Plasma Osteoprotegerin Levels in the General Population
Relation to Indices of Left Ventricular Structure and Function

Torbjørn Omland, Mark H. Drazner, Thor Ueland, Moeen Abedin, Sabina A. Murphy, Pål Aukrust, James A. de Lemos

Abstract—Osteoprotegerin, a member of the tumor necrosis factor receptor superfamily, has pleiotropic effects on bone metabolism, endocrine function, and the immune system. Myocardial expression and circulating levels of osteoprotegerin are increased in heart failure. The relationship between osteoprotegerin levels in the general population and indices of left ventricular structure and function is unknown. Plasma osteoprotegerin levels and cardiac MRI indices of left ventricular structure and function were available in 2715 subjects (median age: 44 years; 45% male) enrolled in the Dallas Heart Study. The associations between osteoprotegerin concentration and indices of left ventricular structure and function were assessed by linear regression analysis, adjusting for possible confounders. By gender-specific linear regression analysis, higher osteoprotegerin levels were significantly associated with higher left ventricular mass, left ventricular wall thickness, left ventricular concentricity index, and lower left ventricular ejection fraction ($P<0.001$ for all). After adjustment for age, race, fat-free mass, fat mass, hypertension, diabetes, coronary artery disease, estimated glomerular filtration rate, hypercholesterolemia, smoking status, hormone replacement therapy, coronary artery calcium score $>10$, and presence of aortic plaque, osteoprotegerin remained significantly associated with each of these left ventricular indices among male subjects ($P<0.05$ for each). Among female subjects, higher osteoprotegerin was independently associated with higher left ventricular end-systolic volume and lower ejection fraction ($P<0.0001$ for each) but not with indices of left ventricular hypertrophy. These findings are compatible with the theory that osteoprotegerin may play a pathophysiological role in the development of left ventricular hypertrophy and systolic dysfunction. (Hypertension. 2007;49:1392-1398.)

Key Words: osteoprotegerin • left ventricular • hypertrophy • hypertension • heart failure

Increased left ventricular mass, as assessed by electrocardiography or echocardiography, is a powerful and independent risk factor for subsequent cardiovascular events. Although contemporary pharmacological treatments, including neurohormonal antagonism with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, delay progression of left ventricular (LV) hypertrophy and deterioration of LV systolic function, the risk of cardiovascular and cerebrovascular complications remains high.

The pathophysiological mechanisms underlying the development of pressure-induced LV hypertrophy are complex. Traditionally, neurohormonal activation, including activation of the renin–angiotensin–aldosterone system, has been considered crucial for the hypertrophic process. More recently, inflammatory mediators have also been implicated in this process. Studies in animals have shown that overexpression of inflammatory cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor-α, induces LV hypertrophy. Moreover, increased levels of circulating markers of inflammation, including C-reactive protein (CRP), have been associated with LV hypertrophy in patients with hypertension, diabetes, and renal failure.

Osteoprotegerin (OPG) is a soluble member of the tumor necrosis factor receptor superfamily with pleiotropic effects on bone metabolism, endocrine function, and the immune system. OPG inhibits osteoclastogenesis by binding the receptor activator of nuclear factor κB ligand (RANKL), acting as a decoy receptor to competitively inhibit RANKL interaction with its receptor, receptor activator of nuclear factor κB (RANK). Recently, the OPG/RANKL/RANK axis has been implicated in the development of ventricular failure and been shown to predict survival in patients with postinfarction heart failure. Based on this information, we hypothesized that circulating levels of OPG would associate with indices of LV mass, dimensions, and function in the general population. Using cardiovascular MRI, a method that

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permits accurate, unbiased determination of LV anatomy and function without geometric assumptions regarding ventricular shape, we related circulating OPG levels to cardiac MRI findings, adjusting for potential confounders.

Methods

Patient Population

The Dallas Heart Study is a population-based, multiethnic sample of Dallas County, Tex, residents aged 18 to 65 years, collected between July 2000 and September 2002. Details of the study design and characteristics of the subject cohort have been reported previously.16 The probability sample was obtained from a randomly selected pool of 841,943 eligible subjects who were oversampled to enrich the ethnic diversity of the cohort. The initial home visit included a detailed survey for health information and measurement of weight, heart rate, and blood pressure. Subjects aged 30 to 65 years who completed the initial home visit were invited for a second visit to collect fasting blood and urine samples. If they completed the second visit, subjects were asked to return for a third detailed clinic visit. At the third visit, subjects aged 30 to 65 years underwent sophisticated imaging studies, including cardiac MRI and dual-energy x-ray absorptiometry scanning. No significant differences were noted in demographics, medical history, blood pressure, or body mass index between subjects participating in the home interview (n=6101) and the phlebotomy visit (n=3557). Moreover, standard laboratory values were similar between those participating in the phlebotomy (n=3557) and clinic (n=2971) visits. For purposes of the present analyses, we included all of the patients who had measurement of OPG and underwent a cardiac MRI (n=2715). The investigation was approved by the University of Texas Southwestern Institutional Review Board, and all of the participants provided written, informed consent. The study adheres to the principles outlined in the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001. All of the procedures followed were in accordance with institutional guidelines.

