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Factors involved in vascular calcification and atherosclerosis in maintenance haemodialysis patients

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Abstract

Background. Atherosclerosis and vascular calcifications are common causes of morbidity and mortality in maintenance haemodialysis patients. In addition to the well-known traditional risk factors, uraemia-specific factors appear to enhance dramatically the progression of the pathological processes involved. The aim of the present study was to evaluate the degree of atherosclerosis and vascular calcifications in chronic haemodialysis patients using non-invasive imaging methods, and to identify potentially involved factors.

Methods. The study included 73 patients (36 females, 37 males), aged 25–75 years, who were on haemodialysis treatment for 12–275 months (mean dialysis vintage 73.8 months). We assessed the following circulating parameters: calcium (Ca), phosphorus, 'intact' parathyroid hormone (iPTH), 25OH vitamin D, lipids, oxidized LDL (ox-LDL), Lp(a), homocysteine, leptin, IL-1-β, IL-6, CRP, TGF-β, TNF-α, (PDGF), advanced oxidation protein products (AOPP) and myeloperoxidase activity (MPO). Coronary artery calcification score (CACS) was assessed using multi-row spiral CT (MSCT). Intima–media thickness index of the common carotid artery (CCA-IMT) and presence of cervical artery atherosclerotic plaques were evaluated by ultrasonography.

Results. Coronary artery calcifications were observed in 79.5% of the patients, with CACS ranging from 0 to 4987. In univariate analysis, a positive correlation was observed between CACS and age, BMI, iPTH, CRP, IL-6 and CCA-IMT, whereas an inverse correlation existed with 25OH vitamin D, TGF-β and PDGF. CCA-IMT ranged from 0.4 to 1.1 mm. It was positively correlated, in univariate analysis, with age, CACS, CRP and Il-6, and negatively with 25OH vitamin D, TGF-β and PDGF. Only CACS remained as independent predictive factor of CCA-IMT in multivariate analysis. Atherosclerotic plaques were found in the carotid arteries of 53 patients (72%). The number of plaques was positively correlated with age, CACS, phosphorus, MPO, CRP and IL-6, and inversely with 25OH vitamin D in univariate analysis. In multivariate regression analysis, only age and CACS remained as independent variables.

Conclusion. In addition to classic risk factors, the degree of atherosclerosis and vascular calcification in our dialysis patient population were associated with several factors that are frequently abnormal in advanced chronic renal failure, but except age, all of them were interdependent. Notably, as in the general population, CACS was an independent predictor of the degree of atherosclerosis in haemodialysis patients.

Keywords: atherosclerosis; common carotid artery intima–media thickness (CCA-IMT); coronary artery calcification score (CACS); haemodialysis; inflammation; oxidative stress

Introduction

Atherosclerosis is a chronic disease process that takes place in the intima–media layer of the arterial wall. A variety of cellular elements are involved in this process including endothelial cells, myocytes, fibroblasts, macrophages, lymphocytes and platelets, as well as a host of compounds produced by and acting on them and their environment, such as cytokines, adhesion molecules, growth factors, oxidative and glycative modifications of lipoproteins and other proteins.

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In addition, numerous systemic and general factors also play an important role, including age, blood pressure, diabetes and smoking [1,2]. Patients with chronic kidney disease (CKD) stage 5 have a much higher prevalence of atherosclerosis than the general population with no renal function impairment [3,4]. This high prevalence is associated with a dramatic increase in cardiovascular mortality [5]. The latter is, however, not only due to atheromatous changes of the arterial intima but also due to remodelling of the arterial media, leading to arteriosclerosis with the functional correlate of increased arterial stiffness.

In Poland, the mortality of patients with CKD stage 5 treated by maintenance haemodialysis does not differ from that of other European countries. Its prevalence ranges from 10 to 15% per year [6,7]. Since the high mortality rate in these patients is mainly due to cardiovascular disease, the search for all possibly involved factors has become intensive in recent years [8,9]. This has led to the discovery of a number of uraemia-associated factors enhancing the rate of atherosclerosis progression. Some of them are also encountered in the general population, but often are phenotypically different or of lesser degree of severity, such as lipid disturbances, hyperuricaemia, anaemia, coagulation anomalies, hypoalbuminaemia, hyperhomocysteinaemia, insulin resistance, oxidative stress and chronic microinflammation. Others appear to be more specifically linked to CKD, including uraemic toxins, hypervolaemia, intravenous iron therapy for the correction of anaemia, and disturbances of calcium–phosphate metabolism and their treatment. The latter may be responsible, at least in part, for the rapid progression of arterial calcium deposits in CKD stage 5 patients [2,10]. Whether this calcification process is mainly located in the intima or the media, or both, is often difficult to evaluate in the clinical setting with presently available diagnostic tools.

