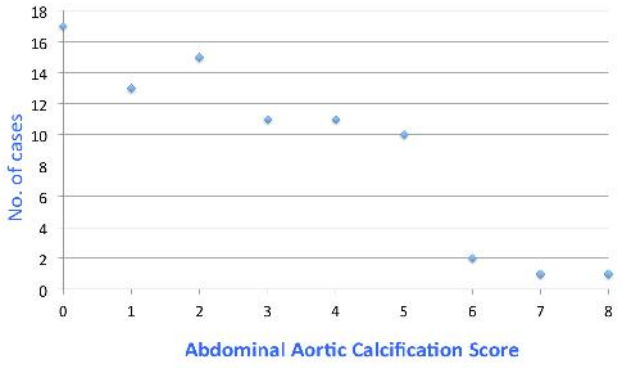

Fig 1 Abdominal aortic calcification score among the study group

There was a significant positive correlation between aortic calcification score on one hand and age, serum FGF23, and serum phosphorus on the other hand (Table 2 and Fig.2).

Table 2 Correlation between calcification score and chemical parameters.

	Calcification Score	
	r	*P*-value
FGF23	*0.800*	*<0.001 **
iPTH	*0.215*	*0.054*
Corrected Calcium	*0.119*	*0.289*
PO4	*0.319*	*0.004 **
ALP	*0.268*	*0.016**

FGF23 (fibroblast growth factor 23), iPTH(intact parathyroid hormone), Ca (Calcium), PO4 (Phosphate),ALP (Alkaline phosphatase).

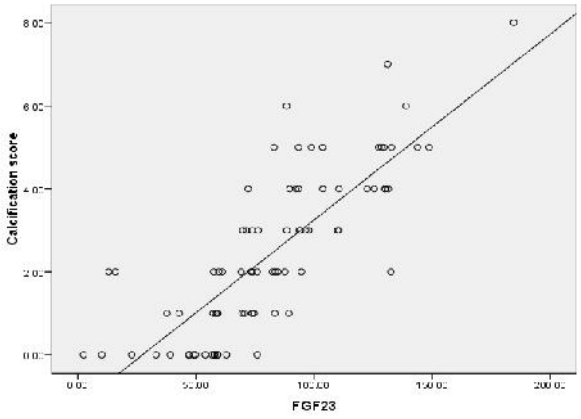

Fig 2 Correlation between Calcification score and fibroblast growthfactor23.

There was a significant correlation between FGF23 and both intact PTH and PO4 (Fig.3,4).

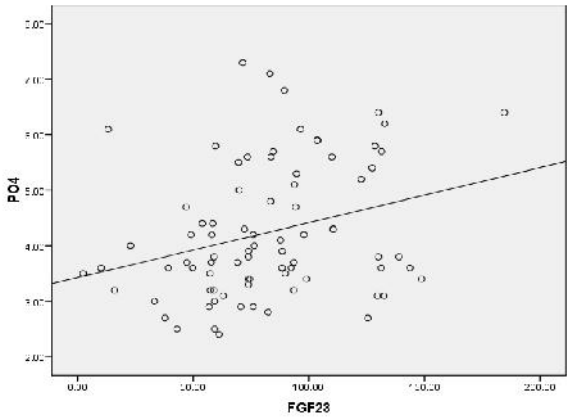

Fig 3 Correlation between Fibroblast growth factor and phosphorus

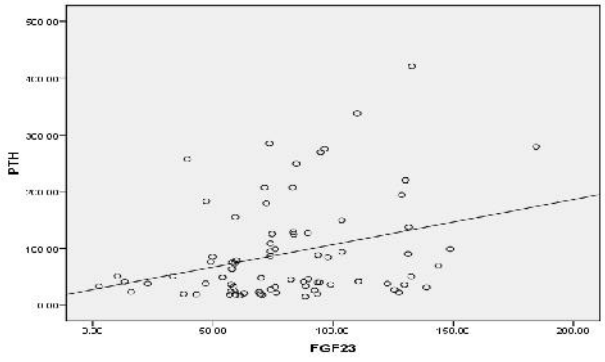

Fig 4 Correlation between Fibroblast growth factor 23 and intact parathormone hormone.

