



Risk factors for abdominal aortic calcifications in chronic hemodialysis patients

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Abstract

Introduction: Cardiovascular disease represents the leading cause of death in chronic hemodialysis (HD) patients; in this field, abdominal aortic calcifications (AAC) which represent a predictor of cardiovascular events are associated with cardiovascular morbidity and mortality.

Objectives: The purpose of our study is to determine the prevalence and factors associated with AAC.

Patients and Methods: This cross-sectional study including 40 chronic HD patients for more than six months having benefited from screening for AAC by profile abdominal x-ray without preparation. The AAC were evaluated according to the Kauppila score (ScK). Demographic, biological and radiological data were collected and then analyzed to assess the prevalence of AAC. Patients were divided into two groups according to ScK, highly calcified (ScK ≥ 12) and slightly or moderately calcified (ScK < 12), in order to determine the associated factors to severe AAC.

Results: The mean age was 58 ± 16 years, 55% were women, and the median of HD duration is 82 months. The prevalence of AAC was 65% and the median score of AAC was four. Patients with highly AAC (ScK ≥ 12) represented 27.5% of population and slightly or moderately AAC (ScK < 12) represented 72.5%. The factors associated with severe AAC retained in the univariate analysis were age ($P=0.029$), phosphoremia ($P=0.027$), duration of dialysis ($P=0.047$) and calcemia ($P=0.035$). Only duration of dialysis ($P=0.042$), age ($P=0.018$) and phosphoremia ($P=0.044$) remained statistically significant in multivariate.

Conclusion: AAC are associated with advanced age, long duration of dialysis, and phosphocalc balance abnormalities. Profile abdominal x-ray without preparation is currently recommended by the KDIGO (kidney disease improving global outcomes) for early detection and follow-up of vascular calcifications on HD, which should be considered for any patient.

Keywords: Calcifications, Abdominal aorta, Hemodialysis.

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Introduction

Cardiovascular disease is the leading cause of death in patients with chronic renal failure due to accelerated atherosclerosis processes and calcifications of their arteries (1). Long considered a simple benign radiological discovery, vascular calcifications are now recognized as a risk factor of cardiovascular events, whether in the general population or in chronic kidney disease (CKD) (2-4). In whom they are associated with high morbidity and mortality (5). In addition to the traditional risk factors for atherosclerosis, many factors linked to chronic uremia and dialysis are implicated in the pathogenesis of vascular calcifications of dialysis patients (6,7). The prevalence of abdominal aortic calcifications (AAC) is high varies between 60% and 90% (8,9) but its severity, unlike coronary calcification, is less well documented, the various works devoted to vascular calcifications are rare (9) and discordant due to the heterogeneity of the assessment methods. Atherosclerosis in the coronary

arteries and other vessels is correlated with the extent of lesions in the aorta that is why a system for quantifying calcification has been described by Kauppila et al. This system is based on lateral view of lumbar spine radiographs and the calculation of the ACC score.

The presence of vascular calcifications in the aorta is associated with cardiovascular mortality and global mortality from any causes (10), hence the need for early detection and regular monitoring given the risk of progression (9).

KDIGO (kidney disease improving global outcomes) 2017 guidelines suggests that a lateral view of lumbar spine radiographs can be used to detect the presence of aortic calcifications as reasonable alternatives to computed tomography (11).

Multicut scanners allow an exact and global determination of vascular calcifications using calcification scores, the most used of which is the Agatston score. However, they are costly and not very suitable for

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■ Implication for health policy/practice/research/medical education

In a study on 40 chronic hemodialysis individuals, we found vascular calcifications are common in hemodialysis patients. These calcifications are associated with advanced age, long duration of dialysis and hyperphosphatemia.

screening and for universal use in all dialysis patients (12).

Objectives

In order to describe the prevalence and identify the risk factors for AAC in chronic hemodialysis (HD) patients, we conducted a screening study based on profile abdominal radiography.

Patients and Methods

Study design

This is a transverse monocentric descriptive and analytical screening study, carried out over a period of 30 days from March 2019 to April 2019 at the Department of nephrology dialysis and kidney transplantation at Mohammed V military teaching hospital, including the 40 chronic HD patients in the HD unit having benefited from a screening for calcifications of the abdominal aorta by profile abdominal radiography. Inclusion criteria were; Age ≥ 18 years and duration of dialysis ≥ 6 months. Exclusion criteria: inability to perform the radiological examination and patient's refusal. Clinical, biological and therapeutic data were collected, based on the review of medical records and dialysis data as well as on the history in order to complete a digitized information sheet.