Several methods can be employed to examine the progression of atherosclerosis and calcification [11,12]. To determine the degree of atherosclerosis, we have applied ultrasonography to the common carotid artery and measured intima–media layer thickness (CCA-IMT), an early reflection of the disease, as well as presence of atherosclerotic plaques, a reflection of more advanced atheromatous disease. Moreover, we have used multi-row spiral computed tomography (MSCT) with programmed calcium scoring to evaluate coronary artery calcification using CACS. Several groups confirmed the usefulness of MSCT in the evaluation of coronary artery calcification as compared with the more expensive electron beam computed tomography (EBCT) technique [11–13].

The aim of the present study was to evaluate atherosclerosis and arterial calcification in CKD stage 5 patients on maintenance haemodialysis using non-invasive, diagnostic imaging methods, and to examine possible associations with atherogenic factors, some of which may be relatively specific for such patients.

Patients and methods

The study included an unselected population of 73 maintenance haemodialysis patients, 36 females and 37 males, aged 25–75 years (mean 49.5 years). The causes of end-stage renal disease were chronic glomerulonephritis in 25, polycystic kidney disease in eight, amyloidosis in three patients, lupus nephritis in two, and unknown in 24 patients. Haemodialysis treatment duration was 12–275 months (mean 73.8 months). Haemodialysis sessions were performed three times for 4 h per week using polysulphone membrane dialysers. The dialysate contained the following ion concentrations: Na 138, K 2.5, Ca 1.25 and bicarbonate 31 mmol/l. Patients with a history of acute cardiovascular episodes or arrhythmias, diabetes mellitus, neoplastic disease, and active infection or non-infectious overt inflammation were excluded from the study. The patients were informed about the purpose and nature of the study and gave written consent. The study protocol was accepted by the local University's Ethics Committee. Owing to the limited number of diabetic patients in our centre those patients have not been included in the study.

Biochemical analyses including serum calcium, phosphorus and lipid profile were done by standard methods using Hitachi 917 multianalyser; Lp(a) was determined using immunonephelometric analyser Behring Nephelometer 100, Dade Behring Company. Oxidized LDL (ox-LDL), TGF-β and PDGF were evaluated by Elisa method using spectrophotometer ELx800 BIO TEK Instruments, Inc. Serum levels of 'intact' PTH (iPTH), homocysteine, IL-1-β, IL-6, CRP and TNF-α were assessed using chemiluminescence apparatus Immulite 2000 (Diagnostic Product Corporation, Los Angeles, CA). Serum leptin was measured by the Elisa method. Serum 25OHD was measured by RIA (DiaSorin, Stillwater, MN [14]). Serum AOPP concentration and myeloperoxidase (MPO) activity were evaluated as described previously [15,16]. All biochemical samples were drawn before the mid-week haemodialysis session.

Imaging techniques comprised the assessment of calcifications in coronary arteries by multi-row spiral CT (MSCT) Somaton Plus 4 Volume Zoom, using a calcium scoring program (Siemens Company, Nürnberg, Germany). The Agatston scale [17], as modified by Mayo Clinic group in 1999 [18], was employed to interpret the results, using CACS expressed in Hounsfield units (HU). Ultrasonography was employed to measure thickness of intima–media layer and to detect presence of atherosclerotic plaques of the common carotid artery (CCA-IMT), using Acuson 128 XP/10 apparatus with B-mode programme, colour and power Doppler (with linear probe at frequency of 7.5 MHz).

Fifty-five patients (75%) received a mean daily dose of 2.31 g calcium carbonate as phosphate binder, and 21 patients (28%) received 1.44 g aluminium hydroxide. Thirty-three patients (46%) received a mean weekly dose of 1.65 mcg active vitamin D_3 (alfacalcidol).

Owing to lack of normal distribution (Shapiro–Wilk test $P < 0.05$ for CACS), all results obtained were assessed by non-parametric tests and presented as mean, SD, median and interquartile range, as appropriate. Independent variables were compared using the Mann–Whitney *U*-test; comparisons of multiple independent variables were made by Kruskall–Wallis test, and correlations between variables by the Spearman *R*-coefficient.

Results

Clinical characteristics and serum biochemistry are summarized in Table 1.

