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Serum Osteoprotegrin (OPG) in Subclinical Atherosclerosis in Systemic Lupus Erythematosus

Adnan N. Kiani[1], **Pal Aukrust**[2], **Thor Ueland**[2], **Ivana Hollan**[3], **Erik Barr**[4], **Laurence S Magder**[4], and **Michelle Petri**[1]

[1]Johns Hopkins University School of Medicine, Division of Rheumatology [2]Oslo University Hospital [3]Lillehammer Hospital of Rheumatic Diseases [4]University of Maryland

Abstract

Introduction—Osteoprotegerin (OPG) is a member of the tumor necrosis factor (TNF) receptor family. It has recently been demonstrated that OPG is produced by a variety of tissues, including the cardiovascular system (heart, arteries, veins), lung, kidney, immune tissues, and bone. The OPG–RANKL signaling pathway is strongly related to vascular calcification. We determined the association of this biomarker with subclinical atherosclerosis in SLE.

Methods—We measured OPG and markers of subclinical atherosclerosis (coronary artery calcium CAC, carotid intima-media thickness (cIMT) carotid plaque) in 166 SLE patients (91% female, 64% Caucasian, 31% African-American, 5% others, mean age 45 yrs). Subgroups of patients with different levels of OPG level were compared with respect to average levels of CAC, cIMT, and with respect to presence of carotid plaque. Age was adjusted for using multiple regression.

Results—OPG was highly correlated with age ($p<.0001$). Those with higher levels of OPG tended to have higher measures of CAC, cIMT, and more carotid plaque. However, after adjustment for age, these associations, while still positive, were no longer statistically significant.

Conclusion—In our study much of the association observed was due to confounding by age, and after adjusting for age, our findings do not rule out the possibility of a null association.

Keywords

Systemic lupus erythematosus; inflammation; atherosclerosis; OPG; CT

Adnan N. Kiani M.D. M.P.H., Assistant Professor of Medicine, Johns Hopkins University, School of Medicine, 1830 East Monument Street Suite 7500, Baltimore MD 21205, USA.
Pal Aukrust, Oslo University Hospital, Oslo Norway, paukrust@ous-hf.no
Thor Ueland, Oslo University Hospital, Oslo Norway, thor.ueland@medisin.uio.no
Ivana Hollan M.D, Lillehammer Hospital of Rheumatic Diseases, Oslo Norway, ivana.hollan@gmail.com
Erik Barr B.A, M.S, Research and Data Analyst, University of Maryland, Baltimore MD 21201, ebarr@epi.umaryland.edu
Laurence S. Magder M.P.H. Ph.D., Professor of Epidemiology and Public Health, University of Maryland, Baltimore MD 21201
Michelle Petri M.D. M.P.H., Professor of Medicine, Johns Hopkins University, School of Medicine, Division of Rheumatology, 1830 East Monument Street Suite 7500, Baltimore MD 21205, USA.

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Introduction

Osteoprotegerin (OPG), a member of the tumor necrosis factor (TNF) receptor family, has been identified as a regulator of bone resorption (5). OPG is produced by a variety of organs and tissues, including the cardiovascular system (heart, arteries, veins), lung, kidney, and immune tissues, and bone (5,6). The expression and production of OPG is complex and is regulated by various cytokines and hormones (7). Human microvascular endothelial cells (HMVEC) express transcripts for OPG, and tumor necrosis factor- and interleukin-1 increase OPG expression 5–40-fold in HMVEC (8). Increased plasma levels of OPG have been found in patients with diabetes mellitus (9,10,11) and have also been associated with diabetic microvascular manifestations (11). Increased OPG levels have been seen in various autoimmune conditions including rheumatoid arthritis, Kawasaki's disease and Crohn's disease (12,13,14). We have previously shown OPG to be associated with measures of lupus nephritis (15).

Serum OPG has been implicated in the development of atherosclerosis in the general population. High levels were not only associated with overall cardiovascular mortality but were a novel marker for stroke in women (9). Other studies have shown high levels of OPG to be associated with cardiovascular disease (16,17). In a study of 201 patients who underwent coronary angiography due to stable chest pain, serum OPG levels were greater in patients with significant stenosis versus those without. There is also one study showing and independent association of OPG with subclinical atherosclerosis in SLE, but that study was restricted to premenopausal women (18). In another study plasma levels of OPG were significantly higher in patients with coronary and inflammatory rheumatic disease than in patients with coronary artery disease alone (19).

