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Preclinical vascular damage in white postmenopausal women: the relevance of osteoprotegerin

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Abstract

Osteoprotegerin (OPG) has recently been implicated in human atherogenesis. Abdominal obesity represents an established risk factor for the onset and development of atherosclerotic damage. The aim of the present study was to investigate the link between OPG and abdominal fat and the relationship to precocious features of atherosclerotic disease such as brachial flow-mediated vasodilation (FMV) and the intima-media thickening (IMT) in 195 white postmenopausal women (age range, 43-75 years). The study population was divided into 2 groups: group 1—waist circumference <80 cm and group 2—waist circumference ≥80 cm. Group 2 had higher menopausal years, body mass index, low-density lipoprotein cholesterol, triglycerides, C-reactive protein, and carotid IMT. High-density lipoprotein cholesterol was higher in group 1. Afterward, these groups were divided on the basis of a cutoff value of OPG (6.85 pmol/L) that was the median of its distribution: patients with OPG ≤6.85 pmol/L were OPG^-, and those with OPG >6.85 pmol/L were OPG^+. The OPG^+ subjects in both had lower brachial FMV and higher carotid IMT in comparison with OPG^- subjects. At the multivariate regression analysis, waist circumference, high-density lipoprotein cholesterol, C-reactive protein, and OPG were predictors of carotid mean IMT ($\beta = 0.55$, $P = .001$; $\beta = -0.14$, $P = .001$; $\beta = 0.16$, $P = .001$; and $\beta = 0.14$, $P = .05$, respectively) and age, OPG, low-density lipoprotein cholesterol, and brachial diameter of brachial FMV ($\beta = -0.13$, $P = .05$; $\beta = -0.25$, $P = .001$; $\beta = -0.14$, $P = .024$; and $\beta = 0.48$, $P = .001$, respectively). The conclusions are as follows: first, OPG levels did not appear to be conditioned by a risk factor such as abdominal obesity; and second, OPG levels are mainly linked to the evidence of vascular damage. On this basis, we could speculate that OPG levels may be considered not a cardiovascular risk condition but a defense against atherosclerotic progression.

1. Introduction

Osteoprotegerin (OPG) represents a key factor in bone remodeling. It is a member of the tumor necrosis factor family and is a decoy receptor activator of nuclear factor–κB ligand and tumor necrosis factor–related apoptosis-inducing ligand [1]; it also protects bone from excessive resorption by inhibiting the terminal stages of osteoclastogenesis. Moreover, recently, it has been implicated in human atherogenesis [2,3]. Several observations suggested that higher OPG levels are associated with evidence of coronary atherosclerosis, severity of the disease, and cardiovascular mortality [4-6].

Abdominal obesity represents an ongoing worldwide epidemic problem because of its rising prevalence and its association with diabetes, hypertension, and metabolic syndrome, thus exponentially increasing cardiovascular risk in affected people [7-9]. Moreover, abdominal obesity plays a critical role in the early stages of atherosclerotic process, mainly, modulating the activation of endothelial synthesis of cytokines and vascular smooth muscle cell proliferation [10,11]. The precocious stages of atherosclerosis are identified in a functional impairment of endothelial surface with a consequent impairment of arterial capacity to vasodilate and in the thickening of intima-media space [12,13].

It is known that menopausal age is characterized by hormonal changes as consequence of estrogenic fall mainly involving the bone metabolism, the redistribution of fat to the upper body depot, and the evidence of an increased risk for cardiovascular events [14].

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On this basis, we decided to investigate in postmenopausal white women the potential links among OPG, as indicator of bone remodeling, abdominal fat accumulation, and the precocious features of atherosclerotic disease such as brachial endothelial function and the intima-media thickening (IMT) of large arteries.

2. Study design

We enrolled 195 white (age range, 43-75 years) postmenopausal women who were referred to our osteoporosis section. All patients underwent clinical evaluation and measurement of body mass index (BMI) and waist circumference; for the latter, we assumed a value of 80 cm to indicate the presence of abdominal obesity in concordance with the International Diabetes Federation Consensus for Europids [15]. Lumbar bone mineral density estimation, performed by dual-energy x-ray absorptiometry, showed that all subjects were not osteoporotic (T-score >−2.5 SD). Smoking habits were assessed by questionnaire. *Arterial hypertension* was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg, or antihypertensive treatment. *Diabetes mellitus* was defined as fasting serum glucose levels ≥7.0 mmol/L in at least 2 occasions or current treatment with insulin or oral hypoglycemic agents. *Dyslipidemia* was defined as serum low-density lipoprotein (LDL) cholesterol ≥6.2 mmol/L, high-density lipoprotein (HDL) cholesterol <1.0 mmol/L, triglycerides ≥2.3 mmol/L, or current hypolipidemic drug treatment. Assessment of brachial flow-mediated vasodilation (FMV) and IMT of carotid arteries was performed in all subjects. The study was approved by the ethical committee of our institution.

