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Risk Factors for Cardiovascular Calcifications in Non-Diabetic Caucasian Haemodialysis Patients

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Key Words

Calcification inhibitor · Calcification score · Dialysis · End-stage renal disease · Ethnicity · Haemodialysis patients · Non-diabetic Caucasian HD patients · Vascular calcification

Abstract

Background/Aims: Dialysis patients display an increased mortality which is associated with cardiovascular calcifications. Diabetes mellitus and ethnicity are known factors that affect the extent of cardiovascular calcifications. However, most studies have investigated mixed cohorts with diabetics and/or mixed ethnicity. ***Methods:*** Cardiovascular calcifications were assessed in non-diabetic Caucasian haemodialysis patients by the semiquantitative Adragao calcification score (X-ray pelvis and hands) and a novel composite calcification score encompassing the Adragao score as well as calcifications detected by X-ray of the fistula arm, echocardiography of heart valves and carotid ultrasound. ***Results:*** Using multivariate analysis, age, male gender, dialysis vintage, lower Kt/V, calcium-phosphate product, smoking and high-sensitivity CRP were independent risk factors for cardiovascular calcifications as assessed by the Adragao or the composite score. Pulse wave velocity was independently related to both calcification scores. Body mass index, cholesterol, triglycerides, iPTH and serum levels of fetuin-A and uncarboxylated matrix Gla protein were not associated with cardiovascular calcifications. ***Conclusions:*** In our cohort of non-diabetic Caucasian haemodialysis patients, age, male gender, dialysis vintage, smoking, calcium-phosphate product, high-sensitivity CRP and lower Kt/V were independent risk factors for cardiovascular calcifications. Whether lowering the calcium-phosphate product and increasing dialysis efficiency can reduce cardiovascular calcifications in dialysis patients remains to be determined.

Introduction

Dialysis patients exhibit a dramatically increased total and cardiovascular mortality when compared with the normal population [1]. Cardiovascular calcifications are

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important predictors of mortality in end-stage renal disease (ESRD) patients on renal replacement therapy [2–7]. Traditional risk factors can only partly explain the increased risk for the development of cardiovascular calcifications [8–10]. Many factors have been investigated and proposed as risk factors for the accelerated cardiovascular calcifications in patients with chronic kidney disease, but most studies have investigated mixed cohorts with diabetic patients and/or different ethnic groups [11–13]. Both diabetes mellitus and, to a lesser degree, ethnicity are known factors which influence cardiovascular calcifications [14–17]. However, studies investigating the influence of risk factors without the impact of diabetes and/or ethnicity are lacking in Caucasians except one small study which, with the exception of age, failed to identify independent predictors for cardiovascular calcifications [18]. Thus, the main objective of this study was to apply semiquantitative calcification scores such as the Adragao score and a novel extended composite score to investigate risk factors for cardiovascular calcifications in a cohort of non-diabetic Caucasian haemodialysis patients.

Table 1. Baseline characteristics of the study population (number, percent; or mean ± SD; range given for age)

Demographic parameters	
Number of patients	194
Age, years	59 ± 11 (32–82)
Male/female	103/91
Dialysis vintage, years	7 ± 5
Body mass index, kg/m^2	23 ± 4
History of smoking	61 (32%)
Aetiologies for ESRD	
Hypertensive nephrosclerosis	109 (56%)
Glomerulonephritis	28 (14%)
Autosomal dominant polycystic kidney disease	21 (11%)
Pyelonephritis, tubulointerstitial disease, obstructive nephropathy	24 (12%)
Systemic lupus erythematosus	5 (3%)
Balkan endemic nephropathy	7 (4%)
Medications	
Calcium carbonate	146 (75%)
Aluminium hydroxide	20 (10%)
Calcium carbonate + aluminium hydroxide	19 (10%)
No phosphate binder	9 (5%)
1,25-OH-vitamin D_3	136 (70%)
25-OH-vitamin D_3	12 (6%)
Warfarin	4 (2%)
Calcium antagonists	77 (40%)

Subjects and Methods

In the cross-sectional BASCH study (Belgrade Aachen Study on cardiovascular Calcification in Haemodialysis patients) we included haemodialysis patients from one single centre (Zvezdara University Medical Centre, Belgrade) [7]. All chronic haemodialysis patients were eligible to enter the study if they agreed to participate. After exclusion of all diabetic patients, 194 non-diabetic patients remained to be investigated (table 1). Patients were enrolled between December 2003 and January 2005. Gender was equally distributed (103 male, 91 female). The study protocol was approved by the Ethics Committee of the Zvezdara University Medical Centre, Belgrade, and each patient gave informed consent.