To further investigate the association of OPG with atherosclerosis in a general SLE population we investigated whether serum OPG was associated with subclinical measures of atherosclerosis, including coronary artery calcium (CAC) score, the occurrence of carotid plaque and carotid intima-media thickness (cIMT) at the baseline visit of patients participating in a randomized double-blind placebo-controlled trial of atorvastatin 40 mg versus matching placebo (20).

Methods

In this study, we analyzed baseline data from LAPS (a randomized double-blind placebo-controlled trial of atorvastatin 40 mg versus matching placebo), described elsewhere (20).

Study Participants

Study participants were members of the Hopkins Lupus Cohort who chose to participate in a randomized double-blind placebo-controlled trial of atorvastatin 40 mg versus matching placebo (20). Patients with a history of an atherosclerotic event (such as angina or myocardial infarction), were excluded. Of the two hundred patients enrolled in this trial, complete baseline data (including coronary artery calcium, cIMT, OPG levels) were available for 166 patients. All patients gave informed consent and the study was approved by

the Johns Hopkins University School of Medicine Institutional Review Board (NCT 00120887).

Coronary artery calcium was assessed by multidetector computerized tomography and cIMT and carotid plaque were assessed by carotid duplex ultrasound.

Measurement of Coronary Artery Calcification

Coronary artery calcification scores were calculated using Agatston scoring. Coronary artery calcification was assessed by multidetector computerized tomography with a Siemens Volume Zoom Scanner (Siemens Medical Solutions Malvern, Pa) using a 2.5 mm collimation and a slice width of 3 mm, with both scans done on the same machine. Data were reloaded into Siemens Leonardo workstation, using the Siemens calcium scoring software. Coronary artery calcification was quantified using a standard scoring system, available as part of the scanner software package (21). There is excellent reproducibility of coronary artery calcification using computed tomography (22).

Measurement of Carotid intima-media thickness and Carotid plaque

cIMT was measured using high resolution B-mode ultrasound to image the right and left common carotid arteries using a single ultrasound machine (Philips Medical Systems Sonos 5500) with a linear array 8-MHz scan head with standardized image settings, including resolution mode, depth of field, gain, and transmit focus. Digital imaging and communications in medicine (DICOM) images from a diastolic frame of the cine-loop recording were electronically stored and transferred via optical disk to an off-line work station for analysis. cIMT thickness was measured between the lumen intima and media-adventitia interfaces of the far wall of the common carotid artery (the 1 cm segment proximal to the bifurcation) by a single reader using an automated edge detection system. The mean intima-media thickness of this one cm segment was measured on two separate images of the left and the right common carotid artery at the peak of the R wave on a simultaneous electrocardiogram tracing. The mean of these four measurements was used as the intima-media thickness. We chose this location because of its demonstrated reproducibility compared with measurements of cIMT thickness at other sites (23,24). Both patients and providers were blinded to the intima-media thickness results until the 2-year follow-up examination was completed and each examination was considered as an independent study. Provider did not know the previous intima-media thickness results.

Carotid plaque was defined as focal protrusion into the lumen with a thickness at least 50% greater than the surrounding intima-media thickness (25,26).

Measurement of Osteoprotegrin

OPG was measured by EIA on stored serum sera. OPG was measured by EIA (R&D systems, Stillwater, MN) on stored serum sera (−80C, <3 freeze thaw cycles) as previously described and validated (27).

Statistical Methods

To assess the association between patient characteristics and OPG levels, we log-transformed the OPG measures (due to the skewness of the distribution) and compared patient subgroups with respect to mean log-transformed OPG. Statistical significance was based on an F-test from an ANOVA model. To assess the association between OPG and atherosclerosis, we divided the patients into subgroups based on tertials of OPG and compared these groups with respect to mean log-transformed coronary plaque score, mean intima-media thickness, and proportion with carotid plaque. To assess these associations, adjusting for age, we used multiple linear regression or logistic regression as appropriate. In these models, age was included as a continuous variable. In the analysis of coronary plaque score we transformed the score as log(score+1) so that those with a score of 0 were included in the analysis with a value of 0.

Results

The SLE patients were 91% female, 64% Caucasian, 31% African-American, and 5% other ethnicity. The mean age was 45 ± 11.3 years. The cumulative revised American College of Rheumatology classification criteria included: malar rash 62%, discoid rash 23%, photosensitivity 63%, oral ulcers 58%, arthritis 82%, serositis 52%, renal disorder 44%, neurologic disorder 10%, immunologic disorder 87% and ANA positivity 98%.

