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Age-independent association between arterial and bone remodeling in mild-to-moderate chronic kidney disease

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Abstract

Background. Damages to large arteries are related to bone disease in end-stage renal disease and contribute to cardiovascular mortality. An outward remodeling and stiffening of carotid artery already exist at an earlier stage of chronic kidney disease (CKD). We made the hypothesis that bone disease could be associated with the carotid outward remodeling in parallel with the decline of renal function in this population.

Methods. One hundred and seven patients (60.4 ± 14.6 years) with CKD (mean glomerular filtration rate = 34 ± 17 mL/min/1.73 m^2) were included in this cross-sectional study. Common carotid artery diameter, intima–media thickness and carotid stiffness were determined with an echotracking system. Bone evaluation was performed by bone densitometry and the measurement of a bone-remodeling marker, bone-specific alkaline phosphatase (BSALP).

Results. After adjustment for age, sex, mean blood pressure, carotid pulse pressure and glomerular filtration rate, bone mineral densities measured at the radius, hip and lumbar spine were significantly and negatively correlated with carotid internal diameter ($P = 0.0001$, $P = 0.0003$, $P = 0.01$, respectively). This association exists only in patients with glomerular filtration rate $\leq$38 mL/min/1.73 m^2. BSALP was independently and positively correlated with carotid internal diameter and explained 13% of the variance.

Conclusions. Bone mineral density and serum marker of bone remodeling are independently correlated with arterial remodeling in CKD patients suggesting a crosstalk between kidney, arterial wall and bone.

Keywords: arterial remodeling; arterial stiffness; bone mineral density; chronic kidney disease; echotracking

Introduction

Damages to large arteries and mineral and bone disease (MBD) contribute in a large part to morbidity in end-stage renal disease (ESRD) patients [1–3]. In advanced renal disease [4,5] and in elderly subjects [6–9], an age-independent association was observed between bone and arterial disease suggesting the existence of a bone–vascular axis.

We have previously described an outward remodeling and stiffening of large arteries in mild-to-moderate chronic kidney disease (CKD) [10], but its association with bone remodeling has never been investigated.

We hypothesized that bone mineral density (BMD) and serum markers of bone remodeling could be altered in parallel with structural and functional abnormalities of large arteries observed in patients with CKD stages 2–5, and that this association could be dependent on the severity of glomerular filtration rate (GFR) alteration. We took advantage of the simultaneous measurement of arterial parameters, renal function and BMD with reference techniques in patients with CKD to test this hypothesis.

Subjects and Methods

Patients

From February 2006 to February 2007, 122 patients with CKD stages 2–5, not yet on dialysis, belonging to the REN-ART study [10] were included in the present study. None of them were included in the previous report. Briefly, REN-ART study population is a subset of the NEPHROTEST cohort that is a prospective cohort including all adult CKD patients who underwent a yearly extensive check-up in two departments of physiology and nephrology in the Paris area, as previously described [11,12]. To be eligible, patients had to be 18 years or older and neither be on dialysis nor have received a kidney transplant. Pregnant women were excluded. Cardiovascular risk factors were defined according to international guidelines (K-DOQI). Fifteen patients receiving drugs interfering with BMD were discarded from the analysis: bisphosphonate ($n = 4$), anti-tumour chemotherapy ($n = 3$) and use of oral corticosteroid therapy (daily dose equivalent $\geq$5 mg of prednisone for more than 3 months, $n = 10$). The underlying renal diseases were pure hypertensive nephropathy ($n = 35$), IgA nephropathy ($n = 14$), diabetic glomerulopathy ($n = 12$), vasculitis ($n = 3$), focal segmental glomerulosclerosis ($n = 2$), chronic interstitial nephritis ($n = 16$) and polycystic kidney disease ($n = 2$), and the cause was unknown in 38 patients. The study was conducted in accordance with Good Clinical Practice guidelines. All patients gave their written informed consent for participating in the NEPHROTEST cohort and the REN-ART study, and the REN-ART study was approved by the Comité de Protection des Personnes of Saint Germain en Laye, France.

Arterial parameters

All patients were studied in a quiet room with controlled temperature of 22 $\pm$ 1°C as previously described [13,14]. Blood pressure was monitored with an oscillometric method (Colins®, BP 8800, Colin Corporation Ayashi, Komaki, Japan).