Assessment of factors potentially involved in coronary artery calcification

The CACS of the 73 haemodialysis patients ranged from 0 to 4987 HU (Table 2). CACS findings were expressed per four patient subgroups, according to Rumberger subdivision [12]: group I, 0–10 HU; group II, 11–100 HU; group III, 101–400 HU; and group IV, >400 HU (Figure 1).

Univariate analysis revealed positive correlations between CACS and the following parameters: age, BMI, iPTH, CRP, IL-6 and CCA-IMT. Inverse correlations were found between CACS and 25OH vitamin D, TGF-β as well as PDGF, as shown in Table 3 and Figures 2 and 3. No correlations were identified for the following parameters: total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, homocysteine, leptin, Lp(a), total calcium, phosphorus, Ca × phosphorus product, TNF-α, IL-1, AOPP, MPO or ox-LDL. Using multivariate regression analysis between CACS and the aforementioned parameters tested in the entire patient population, only age ($R = 0.295$) and CCA-IMT ($R = 0.285$) remained independent predictors of CACS (R of model 0.58, $P = 0.003$).

A subgroup of 15 patients (20.5%) presented with no coronary artery calcifications. Using the Mann–Whitney U-test, these patients had significantly lower values of body surface area ($P < 0.05$), serum iPTH ($P < 0.005$), as well as circulating ox-LDL

Table 2. Coronary artery calcification score (CACS) values (density of more than 130 Hounsfield units)

Parameter	Mean ± SD	Median/range	Interquartile range
CACS HU[a]	610 ± 999	167 (0–4987)	785

[a]Hounsfield units.

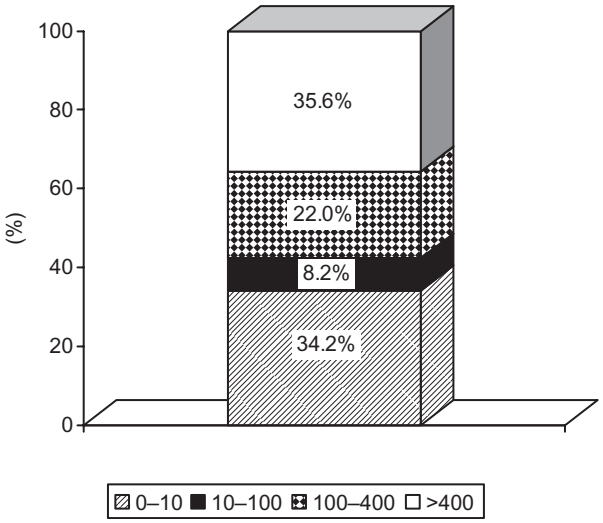

Fig. 1. Coronary artery calcification score (CACS) distribution in coronary arteries of the entire patient cohort.

Table 1. Clinical characteristics and serum biochemistry

Parameter	Mean	Median	Range	Interquartile range	SD	Normal value
Age, years	49.5	47.0	25–75	16	11.7	
BMI, kg/m^2	22.8	22.5	16.8–31.6	3.86	3.12	20–25
Time on dialysis, months	73.8	58	12–275	28	53.1	
Total cholesterol, mmol/l	4.71	4.6	2.68–6.94	1.07	0.92	3.2–5.2
HDL cholesterol, mmol/l	0.91	0.9	0.48–1.76	0.37	0.27	>1.2
LDL cholesterol, mmol/l	2.62	2.6	0.59–4.38	1.00	0.79	0.2–3.4
Triglycerides, mmol/l	2.64	2.4	0.76–8.80	1.39	1.46	0.2–2.0
Homocysteine, μmol/l	28.3	26.2	12.2–86.6	13.2	11.2	5–12
Leptin, ng/ml	30.9	18.6	0.93–162	26.4	37.7	1–8
Lp(a), g/l	0.17	0.1	0.01–1.21	0.20	0.22	0.02–0.72
Ca, mmol/l	2.24	2.2	1.64–2.67	0.21	0.19	2.02–2.61
P, mmol/l	1.81	1.8	1.04–2.50	0.56	0.34	0.87–1.45
Ca × P, mmol^2/l^2	4.06	4.2	2.20–5.74	1.20	0.84	<4.4
IPTH, pg/ml	429	360	11.5–1628	393	341	12–65
25OH Vitamin D, ng/ml	25.3	24.0	3.50–54.5	16.0	11.8	
CRP, mg/dl	1.09	0.39	0.01–5.98	0.95	1.55	0–1.1
TNF-α, pg/ml	10.29	9.90	5.00–20.7	3.05	2.75	<8.1
IL-1, pg/ml	36.1	19.8	0.70–207	25.5	44.2	<5.0
IL-6, pg/ml	6.30	4.4	1.35–40.8	3.68	6.92	<4.1
TGF-β, ng/ml	11.30	10.1	4.05–27.7	5.25	5.05	1.56–3.24
PDGF, pg/ml	478	323	42.4–2147	427	375	<129
AOPP[a], μmol/l	157	131	37.3–501	73.8	92.2	
MPO[b], μg/ml	4.90	4.8	1.78–9.76	1.21	1.17	
ox-LDL[c], U/l	49.2	46.9	28.8–166	15.5	17.4	40–80