After multivariate regression analysis, aortic calcification score showed positive correlation with age and FGF23(Table 3)

Table 3 Correlation with calcification score using multivariate regression analysis

	Model	Unstandardized Coefficients		Standardized Coefficients	t	*P*-value
		B	Std. Error	Beta		
Calcification score	(Constant)	-3.017-	.459		-6.566-	<0.001
	FGF23	.029	.004	.520	7.938	<0.001
	Age	.035	.009	.248	4.102	<0.001
	PO4	.119	.098	.074	1.222	.226
	ALP	.002	.001	.090	1.519	.133

FGF23 (fibroblast growth factor 23), PO4 (phosphorus) and ALP (Alkaline phosphatase)

DISCUSSION

Cardiovascular calcifications affect most of the CKD patients with highest mortality rate compared to other chronic disease[9]. Most of this calcification is related to disturbed renal phosphate handling**.** In a previous pilot study performed by our group, VC was encountered in 100% of the small number of patients starting dialysis [8]. This alarming result has stimulated the study group to expand the size of the incident hemodialysis patient for proper evaluation. In this new study, the prevalence of AAC in incident hemodialysis patients is 79 %. This prevalence agrees with that of a 3-year follow-up study of 742 patients with nondialysis CKD stages 3-5 from 39 centers in Spain [10]. By revising the literature, we failed to encounter other studies that looked for the prevalence of AAC in incident hemodialysis patients using CT scanning for this evaluation. Goldsmith *et al* indicated that aorto-iliac calcification as detected by plain radiography in 39% of patients at the onset of dialysis. These discrepancies in the results can be related to the method used for detection [11]. Another study was done to detect frequency of abdominal aortic calcification in 45 of Iraqi patients on regular hemodialysis for less than 1 year by using lateral abdominal x-ray. The prevalence of AAC in this cohort study was 18.5% [12]. A lateral lumbar X-ray to assess severity of AAC is not as sensitive as other modalities such as CT [13].

In spite of exclusion of CKD patients that are more prone to VC, namely, diabetic patients and patients with history of oral anticoagulants intake and those with history of hyperparathyroidism, the prevalence of AAC is still very high. Being a strong predictor of major cardiovascular events in dialysis population [14], this alarming finding should stimulate the medical community for energetic procedures aiming at inhibition of development of this devastating pathology starting by the very early stage of CKD.

It became evident that traditional risk factors for atherosclerosis, such as dyslipidaemia, diabetes, hypertension, smoking, gender and age, only partly explain the calcification that seems to be more linked to the uraemic milieu and abnormalities in mineral metabolism [2]. It has been suggested that disturbances in bone and mineral metabolism cause vascular calcification [3].

The present study confirmed the significant correlation between AAC and age. In a comprehensive systematic review of 30 studies over a period of 20 years, it was demonstrated that age was one of the main associations with vascular calcifications in patients with ESRD [15]. Another study on 140 prevalent hemodialysis patients with a mean age of 55 years and dialysis vintage of 2.7 years, AAC was significantly correlated to age [16].

FGF23 has been independently linked to VC in patients on dialysis and in predialysis patients [8,17]. In the present study, FGF23 level is elevated in incident HD patients and significantly and independently correlates with AAC. Other studies have confirmed that FGF23 was elevated in incident HD patients [18].

The results revealed a positive correlation between FGF23 and PTH, which is also proven by Krajisnik *et al*. [19].The increase in FGF23 represents an appropriate compensatory mechanism to maintain phosphate balance in the early stages of CKD and thus, along with PTH, to prevent serum phosphate from rising until the late stages of CKD [19]. However, the evolving evidence disclosed a paradoxical action of FGF23 in the pathogenesis and progression of VC [20,21].

Limitations

We were limited by a small sample size and lack of information for medication. Several laboratory parameters that are important in the context of vascular calcification were not available, such as serum vitamin D and fetuin-A. Moreover, AAC could be the result of prolonged low-grade inflammation. In this context highly sensitive C-reactive protein (hsCRP) and Interleukin-6are important,

CONCULSION

The frequency and severity of AAC are significant in incident hemodialysis patients. The frequency of AAC is directly related to the age. The only biochemical parameter with a statistically significant effect on the frequency and severity of AAC in incident hemodialysis patients is FGF23. Hypertension was noticed in most patients with AAC. FGF23 was significantly elevated in incident hemodialysis patients with significant correlation with iPTH and phosphourus.

Conflict of interest: The authors have declared that no conflict of interest exists.

Human and Animal Rights: 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.
We also obtained the IRB approval of the local ethical committee of Internal Medicine Department in our institution.

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

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