2.1. Laboratory determinations

Blood was drawn in the morning after a 13-hour fast. The following parameters were determined: fasting blood glucose, total cholesterol, triglycerides (enzymatic colorimetric method), and HDL cholesterol (enzymatic colorimetric method after precipitation with polyethylene glycol). Low-density lipoprotein cholesterol was calculated from the Friedewald equation.

Plasma C-reactive protein (CRP) concentrations were measured using the latex-enhanced CRP assay (High-Sensitivity CRP Assay; Dade Behring, Marburg, Germany). The interassay coefficient of variation for plasma CRP was 2% at both low and high concentrations.

Serum was separated and stored at −80°C. Serum OPG levels were measured by enzyme-linked immunosorbent assay (Biovendor Laboratory Medicine, Brno, Czech Republic). It is a biotin-labeled antibody based on the direct sandwich technique. The intra- and interassay coefficients of variation were 5.6% and 6.7%. The *sensitivity*, defined as the mean ± 3 SD of the zero standard, was calculated to be 0.13 pmol/L.

2.2. Carotid IMT

Carotid artery IMT was assessed by an ultrasound device (HDI 3500; ATL Philips Medical System, Best, Netherlands) equipped with a linear multifrequency 5- to 12-MHz transducer, as already described [13]. Subjects were examined in the supine position, and all measurements were obtained at end-diastole by electrocardiographic triggering. The ultrasound images have been stored on a Super Video Home System videotape and analyzed using an image processing workstation (AMS System, Malmö, Sweden). On a longitudinal 2-dimensional ultrasound image of the carotid artery, the near and far arterial walls are displayed as 2 bright white lines separated by a hypoechogenic space. The distance between the leading edge of the first bright line on the far wall (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface) indicates the IMT of the far wall. For the near wall, IMT was calculated as the distance between the trailing edge of the first bright line and the trailing edge of the second bright line. A 1.5-cm segment of the common carotid artery (immediately caudal to the bifurcation), the bifurcation of the common carotid artery, and the proximal 1.5-cm segment of the internal carotid artery were considered.

Each subject was characterized by mean carotid IMT (*C mean*—defined as the average of all the automated IMT readings: common, bifurcation and internal carotid arteries, right and left side, far and near wall). We also calculated the mean IMT of each segment, including common carotid (*CC mean*) and internal carotid (*IC mean*). The intraobserver coefficient of variation was 2.4% in the carotid district (mean ± SD of the difference, 0.018 ± 0.031 mm), and the corresponding interobserver values were 3.5.6% in the carotid district (0.028 ± 0.032 mm).

2.3. Assessment of brachial FMV

Flow-mediated vasodilation was assessed on the brachial artery by ultrasonography [16]. Details of the method are reported elsewhere [12]. The brachial artery was scanned longitudinally just above the antecubital crease using a linear multifrequency 5- to 12-MHz transducer (HDI 3500, Advanced Technology Laboratories). Diameter of the brachial artery was measured at the R wave of the electrocardiogram on the interface between media and adventitia of the anterior and posterior wall. Hyperemia was induced by inflation of a pneumatic cuff at 230 to 250 mm Hg for 4 minutes on the most proximal portion of the forearm. Arterial diameter measurement was repeated 45 to 60 seconds after sudden deflation of the cuff. *Flow-mediated vasodilation* was expressed as the relative increase in brachial artery diameter during hyperemia and defined as 100 × [(posthyperemic diameter − basal diameter)/basal diameter]. The intraobserver between-occasion reproducibility of FMV in our laboratory was assessed in 10 subjects examined 2 days apart. The mean ± SD difference between the 2 examinations was 1.0% ± 1.5%.