The end-diastolic internal diameter, stroke change in diameter and IMT were measured on the right common carotid artery (CCA) with a high-precision echotracking device (Wall Track System®, Esaote, Maastricht, The Netherlands), as previously described and validated [13,14]. The end-diastolic diameter was normalized to BSA as previously described [10].

The right CCA pressure waveform was recorded non-invasively by aplanation tonometry, using the Sphygmocor® device (Atcor Medical, Sydney, Australia), as previously described and validated [15], and the local carotid artery pulse pressure (CPP) was used for further calculations.

The wall cross-sectional area (WCSA) was calculated as WCSA $= \pi(R_e{}^2 - R_i{}^2)$ where R_e and R_i are the values of diastolic external and internal radii, respectively. The wall to lumen ratio was calculated in diastole as 2 h_d/D_d, where h_d and D_d are the values of wall thickness and internal diameter during end-diastole. The circumferential wall stress ($\sigma\theta$, kPa) was calculated according to Lamé's equation as $\sigma\theta = (\text{MBP}\cdot D_m)/2h_m$, where MBP is the mean blood pressure (MBP), and D_m and h_m are the mean values of the internal diameter and wall thickness during the cardiac cycle [15].

Carotid distensibility was determined from systolic–diastolic variations in the arterial cross-sectional area (ΔA) and local pulse pressure (ΔP) as previously described [14], assuming the lumen to be circular. The cross-sectional distensibility coefficient (DC) was calculated as DC $= \Delta A/A\Delta P$. The cross-sectional compliance coefficient (CC) was calculated as CC $= \Delta A/\Delta P$. The carotid stiffness (Cstiff) was calculated as Cstiff $=$ $(\text{DC})^{-1/2}$. Incremental Young's elastic modulus (Einc) was calculated as Einc $= [3(1 + A/\text{WCSA})]/\text{DC}$ where A is the diastolic lumen area [14,15].

Bone densitometry

BMD was assessed by dual-energy x-ray absorptiometry using Hologic QDR4500W (fan beam) (Hologic, Waltham, Massachusetts, USA) at the lumbar spine (L1-L4), left proximal femur (femoral neck and total hip) and nondominant radius. Radius analyses were performed at the one-third radius (junction of the proximal two-third and the distal one-third of the radius) and ultradistal radius. If the patients had a history of fracture or hip joint replacement, the contralateral side was scanned ($n = 2$).

All BMD scans were reviewed centrally by a single skilled investigator, blinded to the arterial parameters, renal function and metabolic parameters to ensure that correct placement and analysis were performed according to the manufacturer's recommendations.

BMD measurements were expressed in g/cm^2. We derived *T*-scores and *Z*-scores at the lumbar spine from IOG curves for women (established from three French populations, Isos, Ofely and Genset) and from the manufacturer's reference populations for men; at the proximal femur from the NHANES III reference population for women and men [16]; at the radius from the Ofely reference population for women [17] and from the manufacturer's reference populations for men.

In our unit, the coefficients of variation for BMD at the proximal femur were 1.80% for the femoral neck and 1.42% for the total hip. The coefficients of variation were 0.97% at the lumbar spine, 1.57% at the one-third radius and 2.60% at the ultradistal radius.

GFR measurements

GFR was determined by the renal clearance of ^{51}Cr–EDTA, as previously described [10,18]. Briefly, 1.8–3.5 MBq of ^{51}Cr–EDTA (GE Healthcare, Velizy, France) was injected intravenously as a single bolus. After allowing 1 h for distribution of the tracer in the extracellular fluid, average renal ^{51}Cr–EDTA clearance was determined in 5–6 consecutive 30-min clearance periods.

Biological variables

Total calcium was determined by atomic absorption spectrometry (model 3110, Perkin-Elmer, Norwalk, CT), ionized calcium by a specific electrode (model ABL 725, Radiometer, Copenhagen, Denmark) and phosphate by colorimetry (phosphomolybdate assay). Parathyroid hormone (PTH) was measured by a two-site immunometric method (automatic immunoanalysis assay, Elecsys, Roche, Bale) calibrated to the Nichols-Allegro Intact PTH assay, 25-hydroxy-vitamin D and 1.25 dihydroxyvitamin D by radiocompetition (Diasorin, Antony, France and ImmunoDiagnostic Systems Eurl, Paris, respectively). Plasma bone-specific alkaline phosphatase (BSALP) was measured by a radioimmunoassay (Immunodiagnostic Systems Eurl, Paris).

