Osteoprotegerin as a marker of cardiovascular risk in patients on peritoneal dialysis

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KEY WORDS

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ABSTRACT

INTRODUCTION Arterial thickening contributes to elevated cardiovascular risk in patients on maintenance renal replacement therapy. The common carotid artery intima-media thickness (CCA-IMT) is an early atherosclerotic marker and may be used to assess the stratification of atherosclerotic advancement and resultant arterial calcification.

OBJECTIVES The aim of the study was to evaluate the associations between atherosclerotic changes in the common carotid arteries expressed as the CCA-IMT and the body mass index (BMI), serum lipid levels, C-reactive protein (CRP), and selected bone metabolism parameters including phosphorus, calcium, intact parathormone (iPTH), alkaline phosphatase, osteopontin, osteoprotegerin, osteocalcin, fetuin A, and fibroblast growth factor-23 (FGF-23) in patients treated with peritoneal dialysis.

PATIENTS AND METHODS The study included 67 patients with chronic kidney disease (36 men and 31 women) aged 53 ± 13 years (range, 19–75 years) treated with peritoneal dialysis for 30 ± 24 months. The CCA-IMT was assessed by ultrasonography using Acuson 128/10 XP. The BMI was calculated using the Quetelet formula. Serum lipid levels, phosphorus, calcium, iPTH, alkaline phosphatase, and CRP were measured using standard laboratory methods, while fetuin A, osteocalcin, osteoprotegerin, osteopontin, and FGF-23 using commercial enzyme-linked immunosorbent assay kits.

RESULTS Positive correlations were observed between CCA-IMT and age ($r = 0.54$, $P < 0.0001$), BMI ($r = 0.39$, $P = 0.003$), and osteoprotegerin ($r = 0.38$, $P = 0.004$). In a multiple regression analysis, age ($r = 0.41$, $P = 0.01$), osteocalcin ($r = 0.34$, $P = 0.04$), and log-transformed osteoprotegerin values ($r = 0.38$, $P = 0.02$) remained independently associated with the CCA-IMT. The highest CCA-IMT values (0.85 ± 0.21) were observed in patients with osteoprotegerin concentrations in the upper tertile. Osteoprotegerin concentrations strongly and positively correlated with the duration of dialysis treatment ($r = 0.55$, $P < 0.0001$).

CONCLUSIONS The CCA-IMT has been shown to be a reliable noninvasive measure of subclinical atherosclerosis and, therefore, of associated increased vascular risk. Elevated serum osteoprotegerin levels may be useful as a prognostic marker of cardiovascular risk in dialyzed patients.

INTRODUCTION Cardiovascular disease is one of the main causes of death in patients on renal replacement therapy. Morbidity at the start of dialysis significantly predicts its prevalence in the subsequent stages of treatment. Ultrasonography of the common carotid artery intima-media thickness (CCA-IMT)[1-5] may be used to assess the progress of atherosclerosis. The CCA-IMT is considered a strong predictive factor of cardiovascular events in the general population.[1,6] Progression of atherosclerotic changes in the carotid arteries reflects the atherosclerotic burden of other arteries.[1,7] In patients with end-stage renal disease, atherosclerotic plaques contain the increased amounts of calcium-phosphate deposits compared with those without renal insufficiency.

In these patients, deposits surround inflammatory cell infiltrations, lipoproteins, and protein bone matrix in the areas of vascular and valvular calcifications.[3,8-10]

In the last decades, novel markers emerged that play an important role in the development of soft tissue calcifications. These include inhibitors of extraosseous calcification (such as fetuin A), multifunctional proteins (such as osteoprotegerin and osteopontin), and bone parameters (such as osteocalcin and fibroblast growth factor-23 [FGF-23]).[11-14]

Osteoprotegerin is a key cytokine that belongs to the tumor necrosis factor receptor superfamily and has a wide spectrum of pleiotropic effects on bone metabolism and endocrine function.[15] It acts as a soluble decoy receptor for the receptor activator of nuclear factor κB ligand (RANKL), inhibiting differentiation of osteoclasts. Although the action of osteoprotegerin in blood vessels is not fully understood, its increase has been associated with higher mortality in diabetes, coronary artery disease, acute coronary syndrome, and silent myocardial ischemia.[15-18]