2.4. Statistical analysis

Data are presented as mean ± SD. The study population was divided into 2 groups: group 1—waist circumference

Table 1
Characteristics of the subjects divided on the basis of waist circumference (group 1, <80 cm; group 2, ≥80 cm)

	Group 1	Group 2
	n = 80	n = 115
Age (y)	60 ± 3	62 ± 5 *
Menopausal (y)	12 ± 6	12 ± 5
BMI (kg/m^2)	23 ± 2.8	29 ± 3.8 **
Total cholesterol (mmol/L)	6.79 ± 0.91	6.81 ± 1.32
LDL cholesterol (mmol/L)	5.05 ± 0.88	5.47 ± 1.37 *
HDL cholesterol (mmol/L)	1.76 ± 0.39	1.35 ± 0.31 **
Triglycerides (mmol/L)	1.37 ± 0.72	1.75 ± 1.03 **
Glucose (mmol/L)	4.95 ± 0.62	5.06 ± 0.96
CRP (mg/dL)	2.7 ± 3.1	4.3 ± 3.5 **
OPG (pmol/L)	8.04 ± 3.4	9.1 ± 4.6
Brachial diameter (mm)	3.1 ± 1.2	3.3 ± 1.1
Brachial FMV (%)	7.5 ± 2.1	5.1 ± 1.8
Basal brachial flow (mL/m)	124 ± 33	134 ± 24
Posthyperemic flow (mL/m)	267 ± 16	274 ± 31
C mean (mm)	0.92 ± 0.17	1.20 ± 0.13 **
CC mean (mm)	0.87 ± 0.16	1.13 ± 0.13 **
IC mean (mm)	0.98 ± 0.19	1.26 ± 0.14 **
Diabetes (%)	5	8
Hypertension (%)	48	77 *
Smoking (%)	15	14
Hypercholesterolemia (%)	85	82
Hypertriglyceridemia (%)	15	23

* $P < .05$.
** $P < .01$.

<80 cm and group 2—waist circumference ≥80 cm. Afterward, these groups were divided on the basis of a cutoff value of OPG (6.85 pmol/L) that was the median of its distribution: patients with OPG ≤6.85 pmol/L were OPG$^-$, and those with OPG >6.85 pmol/L were OPG$^+$. Student *t* test was performed to compare parametric variables between groups; differences between categorical variables were tested by χ^2 test. Univariate association between study variables was performed by Pearson and Spearman correlation.

Multiple regression analysis was performed including brachial FMV and C mean IMT as dependent variables; the analysis was performed in the entire group. The independent variables of the model were age, waist circumference, triglycerides, HDL cholesterol, LDL cholesterol, CRP, and OPG. The FMV model also included brachial artery diameter. Data were stored by SPSS release 13.0 (SPSS, Chicago, IL).

3. Results

Demographic, clinical, and laboratory parameters of 195 patients divided on the basis of waist circumference (<80 cm = group 1, ≥80 cm = group 2) are reported in Table 1. Group 2 had higher menopausal years, BMI, LDL cholesterol, triglycerides, CRP, C mean, CC mean, and IC mean. The HDL cholesterol was higher in group 1; no difference emerged in OPG levels.

As shown in Table 2, when these 2 groups were divided on the basis of the OPG median value, it was evident that OPG$^+$ subjects of group 1 had a significant reduction of brachial FMV; in OPG$^+$ patients of group 2, brachial FMV was significantly lower and C mean, CC mean, and IC mean were significantly higher in comparison with OPG$^-$ subjects.

At the univariate analysis, brachial FMV had negative correlation with age, waist circumference, LDL cholesterol, and CRP; C mean IMT was negatively related to HDL cholesterol and had a direct correlation to age, waist

Table 2
Characteristics of groups 1 and 2 divided on the basis of OPG median value (OPG$^-$, under the median; OPG$^+$, over the median)