Cardiac Imaging Studies

Cardiac MRI was performed using a 1.5 T MRI system (Philips Medical Systems), as described previously.17 LV end-diastolic volume, end-systolic volume, and ejection fraction were calculated from short-axis sequences. Consecutivity index was defined as the ratio of LV mass/LV end-diastolic volume. To determine interobserver variability, patients were scanned once, taken off the scanner briefly, and then rescanned. Interobserver difference for LV mass was 9.2±5 g (n=15), intraobserver difference was 10.5±8.6 g (n=8), and interscan variability was 4.9±10.9 g (n=8). Interobserver difference for LV end-systolic volume was 2.6±2.7 mL, intraobserver difference was −2.7±0.4 mL, and interscan variability was 0.3±3.5 mL. Interobserver difference for LV end-diastolic volume was −3.0±9.4 mL, intraobserver difference was −2.7±3.2 mL, and interobserver variability was −2.3±8.9 mL. Interobserver difference for LV ejection fraction was −3±4%, intraobserver difference was 1±1%, and interscan variability was −1.3±2.5%. Coronary artery calcium was measured by electron beam CT scan in all of the subjects as described previously and was considered present if the Agatston score was ≥10.18 Aortic plaque was measured by MRI (n=2406) as described previously and categorized as present or absent.18

Laboratory Measurements

After an overnight fast, venous blood was collected into EDTA tubes and centrifuged at 1430g for 15 minutes at 4°C. The plasma component was removed and frozen at −80°C until assays were performed. OPG measurements were performed in duplicate on thawed samples. Plasma OPG was quantified by an enzyme immunoassay using commercially available matched antibodies (R&D Systems). The intraassay and interassay coefficients of variation were 3.6% and 10.6%, respectively. The sensitivity, defined as the mean±3 SD of the 0 standard, was calculated to be 15 pg/mL.14 CRP measurements were performed using a commercially available high-sensitivity assay (Roche Diagnostics). N-terminal pro-B-type natriuretic peptide (Eliksys, Roche Diagnostics) and B-type natriuretic peptide (Biosite Inc) were measured using well-validated commercially available assays. The coefficient of variation for the B-type natriuretic peptide assay averaged 11.2% at a concentration of 30 ng/mL and 5.8% at concentrations >60 ng/mL, and the coefficient of variation for the N-terminal pro-B-type natriuretic peptide assay was 3.3% at a concentration of 282 ng/mL and 3.0% at a concentration of 6012 ng/mL.

Definitions of Variables

Sex, ethnicity, and age were self-reported. Complete medication profiles were obtained at the first visit. Hypercholesterolemia was defined as a calculated low-density lipoprotein cholesterol ≥160 mg/dL on a fasting sample, direct low-density lipoprotein ≥160 mg/dL on a nonfasting sample, total cholesterol ≥200 mg/dL, or use of statin medication. Hypertriglyceridemia was defined as a fasting triglyceride concentration ≥200 mg/dL, and low high-density lipoprotein was defined as high-density lipoprotein <40 mg/dL in males and <50 mg/dL in females. Five sequential blood pressure measurements were averaged for the first subject visit. Hypertension was defined as an average systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication. Diabetes was defined by a fasting glucose level ≥126 mg/dL, a nonfasting serum glucose level ≥200/mL, or use of any hypoglycemic medication.

