Low Serum Levels of Soluble RANK Ligand Are Associated With the Presence of Coronary Artery Disease in Men

To the Editor:

Receptor activator of nuclear factor-kB ligand (RANKL) and osteoprotegerin (OPG) represent the ligand and decoy receptor, respectively, of a pleiotropic cytokine system that regulates bone metabolism and vascular biology.1 Elevated OPG serum levels have recently been shown to be associated with increased cardiovascular mortality in postmenopausal women.2 In the September 3, 2002 issue of Circulation, Jono et al3 reported increased OPG serum levels in 201 Japanese patients with coronary artery disease (CAD) and a positive correlation of OPG serum levels with the severity of CAD. In a cohort of 522 white men who underwent coronary angiography, we have confirmed that OPG serum levels are highest in those with advanced CAD,4 indicating that these findings are independent of geographic and ethnic differences.

However, because OPG acts by neutralizing the ligand, RANKL, we hypothesized that serum levels of soluble RANKL (sRANKL) are also altered in CAD. To test this hypothesis, we assessed sRANKL serum levels in a well-characterized cohort consisting of 346 age-matched white men (mean age 59.7±8.8 years) undergoing coronary angiography for suspected CAD. Of those, 106 men had no coronary or luminal irregularities, and 240 patients were found to have CAD. Serum levels of sRANKL were measured by an ELISA system (Biomedica) that detects free sRANKL, but not sRANKL complexed to OPG. Soluble RANKL serum levels were significantly lower in patients with CAD (0.50±0.56 pmol/l) compared with those without CAD (0.60±0.60 pmol/l, P=0.009), but in contrast to OPG serum levels, were not correlated with the severity of CAD. Moreover, sRANKL serum levels were not correlated with age, creatinine serum concentrations, body mass index, or the presence of diabetes, arterial hypertension, or hyperlipidemia. They were, however, correlated negatively with OPG serum levels (r=-0.19, P=0.01).

Thus, although OPG serum levels increase with progression of CAD,3,4 our data indicate that sRANKL serum levels are lower in patients with CAD. These concurrent changes of sRANKL and OPG result in a net decrease of the RANKL-to-OPG ratio. Because a high RANKL-to-OPG ratio is associated with profound arterial calcification in OPG-deficient mice that can be rescued by administration of an OPG transgene,5 the findings of low sRANKL-to-OPG ratios in men with CAD are unexpected, and may represent an insufficient counter-regulatory mechanism that needs to be further evaluated.

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Response
We thank Drs Schoppe, Schaefer, and Hofbauer for their comments about our study of the association between serum osteoprotegerin (OPG) levels and the severity of coronary artery disease (CAD).6 They have confirmed that serum OPG levels are significantly greater in patients with advanced CAD than in those without CAD. Interestingly, they found that the serum levels of soluble receptor activator of nuclear factor-kB ligand (RANKL) were significantly lower in patients with CAD than in those without CAD, and that serum soluble RANKL levels were correlated with serum OPG levels. In histological study, RANKL and OPG immunoreactivity was demonstrated in the nondiseased vessel wall and in the early atherosclerotic lesions in human tissues.2 RANKL was present in the extracellular matrix surrounding the calcium mineral deposits of the plaques. Moreover, RANKL transcripts are detected in the calcified arteries of OPG deficient mice.3 These findings suggest that RANKL may be involved in the regulation of mineralization in atherosclerotic lesions. The RANKL/OPG system may have an important role in the regulation of vascular disease. RANKL, OPG, and RANKL-to-OPG ratio measurement in the serum may help to evaluate the activity of vascular disease.

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