	Group 1		Group 2	
	OPG$^-$	OPG$^+$	OPG$^-$	OPG$^+$
	n = 23	n = 57	n = 77	n = 38
Age (y)	60 ± 4	61 ± 3	60 ± 4	63 ± 6
Menopausal (y)	12 ± 6	12 ± 5	11 ± 4	13 ± 6
BMI (kg/m^2)	22 ± 2.3	24 ± 3.2 *	27 ± 2.2	31 ± 3.1 **
Total cholesterol (mmol/L)	6.76 ± 1.04	6.82 ± 1.14	6.68 ± 1.09	6.94 ± 1.43
LDL cholesterol (mmol/L)	4.74 ± 0.09	5.36 ± 1.03	5.23 ± 1.15	5.71 ± 1.44
HDL cholesterol (mmol/L)	1.74 ± 0.42	1.78 ± 0.44	1.38 ± 0.39	1.32 ± 0.31
Triglycerides (mmol/L)	1.39 ± 0.76	1.35 ± 0.74	1.65 ± 1.12	1.85 ± 1.29
Glucose (mmol/L)	4.89 ± 0.73	5.01 ± 0.72	4.93 ± 1.03	5.19 ± 1.21
CRP (mg/dL)	2.5 ± 3.5	2.9 ± 3.3	4.1 ± 3.8	4.5 ± 3.9
Brachial diameter (mm)	2.9 ± 1.0	3.2 ± 1.2	3.0 ± 0.8	3.6 ± 1.8
Brachial FMV (%)	8.2 ± 2.0	6.8 ± 1.8 *	6.1 ± 1.0	4.1 ± 0.8 *
Basal brachial flow (mL/m)	128 ± 28	126 ± 33	131 ± 19	137 ± 24
Posthyperemic flow (mL/m)	264 ± 24	270 ± 18	270 ± 33	278 ± 29
C mean (mm)	0.90 ± 0.19	0.94 ± 0.20	1.15 ± 0.13	1.25 ± 0.11 *
CC mean (mm)	0.85 ± 0.20	0.89 ± 0.19	1.09 ± 0.16	1.18 ± 0.19 *
IC mean (mm)	0.98 ± 0.19	0.98 ± 0.22	1.21 ± 0.16	1.31 ± 0.11 *

* $P < .05$.
** $P < .001$.

Table 3
Univariate correlation among serum OPG levels, brachial FMV, C mean IMT, and study parameters in all patients

	FMV		C mean IMT	
	r	*P*	*r*	*P*
Age	−.17	<.05	.170	<.05
Postmenopausal years	−.02	NS	.112	NS
Waist circumference	−.15	<.05	.781	<.001
BMI	.04	NS	.604	<.001
LDL cholesterol	−.16	<.05	.195	<.001
HDL cholesterol	−.0.2	NS	−.562	<.001
Triglycerides	−.04	NS	.217	<.001
CRP	−.14	<.05	.426	<.001
OPG	−.25	<.001	.310	<.001

NS indicates not significant.

circumference, BMI, LDL cholesterol, triglycerides, and CRP (Table 3). Osteoprotegerin was positively related to C mean IMT and inversely related to brachial FMV (Table 3, Fig. 1).

At the multivariate regression analysis, waist circumference, HDL cholesterol, CRP, and OPG were predictors of C mean IMT ($\beta = 0.55$, $P = .001$; $\beta = -0.14$, $P = .001$; $\beta = 0.16$, $P = .001$; and $\beta = 0.14$ $P = .05$, respectively) and age, OPG, LDL cholesterol, and brachial diameter of brachial FMV ($\beta = -0.13$, $P = .05$; $\beta = -0.25$, $P = .001$; $\beta = -0.14$, $P = .024$; and $\beta = 0.48$, $P = .001$, respectively).

4. Discussion

The main findings of the present study are that OPG levels did not differ in postmenopausal women with and without abdominal obesity and that higher OPG levels seem to distinguish women with a more evident atherosclerotic damage.

Initially, OPG was mainly linked to the bone homeostasis; in fact, it acts as a decoy receptor of the receptor activator of nuclear factor–κB ligand, which is a key regulator of osteoclastogenesis, and inhibits osteoclastogenesis by binding to receptor activator of nuclear factor–κB ligand [17,18]. The role of OPG in cardiovascular diseases is quite debated, and there is evidence that OPG levels are associated with the severity of coronary artery disease and cardiovascular mortality [5,6] and that these are increased in patients affected by diabetes [2]. We decided to investigate the relevance of an important cardiovascular risk condition such as abdominal obesity on the preclinical damage of large vessels and its link with OPG levels in a cohort of postmenopausal women without history of overt cardiovascular disease.

As expected, women with higher waist circumference showed an increased IMT. It is known that abdominal obesity prejudices vascular surface by several mechanisms as an unfavorable lipid profile promoting an inflammatory status and by its association with other cardiovascular risks, that is, diabetes and hypertension. No significant difference emerged in OPG levels. To exclude the potential influence of metabolic syndrome (ie, coexistence of 3 or more factors such as high triglyceride levels, low high-density lipoproteins, high fasting glycemia, hypertension, and abdominal obesity), we evaluated the vascular characteristics of metabolic syndrome patients; nevertheless, no significant differences emerged between this small group (n = 26) and the rest of patients (unpublished data).

