



# *Multi-detector row CT scan for assessing coronary artery calcification in hemodialysis*

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## SUMMARY

Vascular calcification is a strong predictor of cardiovascular and all-cause mortality. Coronary artery calcification is more frequent, more extensive and progresses more rapidly in CKD than in general population. They are also considered a marker of coronary heart disease, with high prevalence and functional significance. It suggests that detection and surveillance may be worthwhile in general clinical practice. New non-invasive image techniques, like Multi-detector row CT, a type of spiral scanner, assess density and volume of calcification at multiple sites and allow quantitative scoring of vascular calcification using calcium scores analogous to those from electron-beam CT. We have assessed and quantified coronary artery calcification with 16 multidetector row CT in 44 patients on hemodialysis and their relationship with several cardiovascular risk factors. Coronary artery calcification prevalence was of 84% with mean calcium score of  $1,580 \pm 2,010$  ( $r 0.9.844$ ) with calcium score  $> 400$  in 66% of patients. It was usually multiple, affecting more than two vessels in more than 50%. In all but one patient, left anterior descending artery was involved with higher calcium score level at right coronary artery. Advanced age, male, diabetes, smoking, more morbidity, cerebrovascular disease previous, and calcium-binders phosphate and analogous vitamin D treatment would seem to be associated with coronary artery calcification. Coronary artery calcification is very frequent and extensive, usually multiple and associated to modifiable risk factors in hemodialysis patients. Multi-detector-row CT seems an effective, suitable, readily applicable method to assess and quantify coronary artery calcification.

Key words: **Coronary artery calcification. Multidetector row CT. Calcium score. Cardiovascular. Hemodialysis.**

## VALORACIÓN DE LAS CALCIFICACIONES CORONARIAS

### RESUMEN

La calcificación vascular es un potente predictor de mortalidad cardiovascular y global. Las calcificaciones de las arterias coronarias en pacientes renales son más frecuentes, más extensas y progresan más rápidamente que en la población general y constituyen un marcador de enfermedad coronaria de elevada prevalencia y significación funcional. La aparición de nuevas técnicas de imagen, como el TAC multidetector, permiten detectar y cuantificar las calcificaciones vasculares utilizando un

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score de calcificación similar al score de calcio del TAC emisor de electrones. Mediante TAC helicoidal de 16 filas de detectores hemos evaluado y cuantificado la presencia de calcificación de arterias coronarias y su relación con diferentes factores de riesgo cardiovascular en 44 pacientes en hemodiálisis. La prevalencia de calcificación fue del 84%, con un score de calcio medio de  $1.580 \pm 2.010$  ( $r 0.9.844$ ). El 66% de los pacientes presentaban valores de score de calcio  $> 400$ . La calcificación coronaria era por lo general múltiple, afectando a más de 2 vasos y de manera prácticamente constante a la arteria descendente anterior (97%) aunque la arteria coronaria derecha presentó valores de score de calcio más elevados. La calcificación coronaria se relacionó con edad avanzada, sexo masculino, diabetes, mayor comorbilidad, tabaquismo, antecedentes de enfermedad cerebrovascular y tratamiento con quelantes del fósforo que contenían calcio y análogos de la vitamina D. La calcificación de las arterias coronarias es muy frecuente y extensa, normalmente múltiple y asociada a factores de riesgo cardiovascular modificables en los pacientes en hemodiálisis. El TAC Multidetector parece un método eficaz, fácil de reproducir y cómodo para el paciente que permite detectar y cuantificar las calcificaciones coronarias.

Palabras clave: **Calcificación coronaria. TAC multidetector. Score de calcio. Enfermedad cardiovascular. Hemodiálisis.**

## INTRODUCTION

Cardiovascular disease (CVD) is the main mortality cause among patients with chronic renal disease (CRD),<sup>1</sup> being currently considered that the presence of vascular calcifications plays a relevant role in CRD-associated cardiovascular risk. Vascular calcifications (VC) are present in most of uremic patients. VC are more frequent, they start earlier, are more extensive, and progress more rapidly than in the general population. Besides, they are associated with modifiable risk factors, they have structural and functional consequences, and are directly related with morbimortality. In clinical practice, chest, pelvis, spine, and hands X-Rays, xeroradiography, coronary angiography, ultrasound, eye fundus inspection, echocardiogram, calculation of the pulse pressure, artery histological examination, and CT scan are used to assess them.