Calcification Assessment

Cardiovascular calcifications were assessed by X-ray and ultrasound. X-rays of the pelvis, hands and AV fistula arm were performed and obvious vessel calcifications were counted. In addition, echocardiography of the mitral and aortic heart valve and ultrasound of both carotid arteries were used for the detection of cardiovascular calcifications. Moreover, we calculated two semiquantitative calcification scores. First, we determined the Adragao score by analysing conventional X-rays of pelvis and hands in 188 patients [5]. In brief, X-rays of the pelvis and one hand were divided into four sections by a median vertical line and horizontal line just above the upper rim of the femoral heads and the metacarpal bones, respectively. The presence of linear vascular calcifications in each quadrant was counted as 1 point, thus a maximum of 8 points could be achieved. Second, we created an extended composite calcification score where not only calcifications of pelvis and hands but also calcifications of the fistula arm plus neighbouring arteries, mitral and aortic heart valves and both carotid arteries were accounted for (n = 174). Each site of calcification assessment was counted as 1 point. Thus, a maximum score of 15 points could be obtained: Adragao (pelvis 4, hands 4), fistula arm, i.e. fistula itself with one (upper arm) or two (lower arm) neighbouring arteries (2 or 3), mitral plus aortic valves (2) and carotid arteries (2). Concerning the X-ray of the AV fistula, not only the AV fistula itself but also neighbouring arteries were counted. As the AV fistula can be situated either in the lower or the upper arm the number of arteries can be one (upper arm) or two (lower arm). Thus a maximum score of 2 (upper arm: AV fistula plus one artery) or 3 (lower arm: AV fistula plus two arteries) can be obtained. X-ray images were assessed by two experienced physicians blinded to the patient's condition.

Functional Assessment and Assessment of Intima-Media Thickness

To determine functional parameters, we measured systolic and diastolic blood pressure, pulse pressure (mean value), pulse wave velocity (PWV), left ventricular function by echocardiography and intima-media thickness (IMT) as previously described [7].

Briefly, a Complior SP system (Artech Medical, Pantin, France) was used to assess the PWV in 168 patients (the other patients had to be excluded due to kidney transplantation, transfer to another dialysis centre, or death, respectively). PWV was measured utilizing two sensors (one carotid, one femoral) simultaneously to de-

Table 2. Serum and dialysis parameters of the study population (mean ± SD)

Serum parameters	
Serum protein, g/l	67.2 ± 5.1
High-sensitivity C-reactive protein, mg/l	9.61 ± 17.84 (median 3.32)
Serum fetuin-A, g/l	0.56 ± 0.15
Calcium, mmol/l	2.29 ± 0.18
Phosphate, mmol/l	1.61 ± 0.42
Ca × PO_4 product, $mmol^2/l^2$	3.71 ± 1.06
iPTH, pg/ml	380 ± 482 (median 191)
Triglycerides, mmol/l	2.27 ± 1.30
Total cholesterol, mmol/l	5.17 ± 1.15
Dialysis parameters	
Kt/V	1.29 ± 0.18
Dialysis, h/week	12.3 ± 1.4
Dialysate calcium, mmol/l	1.6 ± 0.2

termine the velocity of the pulse in relation to the distance between the femoral artery and the suprasternal notch. Two measurements were performed by two observers.

Baseline echocardiography was performed with an Aspen-Acuson device (Mountain View, Calif., USA) equipped with a 2.5-MHz probe allowing M-mode, two-dimensional, and pulsed Doppler measurements (n = 182). Measurements were made according to the recommendations of the American Society of Echocardiography [19].

B-mode ultrasonography of the carotid arteries was performed using Aloca SSD 2000 system (Tokyo, Japan) equipment with 7.5-MHZ linear transducers. A trained investigator scanned both common carotid arteries, 4 cm from the bulbs, the carotid bulbs and the first 2 cm of the internal and external carotid arteries. IMT and lumen diameter measurements were performed in a plaque-free area. IMT was measured as the distance between adventitia and the lining of the arterial lumen/intima (mm). It was measured four times on both sides and the mean of these measurements was recorded. Calcified carotid plaques were defined as echogenic structures showing an acoustic shadow and with protrusion into the lumen with focal widening that was 50% greater than the IMT of adjacent sites [7].

