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Original Article

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Coronary artery calcification is related to coronary atherosclerosis in chronic renal disease patients: a study comparing EBCT-generated coronary artery calcium scores and coronary angiography

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Abstract

Background. Coronary artery calcification (CAC) measured by electron beam computed tomography (EBCT) correlates with plaque burden, vessel stenosis and is predictive of future cardiac events in the general population. Extensive CAC has been described recently in dialysis cohorts. For the first time we studied the relationship between CAC and coronary angiographic findings in patients with chronic renal failure, on dialysis and after renal transplantation.

Methods. We studied 46 patients who all had an EBCT-derived Agatston coronary calcium score and a diagnostic coronary angiogram within a 12-month period. The mean age was 55.7 ± 13.2 (SD) years (range 29–80). The mean duration of dialysis was 54.4 months (range 1–372).

Results. The mean CAC was 2370 ± 352.8. The mean CAC in patients with an abnormal coronary angiogram ($n = 35$) was 2869.6 ± 417.9, while that in patients with a normal coronary angiogram ($n = 11$) was 559.4 ± 255.1 ($P = 0.001$ for the inter-mean comparison). Total CAC correlated with the number of diseased vessels ($P = 0.0001$) and with severity of atherosclerosis in all the vessels ($P = 0.0001$). The individual coronary artery calcification score correlated well with the severity of atherosclerotic coronary disease ($P < 0.0001$ for all) in the left anterior descending, right coronary and circumflex arteries. Running a multivariate regression analysis for atherosclerosis burden, we found that the only predictor was CAC ($r = 0.34$, $P = 0.0001$).

Conclusion. CAC is common and more severe in patients with chronic kidney disease. Although in chronic kidney disease patients CAC can occur in the absence of occlusive coronary atherosclerosis, our data suggest that, as in the general population, CAC in chronic kidney disease patients is associated with obstructive atherosclerosis and may therefore be associated with a worse outcome.

Keywords: coronary angiography; coronary artery calcification; electron beam computed tomography (EBCT)

Introduction

The life expectancy of end-stage renal disease (ESRD) patients is significantly reduced, with premature cardiovascular disease (CVD) contributing to about half of the deaths [1,2]. The risk of death increases 500- to 1000-fold in dialysis patients of 15–25 years of age. Even after transplantation, the risk of death is >5-fold that of the age-matched general population [3]. Traditional CVD risk factors such as hypertension, left ventricular hypertrophy, dyslipidaemia and hyperhomocystinaemia are very frequently present in renal cohorts, but these fail to explain more than a part of the accelerated mortality rates. There are specific additional risk factors related to ESRD that contribute to the development of accelerated atherosclerosis and uraemic arteriopathy [4,5].

Many novel CVD risk factors in ESRD have been identified, with much interest currently in serum calcium and phosphorus levels, calcium–phosphorus ion product and parathyroid hormone (PTH) [6]. There is intense interest in the relationship between calcium homeostasis, ectopic calcification (in heart and great vessels), and functional and structural changes that predispose to adverse cardiovascular outcomes [5].

In dialysis patients, both atheromatous plaque calcification and calcification in the media of the vessel wall (arteriosclerosis and increased vessel stiffness)

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are common and are related to hypertension, duration of dialysis, oral calcium intake and disturbed calcium–phosphate homeostatis [7,8]. Cardiac calcification (valves, arteries, mycoardium and pericardium) is also common and occurs significantly more frequently than in the general population [9]. Coronary artery calcification (CAC) is seen in the general population only in the context of atherosclerosis; however, several recent reports have demonstrated widespread premature and rapidly progressive CAC in patients on dialysis [7,10,11]. Oh *et al*. demonstrated vascular calcification in 92% of 39 patients aged between 19 and 39 with childhood onset renal failure [12].

The reasons for this excessive arterial calcification, and for rapid progression of calcification on dialysis, are not fully understood. There is some evidence that this tendency may not be inevitable, as a recent study has shown that avoidance of calcium-containing oral phosphate binders, and reduction in positive calcium balance and hypercalcaemia, may reduce progression of CAC in dialysis patients [13]. However, until now, the implications of the presence of CAC in renal failure patients have not been known. Therefore, to know more about the relationship between CAC and coronary artery disease (CAD) atherosclerotic burden, we studied the relationship between the electron beam computed tomography (EBCT)-derived CAC score and the atherosclerotic burden from coronary angiography (CA) in a cohort of patients with chronic renal failure.