Statistical Analysis

Categorical data are reported as proportions and continuous data as median values with interquartile ranges (25th to 75th percentile). Because circulating levels of OPG were significantly higher in female than in male study subjects, demographic variables and cardiovascular risk factors were compared across sex-specific quartiles of OPG using the Pearson χ² trend test for categorical variables and the test for trend across ordered groups for continuous variables. Associations between OPG levels, log transformed to account for skewness of the OPG distribution, and indices of LV structure and function were determined using a series of univariable and multivariable linear regression models. The first model (see Table 5) adjusts for conventional risk factors for LV hypertrophy and coronary artery disease, that is, age, race, fat-free mass, fat mass, hypertension, diabetes, coronary artery disease, glomerular filtration rate estimated using the Modification of Diet in Renal Disease equation (glomerular filtration rate=186×creatinine⁻¹·⁰⁴⁰×age⁻⁰·⁸⁰⁰×constant[constant=1 for a white male and is multiplied by 0.742 for females and multiplied by 1.21 in African Americans]), total cholesterol, smoking, and hormone replacement therapy (in women). To assess whether OPG provides additional information to the most widely used inflammatory marker, the second model (see Table 5) adjusts for conventional risk factors and CRP. To document that the association between OPG and LV function and structure was not secondary to coronary artery disease, the last model (see Table 5) adjusts for conventional cardiovascular risk factors and markers of coronary and aortic calcification, that is, coronary artery calcium score >10 and prevalent aortic plaque. To assess potential effect modification by sex on the association between OPG and LV mass indices, a series of 3-factor analyses was performed and the change in stratum-specific estimates evaluated.

Results

Patient Characteristics

The characteristics of study subjects according to sex-specific OPG quartile are presented in Table 1. OPG levels were higher among women than among men (1281 pg/mL [range: 938 to 1750 pg/mL] versus 1114 pg/mL [range: 827 to 1439 pg/mL]; P<0.001); thus, all of the analyses are presented in
sex-specific quartiles. Study subjects with higher OPG levels were more likely to be older, to be postmenopausal, to be using hormone replacement, and to be of nonwhite ethnicity. Moreover, higher OPG levels were associated with some conventional coronary risk factors, including current smoking, hypercholesterolemia, a diagnosis of diabetes mellitus, hypertension, increased pulse pressure, and family history of coronary heart disease, but only weakly related to others, including body mass index. OPG levels were also associated with other biochemical risk markers, including CRP and BNP.

### Relation to LV Structure and Function
Cardiac MRI and electron beam CT findings by sex-specific OPG quartiles are presented in Table 2. Sex-specific predictors of LV mass are presented in Table 3. By sex-specific, univariable linear regression analyses, OPG was positively associated with LV mass, LV mass indexed to fat-free mass or body surface area, LV wall thickness, and LV concentricity index; OPG was inversely associated with LV ejection fraction (Table 4). The association between OPG and LV end-systolic volume was borderline significant, and there was no significant association between OPG and LV end-diastolic volume. After adjustment for potential confounders in sex-specific multivariable models, OPG remained significantly associated with LV mass, LV wall thickness, and LV concentricity index in men but not women (Table 5). However, higher levels of OPG were independently associated with other biochemical risk markers, including CRP and BNP.
associated with higher LV end-systolic volume and lower ejection fraction in both sexes.

To elucidate whether specific covariables affected the association between OPG and LV mass differentially in males and females, individual variables were added to the linear regression model in which log OPG was the independent variable and LV mass the dependent variable. In this model, the \( \beta \)-coefficient (SE) for LV mass in males was 6.3 (2.3) and in women was 6.3 (1.5). Addition of fat-free mass to the model strengthened the association in males but not in females (\( \beta \)-coefficient [SE] for LV mass in males versus females: 9.5 [1.8] versus 4.7 [1.1]). The remaining variables altered the OPG-LV mass relationship equally in both sexes or to a lesser extent (data not shown).

**Discussion**

The important new information obtained from the current study is that OPG, a soluble member of the tumor necrosis factor receptor superfamily with pleiotropic effects on bone metabolism, endocrine function, and the immune system, is independently associated with LV function in both sexes and with LV hypertrophy and concentric remodeling in male subjects drawn from the general population. Recent epidemiological and clinical evidence from human studies suggest that the OPG/RANK/RANKL axis is linked to vascular disease. Elevated serum OPG levels have been associated with the progression of vascular calcification, with the presence and severity of coronary artery disease, with cardiovascular mortality in elderly women, and in patients with chronic renal failure, and with future cardiovascular events in the general population. However, to the best of our knowledge, this is the first study reporting a relation between OPG and LV mass and between OPG and LV systolic function in a population-based study.