[a]Advanced oxidation protein products.
[b]Myeloperoxidase.
[c]Oxidized LDL.

($P < 0.05$) in comparison with the patient subgroup with coronary artery calcifications. The remaining parameters did not differ between the two subgroups.

Assessment of factors potentially involved in atherosclerosis

CCA-IMT of the entire patient cohort ranged from 0.4 to 1.1 mm. In univariate analysis, CCA-IMT was directly correlated with age, CACS, CRP and IL-6, and negatively with 25OH vitamin D, TGF-β and PDGF (Table 4). No correlations were found for the following parameters: total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, homocysteine, leptin, Lp(a), total calcium, phosphorus, Ca × phosphorus product, TNF-α, IL-1, AOPP, MPO or ox-LDL. In multivariate analysis, only CACS remained as an independent predictive factor of CCA-IMT (Table 5).

Presence of plaques in common carotid arteries was visualized in 53 haemodialysis patients (72%), with a maximum number of 7, a median of 1 and an interquartile range of 3. In univariate analysis, the number of atherosclerotic plaques correlated significantly with age, CACS and serum phosphorus, 25OH vitamin D, MPO, CRP and IL-6. In multivariate regression analysis, only age (β = 0.24) and CACS (β = 0.29) remained independent factors.

Table 3. Correlation analysis results between coronary artery calcification score (CACS) and selected parameters in entire population (Spearman's *R*-coefficient)

Parameter	*R*	*P*-value
Age	**0.42**	**<0.00025**
BMI	**0.28**	**0.01**
Time on dialysis	0.07	NS
Total cholesterol	−0.09	NS
LDL cholesterol	0.05	NS
HDL cholesterol	−0.11	NS
Triglycerides	0.01	NS
Homocysteine	0.11	NS
Leptin	−0.16	NS
Lp(a)	0.06	NS
Ca	0.09	NS
Ca × P	0.04	NS
P	0.17	NS
iPTH	**0.37**	**<0.05**
25OH vitamin D	**−0.30**	**<0.01**
CRP	**0.43**	**<0.0005**
TNF-α	0.16	NS
IL-1	0.01	NS
IL-6	**0.26**	**<0.02**
TGF-β	**−0.28**	**<0.02**
PDGF	**−0.28**	**<0.02**
AOPP[a]	0.14	NS
MPO[b]	0.06	NS
Ox-LDL[c]	0.12	NS

[a]Advanced oxidation protein products.
[b]Myeloperoxidase.
[c]Oxidized LDL.

The subgroup of 15 patients (20.5%) without coronary artery calcification (CACS=0) presented with significantly lower IMT-CCA values ($P < 0.04$) and fewer number of atherosclerotic plaques ($P < 0.03$) than the subgroup of 58 patients (79.5%) with coronary artery calcification.

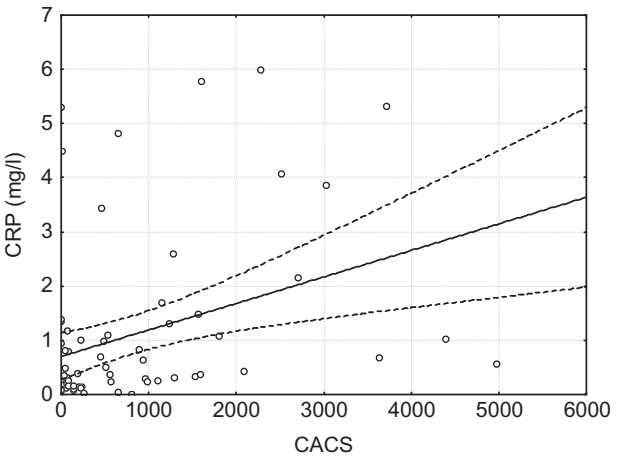

Fig. 2. Correlation between coronary artery calcification score (CACS) and serum CRP in the entire patient cohort ($R = 0.43$, $P < 0.0005$).