Methods

Study subjects

Over a period of 2 years (May 2001–May 2003), 82 patients from our renal unit were invited to participate in a study comparing diagnostic CA and EBCT findings. Patient selection for diagnostic CA was done on clinical grounds: for renal transplantation evaluation, for symptoms of rest, or exertional, chest pain or recent myocardial infarction. A total of 62 agreed to undergo EBCT and, of these, 46 (33 males and 13 females) were able to have their diagnostic CA within 12 months of the EBCT scan. CA preceded EBCT in 36 cases, and followed it in 10. Only the results of these 46 patients' have been analysed. All of the studied patients had renal impairment: 16 were on haemodialysis, four on continuous ambulatory peritoneal dialysis, eight had chronic kidney disease not requiring dialysis (glomerular filtration rate <25 ml/min) and 18 were post-renal transplantation (all but two of these had been dialysed for significant periods pre-transplantation).

The causes of renal failure in the 46 patients included glomerulonephritis in 18, diabetes in 12, Alport's disease in four, renovascular disease in five, polycystic kidney disease in three, and reflux nephropathy and hypertension in two patients each.

All the patients had their EBCT and CA within 12 months of each other. Baseline data on height and weight were measured at the time of EBCT. Information about systolic and diastolic blood pressure (BP), the duration of chronic renal disease, and previous parathyroidectomy was gathered. The time-averaged systolic and diastolic BP, calcium, phosphorus, PTH, calcium–phosphorus product, albumin and C-reactive protein (CRP) were derived from 12–84 months of routine biochemical information (see Table 1). Medication charts for the preceding 1–8 years (on dialysis) were reviewed to calculate the daily dose of calcium-containing phosphate binder, and the total cumulative exposure to calcium-containing oral phosphate binders. The diagnosis of atherosclerotic vascular disease was reached by clinical diagnosis of CAD in 35 patients (a history of myocardial infarction in 21 patients, angina pectoris in 31 patients, or evidence of obstructive coronary disease by previous angiography and nuclear imaging in 35 patients). Cerebrovascular disease (a history of thrombotic stroke or transient ischaemic attack) was known about in five patients, and peripheral vascular disease (a history of claudication, lower extremity revascularization or abnormal ultrasonic angiology studies of aorto-iliac regions) was evident in 21 patients.

EBCT protocol

All subjects underwent EBCT at the Imatron Unit, Royal Brompton Hospital on a C-100 scanner (Imatron: South San Francisco, CA) [14]. Images were performed with 100 ms scanning time and a single slice thickness of 3 mm. Thirty-six to 40 tomographic slices were obtained for each subject

Table 1. Patient characteristics

	n	Mean	Median	SD	Minimum	Maximum
Age (years)	46	55.7	59.0	13.2	29.0	80.0
Weight (kg)	46	72.3	70.0	16.0	48.0	135.0
Dialysis duration (months)	38	54.4	23.5	78.7	1.0	372.0
Transplant duration (months)	22	80.8	44.5	81.4	3.0	276.0
Time-averaged CRP (mg/l)	46	19.2	9.5	25.0	1.0	151.0
Albumin (g/l)	46	35.4	35.0	4.3	22.0	43.0
Cholesterol (mmol/l)	45	4.9	4.8	1.2	1.8	8.0
Time-averaged calcium (mmol/l)	46	2.4	2.4	0.13	2.2	2.8
Time-averaged phosphate (mmol/l)	46	1.5	1.5	0.33	1.0	2.5
Serum calcium–phosphorus ion product ($mmol^2/l^2$)	46	3.6	3.6	0.80	2.3	5.5
PTH level (nmol/l)	33	315.9	200.0	337.7	5.1	1213.3
Systolic blood pressure (mmHg)	46	143.9	138.5	28.9	90.0	219.0
Diastolic blood pressure (mmHg)	46	74.9	70.0	13.3	50.0	104.0

during two breath-holding sessions. Tomographic imaging was electronically triggered at 80% of the R–R interval, to minimize cardiac movement, and proceeded from the carina to the diaphragm. The intra-assay coefficient of variation for the scoring was <5%.

The acquired images were scored with the use of Imatron software by a single radiologist blinded to the clinical or angiographic history of the patient. As originally described by Agatston [14], the degree of CAC was calculated by multiplying the area of each calcified lesion by a weighting factor corresponding to the peak pixel intensity for each lesion to yield a lesion-specific calcification score. The sum of the scores for each arterial segment, and for all arterial lesions, was used for analysis. We examined the proximal segments of four vessels: left main stem, left anterior descending artery, circumflex artery and right coronary artery. Figure 1 shows the EBCT CAC findings in one of the patients from this study.