Because of the cross-sectional design of our study, we cannot deduce whether higher OPG is causally linked to an increase in LV mass and decrease in LV function or whether it merely represents an epiphenomenon. However, the study subjects were drawn from a general population sample with a low prevalence of pre-existing disease, and in male subjects the association between OPG and LV mass indices persisted after statistical adjustment for potential confounders, including a history of hypertension, diabetes, and coronary heart disease. Moreover, a plausible biological link exists between

<table>
<thead>
<tr>
<th>Variable</th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>P Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>743</td>
<td>740</td>
<td>741</td>
<td>741</td>
<td></td>
</tr>
<tr>
<td>Coronary artery calcium score &gt;10</td>
<td>100 (15)</td>
<td>108 (16)</td>
<td>152 (22)</td>
<td>220 (32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Aortic plaque present</td>
<td>200 (32)</td>
<td>229 (37)</td>
<td>243 (41)</td>
<td>294 (53)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>154 (129, 185)</td>
<td>155 (130, 187)</td>
<td>159 (132, 189)</td>
<td>165 (138,195)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV mass/BSA, g/m²</td>
<td>81 (71, 92)</td>
<td>80 (71, 92)</td>
<td>81 (71, 94)</td>
<td>84 (74, 98)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV end-diastolic volume, mL</td>
<td>100 (85, 117)</td>
<td>100 (87,116)</td>
<td>98 (85, 115)</td>
<td>97 (83, 114)</td>
<td>0.016</td>
</tr>
<tr>
<td>LV end-diastolic volume/BSA, mL/m²</td>
<td>53 (47, 60)</td>
<td>52 (46, 59)</td>
<td>52 (45, 58)</td>
<td>51 (44, 59)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV end-systolic volume, mL</td>
<td>26 (20, 33)</td>
<td>27 (20, 35)</td>
<td>27 (21, 35)</td>
<td>27 (20, 35)</td>
<td>0.088</td>
</tr>
<tr>
<td>LV end-systolic volume/BSA, mL/m²</td>
<td>14 (11, 17)</td>
<td>14 (11, 18)</td>
<td>14 (11, 17)</td>
<td>14 (11, 18)</td>
<td>0.119</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>74 (69, 78)</td>
<td>73 (68, 77)</td>
<td>72 (67, 77)</td>
<td>72 (67, 77)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BSA indicates body surface area. Continuous variables reported as median (25th, 75th percentiles) and categorical values as number (percentage of quartile).

**TABLE 3. Predictors of LV Mass: Sex-Specific, Multivariable Analyses**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male Coefficient (SE)</th>
<th>Male P</th>
<th>Female Coefficient (SE)</th>
<th>Female P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log osteoprotegerin, pg/mL</td>
<td>5.6 (1.8)</td>
<td>0.002</td>
<td>1.8 (1.1)</td>
<td>0.095</td>
</tr>
<tr>
<td>Age, y</td>
<td>-0.004 (0.1)</td>
<td>0.97</td>
<td>0.17 (0.08)</td>
<td>0.044</td>
</tr>
<tr>
<td>White race</td>
<td>-5.1 (2.2)</td>
<td>0.021</td>
<td>-3.4 (1.5)</td>
<td>0.026</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>0.002 (0.0001)</td>
<td>&lt;0.001</td>
<td>0.03 (0.0001)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>-0.0002 (0.0002)</td>
<td>0.28</td>
<td>-0.0004 (0.00008)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23.2 (2.5)</td>
<td>&lt;0.0001</td>
<td>16.8 (1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>-0.9 (3.3)</td>
<td>0.79</td>
<td>-3.2 (2.2)</td>
<td>0.135</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>24.0 (5.2)</td>
<td>&lt;0.0001</td>
<td>11.1 (4.5)</td>
<td>0.014</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, mL/min</td>
<td>0.6 (0.4)</td>
<td>0.17</td>
<td>0.08 (0.03)</td>
<td>0.004</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>-0.03 (0.03)</td>
<td>0.29</td>
<td>0.002 (0.02)</td>
<td>0.89</td>
</tr>
<tr>
<td>Smoking</td>
<td>5.2 (2.2)</td>
<td>0.016</td>
<td>7.9 (1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>NA</td>
<td>NA</td>
<td>-4.1 (1.7)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

NA indicates not applicable.
inflammation, pressure overload and LV hypertrophy. In spontaneously hypertensive rats and in experimental renovascular hypertension in rats, macrophages accumulate in the perivascular space in close proximity to collagen-producing fibroblasts. In a suprarenal abdominal aortic banding rat model, pressure overload induces rapid induction of endothelial cell activation and macrophage accumulation in the perivascular area. In humans, increased CRP levels have been linked to LV hypertrophy in diabetics, and microalbuminuria accompanied by biochemical evidence of low-grade inflammation has been associated with the presence of concentric hypertrophy in nondiabetic hypertensive patients. Taken together, these observations suggest that pressure overload generates a potent proinflammatory stimulus.