Fetuin A is the main inhibitor of hydroxyapatite formation in the body fluids.[19-21] Wang et al.[21] have shown a 6% lower risk of vascular calcification per 0.01 g/l rise of fetuin A concentration in patients on peritoneal dialysis. Dialyzed patients tend to have decreased levels of fetuin A compared with the group of patients with normal renal function.[2] Fetuin A is postulated to be an independent predictive factor of cardiovascular death, because decreased levels are associated with a significantly shorter survival in dialyzed patients.[19,21]

Arterial calcification, such as osteogenesis, involves a complex interaction of various cells that produce matrix vesicles and subsequent mineralization. Osteocalcin could play a pivotal role both in bone mineralization and vascular calcification.[22]

On the other hand, osteocalcin has several hormonal features and is secreted into general circulation from osteoblastic cells. This protein has been associated with high bone turnover and decreased bone mineral density in a variety of clinical settings. Pathological studies in humans showed higher osteocalcin levels in calcified atherosclerotic plaques and calcified cardiac valves than in noncalcified vasculature.[22,23]

Elevated phosphorus and intact parathormone (iPTH) levels in uremic patients contribute to vascular remodeling. The recently discovered FGF-23 is one of the most important regulators of calcium-phosphate metabolism. It is a bone-derived protein that promotes renal phosphorus wasting and inhibits conversion of 25-hydroxyvitamin D to the active 1,25-hydroxyvitamin D form. FGF-23 levels are extremely high in hemodialysis patients and are independently associated with increased mortality in these population.[24,25] In most hemodialyzed patients, serum FGF-23 concentration is more than 100-fold higher than in controls.[25]

The aim of the study was to evaluate the relationship of the atherosclerotic lesions in the carotid arteries expressed as the CCA-IMT and selected biochemical parameters associated with bone and mineral metabolism (fetuin A, osteocalcin, FGF-23, osteopontin, osteoprotegerin) with reference to classic atherosclerotic risk factors in patients on peritoneal dialysis.

PATIENTS AND METHODS The study group consisted of 67 patients with chronic kidney disease (CKD) (36 men and 31 women), aged 53 ±13 years (range, 19–75 years), and treated with peritoneal dialysis for 30 ±24 months (range, 4–100 months). Patients were included consecutively during 6 months. The inclusion criteria were as follows: age >18 years, continuous ambulatory peritoneal dialysis or automatic peritoneal dialysis, stable clinical course for at least 2 months before being included into the study, and a negative history of neoplastic diseases. The informed consent was obtained from each patient. The study protocol was approved by an institutional ethics committee.

The CCA-IMT was measured by a single investigator according to the current guidelines. It was visualized in the B presentation using Acuson 128/10 XP the linear 5/7 MHz head. Morning fasting blood samples were obtained during routine control examinations.

The following routine laboratory tests were performed in the Diagnostic Department, University Hospital: peripheral blood cell count, serum lipid levels (total cholesterol, high- and low-density lipoprotein, triglycerides), calcium, phosphorus, iPTH, and alkaline phosphatase. The serum concentrations of selected bone metabolism proteins were assessed using the commercially available enzyme-linked immunosorbent assay kits, including fetuin A (Human Fetuin A Elisa Kit, Epitope Diagnostics, United States), osteocalcin (METRA, Germany), osteoprotegerin (Human Osteoprotegerin Elisa Kit, Biomedica, Wien, Austria), osteopontin (Quantikine Human Osteopontin Elisa kit, R&D Systems, United Kingdom), and FGF-23 (Human FGF-23 Elisa kit, Immutopics, United States). The serum concentration of C-reactive protein (CRP) was determined by an immunonephelometric assay using Nephelometer BNII (Simens, Heathcare Diagnostics, Germany). The reference ranges for laboratory tests are presented in TABLE 1.

Continuous variables were assessed for normality by the Kolmogorov-Smirnov test. Means ± standard deviations are shown for normally distributed variables and medians (interquartile ranges) for nonnormal distributions. The Spearman coefficient was used to assess correlations between continuous variables. A multiple linear regression was applied to assess the effect of multiple variables on the CCA-IMT; right-skewed variables were log-transformed before the analysis. Partial correlation coefficients and P value were reported for each independent variable. Differences

TABLE 1 Clinical and biochemical characteristics of the study group including risk factors for cardiovascular disease, common carotid artery intima-media thickness, and selected biochemical parameters