Calcification accounts for 20%-30% of the atherosclerotic plaque and is an important part of the global atherosclerotic process. This association is the basis for using non-invasive and sensitive radiological methods to detect calcium deposition in the coronary arteries as an indicator of the atherosclerotic plaque. Among these methods, there is electron beam-emitting CT scan and spiral CT scan.

The aim of this study was to describe the prevalence and degree of calcification of the coronary arteries by means of Multi-detector CT Scan and its distribution by cardiovascular risk factors in hemodialysis patients.

## MATERIAL AND METHODS

A cross-sectional observational study has been performed in 44 patients on regular hemodialysis therapy.

The inclusion criterion was being on regular hemodialysis for at least 3 months. We excluded those patients with coronary metallic stents and/or the presence of arrhythmia such as frequent extrasystoles or not controlled atrial fibrillation since both the presence of metallic stents and alterations in cardiac rhythm may produce image artifacts that may render difficult and limit the quantification of the calcium score.

The following cardiovascular risk factors were determined in every patient: AHT, dyslipidemia, overweight (BMI > 25), cigarette smoking, diabetes mellitus, anemia (Hb < 11 g/dL), hyperparathyroidism (i-PTH > 300 pg/mL), hyperphosphatemia (PO4s > 5.5 mg/dL), and personal history of coronary disease and/or cerebrovascular disease. We calculated the compounded Charlson's comorbidity index adjusted for CRD.

About hyperparathyroidism and/or hyperphosphatemia management, we quantified the dose of elemental calcium that was contained in chelating agents and the doses of vitamin D analogues that were administered to the patients.

We calculated the mean systolic blood pressure (SBP), diastolic blood pressure (DPB), and pulse pressure (PP) gathered from three consecutive hemodialysis sessions (predialysis), and the following blood analytical parameters were determined: Hb, Ca, P, i-

**Table I.** Demographical and clinical characteristics of the patients

	<b>Patients (n = 44)</b>	<b>No calcification (n = 7) (16%)</b>	<b>Coronary calcification (n - 37) (84%)</b>	<b>p</b>
Age (years)	M 68	57 ± 13	71 ± 10	0.003
Permanence on HD (months)	M 33	28 ± 18	31 ± 28	NS
Gender				
Female	14	5 (72%)	9 (24%)	
Male	30	2 (28%)	28 (76%)	0.01
Etiology of CRD				
Diabetes Mellitus	13	0	13	
Vascular	9	0	9	
Unknown	6	0	4	
Tubulointerstitial	6	1	1	0.015
CGN	5	2	3	
Tumoral	5	0	5	
Charlson's Index		4 ± 3	8 ± 4	0.004
PP		57 ± 19	65 ± 17	NS

PP = Pulse pressure.

PTH, albumin, bicarbonate, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and Kt/V (second generation Daugirdas).

The patients were examined by means of multi-detector spiral CT scan (LightSpeed 16 GE®). The quantification of the different coronary arteries was done by using Agatston's method measuring the calcium score (CAS). According to the CAS, the patients were classified in three groups: «No calcification» when the CAS = 0; «light-moderate calcification» with CAS = 1-400; and severe calcification with CAS > 400.

### Statistical analysis

The descriptive analysis of the different frequencies is summarized by mean and standard deviation, expressed as mean ± SD, and in some cases we used the range as a dispersion measures. Mean comparison was done by the Student's t test for independent dichotomous variables, and variance analysis for categorical variables. We also used the chi-squared test to study the relationship between quantitative variables and the presence of calcification and its degree. The calculation of the confidence interval for the prevalence of coronary calcification was done by suing binomial distribution. All the analyses were done using the SPSS software, v. 10.0 at the Clinical Epidemiology Unit of La Princesa University Hospital. In all cases we considered as being statistically significant p values < 0.05.

### RESULTS

A total of 44 patients (14 females and 30 males), all Caucasian but one male of Afro-American origin have been included. The mean age was 68 years (r: 34-88), with a mean stay on hemodialysis of 29 months (r: 3-106).