Protocol for coronary angiography

Diagnostic CA was performed in one centre always using the Judkins technique. The angiographic findings were reported by different cardiologists in our centre, but all were blinded to the EBCT score results. Significant occlusive disease was defined as >50% luminal narrowing of any epicardial coronary artery. The degree of severity of atherosclerosis or atherosclerosis burden was calculated by adding the percentages of the most severe lesion in each artery (thus the range was 0–400% as we were studying four vessels).

Statistical analysis

All values are expressed as mean ± SE unless stated in the text. Spearman's ρ correlation (non-parametric) coefficient was used for bivariate correlation calculations. Bivariate partial correlations were used to correct for possible confounders. Comparisons between groups were made using the Mann–Whitney test. Kruskal–Wallis test was used to compare more than two not normally distributed means. We ran a multivariate regression analysis to look for correlates of coronary atherosclerosis. SPSS 11.5 was the statistical program used. A P-value of <0.05 was considered to be statistically significant.

Results

Baseline characteristics of the patients are outlined in Table 1. The mean age of the 46 patients was 55.7 ± 13.2 (SD) years (range 29–80). There were 13 females and 33 males. The mean duration of dialysis was 54.4 months (range 1–372). The median gap between CA and EBCT scanning was 6 months (range 0.1–12).

Total calcium score

The mean calcification score of the 46 patients was 2370 ± 352.8 (median = 1866, range 1–7699). The mean calcium score in patients with an abnormal CA was 2869.6 ± 417.9 (median = 2115, range 3–7699), while the mean calcium score in patients with a normal CA was 559.4 ± 255.1 (median = 150.5, range 1–2447). When compared, those two means were significantly different ($P = 0.001$).

Total calcium score strongly correlated with the number of diseased vessels ($P = 0.0001$, $r = 0.546$), i.e. as the calcium score increased, the number of diseased arteries increased. We divided our patients into three categories. The first category was normal coronary arteries (11 patients); the second category, one and two vessel disease (15 patients); and the third category, three or four vessel disease (20 patients). The average calcium score in the first category was 619.1 ± 238.3 (median = 243, range 1–2447), in the second category it was 1949.8 ± 417.7 (median = 1902, range 142–5661), and in the third it was 3739.55 ± 629 (median = 3273, range 4–7699) (Figure 2). The CAC scores for these

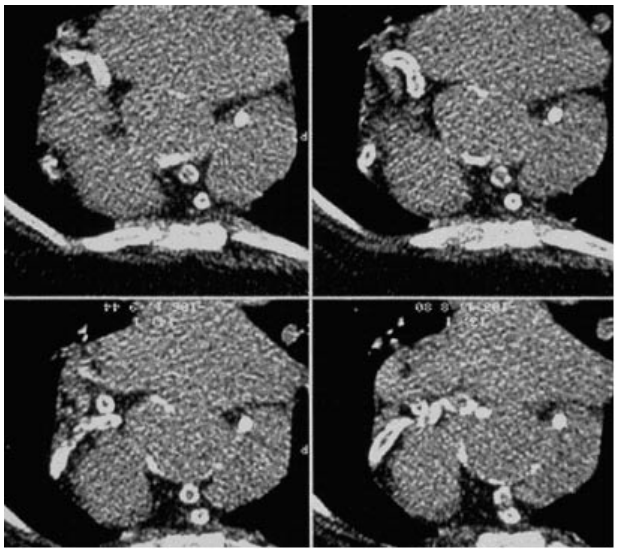

Fig. 1. EBCT scan findings from one of the 46 patients in the study: extensive triple vessel calcification.

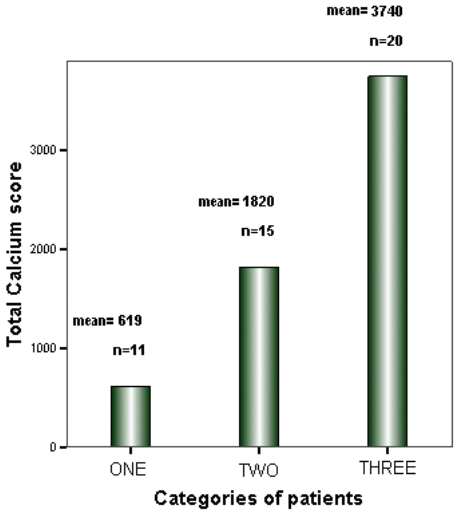

Fig. 2. Bar chart showing the mean calcium in three categories of patients (labelled ONE, TWO and THREE). No vessel disease ($n = 11$), one and two vessel disease ($n = 15$) and three and four vessel disease ($n = 20$). $P = 0.01$ for each inter-mean comparison.