Parameter		Patients on peritoneal dialysis (n = 67)		Reference values[b]
		number (percentage) or mean values[a]	minimum–maximum	
age, y		53 ±13	19–75	–
duration of dialysis, mo		30 ±24	4–100	–
male sex		36 (53.7)	–	–
hypertension		56 (83.6)	–	–
blood pressure, mmHg	systolic	149 ±18	105–180	–
	diastolic	90 ±12	60–115	<80
	mean	109 ±12	83–133	–
	pulse pressure	58 ±17	25–110	–
BMI, kg/m²		25.3 ±4.1	17.2–34.2	20–25
total cholesterol, mmol/l		5.45 ±1.18	2.97–9.02	3.2–5.2
HDL cholesterol, mmol/l		1.40 ±0.34	0.84–2.39	0.9–3.0
LDL cholesterol, mmol/l		3.13 ±0.99	0.95–6.35	0.2–3.4
triglycerides, mmol/l		2.03 ±0.90	0.59–5.28	0.2–2.3
ischemic heart disease		23 (34.3)	–	–
left ventricular dysfunction		33 (49.3)	–	–
peripheral artery disease		21 (31.3)	–	–
diabetes		11 (16.4)	–	–
current smokers		14 (20.9)	–	–
number of cigarettes per day		15 ±3	5–30	–
CCA-IMT, mm		0.76 ±0.21	0.40–1.30	–
osteocalcin, ng/ml		64.9 (38.9–70.5)	8.1–106.2	3.4–9.1
osteopontin, ng/ml		1340 ±742	85–3092	49.2–175.0
osteoprotegerin, pmol/l		9.49 (7.88–13.02)	3.58–27.48	2.5–12.8
fetuin A, g/l		0.27 (0.23–0.34)	0.12–0.81	0.26–0.35
FGF-23, RU/ml		2648 (768–10,845)	15–38,798	no data
iPTH, pg/ml		406 (196–806)	3–2474	150–300
calcium, mmol/l		2.29 ±0.22	1.59–2.68	2.1–2.4
phosphorus, mmol/l		1.76 ±0.50	0.79–2.90	1.1–1.8
alkaline phosphatase, U/l		240 (174–360)	99–1070	91–258
CRP, mg/l		5.37 (1.49–10.60)	0.16– 80.40	0.16–3.17

a   mean ± standard deviation for normally distributed variables or median (interquartile range) for nonnormally distributed variables

b   routine laboratory reference values for lipids, CRP, and alkaline phosphatase; target values for end-stage renal disease patients in the case of iPTH, calcium, phosphorus; reference values defined by the laboratory for fetuin A and osteoprotegerin; values reported by the manufacturers for other laboratory tests

Abbreviations: BMI – body mass index, CCA-IMT – common carotid artery intima-media thickness, CRP – C-reactive protein, FGF-23 – fibroblast growth factor-23, HDL – high-density lipoprotein, iPTH – intact parathormone, LDL – low-density lipoprotein

between the groups were assessed with the analysis of variance and Tuckey post-hoc test. The results were considered statistically significant at a *P* less than 0.05. The Statistica 9.0 package was used for calculations.

RESULTS   The clinical and biochemical characteristics of studied patients, including the major cardiovascular risk factors are shown in **TABLE 1**. The majority of patients (>80%) had hypertension; about half of the group were diagnosed with left ventricular dysfunction; and about one-third suffered from ischemic heart disease or peripheral artery disease. The majority of patients showed high concentrations of osteocalcin,

osteopontin, and osteoprotegerin. Fetuin A was generally within the reference range, although in most patients it was close to the lower reference limit. FGF-23 levels in our study were higher than those reported in the literature (**TABLE 1**).[13,24,25]