The most common etiology for renal disease was diabetes mellitus (30%), followed by vascular nephropathy (20%).

About risk factors studied, 13 patients were diabetic, accounting for 30% of all patients, 41/44 (93%) were hypertensive, 19 (43%) patients had a history of coronary disease, 12 patients (27%) had a history of cerebrovascular disease, 16 (36%) were overweighted, 32 (72%) were smokers, and 19 (43%) had dyslipidemia. Calcium-phosphate metabolism impairments were very common with half of the patients (22/44) having hyperphosphatemia and secondary HPT was present in 17 patients (38%).

The demographic and clinical characteristics of the patients are shown in Table I.

The multi-detector CT scan showed the presence of calcifications of the coronary arteries in 37 patients, which accounts for a prevalence of 84% [95% CI 72.15-96.03] and only 7 patients (16%) did not show calcifications (CAS = 0). Slight-moderate calcification (CAS 1-400) was found in 7 patients (15.9%) and severe calcification (CAS > 400) in 30 patients (66.6%).

The CAS was quantified for the different coronary arteries: main branch of the left coronary artery, ante-

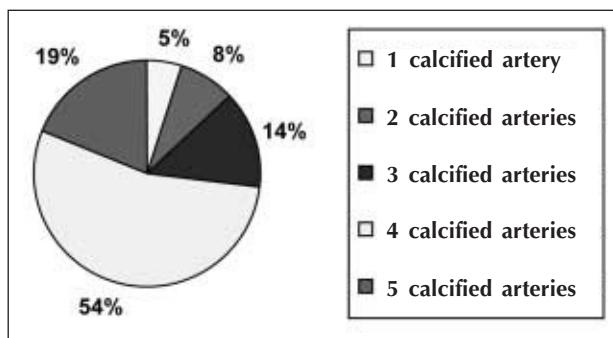


Fig. 1.—Distribution of coronary calcification by number of involved arteries.

rior descending artery, circumflex, right coronary artery, and posterior descending artery. All patients but one presenting calcifications had a calcification of the anterior descending artery, although the CAS were slightly higher at the right coronary artery ( $551 \pm 617$  vs.  $641 \pm 1015$ ). By contrast, the posterior descending artery was calcified in only 9 patients (20%) and always with a slight to moderate degree (CAS  $27 \pm 90$ ). Most frequently, calcification of the coronary arteries was multiple, with involvement of more than one vessel in 95% of the patients, and practically half of them (54%) presented involvement of 4 coronary arteries (Graph 1). The mean CAS value was  $1.586 \pm 2.010$  (r: 0-9,844). The CAS results are shown in Table II. The mean Charlson's index (Chl) was  $7 \pm 4$  (r: 0-16). Those patients with no calcifications had mean Chl values of  $4 \pm 3$ , in the group with slight-moderate calcification it was  $6 \pm 4$ , and in sever calcification this value was  $8 \pm 4$  ( $p = 0.004$ ). For HPT and/or hyperphosphatemia management, 79.5% of the patients were on calcium chelators, calcium carbonate (mean  $2.6 \pm 1.5$  g of elemental calcium) or calcium acetate

(mean of  $0.9 \pm 0.7$  g of elemental calcium), and 52.3% of the patients were on phosphate-chelating agents without calcium either as sevelamer hydrochloride (mean dose  $3.40 \pm 1.95$  g) or either as aluminum hydroxide (mean dose  $2.0 \pm 1.26$  g). Besides, 16 patients (36.3%) required both types of chelators. Together with these medications, 20% also took vitamin D analogues with a mean dose of  $2.0 \pm 2.5$  mg orally or  $5.0 \pm 3.0$  mg intravenously.

We have possibly found a not random distribution and thus suggesting a relationship between the degree of coronary calcification and male gender ( $p = 0.011$ ), presence of diabetes ( $p = 0.015$ ), advanced age ( $p = 0.003$ ), cigarette-smoking ( $p = 0.03$ ), previous cerebrovascular disease ( $p = 0.01$ ), and treatment with phosphate chelators containing calcium content ( $p = 0.03$ ) and vitamin D ( $p = 0.04$ ). Patients with no coronary calcifications presented higher HDL-CHOL levels ( $p = 0.02$ ) and higher Kt/V ( $p = 0.02$ ). The analysis of these possible relationships with total CAS is shown in Tables III and IV.