Statistical analysis

Statistics were performed using the NCSS 2004 software (Gerry Hintze, Kaysville, UT, USA). Data were expressed as mean ± standard deviation. Variable selection was performed according to the following procedure. We first included classical determinants of arterial parameters (age, MBP, central pulse pressure). Univariate regression analyses were used to determine which additional parameters should be included in the multiple regression analyses for the determinants of arterial parameters or potential confounding variable for BMD. Because of multiple testing, we used the Bonferoni correction and interpreted as significant only $P \leq 0.0055$. Multivariate analysis was conducted using robust multiple regression followed by stepwise regression.

Results

Characteristics of the studied population

The clinical characteristics of the patients are summarized in Table 1. The 107 patients (60.4 ± 14.6 years) included in the study had CKD stages 2–5, according to the KDIGO classification [19] (mean GFR 34 ± 17 mL/min/1.73 m^2).

The mineral metabolism parameters, including BMD values, are presented in Table 1. One third of the patients had a history of bone fracture, 30% of patients had osteopenia (−2.5 SD<*T*-score < −1 SD) and 34% of patients had BMD values consistent with osteoporosis (*T*-score ≤ −2.5 SD).

The arterial blood pressure and arterial characteristics are presented in Table 2. Characteristics of the present population were very close to those previously published [10], and confirmed the specific arterial phenotype observed in CKD patients (an outward remodeling of the CCA, without arterial wall thickening, leading to increased circumferential wall stress and a moderate increase in carotid stiffness).

Relationship between carotid internal diameter and BMD in CKD patients

In univariate analyses, the carotid internal diameter was significantly and positively correlated with MBP, and negatively correlated with GFR and BMD measured at any site (one-third radius, total hip and lumbar spine) ($P < 0.0055$) (Table 3), the lower the BMD, the larger the diameter.

Independently of age, sex, MBP, carotid pulse pressure (CPP) and GFR, BMDs measured at the one-third radius, total hip and lumbar spine were significantly and negatively correlated with carotid internal diameter ($P = 0.0001$, $P = 0.0003$, $P = 0.01$, respectively) (Table 4). BMD measured at the one-third radius explained 12% of the variance of carotid internal diameter.

Table 1. Characteristics of the studied population

Parameters	Mean ± SD	Reference values
$n = 107$		
Age (years)	60.4 ± 14.6	
Sex ratio M/W (%)	75/25	
BMI (kg/m^2)	25.8 ± 5.0	
BSA (m^2)	1.84 ± 0.23	
Menopausal status (% women)	66	
Hypertension (%)	98	
Diabetes (%)	19	
Dyslipidaemia (%)	72	
Active smoking (%)	17	
Hip fracture (*n* patients)	1	
Vertebral fracture (*n* patients)	2	
Radius fracture (*n* patients)	8	
Others fracture (*n* patients)	29	
SBP (mmHg)	134 ± 17	
MBP (mmHg)	92 ± 11	
DBP (mmHg)	71 ± 10	
HR	66 ± 11	
Measured GFR (mL/min/1.73 m^2)	34 ± 17	
Serum total calcium (mmol/L)	2.26 ± 0.11	2.09–2.52
Ionized calcium (mmol/L)	1.25 ± 0.06	1.15–1.32
Serum phosphate (mmol/L)	1.11 ± 0.25	0.82–1.39
Serum 25(OH) vitamin D (nmol/L)	52.7 ± 27.0	>75
Serum 1,25(OH)$_2$ vitamin D (pmol/L)	63 ± 35	66–167
Parathyroid hormone (pmol/L)	11.8 ± 13.1	11–57
Bone-specific alkaline phosphatase (UI/L)	13.0 ± 7.4	<20
Bone mineral density (g/cm^2)		
One-third radius	0.740 ± 0.096	
Total hip	0.933 ± 0.163	
Lumbar spine	0.955 ± 0.161	
T-scores for bone mineral density (SD)		
One-third radius	−0.83 ± 1.55	
Total hip	−0.52 ± 0.97	
Lumbar spine	−1.05 ± 1.47	
Z-scores for bone mineral density (SD)		
One-third radius	0.42 ± 1.46	
Total hip	0.2 ± 0.94	
Lumbar spine	−0.34 ± 1.46	

BMI, body mass index; BSA, body surface area; SBP, systolic blood pressure; MBP, mean blood pressure; DBP, diastolic blood pressure; HR, heart rate; GFR, glomerular filtration rate, measured with ^{51}Cr–EDTA clearance; SD, standard deviation.