Circulating OPG levels appear to be a stable and reliable marker not only of bone homeostasis and vascular calcification, but also of inflammation, and the ability of OPG to predict LV mass may also reflect its ability to mirror pressure-independent inflammatory mechanisms in the development of LV dysfunction. OPG was originally identified as a candidate mediator for paracrine signaling in bone metabolism. We have shown previously that both experimental and clinical heart failure are associated with increased expression of the OPG/RANKL/RANK axis. The robust association between LV ejection fraction and OPG levels observed in this large, population-based sample extends previous observations made in small groups of animals and patients with manifest heart failure. Importantly, our current findings demonstrate that OPG levels are elevated in subjects with only mildly impaired ventricular systolic function, suggesting that OPG/RANKL/RANK system activation is an early phenomenon in the process of ventricular dysfunction and heart failure development.

Because OPG circulates at much higher levels than RANKL, it may be a more stable overall measure of RANKL/ RANK activity and more suited for clinical use than quantification of circulating RANKL concentrations. Our observations are compatible with the theory that activation of the OPG/RANKL/RANK system may not only be a marker of development of heart failure but also a mediator in this process, at least partly, by promoting matrix degradation, inflammation, and ventricular remodeling. In addition, recent data suggest that OPG is not only a modulator of RANKL, but may also have RANKL-independent effects, such as induction of monocyte chemotaxis. Moreover, OPG could act as a survival factor for serum-deprived smooth muscle cells, and if a similar mechanism is operative in cardiomyocytes, it could be of relevance for the development of LV hypertrophy.

Although the current study was not designed to identify the source(s) of circulating OPG, recent studies suggest that the cardiovascular system may be an important contributor to circulating OPG levels. We have recently shown strong OPG immunostaining within the failing human myocardium, and it is possible that the association of circulating OPG levels with LV mass and function may reflect the contribution of the myocardium itself to circulating OPG levels.

The crude relationships between OPG and LV mass were not markedly different in men and women. The reason for the weaker associations between OPG and LV mass in women after adjustment for potential confounders remains unclear. Adding individual covariables to the OPG-LV mass model did not reveal specific variables that could fully explain the attenuation of the relationship in females. However, the differential effect of adjustment for fat-free mass may suggest that this variable may play a role. In general, women had higher OPG levels than men, which may suggest important interactions between sex steroids and the OPG/RANKL/RANK axis. Accordingly, exploration of the association between OPG and sex hormones may be required to understand the differential associations between OPG and LV mass between sexes.

In the current study, use of hormone replacement therapy was associated with higher OPG levels. This finding is in line with other cross-sectional studies of patients with Crohn disease between 18 and 50 years and elderly women but apparently in contrast to the results of intervention studies examining the effect of hormone replacement therapy. Potential explanations for this apparent discrepancy include differences in study populations and methodology for assessing OPG activity. However, we believe the most likely explanation is related to the confounding effect of an associ-
ation between altered bone metabolism and the use of hormone replacement therapy in cross-sectional studies. In other words, women with disturbances in bone metabolism may have higher OPG levels and may also be more frequent users of hormone replacement therapy. Several studies have examined the association between OPG and blood pressure with conflicting results. In the current study, we found a weak but highly significant association between OPG and blood pressure. Because our data are population based and compose the largest cohort examining the association between OPG and blood pressure, we believe that these findings are important. However, we cannot conclude based on the current data that OPG is related to blood pressure in other ethnic groups than those included in the Dallas Heart Study.

**Strengths and Limitations**

Strengths of the current study include the use of an accurate method for estimation of LV structure and function in a large sample of subjects drawn from the general population. Limitations include the cross-sectional design, which does not provide information concerning the temporal sequence of OPG elevation, and the development of LV hypertrophy and dysfunction.

### Perspectives

We have shown that in a large contemporary study of subjects drawn from the general population, plasma OPG levels are independently associated with indices of LV hypertrophy in male but not female subjects. In contrast, OPG levels are independently and inversely associated with LV systolic function in both sexes. These findings are compatible with the theory that the OPG/RANKL/RANK system may play a pathophysiological role in the development of hypertrophy and systolic impairment of the left ventricle, which may contribute to the association between OPG and cardiovascular outcomes observed in recent cohort studies. However, serial measurement of OPG and LV function and structure will be required to further elucidate whether the OPG/RANKL/RANK system is likely to be a pathophysiological mediator or merely an epiphenomenon.

### Conclusions

This population-based study provides strong evidence that OPG is independently associated with indices of LV function in both sexes and with indices of LV hypertrophy in male but not female subjects.
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Disclosures
P.A. and T.U. are listed as coinventors on a pending patent application on the use of osteoprotegerin as a prognostic marker in cardiovascular disorders. The remaining authors report no conflicts.

References
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