## DISCUSSION

VC is a potent predictor of cardiovascular and global mortality.<sup>2,3</sup> Calcifications of the coronary arteries (CCA) are present in most of renal patients, even in young patients, are more frequent in diabetics and dialysis, may occur at early phases of CRD and progress rapidly.<sup>4-9</sup>

From a clinical perspective, one of the most important aspects is the difficulty for quantifying calcifications and analyzing their progression, thus the current interest in new imaging methods such as multi-detector CT scan.

**Table II.** Calcification of the coronary arteries

Coronary artery	CAS $M \pm DS$	CAS Range	No calcification N	No calcification %	Slight-moderate calcification N	Slight-moderate calcification %	Severe calcification N	Severe calcification %
<b>Left coronary territory</b>								
MLB	$83 \pm 146$	0-832	14	32	29	65	1	2
ADA	$551 \pm 617$	0-2,442	7	16	15	37	21	48
CxA	$309 \pm 617$	0-3,088	12	27	22	50	10	23
<b>Right coronary territory</b>								
RCA	$642 \pm 1,015$	0-4,742	13	30	13	30	18	40
PDA	$27 \pm 90$	0-368	35	80	9	20	0	0

Abbreviations: CAS = Calcium score; MLB = Main left branch; ADA = Anterior descending artery; CxA = Circumflex artery; RCA = Right coronary artery; PDA = Posterior descending artery.

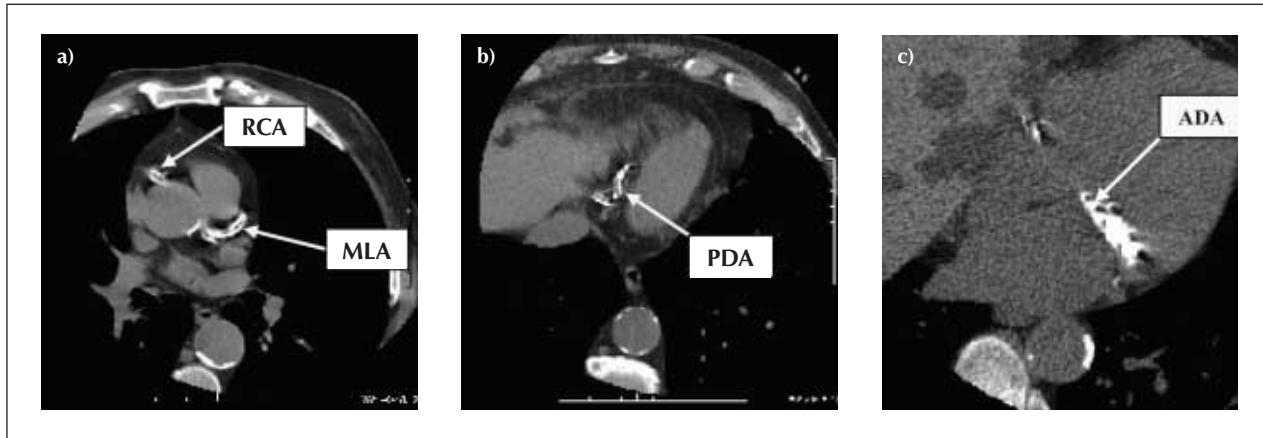


Fig. 2.—Multi-detector CT scan images. The arrows indicate the calcified coronary arteries (RCA = right coronary artery; MLA = main left artery; ADA = anterior descending artery; PDA = posterior descending artery).