Biochemistry

Blood was drawn from the arterial site after a long dialysis interval just before dialysis commenced (non-fasted state). Biochemical analysis of serum risk factors (calcium, phosphate, lipids, etc.) was performed by standard laboratory procedure using an automated analyser. Intact PTH was assessed by a second-generation chemiluminescence assay (Diagnostic Product Corp., Los Angeles, Calif., USA; normal range 10–60 pg/ml). Serum analysis for high-sensitivity CRP (hsCRP) was performed by particle-enhanced immunonephelometry using a standard 'CardioPhase hsCRP' for 'BNII' (Dade Behring Holding GmbH, Liederbach, Germany). The nephelometric method for AHSG serum was adopted from a serum ELISA method as previously described [20]. The ELISA measurement of undercarboxylated matrix Gla protein was conducted as previously described [21]. Calcium and phosphate measurements were calculated as mean values from four measurements within 4 months before the start of the study. All other parameters were single measurements at the beginning of the study.

Statistical Analysis

Continuous variables were summarized by means and corresponding standard deviations. Categorical variables were summarized by absolute and relative frequencies. We stratified patients according to the level of calcification as assessed by both calcification scores into three groups: the first group with absent or very low cardiovascular calcifications, the second with intermediate and the third group with high cardiovascular calcification scores. The thresholds between the latter two were chosen in order to create groups of comparable size. Multivariate statistical analyses were used in order to determine the effect of independent variables on the degree of cardiovascular calcifications (low, medium, high calcification according to the Adragao and composite score). Due to the large number of possible influence variables, the results of univariate statistical analyses (χ^2 for qualitative variables and F-test for quantitative variables to compare the three calcification groups) were used in order to select relevant risk factors (risk factors with a p value of $p \leq 0.1$) for the final multivariate model. An ordinal logistic regression model was used to investigate the influence of the selected risk factors on the degree of cardiovascular calcifications. Multivariate analysis was performed by LOGISTIC procedure (SAS). To assess the validity of both the Adragao and the composite score, a Kaplan-Meier survival analysis was performed. A p value of <0.05 was considered to be statistically significant. Statistical analyses were performed using SAS software, version 9.2.

Results

Cardiovascular Calcifications in Haemodialysis Patients

Characteristics of the dialysis population are given in tables 1 and 2. First we used X-rays and ultrasound for the detection of cardiovascular calcifications at different sites. The majority of the patients exhibited calcifications of the carotid arteries (68%; fig. 1) and half of the patients showed vascular calcifications on the pelvic X-ray (51%), whereas valvular calcifications (40%), calcifications of hand arteries (30%) and AV fistula calcifications (20%; fig. 2) were less frequent (table 3).

Next, we applied the Adragao score in 188 patients with available X-rays of pelvis and hands [5]. According to the Adragao score, three groups were formed, with the first group having a score of 0 (n = 89), the second group a score of 1 and 2 (n = 45) and the third group a score of 3–8 (n = 54). In addition to the Adragao score, we also created a novel composite calcification score, using all

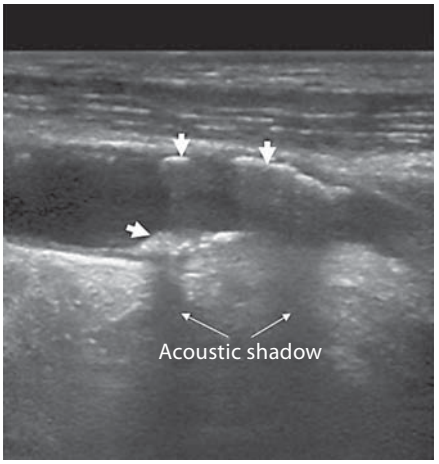

Fig. 1. Ultrasound of calcified carotid plaques with an acoustic shadow.