The relationships between the CCA-IMT and selected bone metabolism markers as well as cardiovascular risk factors were studied using simple correlations as well as a multiple regression. Osteoprotegerin was the only bone marker that significantly correlated with CCA-IMT in a simple analysis (*r* = 0.38, *P* = 0.004) (**FIGURE**). The CCA-IMT also positively correlated with age (*r* = 0.54, *P* <0.0001) and body mass index (BMI) (*r* = 0.39, *P* = 0.003). Consistently, in a multiple
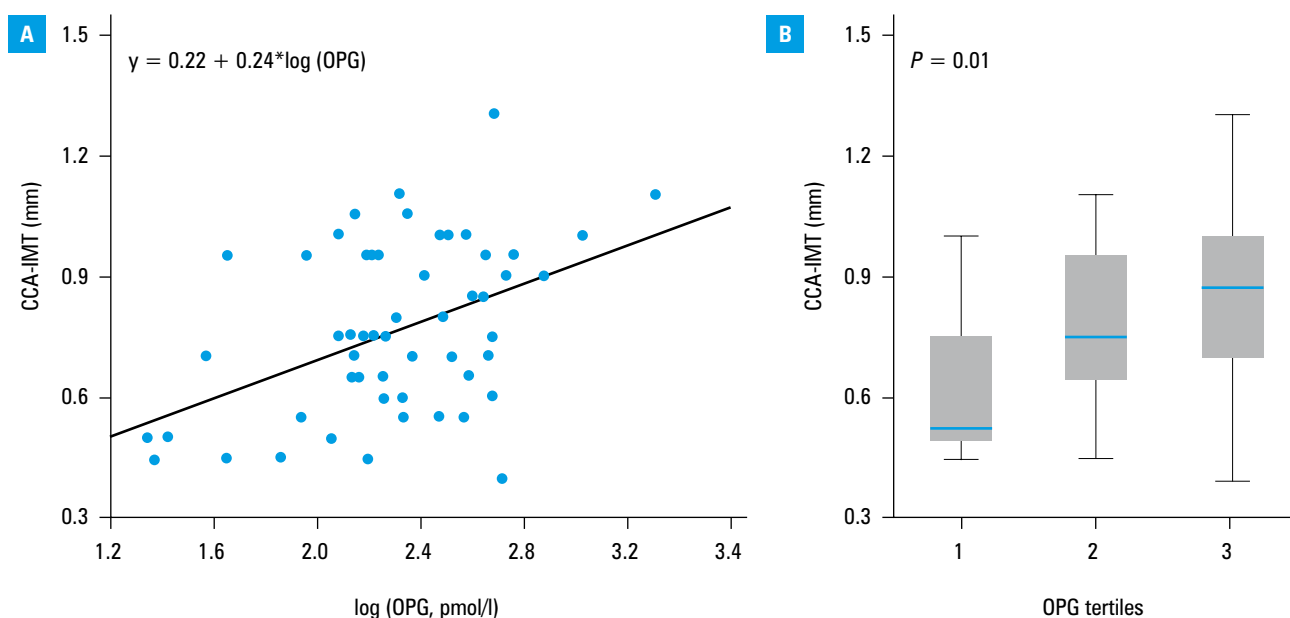
A $y = 0.22 + 0.24*\log(\text{OPG})$

CCA-IMT (mm) vs log (OPG, pmol/l)

B $P = 0.01$

CCA-IMT (mm) vs OPG tertiles

regression model adjusted for the major cardiovascular risk factors, including age, osteoprotegerin (log-transformed), and osteocalcin, were shown to independently predict the CCA-IMT. The inhibitor of extraosseous calcification, fetuin A, did not show a significant association with the CCA-IMT (TABLE 2).

CCA-IMT values varied depending on the osteoprotegerin tertile ($P = 0.01$; FIGURE). Patients with osteoprotegerin in the upper tertile (>11.90 pmol/l) had a significantly higher CCA-IMT compared with patients in the lower tertile (≤8.44 pmol/l) (0.85 ±0.21 vs. 0.64 ±0.20; $P = 0.01$). Osteoprotegerin concentrations strongly positively correlated with the duration of dialysis treatment ($r = 0.55$, $P <0.0001$). However, the duration of dialysis did not directly correlate with the value of CCA-IMT ($r = 0.26$, $P = 0.06$).

DISCUSSION The increased concentrations of calcium and phosphorus and insufficiency of natural calcification inhibitors are among the factors leading to the progression of atherosclerotic lesions especially in patients with CKD.[11,12,14,26]

Our study focused on the interrelationships between the CCA-IMT and selected biochemical parameters associated with bone metabolism. In patients on peritoneal dialysis, age, log (osteoprotegerin), and osteocalcin were found to be independent risk factors positively associated with the CCA-IMT. Of classic risk factors, age and BMI positively correlated with the CCA-IMT.