Moreover, we extended our analysis by dividing these 2 groups of postmenopausal women on the basis of an OPG cutoff value. We observed that in women without abdominal obesity and high OPG levels, there was more evident detriment of endothelial function; on the other hand, women with abdominal obesity and higher levels of OPG were distinguished by a more relevant impairment of brachial endothelial function and thickening of carotid IMT. This observation seems extremely interesting for 2 main reasons: first, OPG levels did not appear to be conditioned

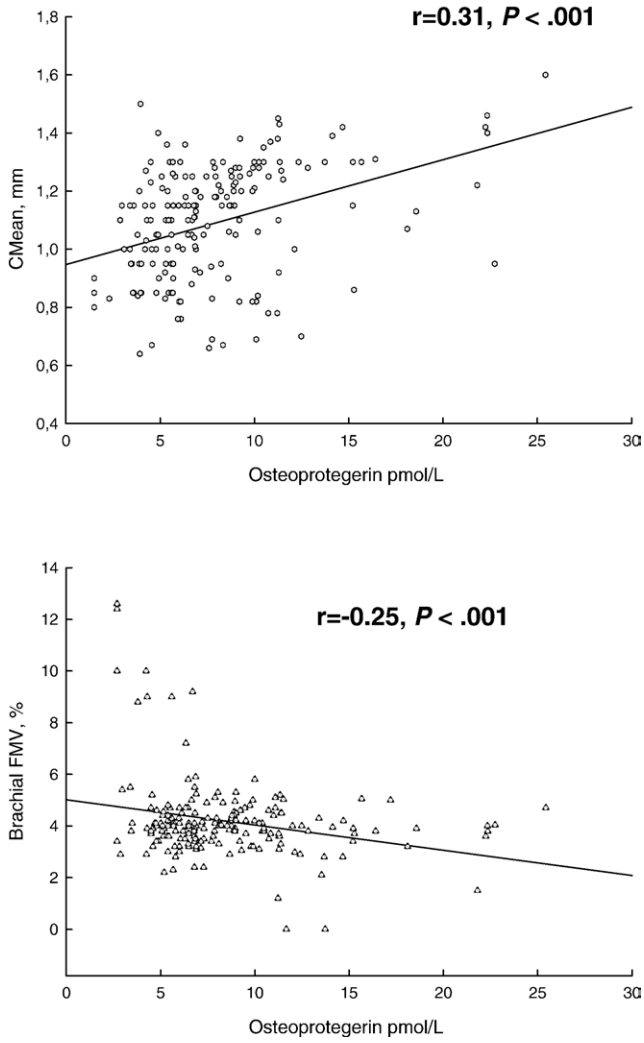

Fig. 1. Univariate correlation between OPG levels and C mean IMT and between OPG levels and brachial FMV.

by a risk factor such as abdominal obesity; and second, OPG levels are mainly linked to the evidence of vascular damage. Experimental evidences have demonstrated the ribonucleic acid and protein expression of OPG in plaque and myocardial tissue [19-21]; moreover, the development of vessel calcification is completely prevented by the OPG gene restoration in animal model [22]. In the same way, it has been observed that OPG acts as an antiapoptotic factor inhibiting specific proinflammatory and proapoptotic signaling pathways [23,24]. In humans, high OPG levels have been reported in patients with stable angina, related to the entity of coronary atherosclerosis. Moreover, there are a number of studies indicating the relationship among OPG levels and cardiovascular risk factors such as diabetes, hypertension, metabolic syndrome, and waist-to-hip ratio [2,25,26]. Recently, prospective studies indicated OPG to be an independent risk factor of carotid atherosclerosis and cardiovascular events [4-6].

In conclusion, our study focused on the association between the preclinical phase of atherosclerosis in postmenopausal women and OPG levels, although this fact opens to 2 opposite explanations: OPG may exert a causal role of atherosclerotic damage; on the other hand, it may be considered as a defense against atherosclerosis. On the basis of the physiology of the menopausal age and the metabolic role of OPG, we are inclined toward the latter interpretation. Large studies will be needed to confirm this observation.

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