Clinical and biological data

The clinical data collected were; age; gender; primary cause of end-stage renal disease (ESRD); duration of dialysis; cardiovascular risk factors: diabetes, hypertension, smoking, dyslipidemia; and history of ischemic heart disease. In addition, a balance sheet including the determination of calcemia, phosphoremia, alkaline phosphatases, intact parathormone (iPTH), and 25-OH vitamin D was carried out.

Therapeutic modalities

Our patients were dialyzed three times a week at the rate of 4 hours per session. The dialysate bath contained 3 mmol/L potassium and 1.50 mmol/L calcium. High permeability polysulfone membranes were used in all patients.

Regarding oral treatment, we used the average daily dose of calcium carbonate in grams per day for each patient and distinguished between patients that took 25-OH vitamin D or 1 alpha-hydroxy-vitamin D3.

Profile abdominal x-ray

The existence of vascular calcifications was assessed by the

abdominal profile radiography carried out in a standing position using equipment allowing to obtain a digital imagery. The x-ray was interpretable when it included:

- The last two thoracic vertebrae and the first two sacral vertebrae.
- The portion of the abdominal aorta between L1 and L4 was analyzed.

Aortic calcifications were sought on the anterior and posterior slopes of each segment and scored according to the score validated by Kauppila and Schousboe.

A rating of 0 to 3 was assigned to these calcifications according to their length:

- 0: no calcific deposits in front of vertebra.
- 1: $< 1/3$ of the segment.
- 2: $1/3-2/3$ of the segment.
- 3: $2/3$ or more of the segment.

The aortic calcium score is obtained by the sum of the 8 points (2 points for each vertebra) and varies between 0 and 24.

The interpretation of the radiological results was carried out by radiologists who were not informed of the clinical and biological data of the patients.

Statistical analysis

First, we performed a descriptive analysis using means and medians for quantitative variables and frequencies for qualitative variables. In a second step, the patients were divided into 2 groups according to the Kauppila score (ScK): highly calcified (ScK ≥ 12) and slightly or moderately calcified (ScK < 12).

The comparison of variables was carried out by the Student test for symmetric quantitative variables, by Mann-Whitney U test for asymmetric quantitative variables, and by the χ^2 test for qualitative variables. The factors correlated with severe calcifications of the abdominal aorta were estimated by regression models; Initially, analysis by univariate logistic regression was carried out to independently obtain a crude association between risk factors and severe AAC. Then the variables which emerged significant in the univariate analysis, were inserted in the multivariate analysis model which allowed us to define a model for predicting severe calcifications of the aorta. Statistical significance is defined as $P < 0.05$. All analyzes were performed with SPSS version 21 software.

Results

This study consisted 40 chronic hemodialysis patients, who had an average age of 58 ± 16 years, while 55% were women. The median duration of hemodialysis was 82 months. Diabetic nephropathy as an etiology of end-stage renal disease was seen in 35% of cases (Table 1).

Around 65% of our patients were hypertensive followed by 37.5% 27.5% and 17.5% for diabetic, ischemic heart disease, and smoking, respectively.

With regard to the treatment influencing the phosphocalcic metabolism; 82% of the patients were

taking elemental calcium carbonate with an average dose of 1.3 g, as phosphorus complexing agent, or for the treatment of hypocalcemia, and 65% were on vitamin D derivatives. Vascular calcifications were observed in 65% of cases and the median AAC score was 4.5.

The patients were divided into two groups according to ScK. Group 1; highly calcified (ScK ≥ 12) represented 27.5% and group 2; slightly or moderately calcified (ScK < 12) represented 72.5%.

The univariate analysis showed that severe AAC was significantly associated with age ($P=0.027$), phosphoremia ($P=0.029$), duration of dialysis ($P=0.047$) and calcemia ($P=0.035$), since there was no significant association between AAC and diabetes, smoking, iPTH and calcium elements (Table 2).

In multivariate analysis, after adjustment for confounding factors, age (OR=1.128, 95% CI: 1.02-1.24, $P=0.018$), duration of dialysis (OR=1.016, 95% CI: 1.001-1.03, $P=0.042$), and phosphoremia (OR=1.016, 95% CI: 1.001-1.03, $P=0.044$) were independently associated with severe AAC (Table 3).