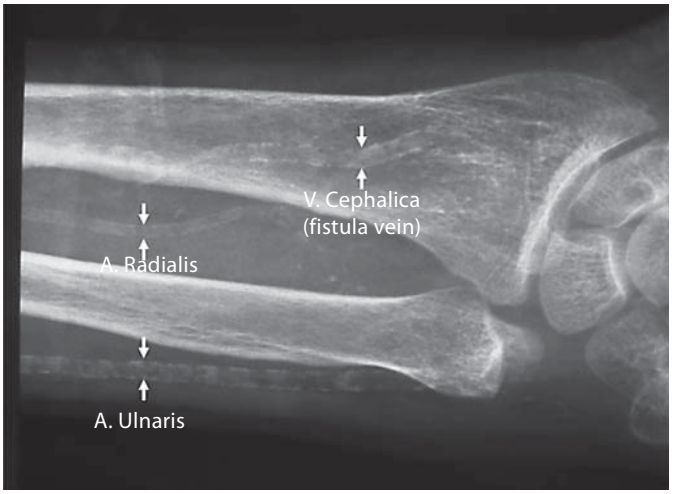

Fig. 2. X-ray of the AV fistula arm with calcification of the AV fistula and both neighbouring arteries.

parameters of the Adragao score plus X-rays of the AV fistula with neighbouring arteries plus ultrasound of carotids and mitral and aortic heart valves (n = 174). Within the composite calcification score we identified a group with a score of 0–2 (n = 84), a second group with a score between 3 and 5 (n = 42) and a third group with a score between 6 and 15 (n = 48).

Both the Adragao and the composite score were validated by using a Kaplan-Meier survival analysis. Patients with more calcifications were more likely to die in both analyses (p = 0.048 and p = 0.023 for the Adragao and composite score, respectively).

Univariate Analysis of Calcification Risk Factors

In the univariate analyses, age (p = 0.02 and p = 0.03, Adragao and composite score, respectively) gender (p = 0.0005 and p = 0.0003), smoking (p = 0.004 and p = 0.08), dialysis vintage (p = 0.02 and p = 0.05), PWV (p = 0.007 and p = 0.007), hsCRP (p = 0.08 and p = 0.005), Kt/V (p = 0.003 and p = 0.005) and positive hepatitis C antibody (p = 0.02 and p = 0.09) were associated with cardiovascular calcifications. Body mass index, intact PTH, cholesterol, triglycerides and serum levels of the calcification inhibitors fetuin-A and undercarboxylated matrix Gla protein were not related to cardiovascular calcifications in our non-diabetic cohort using either score.

Multivariate Analysis of Calcification Risk Factors

Using multivariate analyses, we found that higher age, male gender, smoking, dialysis vintage, increased calcium-phosphate product and reduced Kt/V were independently associated with cardiovascular calcifications as measured by the Adragao score (table 4), whereas higher age, male gender, dialysis vintage, increased hsCRP and reduced Kt/V were independent risk factors for cardiovascular calcifications as determined by the composite score (table 5).

Table 3. Number of visible cardiovascular calcifications per site as detected by plain X-ray of pelvis, hands and AV fistula and by ultrasound of heart valves (aortic and mitral valve) and carotid arteries

Site of cardiovascular calcification	Patients with calcifications, n
Femoral/iliacal arteries (n = 188)	95 (51%)
Wrist/finger arteries (n = 189)	56 (30%)
AV fistula (n = 186)	37 (20%)
Heart valves (n = 165)	73 (40%)
Carotid arteries (n = 189)	129 (68%)

Relation of IMT and PWV to Calcification

Carotid IMT and cardiac ejection fraction were not related to cardiovascular calcification in our cohort using either the Adragao or the composite score. However, PWV was significantly correlated with both the Adragao and composite calcification score (odds ratio (OR) 1.24;

Table 4. Multivariate analysis of risk factors for vascular calcifications (ordinal logistic regression, Adragao score)

	Score 0 (n = 89)	Score 1–2 (n = 45)	Score 3–8 (n = 54)	OR	95% CI	p
Age, years	57 ± 10	61 ± 10	61 ± 11	1.08	1.04–1.11	<0.0001
Male gender	36 (40%)	24 (53%)	40 (74%)	2.75	1.41–5.38	0.003
Smoking	17 (19%)	19 (42%)	22 (42%)	2.32	1.16–4.65	0.017
Dialysis vintage, years	5.74 ± 4.43	7.54 ± 4.41	7.69 ± 4.83	1.13	1.03–1.23	0.006
Ca × PO_4 product, $mmol^2/l^2$	3.55 ± 1.02	3.76 ± 1.02	3.96 ± 1.14	1.75	1.29–2.37	0.0003
Kt/V	1.33 ± 0.18	1.25 ± 0.13	1.23 ± 0.18	0.095	0.01–0.64	0.015
Anti-HCV antibody	16 (18%)	17 (38%)	18 (33%)	1.39	0.59–3.31	0.454
hsCRP, mg/l	7.71 ± 18.91	7.88 ± 10.68	14.31 ± 20.43	1.01	1.00–1.03	0.096
Total cholesterol, mmol/l	5.35 ± 1.27	4.94 ± 1.04	5.01 ± 0.98	0.99	0.75–1.30	0.930