Chonchol et al.[6] reported that patients with "subclinical" carotid artery atherosclerosis have a high risk of developing CKD. During a 2-year follow-up, the CCA-IMT presented as an influential, predictive factor of cardiovascular disease when correlated with classic risk factors such as age, sex, cigarette smoking, systolic and diastolic blood pressure, low-density lipoprotein (LDL) cholesterol, and glycated hemoglobin. Increased CCA-IMT was associated with a higher rate of new cases of CKD. In a group of patients

on peritoneal dialysis, Wang et al.[27] observed correlations between the CCA-IMT and age, diastolic arterial blood pressure, cigarette smoking, acute-phase proteins (such as CRP, fibrinogen), as well as fetuin A and lipoprotein (a). In a study of Szeto et al.[28] in whom 203 patients with stages 3 and 4 of CKD were evaluated, the IMT correlated with age, LDL cholesterol, and CRP. A substantially higher CCA-IMT was noted in patients with diabetes compared with nondiabetic subjects. Japanese investigators showed a correlation between the CCA-IMT and age, duration of diabetes, and arterial hypertension. The value of IMT increased substantially with the progression of CKD (0.87 mm in stage 1, 1.02 mm in stage 2, and 1.11 mm in stage 3 CKD).[29] Yilmaz et al.[30] studied 406 patients with CKD and 58 patients after kidney transplantation without manifestation of cardiovascular disease at the moment of the study. The CCA-IMT was significantly higher in patients with kidney disease compared with the control group (0.9 vs. 0.6 mm) and independently associated with creatinine clearance, mean arterial pressure, and the calcium × phosphorus index. In patients after kidney transplantation, the CCA-IMT considerably decreased reaching the values comparable to controls.

Sigrist et al.,[15] showed in multiple regression that male patients with osteoprotegerin higher than 25 pmol/l and hypoalbuminemia are at a higher risk of death. Subjects with osteoprotegerin levels lower than 25 pmol/l showed a higher rate of diabetes compared with subjects with osteoprotegerin levels higher than 25 pmol/l. The authors found no association between circulating fetuin A and CRP. These data show that osteoprotegerin is associated with vascular damage independently of CRP. Osteoprotegerin is a specific link between vascular calcification and bone resorption. Nitta et al.[17] showed that high serum osteoprotegerin levels may be independently associated with vascular calcification. Patients with increased aortic calcifications had higher calcium

TABLE 2 Multiple regression analysis for the prediction of common carotid artery intima-media thickness

Parameter		Partial correlation coefficient	*P*
age		0.41	0.01
male sex		−0.28	0.09
log (duration of dialysis)		−0.25	0.1
BMI		0.21	0.2
LDL		0.11	0.5
triglycerides		0.28	0.09
calcium × phosphorus		0.16	0.3
osteocalcin		0.34	0.04
osteopontin		−0.14	0.4
log	osteoprotegerin	0.38	0.02
	fetuin A	−0.29	0.08
	FGF-23	−0.14	0.4
	alkaline phosphatase	−0.19	0.2
	iPTH	0.08	0.6
	CRP	0.01	0.9

$R^2 = 0.56$; $P = 0.003$ for the model

Abbreviations: see **TABLE 1**

and CRP levels and lower albumin and iPTH levels compared with patients with a lower degree of calcifications. Patients with increased calcification had higher mean serum levels of osteoprotegerin and osteopontin.

Adamczyk et al.[31] observed that increased serum osteoprotegerin levels and aortic valve calcium score were associated with coronary artery disease in patients with moderate degenerative aortic stenosis. This study showed that enhanced serum osteoprotegerin levels were associated with early valvular calcification.

In our study, in a multiple regression model adjusted for the major cardiovascular risk factors, osteoprotegerin (log-transformed), together with osteocalcin were shown to independently predict the CCA-IMT. Studies suggested that osteoprotegerin may be an inflammatory marker associated with atherosclerosis. The ability of proinflammatory mediators such as tumor necrosis factor α, interleukin 1, and platelet-derived growth factor to enhance osteoprotegerin expression and production in the vascular cells may explain the association of osteoprotegerin concentrations and cardiovascular disease.[18] Osteoprotegerin as a natural decoy receptor for an osteoclast differentiation factor, is produced by osteoblasts in response to PTH. PTH induces the synthesis of RANKL, which in turn plays a pivotal role in osteoclastogenesis by providing an essential signal to osteoclast progenitors through the membrane-anchored receptor activator of nuclear factor κB (RANK). Osteoprotegerin blocks the interaction between RANKL and RANK, inhibits bone resorption, and protects bone tissue against extensive bone deterioration. Increased osteoprotegerin levels in dialysis patients is a reply to high bone resorption, which has a protective function. On the other hand, elevated osteocalcin is a marker of high bone turnover. Osteocalcin can play a pivotal role both in bone mineralization and vascular calcification. The osteoprotegerin / osteocalcin complex may become a useful marker of early development of bone mineral disease and calcification in dialysis patients.