Table 2. Arterial parameters in the studied population

Carotid artery parameters	Mean ± SD
SBP (mmHg)	125 ± 20
MBP (mmHg)	91 ± 10
DBP (mmHg)	72 ± 10
PP (mmHg)	53 ± 17
IMT (m × 10^{-6})	739 ± 157
Internal diastolic diameter (m × 10^{-3}/1.73 m^2)	5.99 ± 0.96
Wall cross-sectional area (m^2 × 10^{-6})	16.5 ± 4,5
Thickness/radius ratio (h/r)	0.23 ± 0.05
Circumferential wall stress (kPa)	54.4 ± 15.8
Distensibility (per kPa × 10)	21.6 ± 11.4
Compliance (mm^2 /kPa × 10)	666 ± 331
Carotid stiffness (m/s)	7.5 ± 1.9
Young's elastic modulus (kPa × 10^3)	0.528 ± 0.253

SBP, systolic blood pressure; MBP, mean blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; IMT, intima–media thickness.

Table 3. Univariate correlations (Spearman Rank test) between carotid internal diameter, intima–media thickness, carotid stiffness and potential determinants

	Carotid internal diameter		Carotid IMT		Carotid stiffness	
Parameters	*R*	*P*	*R*	*P*	*R*	*P*
Age	0.18	NS	0.58	<0.0055	0.61	<0.0055
MBP	0.25	<0.0055	0.13	NS	0.43	<0.0055
Sex	0.21	NS	−0.18	NS	−0.10	NS
Measured GFR	−0.26	<0.0055	0.26	<0.0055	0.06	NS
BSALP	0.37	<0.0055	−0.01	NS	0.009	NS
One-third radius, BMD	−0.27	<0.0055	0.16	NS	−0.10	NS
Total hip, BMD	−0.27	<0.0055	0.06	NS	−0.10	NS
Lumbar spine, BMD	−0.32	<0.0055	−0.03	NS	−0.25	NS

MBP, mean blood pressure; GFR, glomerular filtration rate; BSALP, bone-specific alkaline phosphatase; BMD, bone mineral density; IMT, intima–media thickness; NS, non significant.

Table 4. Multivariate regression analysis of carotid internal diameter determinants

Parameters	In/out	R^2 increment (%)	Beta coeff.	Lower CI	Upper CI	*P*
One-third radius, BMD (g/cm^2)	In	12	−2.87	−5.23	−0.51	0.0001
MBP (mmHg)	Out	–	–	–	–	NS
CPP (mmHg)	In	3.4	0.008	−0.003	0.02	0.03
Sex	Out	–	–	–	–	NS
Measured GFR (mL/min/1.73 m^2)	In	5.6	−0.012	−0.02	−0.002	0.008
Age (years)	Out	–	–	–	–	–
$R^2 = 0.22$						
RMSE = 0.81						
Total hip, BMD (g/cm^2)	In	10.9	−1.60	−2.86	−0.34	0.0003
MBP (mmHg)	Out	–	–	–	–	NS
CPP (mmHg)	In	3.6	0.008	−0.003	0.020	0.03
Sex	Out	–	–	–	–	NS
Measured GFR (mL/min/1.73 m^2)	In	5.7	−0.012	−0.022	−0.003	0.008
Age (years)	Out	–	–	–	–	NS
$R^2 = 0.21$						
RMSE = 0.81						
Lumbar spine, BMD (g/cm^2)	In	5.5	−1.382	−2.534	−0.230	0.01
MBP (mmHg)	Out	–	–	–	–	NS
CPP	Out	–	–	–	–	NS
Sex	In	5.6	0.543	0.125	0.961	0.01
Measured GFR (mL/min/1.73 m^2)	In	4.5	−0.011	−0.021	−0.001	0.02
Age (years)	Out	–	–	–	–	NS
$R^2 = 0.20$						
RMSE = 0.80						

BMD, bone mineral density; MBP, mean blood pressure; CPP, carotid pulse pressure; GFR, glomerular filtration rate; CI, confidence interval; NS, non-significant; RMSE, root mean squared error.