Table 1. Characteristics of the study population

| Data | Results |
|--------------------------------------|-----------------|
| Gender* | |
| Women | 22 (55) |
| Man | 18 (45) |
| Age (years) ** | 58 \pm 16 |
| Duration of dialysis (months) *** | 82 (39-120) |
| Initial nephropathy * | |
| Diabetic nephropathy | 14 (35) |
| Chronic tubulointerstitial nephritis | 8 (20) |
| Vascular nephropathy | 6 (15) |
| Glomerular nephropathy | 6 (15) |
| Indeterminate nephropathy | 6 (15) |
| Hypertension* | 35 (65) |
| Diabetes * | 15 (37.5) |
| Smoking* | 7 (17.5) |
| Ischemic heart disease * | 11 (27.5) |
| Dyslipidemia* | 10 (25) |
| Alkaline phosphatase (U/L) *** | 117 (89-167) |
| Ca (mg/L) ** | 89 \pm 8 |
| P (mg/L) | 40 \pm 16 |
| Intact PTH (pg/mL) | 800 (300-1100) |
| Vitamin D (μ g/L) ** | 31 \pm 15 |
| C-reactive protein (mg/L) | 3.9 (2-7) |
| Kt/V** | 1.75 \pm 1.44 |
| Ca element(g) *** | 1.3 (1-1.5) |
| Vitamin D derivatives * | 35 (65) |
| AAC* | 35 (65) |
| AAC score*** | 4.54 (0-13.75) |

*Expressed in effective (%); ** Expressed as mean \pm standard deviation; *** Expressed in median (quartiles).

Discussion

Vascular calcifications are a major risk factor for morbidity and mortality in chronic HD (5) and AAC are predictive of a large number of severe complications including myocardial ischemia, congestive heart failure, stroke and arteritis of the lower limbs (13,14). These calcifications develop in the early stages of renal failure justifying systematic and repeated cardiovascular explorations(15,16).

The pathogenesis of vascular calcification is complex. There are two types of calcifications, in the intima where the atheroma plaques are located, or in the media of the vessels (5,17). Vascular calcifications, considered as a passive phenomenon due to the unregulated precipitation of calcium and phosphorus. A condition similar to the osteogenesis (18,19). Vascular calcification is a tightly regulated active cellular mechanism involving phenotypic trans-differentiation of the vascular smooth muscle cell into osteoblasts capable of initiating the synthesis of an extracellular matrix (20,21). This situation implying an imbalance between protein calcification inhibitors (Fetuin-A, matrix Gla protein or osteoprotegerin) which are reduced, and pro-calcifying factors. This imbalance explains why vascular calcifications are more frequent, more severe and rapidly progressive in dialysis patients compared to the general population (20,23). The main traditional factors associated with the development of vascular calcifications are age, diabetes, dyslipidemia, hypertension, left ventricular hypertrophy and advanced age (23). The main non-traditional risk factors reported in the literature are secondary hyperparathyroidism, hyperphosphatemia and/or increased calcium burden, hypervitaminosis D, inflammation, genetics and the duration of dialysis (6, 24, 25). The prevalence of vascular calcifications in dialysis patients is high, being between 60 and 90% according to studies (8,9). In our study, this prevalence represents 65% and joins that of the literature.

A multitude of research studies have significantly linked advanced age to the presence of arterial calcifications (26) and their severity in the population of chronic

Table 2. Comparison of risk factors between the two groups

| Factors | Group 1 (n =14) | Group 2 (n =26) |
|----------------------------------|------------------|------------------|
| Age (y) ** | 42 \pm 13 | 67 \pm 9 |
| Duration of dialysis (months)*** | 54 (31; 120) | 90 (57; 141) |
| Diabetes* | 4 (28) | 11 (42) |
| Smoking* | 0 | 7 (27) |
| Calcium (mg/L)** | 88 \pm 5 | 89 \pm 9 |
| Phosphorus (mg/L)** | 43 \pm 15 | 45 \pm 17 |
| PTH (pg/L)*** | 398 (890; 1380) | 687 (315; 1105) |
| Ca elements (g)*** | 1 (1; 1,6) | 1 (1; 1,5) |
| Vitamin D (μ g/L)** | 30 \pm 12 | 31 \pm 17 |

*Expressed in effective (%); ** Expressed as mean \pm standard deviation; *** Expressed in median (quartiles).

Table 3. Risk factors independent of severe AAC

| Factors | Univariate | | | Multivariate | | |
|-------------------------------|------------|---------------|--------------|--------------|----------------|--------------|
| | OR | 95% CI | P | OR adjusted | 95% CI | P |
| Age (years) | 1.07 | (1.009, 1.15) | 0.027 | 1.128 | (1.02, 1.24) | 0.018 |
| Duration of dialysis (months) | 1.01 | (1.001, 1.21) | 0.047 | 1.016 | (1.001, 1.03) | 0.042 |
| Diabetes | 1.83 | (0.45, 7.40) | 0.39 | | | |
| Smoking | 4.95 | (0.89, 27.4) | 0.067 | | | |
| Calcium (mg/L) | 1,11 | (1.007, 1.24) | 0.035 | 1.002 | (0.878, 1.145) | 0.971 |
| Phosphorus (mg/L) | 1.05 | (1.005, 1.10) | 0.029 | 1.08 | (1.002, 1.18) | 0.044 |
| Intact PTH (pg/L) | 1 | (0.99, 1.001) | 0.987 | | | |
| Calcium element (g) | 0.63 | (0.242, 1.66) | 0.356 | | | |
| Vitamin D (ug/L) | 1 | (0.963, 1.05) | 0.72 | | | |

dialysis patients (26-28). The multivariate analysis of our study retained that age is an independent factor in the development of vascular calcifications ($P = 0.01$), which agrees with the data in the literature.