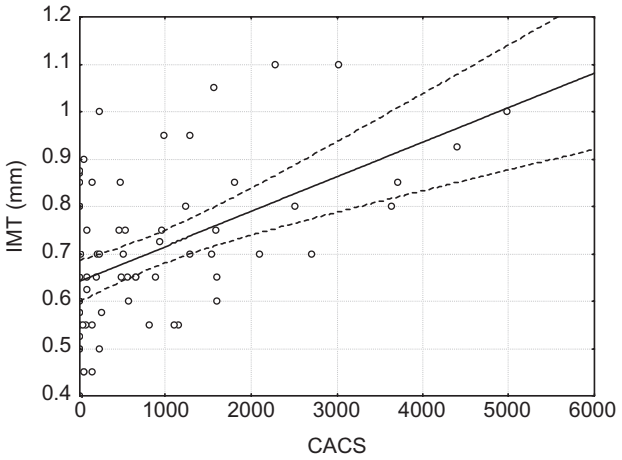

Fig. 3. Correlation between intima–media thickness of the common carotid artery (CCA-IMT) and coronary artery calcification score (CACS) in the entire study population ($R = 0.43$, $P < 0.0002$).

Table 4. Significant correlations between intima–media thickness of common carotid artery (CCA-IMT) and various study parameters in univariate analysis (Spearman's *R*-coefficient)

Parameter	*R*	*P*-value
Age	0.31	<0.01
CACS	0.43	<0.0002
25OH vitamin D	−0.31	<0.01
CRP	0.30	<0.01
IL-6	0.31	<0.01
TGF-β	−0.29	<0.01
PDGF	−0.31	<0.01

Table 5. Univariate correlation of number of atherosclerotic plaques in common carotid arteries with age, coronary artery calcification score (CACS) and several serum parameters

Parameter	*R*	*P*-value
Age	0.41	<0.0005
CACS	0.32	<0.001
Phosphorus	0.24	<0.05
25OH vitamin D	−0.38	<0.001
MPO[a] activity	0.24	<0.05
CRP	0.40	<0.001
IL-6	0.36	<0.005

[a]Myeloperoxidase.

Discussion

The present study showed high values of CACS and IMT-CCA indices in the majority of the haemodialysis patients who agreed to participate. These findings are in agreement with the claim, accepted by many authors, of an acceleration of both vascular calcification and atherosclerosis in association with end-stage renal disease [19,20]. We found coronary artery calcification to be present in 79.5% of the patients. Braun *et al*. [21] using EBCT found a similarly high prevalence of coronary artery calcification (65%) in haemodialysis patients. An even higher percentage was reported by Goodman *et al*. [22] in young adults on haemodialysis treatment (90% of patients aged 20–30 years). MSCT, used to measure CACS was proven to be equivalent to EBCT in a study by Becker *et al*. [11]. Broderick *et al*. [12] presented comparable results, assessing coronary artery calcifications by MSCT together with angiography.

Several research groups have provided evidence for the hypothesis that increased CACS values are indicative of a high risk of cardiovascular disease [8,18]. Of particular concern is the observation that CKD stage 5 patients suffer from a much more rapid progression of vascular calcifications as well as atherosclerotic plaque formation than patients without CKD [8,23] and that the two pathological processes appear to be somehow interrelated in CKD, as they are in the general population [24].

The precise causes underlying the rapid deterioration of the cardiovascular tree remain to be defined. Probably, a variety of factors play a role. As to the accelerated calcification process in CKD patients, we identified several factors to be potentially involved, by univariate analysis, including age, BMI, serum iPTH, CRP, IL-6, 25OH vitamin D, TGF-β and PDGF, and CCA-IMT. Of interest, the relation between iPTH and CACS was positive, not negative, in contrast to recent reports in dialysis patients with predominantly low PTH values. The overall relationship may be best represented by a U-shaped curve, rather than being linear, with both very low and very high circulating PTH levels favouring vascular calcification, but normal PTH values having either no effect or inhibiting it. In multivariate regression analysis, only age and CCA-IMT remained as independent predictors of coronary artery calcification. Such associations have previously been reported by others [21,22].