The carotid internal diameter was significantly higher in patients with lower BMD and lower GFR (Figure 1). As apparent from Figure 1, the correlation between carotid internal diameter and BMD was mainly observed in patients with markedly reduced GFR (< 38 mL/min/1.73 m^2, tertiles 2 and 3). Multivariate analysis in the group of CKD patients with GFR <38 mL/min/1.73 m^2 (tertiles 2 and 3) and in the group of CKD patients with GFR >38 mL/min/1.73 m^2 (tertile 1) showed that BMD measured at the one-third radius is independently correlated with carotid internal diameter only in the first group (GFR <38 mL/min/1.73 m^2) ($P < 0.0001$) (Table 5).

The results were virtually identical when *Z*-scores for BMD were used in the analysis (supplementary data).

Relationship between carotid intima–media thickness, carotid stiffness and BMD in CKD patients

In univariate analysis, carotid intima–media thickness (IMT) and carotid stiffness were significantly correlated with age and GFR, age and MBP, respectively. No relationship was found with BMD measured at any sites (Table 3).

Relationship between carotid internal diameter and serum bone-remodeling marker in CKD patients

BSALP, a serum marker of bone formation was positively correlated with carotid internal diameter in univariate analysis. An independent and positive correlation between BSALP and carotid internal diameter persisted in

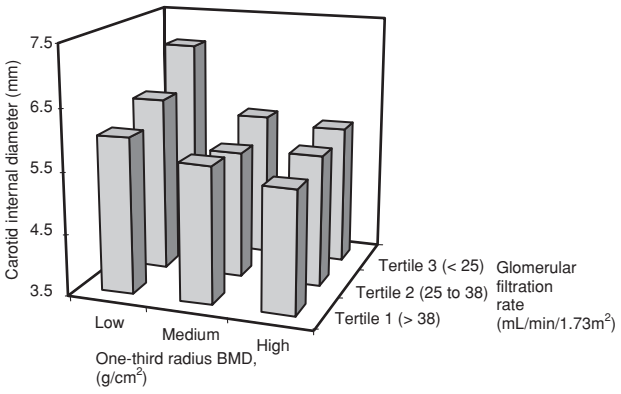

Fig. 1. Carotid internal diameter as a function of tertiles for bone mineral density ($P = 0.003$, linear trend) and tertiles for glomerular filtration rate ($P = 0.03$, linear trend).

Table 5. Multivariate analysis of the relationship between carotid internal diameter and one-third radius BMD in the group of patients with GFR <38 mL/min/1.73 m^2 (group 1) and in the group of patients with GFR >38 mL/min/1.73 m^2 (group 2)

Group	Parameters	R^2 increment (%)	Beta coeff.	Lower CI	Upper CI	P	R^2
1	One-third radius BMD	17.5	−4.17	−6.12	−2.20	<0.0001	0.39
2	One-third radius BMD	<1.0	–	–	–	NS	0.05

All data are adjusted on age, sex, carotid pulse pressure, mean blood pressure, glomerular filtration rate.
CI, confidence interval; NS, non-significant.

Table 6. Multivariate analysis of the relationship between serum marker of bone remodeling and carotid internal diameter

Parameter	R^2 increment (%)	Beta coeff.	Lower CI	Upper CI	P	R^2
BSALP	13	0.03	0.007	0.06	0.003	0.22

All data are adjusted on age, sex, carotid pulse pressure, mean blood pressure, glomerular filtration rate.
BSALP, bone-specific alkaline phosphatase; CI, confidence interval.

multivariate analysis ($P = 0.003$). BSALP explained 13% of the variance of carotid internal diameter (Table 6).

Discussion

In the present study, we demonstrate for the first time an age-independent association between the outward remodeling of carotid artery and bone remodeling in patients with CKD stages 2–5. Carotid internal diameter is independently correlated with BMD measured at three sites and with a serum marker of bone remodeling, BSALP. The carotid internal diameter was larger in CKD patients with lower BMD and with lower GFR. No correlation was found between carotid stiffness and BMD in CKD patients.