Table 5. Multivariate analysis of risk factors for cardiovascular calcifications (ordinal logistic regression, composite score)

	Score 0–2 (n = 84)	Score 3–5 (n = 42)	Score 6–15 (n = 48)	OR	95% CI	p
Age, years	56.75 ± 10.03	61.07 ± 9.90	60.81 ± 11.23	1.06	1.02–1.09	0.002
Male gender	35 (42%)	19 (45%)	37 (77%)	2.32	1.19–4.52	0.014
Dialysis vintage, years	5.84 ± 4.13	7.36 ± 5.29	7.66 ± 4.55	1.13	1.04–1.24	0.005
hsCRP, mg/l	6.18 ± 8.16	6.21 ± 9.79	12.85 ± 17.23	1.04	1.01–1.07	0.012
Kt/V	1.34 ± 0.18	1.27 ± 0.16	1.23 ± 0.19	0.11	0.02–0.70	0.019
Smoking	20 (24%)	12 (29%)	20 (43%)	1.84	0.89–3.83	0.097
Anti-HCV antibody	16 (19%)	15 (36%)	15 (31%)	1.25	0.52–3.02	0.614

95% confidence interval (CI) 1.02–1.49; p = 0.03 and OR 1.22; CI 1.02–1.47; p = 0.03, respectively) as confirmed in a multivariate analysis.

Discussion

In the present study, we performed a comprehensive assessment of the vascular status in a cohort of 188 haemodialysis patients by using two semiquantitative calcification scores to determine risk factors for cardiovascular calcifications in a non-diabetic Caucasian haemodialysis cohort. First, we applied the score described by Adragao et al. [5] to determine the degree of vascular calcifications in hands and the pelvis. We extended this score by also assessing calcifications of the AV fistula and neighbouring arteries, carotid arteries and heart valves to create a novel composite calcification score. This global approach was chosen since there is a clear need for widely available, cost-effective but nevertheless reliable predictive measures of cardiovascular calcifications in chronic kidney disease patients. Additionally, we determined IMT and functional parameters like cardiac function and PWV to describe cardiovascular function in a comprehensive manner.

As diabetic patients often develop extensive cardiovascular calcifications already before they start dialysis [22], diabetes has to be regarded as an important confounder when analysing risk factors contributing to uraemic cardiovascular calcifications. It might thus obscure important dialysis-related factors that could be amenable to therapeutic interventions. Two Japanese studies determined risk factors in both diabetic and non-diabetic dialysis patients and they found that diabetic patients differ in their risk profile when compared to non-diabetic patients [14, 15]. Despite a recent study which failed to detect any influence of ethnicity on coronary calcifications [23], ethnicity has been described as affecting cardiovascular calcifications in patients with normal renal function [16] and in dialysis patients [17]. In both studies,

Caucasians had significantly more coronary calcifications than other ethnic groups [16, 17]. To the best of our knowledge, there is only one small study investigating risk factors for cardiovascular calcifications in a non-diabetic Caucasian dialysis cohort [18], but this study failed to identify any independent risk factors for cardiovascular calcifications except for age. This is probably related to a low number of patients.

The major finding of our study is that by using the Adragao or the novel composite calcification score, age, male gender, dialysis vintage and lower Kt/V were important risk factors for cardiovascular calcifications, while the calcium-phosphate product and smoking were independent risk factors only when applying the Adragao score and hsCRP only when applying the composite score. Basically, these results are in good agreement with previous findings in cross-sectional studies [8, 11, 14, 15].