Values of OPG ranged from 309 to 6709 pmol/L. The mean OPG was 1656 (SD=928). The median was 1402. The distribution was skewed to the right.

Table 1 shows the association between OPG and the patient characteristics based on log-transformed values of osteoprotegin. OPG was highly correlated with age ($p<.0001$). OPG was also associated with hs-CRP ($p=0.0007$). African-Americans had higher OPG compared to Caucasians. However this difference as not statistically significant ($p=0.09$) (Table 1).

Table 2 shows the mean of the log-transformed coronary calcium score in subgroups defined by tertials of the OPG measure. It is evident that the mean coronary plaque score increases with higher levels of OPG, and these differences are statistically significant. Since both coronary plaque and OPG increase with age, this association is due, in part, to confounding by age. The right two columns of the table show the association between OPG and coronary plaque score after adjustment for age in a linear regression model. After adjustment for age, those with medium or high levels of OPG still had higher levels of coronary calcium, however, these differences did not reach statistical significance at the 0.05-level.

Table 3 shows the unadjusted and adjusted association between OPG and the mean cIMT. Similar to what was seen for the coronary calcium score, there was a significant association between OPG and intima-media thickness, but after adjustment for age, this association was strongly attenuated and no longer significant.

Table 4 shows the unadjusted and adjusted association between OPG and presence of carotid plaque. Among those with low OPG levels, only 3 (6%) had carotid plaque. However, among those with high levels of OPG, 16 (29%) had carotid plaque. After adjustment for

age, there is still an estimated increased odds of carotid plaque among those with medium or high levels of OPG (OR=3.1 and 3.2 respectively). However these increases are not statistically significant at the 0.05 level (p=0.11 and 0.10 for medium and high levels respectively).

Discussion

In this novel study of SLE patients, OPG was related to subclinical markers of atherosclerosis in terms of CAC, cIMT and c-plaque. However, these relationships were no longer significant after adjustments for age. Hence, the apparent association between OPG and the subclinical atherosclerosis markers appear to be confounded by its relationship to age, which is also positively related to cardiovascular risk. Thus, our study does not support the notion that OPG is an independent marker of cardiovascular risk in SLE: it might rather be a marker of aging. Indeed, also previous studies in the general population and in SLE patients demonstrated a positive relationship between OPG levels and age (10,28,29,30). Though, a real association between OPG and atherosclerosis cannot be definitely ruled out by our study, e.g. due to a relatively low sample size.

Previous studies indicated that the OPG/RANKL/RANK axis is implicated in atherogenesis (31). High OPG levels have been reported to be associated with a higher prevalence and severity of coronary artery disease (9,12,32). In a study of 490 white women greater than 65 years of age, serum OPG levels were greater among women with diabetes versus those without. These levels were also associated with all cause mortality not confounded by diabetes (OR 1.4, 95% C.I 1.2–1.8) (9).

OPG plays an important role in plaque stability. It binds with TRAIL, which is a potent activator of apoptosis. It therefore inhibits TRAIL induced apoptosis in vascular cells leading to plaque instability. In one study, OPG levels were significantly higher in patients with unstable angina compared to healthy controls (32).

OPG levels have been shown to be higher in patients with SLE. In a study of seventy-nine SLE patients with antiphospholipid antibody syndrome and ninety-two healthy controls, OPG levels were higher in SLE patients with APS and their levels correlated with APS antibodies titers (28). Serum OPG levels positively correlated with both anticardiolipin (aCL-IgG) and ant-beta 2 (αβ2GP1-IgG) ($p=0.026$, $p<0.001$). The mechanism of origin and association of OPG with antiphospholipid antibodies is uncertain but it is hypothesized that since antiphospholipid antibodies are associated with myocardial infarction and cardiac death. Therefore, OPG might be associated with antiphospholipid antibody syndrome.

In a study of 68 rheumatoid arthritis patients with no history of cardiovascular disease vs. controls, serum OPG levels were increased and correlated with cIMT thickness compared to controls (33). In line with hypothesis that ongoing inflammation within plaque and vascular insult may lead to increased OPG levels, our study showed a positive association between hs-CRP and serum OPG. Similar association between serum OPG and hs-CRP has been seen in diabetic patients (34).