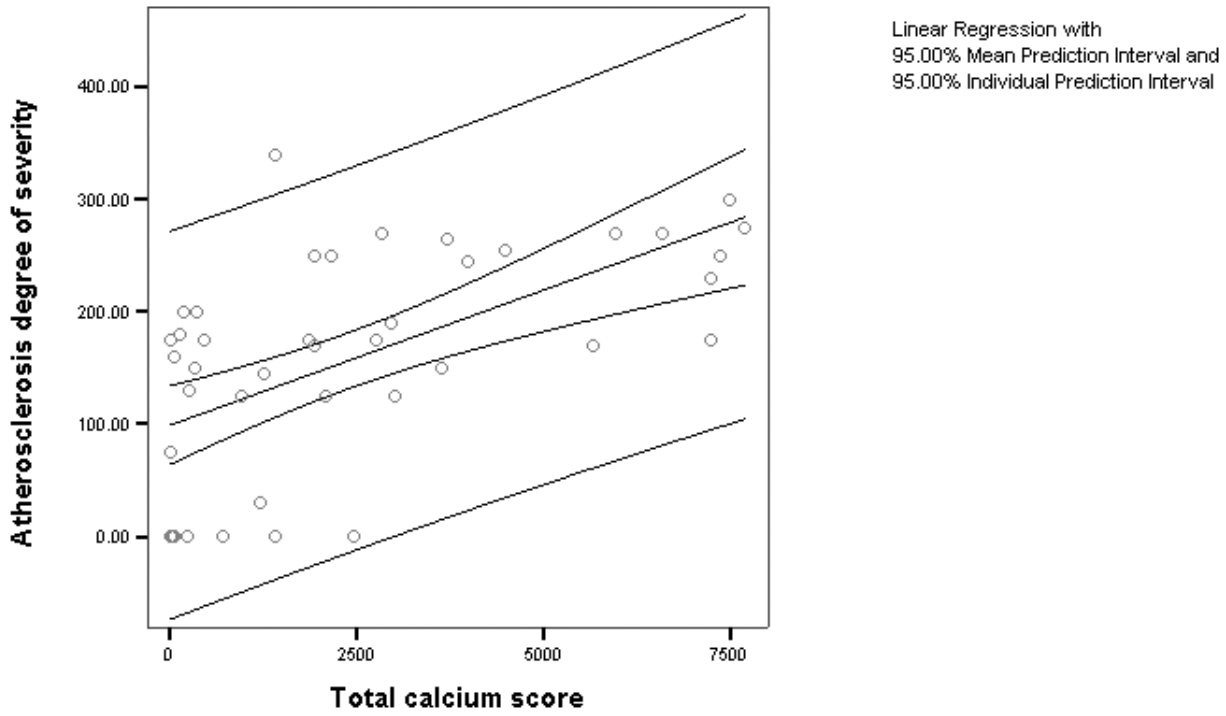

Fig. 3. Scatter plot showing the relationship between severity of obstructive atherosclerosis and total coronary artery calcium score.

CAD categories were each significantly different (Kruskal–Wallis $P = 0.003$).

Total calcium score correlated with total atherosclerotic burden in the four vessel territories (atherosclerosis burden was obtained by adding the percentages of the most severe luminal occlusion in all four vessels); $P = 0.0001$, $r = 0.632$ (see Figure 3).

Running a multivariate regression analysis to identify the best predictor(s) for atherosclerosis burden, we found that the only predictor was CAC ($r = 0.34$, $P = 0.0001$). However, the calcium–phosphorus ion product, time-averaged calcium, time-averaged phosphorus, age, time-averaged CRP, and systolic BP did not predict atherosclerosis burden.