Based on the earlier reports and our own results, it appears that an imaging procedure such as the measurement of CCA-IMT should be considered as a routine, noninvasive tool in the evaluation of atherosclerosis at diagnosis of CKD, at initiation of renal replacement therapy, and during treatment.

Elevated serum osteoprotegerin levels could be a biomarker of cardiovascular risk and prognosis in dialyzed patients. High levels of this protein may promote the progression and instability of atherosclerosis.

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Osteoprotegeryna jako marker ryzyka sercowo-naczyniowego u pacjentów dializowanych otrzewnowo

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SŁOWA KLUCZOWE

dializa otrzewnowa,
osteoprotegeryna,
parametry
metabolizmu
kostnego, wskaźnik
grubości błony
środkowej
i wewnętrznej pnia
tętnicy szyjnej
wspólnej

STRESZCZENIE

WPROWADZENIE   Sztywność naczyń tętniczych przyczynia się do zwiększonego ryzyka sercowo--naczyniowego u pacjentów leczonych nerkozastępczo. Wskaźnik grubości błony środkowej i wewnętrznej pnia tętnicy szyjnej wspólnej (*common carotid artery intima-media thickness* – CCA-IMT) może być użyteczny w ocenie nasilenia zmian miażdżycowych oraz kalcyfikacji naczyń tętniczych.

CELE   Celem badania była ocena zależności między nasileniem zmian miażdżycowych w tętnicach szyjnych wspólnych wyrażonych jako wskaźnik CCA-IMT a wskaźnikiem masy ciała (*body mass index* – BMI), składowymi lipidogramu, białkiem C-reaktywnym (*C-reactive protein* – CRP) oraz wybranymi parametrami metabolizmu kostnego: fosforu, wapnia, parathormonu (iPTH), fosfatazy alkalicznej, osteopontyny, osteoprotegeryny, osteokalcyny, fetuiny A i czynnika wzrostu fibroblastów-23 (*fibroblast growth factor-23* – FGF-23) u pacjentów dializowanych otrzewnowo.

PACJENCI I METODY   Badaniem objęto 67 pacjentów (36 mężczyzn i 31 kobiet) z przewlekłą chorobą nerek w wieku 53 ±13 lat (zakres 19–75 lat), dializowanych otrzewnowo od 30 ±24 miesięcy. Pomiary CCA-IMT zostały wykonane ultrasonograficznie przy użyciu aparatu Acuson 128 XP/10. BMI wyliczono używając wzoru Queteleta. Składowe lipidogramu, fosfor, wapń, iPTH, fosfatazę alkaliczną oraz CRP oznaczono używając standardowych metod laboratoryjnych, zaś fetuinę A, osteokalcynę, osteoprotegerynę, osteopontynę i FGF-23 przy użyciu dostępnych komercyjnie zestawów ELISA.

WYNIKI   Stwierdzono dodatnie korelacje między CCA-IMT a wiekiem (r = 0,54; p <0,0001), BMI (r = 0,39; p = 0,003) oraz stężeniem osteoprotegeryny (r = 0,38; p = 0,004). W analizie regresji wielokrotnej niezależnymi czynnikami predykcyjnymi CCA-IMT były wiek (r = 0,41; p = 0,01), osteokalcyna (r = 0,34; p = 0,04) i log osteoprotegeryna (r = 0,38; p = 0,02). Najwyższe wartości CCA-IMT (0,85 ±0,21) obserwowano u pacjentów ze stężeniem osteoprotegeryny w górnym tercylu. Stężenie osteoprotegeryny silnie korelowało z czasem trwania dializoterapii (r = 0,55; p <0,0001).

WNIOSKI   CCA-IMT jest wiarygodnym nieinwazyjnym wskaźnikiem nasilenia subklinicznych zmian miażdżycowych i związanego z nimi zwiększonego ryzyka powikłań naczyniowych. Podwyższony poziom osteoprotegeryny może być przydatny jako marker prognostyczny w ocenie ryzyka sercowo-naczyniowego u pacjentów dializowanych.

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