This study has several potential limitations. First, due to relatively small sample size could be one of the reasons why our results differ from other studies, the lack of some associations might be due to a Type-2 error. Second, corticosteroids increase RANKL expression and thus decrease OPG levels, we did not look at this association (35). An advantage of our study is the opportunity to examine the relationship between OPG and several markers of atherosclerosis. In our study much of the association observed was due to confounding by age, and after adjusting for age, our findings do not rule out the possibility of a null association.

Acknowledgments

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Key Message

1. OPG was associated with subclinical measures of atherosclerosis.
2. This is the first study to look at three measures of subclinical atherosclerosis including coronary artery calcium, carotid plaque and carotid intima-media thickness.

Table 1

Mean (SD) log OPG by patient characteristics

Characteristic	n	Mean (SD) log OPG	P-value
Age			
<40	49	7.10 (0.48)	
40–49	59	7.27 (0.37)	<0.0001
50+	58	7.48 (0.49)	
Sex			
Female	151	7.30 (0.49)	0.77
Male	15	7.26 (0.19)	
Race			
Caucasian-American	106	7.25 (0.48)	
African American	51	7.41 (0.45)	0.09
Other	9	7.16 (0.41)	
BMI			
<18	3	6.97 (0.25)	
18–25	52	7.26 (0.46)	0.24[1]
25–30	55	7.25 (0.47)	
30+	56	7.38 (0.49)	
Total Cholesterol (mg/dl)			
<200	111	7.25 (0.48)	0.11
200+	55	7.38 (0.46)	
LDL (mg/dl)			
<100	85	7.25 (0.49)	
100–129	45	7.39 (0.49)	0.28
130+	36	7.28 (0.40)	
HDL (mg/dl)			
<40	20	7.23 (0.49)	
40–59	75	7.26 (0.49)	0.38
60+	71	7.35 (0.45)	
High Sensitivity CRP (mg/L)			
<1	43	7.14 (0.44)	0.0007
1–2.9	44	7.18 (0.47)	
3+	79	7.44 (0.45)	
SLEDAI			
0	81	7.32 (0.42)	
1–3	46	7.22 (0.51)	0.46
4+	39	7.33 (0.53)	

[1]P=0.054 for increasing log-opg by increasing BMI (body mass index),

OPG. Osteoprotegrin

SD. Standard deviation

Table 2

Association between OPG and mean log-transformed coronary calcium score

OPG Levels	Unadjusted for Age			Adjusted for Age	
	Mean log-transformed coronary plaque score	Mean Difference relative to low (95% Confidence Interval)	P-value	Mean Difference relative to low (95% Confidence Interval)	P-value
Low (n=55)	0.56	0.0 (Ref. Group)		0.0 (Ref. Group)	
Medium (n=55)	1.29	0.73 (0.03, 1.43)	0.042	0.51 (−0.16, 1.18)	0.14
High (n56)	1.81	1.25 (0.55, 1.94)	0.0005	0.66 (−0.05, 1.37)	0.069

OPG. Osteoprotegrin

Table 3

Association between OPG and carotid intima-media thickness

OPG Levels	Unadjusted for Age			Adjusted for Age	
	Mean carotid intima-media thickness	Mean Difference relative to low (95% Confidence Interval)	P-value	Mean Difference relative to low (95% Confidence Interval)	P-value
Low (n=55)	0.54	0.0 (Ref. Group)			
Medium (n=55)	0.57	0.04 (−0.00, 0.02)	0.069	0.02 (−0.01, 0.05)	0.26
High (n56)	0.60	0.06 (0.03, 0.10)	0.0011	0.02 (−0.01, 0.06)	0.24

OPG. Osteoprotegrin

Table 4

Association between OPG and presence of carotid plaque

OPG Levels	Unadjusted for Age			Adjusted for Age	
	Number (%) with carotid plaque	Odds Ratio (95% confidence interval)	P-value	Odds Ratio (95% confidence interval)	P-value
Low (n=54)	3 (6%)	1.0 (Ref. Group)		1.0 (Ref Group)	
Medium (n=55)	10 (18%)	3.8 (1.0, 14.)	0.054	3.1 (0.8, 12.4)	0.11
High (n=55)	16 (29%)	7.0 (1.9, 25.6)	0.0035	3.2 (0.8, 12.8)	0.10

OPG. Osteoprotegrin