Interestingly, we found that reduced dialysis efficiency, i.e. Kt/V, independently related to the degree of cardiovascular calcifications (both calcification scores). Recently, we could describe a negative correlation between Kt/V and indirect markers of cardiovascular calcifications such as PWV and IMT [24], but there is no other report in the literature describing such a relation between cardiovascular calcifications and dialysis efficiency. What could be potential mechanisms linking calcification with lower Kt/V? First, it could be speculated that higher dialysis efficiency removes not only more phosphate but also uremic toxins. However, in our study we could not detect a significant correlation between Kt/V and serum phosphate levels. Second, lower Kt/V may be associated with malnutrition. However, in our study there was no relation of body mass index either with calcification or Kt/V. Whether a more efficient dialysis may improve calcification status is unknown. The HEMO study failed to show a survival benefit with more efficient dialysis [25], but there was only a small difference in dialysis efficiency between the two groups of that study.

In our study, the risk factors for both calcification scores were similar but not identical. What are possible reasons for this difference? First, the univariate association of some factors with either score could be outweighed by other factors in the multivariate analysis. Second, the scores do not distinguish between different types of calcifications and different types of vascular calcifications (i.e., atherosclerotic, medial artery, and cardiac valve calcifications) in turn are presumably the consequence of different, however overlapping, pathomechanisms [26]. London et al. [2] investigated risk factors for intimal and medial calcifications in dialysis patients and found that the majority of cardiovascular risk factors were related both to intimal and medial calcifications. In this context we have to note that the composite score is composed of calcifications at different sites and detected by different methods. Thus a limitation of our study is that we do not know the relative weight of each calcification score point and site in the composite score. However, in our hands both the Adragao and the composite score appeared comparable as both detected patients at increased mortality risk. From a practical point of view, the composite score does not appear to be superior to the Adragao score and thus the Adragao score, which is based on only two X-rays (pelvis, hands), may be an easy way to examine patients.

Previous studies in dialysis patients have shown a negative relation between cardiovascular calcifications and both calcification inhibitors fetuin-A [27–29] and undercarboxylated matrix Gla protein [30], respectively. In our study, we could not detect such a relationship between cardiovascular calcifications and calcification inhibitors. What are possible reasons for our unexpected finding of a lacking relation between calcification inhibitors and cardiovascular calcifications? First, the cross-sectional character of our study which assesses serum parameters at only one single time-point might miss changes in serum parameters. Second, the calcification score we used describes cardiovascular calcifications semiquantitatively and due to the usage of a simple X-ray technique and ultrasound, we might have missed early stages of cardiovascular calcifications which are already present in the form of microcalcifications. These might be detected by a CT scan but are too small to be visualized by plain X-ray films or ultrasound.

Only PWV, but not IMT, showed a relation to the degree of cardiovascular calcifications as assessed by the Adragao or composite score, respectively. Our finding is in line with studies of Haydar et al. [31] and Blacher et al. [3] which also described a positive relationship between PWV and the degrees of vascular calcifications despite the fact that different methods were used in these studies: Haydar et al. used electron beam computed tomography (EBCT) to quantify coronary calcifications, i.e. a rather sensitive and accurate measurement, while Blacher et al. used a semiquantitative technique to calculate vascular calcifications as we did in our study. Blacher et al. relied more on ultrasound to detect vascular calcifications, while we used plain X-rays alone or in combination with ultrasound. Taken together, patients who want to know about their vascular status but are not willing to agree to the radiation of X-ray may undergo PWV measurement if such a device is available in his/her centre.

Our measures of cardiovascular calcifications can easily be applied in dialysis patients by using standard clinical procedures (i.e. X-ray and ultrasound). Especially those patients who do not have easy access to a cardiac spiral CT (e.g. those with atrial fibrillation or massive obesity) can be assessed concerning their cardiovascular profile and risk. Moreover, these rather simple methods provide a cost-effective measure of cardiovascular calcifications and thus could become a standard screening method for cardiovascular calcifications in dialysis patients. In this context it is important to note that a recent study comparing a simple calcification score with the more sensitive assessment of coronary calcifications by spiral CT found a good correlation between these two assessments [32]. Concerning both the Adragao and the composite score a formal comparison with a coronary heart CT (EBCT or multisclice CT) still has to be performed.

In conclusion, this study suggests that widely available and cost-effective methods such as the Adragao and composite calcification score can be used to assess risk factors for cardiovascular calcifications and are probably useful tools to identify patients at increased mortality risk. In addition to known risk factors, reduced Kt/V was independently associated with cardiovascular calcifications. Future studies should focus on reducing calcium-phosphate product and increasing dialysis efficiency, and smoking cessation is encouraged in dialysis patients to determine whether this can reduce cardiovascular calcifications and improve survival.

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