MDCTS is a type of spiral CT that has multiple rows of detectors. Its main advantage is that it brings high especial resolution (sections < 1 mm wide) and rapidity (20-25 seconds) simultaneously. Thanks to the especial resolution of this method the difficulty that the coronary arteries offer due to their small diameter, complex path, and multiple ramifications is solved

without needing IV contrast media. The rapidity of the MDCTS allows that the whole heart is visualized in just 20-25 seconds while keeping the patient holding his/her breath. It has cardiac synchronism systems that couple X ray emission to a cardiac cycle at end of the diastole. This period coincides with the heart virtually quiet and corresponds with coronary artery

**Table III.** Relationship of total calcium score and independent variables

	No Calcification N %		Slight-moderate calcification N %		Severe calcification N %		Mean CAS	p
	N	%	N	%	N	%		
Diabetes Mellitus								
No	7	100	5	72	17	57	1,333	
Yes	0	0	2	28	13	43	2,094	0.03
Previous cerebrovascular disease								
No	7	100	7	100	12	40	1,265	
Yes	0	0	0	0	18	60	2,470	0.01
Cigarette-smoking								
No	0	0	1	14	11	37	1,454	
Yes	7	100	6	86	19	63	1,635	0.03
Calcium-containing chelating therapy								
No	1	14	0	0	8	27	1,265	
Yes	6	86	7	100	22	72	2,933	0.003
Vitamin D therapy								
No	5	71	5	71	25	83	1,319	
Yes	2	29	2	29	5	17	2,804	0.04
Hyperphosphatemia (mg/dL)								
No	1	14	7	100	14	47	1,416	
Yes	6	86	0	0	16	53	1,750	NS
HPT (pg/dL)								
No	4	57	6	86	17	57	1,225	
Yes	3	43	1	14	13	43	2,182	NS

p < 0.05 statistical significance.

**Table IV.** Relationship of total calcium score and independent analytical variables

	No calcification M ± SD	Slight moderate calcification M ± SD	Severe calcification M ± SD	P <sub>L</sub>
Serum calcium (mg/dL)	9.3 ± 0.9	9.1 ± 0.8	8.9 ± 0.9	NS
Serum phosphate (mg/dL)	6.2 ± 2.0	3.7 ± 0.8	5.3 ± 1.7	NS
Ca × P (mg <sup>2</sup> /dL <sup>2</sup> )	57 ± 16	34 ± 8	46 ± 13	NS
i-PTH (pg/dL)	308 ± 19	186 ± 65	353 ± 318	NS
Hemoglobin (g/dL)	11 ± 2	12 ± 2	11 ± 2	NS
HDL-cholesterol (mg/dL)	56 ± 21	54 ± 20	41 ± 15	0.02
LDL-cholesterol (mg/dL)	105 ± 20	115 ± 51	188 ± 40	NS
Kt/V	1.5 ± 0.3	1.3 ± 0.4	1.2 ± 0.2	0.02
Serum albumin (g/dL)	3.5 ± 0.6	3.7 ± 0.4	3.4 ± 0.6	NS
Venous HCO (mom/mL)	22 ± 4	26 ± 4	21 ± 4	0.04

p < 0.05 statistical significance.

filling. MDCTS with sixteen rows of detectors takes 32 images per second and 0.6-1 mm width sections. Using CAS analogue to those from electron-emission CT scan allow quantifying the calcification of the coronary arteries. Total coronary calcium quantification is a marker of atherosclerosis, allows stratifying the cardiovascular risk of patients with higher accuracy than usual methods. It incorporates a specific software that quantifies CAS. The CAS is obtained by multiplying the area of calcification of a segment by the maximal calcium density in that segment (Agaston's area).<sup>10</sup> The CAS represents the total atherosclerotic plaque load, correlates with the degree of obstructive coronary artery disease and allows predicting the cardiovascular course in the general population. CAS = 0 implies that there is no calcified atherosclerotic plaque, ruling out significant obstructive coronary damage. CAS < 10 indicates that although there exists calcified atherosclerotic plaque it is minimal with little possibility of coronary artery disease. CAS 11-100 represents mild atherosclerotic plaque with moderate cardiovascular risk. CAS de 101-400 establishes that there is atherosclerotic plaque with moderate total calcium load but high risk for cardiac events; CAS >

400 indicates the presence of high total calcium load of the atherosclerotic plaque, with high risk for presenting obstructive arterial disease, symptomatic myocardial ischemia, and future cardiovascular events.<sup>11-14</sup>