Total calcium score also correlated, as demonstrated in other studies, with patient age ($P = 0.01$, $r = 0.541$), dialysis duration ($P = 0.041$, $r = 0.333$), total cumulative exposure to calcium-containing oral phosphate binders ($P = 0.037$, $r = 0.355$) and time-averaged CRP ($P = 0.023$, $r = 0.425$), but not with the time-averaged plasma calcium, phosphate and calcium–phosphorus ion product concentrations (data not shown). After conducting a partial correlation correcting for the above significantly related variables, total calcium score still correlated with the number of diseased vessels ($r = 0.608$) and the severity of atherosclerosis ($r = 0.614$); $P < 0.0001$ for both. Finally, total calcium score was again strongly correlated with previous history of angina and CAD, but not with a previous history of myocardial infarction ($P = 0.004$, $r = 0.435$).

Individual vessel calcium score

Running Spearman's correlation analysis in each vessel, we found that the calcium score in the left main artery correlates weakly with the presence and severity of the disease in that artery; $P = 0.013$, $r = 0.363$. However, it strongly correlated with the severity and presence of disease in the left anterior descending ($r = 0.538$), right coronary ($r = 0.626$) and circumflex artery ($r = 0.521$); $P < 0.001$ for all.

Analysis restricted to transplanted and dialysed patients only

Running the above statistical methods on a restricted subset of patients (20 dialysed, 16 transplanted) still produced strong positive associations between CAC and coronary atherosclerotic burden (data not shown).

Discussion

This is the first study systematically to examine the relationship between CAC determined by EBCT and angiographically proven CAD in chronic kidney disease patients. This is an important issue because although very considerable increases in EBCT-derived CAC scores are reported regularly in chronic kidney disease patients, to date it has not been clear whether this represents medial vascular calcification associated

with arteriosclerosis, intimal atherothesclerotic calcification, or both. The potential importance of this distinction between intimal and medial calcification has been shown by London's group recently, where there was a significant suvival difference [15]. Our data suggest that both processes occur, but that the patients with very high CAC scores have a significant atherosclerotic burden.

Our data were analysed in two complementary ways. The first was the use of the total calcium score (CAC), and we found that it increased linearly with the number of diseased vessels and with the severity of disease in all vessels combined together. Importantly, many patients with normal epicardial coronary arteries had mild CAC (all but one with a score <1000). However, there was a clear relationship between CAC score and atherosclerotic CAD burden—the higher the calcium score, the more severe was the disease, and the more vessels were involved.

The second analysis involved using the CAC score for each vessel alone. Again we found that individual calcium score in a given vessel correlated with the severity of disease in that artery. This correlation was strongest in left anterior descending, right coronary and circumflex vessels, and weaker in the left main stem, but still statistically significant (reflecting the small number of patients whom we studied with main stem disease).

Coronary calcium score is a highly sensitive marker of underlying atherosclerotic disease [16–18], and coronary calcification has been shown to be associated with cardiovascular events in individuals not affected by kidney disease [19,20]. In ESRD, Braun *et al*. [7] evaluated 49 patients with EBCT and they found a significantly greater calcification score than non-ESRD patients with established CAD.

Our findings have shown for the first time that as in non-ESRD patients, the CAC does correlate with CAD burden. However, we have no long-term follow-up of our population to determine whether, as in non-ESRD patients, a high calcium score has adverse prognostic value. Cardiac calcification scores in our cohort were very much higher than those seen in age- and gender-matched non-ESRD patients. It is striking that patients with normal CA findings had a mean calcium score of 559.4 ± 255.1 (median = 150.5, range 1–2447), which in the non-renal setting would be indicative of significant CAD. Accepting the limitations of diagnostic CA, it is reasonable to infer that much if not all of this calcification was in the arterial media. EBCT imaging cannot *per se* differentiate the site (intima *vs* media) of the CAC; this is best achieved either by intravascular ultrasound or by optical coherence tomography.

It is not known whether regression of vascular calcification can occur in medium to large muscular and elastic arteries. In contrast, vascular calcification can regress in smaller (e.g. digital) arteries [8]. Our cross-sectional study, of necessity, cannot address this point, and most of the available literature suggests chronic progression on dialysis; however, it is noteworthy that despite normal calcium–phosphate and PTH parameters, many of the renal transplant patients in our study had scores as high, or higher, than patients currently on dialysis. This does not support the concept of significant regression of vascular calcification simply by normalizing calcium–phosphate metabolism, in contrast, for example, to tumoral calcinosis. It is important to emphasize that measurement of plasma calcium, phosphate or calcium–phosphate product did not accurately predict the presence of calcified atherosclerotic lesions in the coronary arteries of dialysis patients (analogous to the limited value of relying on low-density lipoprotein-cholesterol values to predict atherosclerosis). The current state of knowledge concerning CAC in patients with chronic kidney disease is reviewed elsewhere in detail [21,22].