Interpretation of findings

This study demonstrates an association between bone-remodeling markers and arterial-remodeling parameters in particular the carotid internal diameter. Epidemiological studies have previously demonstrated the predictive value of cardiovascular mortality of carotid internal diameter in ESRD patients [2] and in the general population [20].

Arterial- and bone-remodeling association is related to the alteration of GFR since it was only observed in the group of patients with late stage 3 CKD (GFR <45 mL/min/1.75 m^2) or later stages. No correlation was found between carotid internal diameter and BMD in patients with early stage 3 and stage 2 CKD. This is the first demonstration of the interplay of GFR with the relationship between bone disease and arterial remodeling. This result is in accordance with recent studies suggesting that cardiovascular and metabolic complications occur mainly in patients with GFR <45 mL/min/1.73 m^2 [11,21].

Age could be a potential confounding factor as it is a strong determinant of BMD. The use of *Z*-score of BMD, which is adjusted for age and sex instead of BMD values, and carotid internal diameter-age adjusted did not change the relationship.

BMDs were measured at three sites, the total hip and lumbar spine that are weight-bearing bones and the one-third radius that is a non-weight-bearing bone. The results did not differ between the three sites. The strongest correlations between BMD measurements and arterial remodeling were observed at the one-third radius and the total hip. Since one-third radius BMD has a better predictive value for the risk of fracture than other sites in CKD [22] and better correlates with PTH levels in haemodialysis patients [23], a new observation involving this BMD measurement site in CKD patients is of particular interest. Accordingly, KDIGO recommendations have suggested the distal radius as the preferential site of measurement in CKD patients [24]. Moreover, the BMD measurements at the distal radius and at the proximal femur are less influenced by arterial calcifications. BMD values obtained at these sites are more precise than those obtained at the lumbar spine that could be overestimated by aortic calcifications.

The independent correlation observed between arterial enlargement and BMD suggests a pathophysiological link that may be an excessive turnover of the extracellular matrix, both in bone and in arteries. In accordance with this explanation, we found an independent and positive correlation between a serum marker of bone formation, BSALP and carotid internal diameter. The demonstration of an independent correlation between BSALP and arterial-remodeling complements the results of two previous studies that demonstrate that BSALP have a predictive value of cardiovascular events in CKD patients [3,25].

Relationships between bone metabolism, CKD and large artery remodeling are complex. We can only hypothesize the link between arterial and bone remodeling in CKD. Traditional cardiovascular risk factors such as dyslipidaemia, age, tobacco use [26] and non-traditional cardiovascular risk factors such as inflammatory state [27] and oxidative stress co-exist in CKD [28] and are associated with bone

loss [29]. Moreover, CKD is associated with elevated circulating proteins [30,31] implicated in large arteries remodeling and bone metabolism such as metalloproteinase-9 [32] and osteoprotegerin [33].

In this population of CKD stage 2–5 patients, no relationship was found between osteopenia and arterial stiffness. This contrasts with previous studies in haemodialysis patients [4,5]. We earlier proposed that arterial disease in moderate chronic disease is mainly characterized by an arterial enlargement without thickening and with only moderately increased arterial stiffness [10]. This is confirmed by the present analysis on a different set of patients. In ESRD, increased arterial stiffness and IMT complete the arterial phenotype. Arterial enlargement without thickening adaptation is the first step of arterial disease in CKD and is associated with bone remodeling at an early stage.

Methodological features and limitations of the study

This study is the first one designed to evaluate the relationship between arterial remodeling and bone density with two gold standard methods, an echo-tracking apparatus for measuring arterial parameters and dual-energy x-ray absorptiometry for the measurement of bone density, in a population of patients with CKD stages 2–5, GFR being precisely measured by ^{51}Cr–EDTA clearance.

The major limitation of this study is its observational cross-sectional nature. No causal relationship can thus be drawn from these data. Further experimental studies will be able to identify the nature and the mechanism of the link between arterial and bone remodeling.

Conclusion and perspectives

This cross-sectional study shows that arterial remodeling, more precisely carotid enlargement, is independently associated with low BMD and elevated serum markers of bone remodeling in patients with stage 2–5 CKD. Longitudinal studies are necessary to evaluate the relative value of large arteries and bone remodeling as prognosis markers in CKD.

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Conflict of interest statement. None declared.

Supplementary Data

Supplementary data are available online at http://ndt.oxfordjournals.org.

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