Duration of dialysis is an important factor given the prolonged exposure to a set of risk factors, according to studies, the duration of dialysis is a determining and constant factor for vascular calcifications (8,27,28) which shows our series. Diabetes is known to be an important risk factor for vascular calcification, especially in patients with atherosclerotic plaques. A recent study has shown that hyperglycemia reduces the binding of vitamin D to its receptor, which may increase the risk of soft tissue calcification (29). In our study, diabetes was not defined as a risk factor for AAC as reported by other studies. This can be explained by the control of the glycemic figures. There is a significant association between AAC and phosphatemia in our studied population, in fact in patients with ESRD. Hyperphosphatemia is a major stimulus of cardiovascular calcifications because it can increase, vascular mineralization and constitutes one of the risk factors of vascular calcifications (30,31).

Parathormone excess is associated with uremic toxicity by a disruption of the calcium-calcium metabolism and bone turnover. In case of hyperparathyroidism, the intracellular calcium concentration increases, as do the vascular medial calcifications, especially at the aortic and coronary level (32).

A PTH lower than the KDOQI recommendations could testify to an adynamic bone, recently identified as a major risk of vascular calcification(33).

It seems that the low plasma PTH level is even more significantly associated with the progression of vascular calcification than its high level. This is explained by the fact that the decrease in the level of PTH leads to a decrease in the absorption capacity of calcium and phosphate by the bone, which leads to their elevation in the plasma to serve as a substrate for the calcification process.

However, studies have found no association between markers of bone turnover such as bone alkaline phosphatases and vascular calcifications (34).

In our series, we find that PTH is not identified as a

significant risk factor associated with AAC.

Multi-centric data find that high serum calcium is a vascular risk factor (35). Thus, in some monocentric studies, more than average calcemia ($Ca > 2.6$ mmol/L), appears to be a predictor of the calcification score (36).

Taking calcium phosphorus chelating results in an increase in calcium concentration at the vascular level, with a progression of calcifications (37). This is questioned by other authors (38), who argue that these studies do not demonstrate the biological sequence between calcium intake and intimal plaques.

In our series, neither calcemia nor the intake of calcium chelating is factors associated with calcifications.

Vitamin D acts as a vascular toxin while the administration of vitamin D to treat secondary hyperparathyroidism increases the intestinal absorption of calcium and phosphorus, and raises the levels of calcium and phosphorus levels (5,39). This predisposes to in-vivo formation of calcification plaques (5) and vascular calcifications progression (15,40). In our study, this association is not significant.

Another well-known risk factor for cardiovascular disease and vascular calcifications is smoking. In a clinical study in HD patients, smoking was associated with the presence of vascular calcifications (14). There was no significant association with these factors in our study.

Conclusion

In ESRD patients, vascular calcifications are an active, multifactorial process whose determinants add up and potentiate each other.

Our study has shown that vascular calcifications are common in HD patients. These calcifications are associated with advanced age, long duration of dialysis and hyperphosphatemia.

Screening for AAC using a widely available, less irradiating and sensitive method could be part of the cardiovascular risk assessment in dialysis patients recently recommended by KDIGO.

It is important to detect these often-silent calcifications in order to establish preventive therapeutic strategies focused on adequate monitoring and correction of

disorders of phosphocalcic metabolism and classic cardiovascular risk factors.

Strengths and limitations

Our study presents several points of strength in particular: the prospective nature of the study allowing a considerable reduction of information bias, as well as a representable sample allowing a statistical analysis of quality.

However, it also has certain limitations: presence of other potential confounding factors not measured in our study and therefore not taken into account during the analysis, in this case: inflammatory state, nutritional status.

Authors' contribution

AT, EM and DE were the principal investigators of the study. AT, EM, AS and DE were included in preparing the concept and design. AT and EM revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no interest link

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Mohamed V Military Hospital, Faculty of Medicine and Pharmacy, Mohammed V-Souissi University approved this study. Accordingly, written informed consent was taken from all participants before any intervention. Moreover, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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