In our study, the prevalence of coronary calcification has been very high, 84% [95% CI: 72.15-96.03], and in 68% of the patients coronary calcification was of sever degree (CAS > 400) with a mean CAS of 1586 ± 2010 (r: 475-9,844) in this group, levels that would indicate the presence of obstructive arterial disease with high cardiovascular risk.<sup>6-8,15-20</sup> We have found that in our patients coronary calcification was multiple, in most of the cases involving more than one coronary vessel, and in half of the cases (54%) four coronary arteries. The left descendent coronary artery is the one most frequently calcified, similar to other groups.<sup>8,21</sup> By contrast to the general population where CCA is only seen within the context of arteriosclerosis, in the CRD patient the coexistence of calcification of the atheromatous plaque with calcification of the intermediate layer of the vessel wall (arteriosclerosis and increase of vascular rigidity) is observed, which would explain the high CAS observed in these

**Table V.** Total calcium score of the coronary arteries and its clinical significance

Calcium score	Total plaque load	Possibility of coronary artery disease	Cardiovascular risk
0	No plaque identified	Disease ruled out	Very low
1-10	Minimal	Very low (< 10%)	Low
11-100	Mild	Mild or minimal coronary stenosis	Moderate
101-400	Moderate	Moderate obstructive disease	High
> 400	Extensive	High (> 90% for at least one significant stenosis)	Very high

patients. Unfortunately, the CAS of the coronary arteries mediated by TMD does not differentiate whether the calcification is located at the intimal layer, or the intermediate layer, or both. This differentiation between both would be important since it confers a different composition of the atheromatous plaque and implies differences in patients' survival. A poorer prognosis has been observed if it is located at the intimal layer, but the survival is always worse in the patient presents calcification of any type, as compared to patients without calcification.<sup>3</sup>

The mortality rate of cardiac origin in CRD is 40%, ischemic cardiopathy accounting for 60% of it. Coronary disease is just another manifestation of the atherosclerotic process that renal patients may have, with a prevalence of asymptomatic coronary disease of 20%-40%. Besides, the existence of MI in dialyzed patients indicates a very poor prognosis, with a mortality of 60% within the first year after the infarction, 73% within the second year, increasing to 90% within the third year.<sup>22</sup> CCA is considered a marker of coronary disease. Raggi *et al.* reported that the presence of myocardial infarction, angina, and previous coronary artery disease was more frequent among patients with extensive coronary calcification.<sup>19</sup>

Risk factors for atherosclerosis are several. Some of them are common to the general population, such as advanced age, overweight, and sedentary lifestyle. Others are more prevalent in CRD patients, such as AHT, diabetes mellitus, increased formation of AGE, increased homocysteine levels, oxidative stress, inflammation, accumulation of endogenous inhibitors of nitric oxide synthesis, malnourishment, permanence in dialysis, alterations of calcium-phosphate metabolism, chronic infections, bioincompatible materials and endotoxins from the dialysis water.

The impairments of the mineral metabolism, in particular phosphate and serum calcium, are very common in CRD patients and play an important role in the development of CVD by promoting VC and being associated with higher mortality risk.<sup>23-25</sup> Besides, hyperphosphatemia management and/or secondary HPT have been implicated in the development of VC. Although several groups have associated VC with a high intake of calcium-containing phosphate chelators,<sup>6,26</sup> the «Treat to Goal» study is the first randomized prospective study that has shown that the progression of coronary and aortic calcification may be attenuated, and that the type of phosphate chelators used may have an influence on the extension of the calcification.<sup>17</sup> In spite of the critics this study has received, another study has recently been published comparing calcium carbonate with sevelamer in new hemodialysis patients, also showing progression of CCA in the group receiving calcium-containing che-

lators and absence of progression in the group of patients treated with sevelamer.<sup>27</sup>

Finally, in our study we have found higher total CAS levels among patients receiving calcium-containing phosphate chelators (calcium carbonate or calcium acetate) and vitamin D, with a mean dose of elemental calcium of  $2.6 \pm 1.5$  g/day, higher than the doses recommended in the K-DOQI guidelines.<sup>28</sup>

## CONCLUSIONS

CCA are very frequent and extensive, generally multiple and associated to modifiable risk factors in hemodialysis patients.

Multi-detector CT scan is an effective method, easy to reproduce, and convenient for the patient, allowing for the detection and quantification of coronary calcifications.

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