Taking an arbitrary cut-off point of 1000 for the CAC score, the calculated specificity and sensitivity for the presence of CAD were 44 and 92.8%, respectively, with a positive predictive value of 72% and a negative predictive value of 80%. Of course, we cannot draw a firm conclusion about the potential role of EBCT in the diagnosis and prediction of CAD from a small study such as this, but the data suggest that EBCT should be trialled prospectively alongside nuclear scintigraphic and stress-echocardiographic screening modalities.

Our study was limited principally by a relatively small number of patients (we were able to recruit 46 kidney disease patients over 24 months who had both EBCT and angiography within 12 months of each other) and by their heterogeneity. However, even restricting the analysis to patients on dialysis or after renal transplantation did not materially affect the results. It must also be recognized that CA, although the historical 'gold standard' for coronary imaging, is relatively insensitive to the earlier stages of vascular remodelling (which may be studied better using optical coherence tomography or intravascular ultrasound).

In summary, in our study, we have found that although there is significant calcification in many patients with normal CA findings, the degree of CAD in those patients with occlusive atherosclerosis was well linked to the CAC score using EBCT. Further studies to determine the prognostic, and screening, value of these EBCT-derived scores are urgently required.

Conflict of interest statement. None declared.

References

1. United States Renal Data System. Causes of death. *Am J Kidney Dis* 1998; 32: S81–S88
2. V. Patient mortality and survival in ESRD. *Am J Kidney Dis* 1999; 34: S74–S86
3. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; 32: S112–S119
4. Mailloux LU, Haley WE. Hypertension in the ESRD patient: pathophysiology, therapy, outcomes, and future directions. *Am J Kidney Dis* 1998; 32: 705–719

5. Stenvinkel P, Pecoits-Filho R, Lindholm B. Coronary artery disease in end-stage renal disease: no longer a simple plumbing problem. *J Am Soc Nephrol* 2003; 14: 1927–1939
6. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium × phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis* 1998; 31: 607–617
7. Braun J, Oldendorf M, Moshage W, Heidler R, Zeitler E, Luft FC. Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients. *Am J Kidney Dis* 1996; 27: 394–401
8. Goldsmith DJ, Covic A, Sambrook PA, Ackrill P. Vascular calcification in long-term haemodialysis patients in a single unit: a retrospective analysis. *Nephron* 1997; 77: 37–43
9. Rostand SG, Sanders C, Kirk KA, Rutsky EA, Fraser RG. Myocardial calcification and cardiac dysfunction in chronic renal failure. *Am J Med* 1988; 85: 651–657
10. Goodman WG, Goldin J, Kuizon BD *et al*. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000; 342: 1478–1483
11. Raggi P, Boulay A, Chasan-Taber S *et al*. Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol* 2002; 39: 695–701
12. Oh J, Wunsch R, Turzer M *et al*. Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. *Circulation* 2002; 106: 100–105
13. Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int* 2002; 62: 245–252
14. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990; 15: 827–832
15. London GM, Guerin AP, Marchais SJ, Metivier F, Pannier B, Adda H. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant* 2003; 18: 1731–1740
16. Sangiorgi G, Rumberger JA, Severson A *et al*. Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. *J Am Coll Cardiol* 1998; 31: 126–133
17. Simons DB, Schwartz RS, Edwards WD, Sheedy PF, Breen JF, Rumberger JA. Noninvasive definition of anatomic coronary artery disease by ultrafast computed tomographic scanning: a quantitative pathologic comparison study. *J Am Coll Cardiol* 1992; 20: 1118–1126
18. Mautner SL, Mautner GC, Froehlich J *et al*. Coronary artery disease: prediction with *in vitro* electron beam CT. *Radiology* 1994; 192: 625–630
19. Raggi P, Callister TQ, Cooil B *et al*. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation* 2000; 101: 850–855
20. Arad Y, Spadaro LA, Goodman K, Newstein D, Guerci AD. Prediction of coronary events with electron beam computed tomography. *J Am Coll Cardiol* 2000; 36: 1253–1260
21. Covic A, Ritz E, Goldsmith DJA. Vascular calcification—a stiff challenge for nephrologists. *Kidney Int*, 2004, in press
22. Hujairi N, Goldsmith DJA. Cardiovascular calcifications in dialysis patients—what we do know and what we don't know. *Am J Kidney Dis*, 2004, in press

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