Similarly, many factors might contribute to the enhanced progression of atherosclerosis. The search for possible factors involved in early atherosclerosis development, as reflected by CCA-IMT, led us to identify, by univariate analysis, positive associations with age, CACS and serum CRP, and negative associations with serum IL-6, 25OH vitamin D, TGF-β and PDGF. However, in multivariate regression analysis, only one factor remained, namely CACS.

Finally, concerning the factors potentially involved in more advanced stages of atherosclerosis, as reflected by presence of carotid plaques, we found correlations with age, CACS, serum phosphorus, 25OH vitamin D, MPO, CRP and IL-6 in univariate analysis. However, in multivariate analysis, again, only CACS remained as an independent predictive factor.

Among the many factors involved in the accelerated calcification and atherosclerosis of uraemia, disturbances of calcium × phosphate metabolism associated with secondary hyperparathyroidism appear to play an important role [25,26]. Thus, a relation was noted in the present study population between CACS and serum iPTH. The inverse relation found between coronary artery calcifications and serum 25OH vitamin D probably reflects the role of vitamin D insufficiency or deficiency in the pathogenesis of secondary hyperparathyroidism [27]. The presence of microinflammation in uraemia also appears to predispose to the acceleration of atherosclerosis and cardiovascular complications in dialysis patients [28,29], with CRP being an indicator of inflammation, as it is in the general population [30]. Increased circulating levels of inflammation markers including CRP and IL-6 also were associated with CACS and signs of atherosclerosis in the present study group. Our findings are in agreement with the claim by other research teams that microinflammation enhances atherosclerosis in chronic dialysis patients and that there is also an association between the inflammatory state and coronary artery calcification [31,32].

We found an inverse relation between CACS and serum PDGF and TGF-β, again in accord with previous reports [33]. Concerning PDGF, one must also take into account the influence of the dialysis membrane and dialysis biocompatibility. It is of note that the contribution of this mediator to the process of vessel wall calcification is not yet well explained. There is some evidence that PDGF actually has a proatherogenic effect [34].

The assessment of early atherosclerosis in the present study was based on measurements of CCA-IMT thickness. The magnitude of this indicator appears to depend on vessel wall remodelling during the course of atherosclerosis, as well as on focal calcium and phosphate deposition [23]. CCA-IMT was positively correlated, in multivariate analysis, only with age and CACS, in addition to a direct association

in univariate analysis with serum CRP and IL-6, and to an inverse association with 25OH vitamin D, TGF-β and PDGF. The assessment of advanced atherosclerosis by the presence of atherosclerotic plaques in the common carotid arteries led to a positive finding in 53 patients, i.e. 72% of our study population. This prevalence is in line with previous reports [35].

The association between CCA-IMT and plaque number on the one hand and CACS on the other demonstrates that the vascular deposition of calcium and phosphate parallels the development of atherosclerosis. From a clinical point of view, it is important to underline the recent observation by London *et al.* [23] that, in chronic haemodialysis patients, atherosclerotic plaque (intima) calcification is associated with worse outcome than media calcification of major arteries.

Our study has several limitations. First of all, its cross-sectional nature precludes any formal statement as to the rate of vascular disease progression and limits the analyses to comparisons between highly variable serum parameters and less rapidly changing morphological parameters. Time-varying assessments of serum parameters might have led to more reliable findings. Second, the relatively small number of patients included may have prevented us from identifying independent associations with inflammation, oxidative stress and/or advanced glycation or oxidation end-product formation, as reported by others, which could have been identified in larger patient cohorts. Third, changes in circulating parameters such as markers of inflammation do not necessarily reflect the situation prevailing in atheromatous plaques. A direct assessment *in situ* would lead to either invasive procedures or the use of animal models. Fourth, the present findings may not be valid for chronic dialysis patients with diabetes since those patients were not included in the study. Fifth, we did not examine possible associations between abnormal serum parameters and the well-known functional changes of the vessel wall in CKD patients which result in pathological arterial stiffness. However, one of the strengths of the present study is the concomitant quantitative assessment, in the same haemodialysis patients, of vascular calcification by MSCT and two atherosclerosis parameters, together with a large number of potentially involved biochemical markers. In previous reports, the number of circulating markers and of arterial imaging methods was most often limited to one or two of these parameters.

In conclusion, the present study confirms an independent association of vascular calcification, in addition to the well-known influence of age, with the atherosclerosis process of chronic haemodialysis patients. Whether the association between intima calcification and atherosclerosis reflects a cause–effect relationship or simply two concomitant disease processes remains to be clarified.

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Conflict of interest statement. None declared.

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