INVITED COMMENTARY

Serum measurement of osteoprotegerin – clinical relevance and potential applications

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The tumor necrosis factor ligand superfamily member receptor activator of nuclear factor- κ B (NF- κ B) ligand (RANKL), its cellular receptor, receptor activator of NF- κ B (RANK), and the decoy receptor, osteoprotegerin (OPG) represent a novel cytokine triad with pleiotropic effects on bone metabolism, the immune system, and endocrine functions (1). RANKL is produced by osteoblastic lineage cells and activated T lymphocytes (2–4) and stimulates its receptor, RANK, which is located on osteoclasts and dendritic cells (DC) (4, 5). The effects of RANKL within the skeleton include osteoblast–osteoclast cross-talks, resulting in enhanced differentiation, fusion, activation, and survival of osteoclasts (3, 6), while in the immune system, RANKL promotes the survival and immunostimulatory capacity of DC (1, 7). OPG acts as a soluble decoy receptor that neutralizes RANKL, thus preventing activation of RANK (8). The RANKL/RANK/OPG system has been implicated in various skeletal and immune-mediated diseases characterized by increased bone resorption and bone loss, including several forms of osteoporosis (postmenopausal, glucocorticoid-induced, and senile osteoporosis) (9), bone metastases (10), periodontal disease (11), and rheumatoid arthritis (2). While a relative deficiency of OPG has been found to be associated with osteoporosis in various animal models (9), the parenteral administration of OPG to postmenopausal women (3 mg/kg) was beneficial in rapidly reducing enhanced biochemical markers of bone turnover by 30–80% (12).

These studies have clearly established the RANKL/OPG system as a key cytokine network involved in the regulation of bone cell biology, osteoblast–osteoclast and bone-immune cross-talks, and maintenance of bone mass. In addition to providing substantial and detailed insights into the pathogenesis of various metabolic bone diseases, the administration of OPG may become a promising therapeutic option in the prevention and treatment of benign and malignant bone disease.

Several studies have attempted to evaluate the clinical relevance and potential applications of serum OPG measurements in humans. Yano *et al.* were the first to assess systematically OPG serum levels (by an ELISA system) in women with osteoporosis (13). Intriguingly, OPG serum levels were negatively correlated with

bone mineral density (BMD) at various sites (lumbar spine, femoral neck, and total body) and positively correlated with biochemical markers of bone turnover. In view of the established protective effects of OPG on bone, these findings came as a surprise, and were interpreted as an insufficient counter-regulatory mechanism to prevent bone loss. Another group which employed a similar design (but a different OPG ELISA system) could not detect a correlation between OPG serum levels and biochemical markers of bone turnover (14), but confirmed the negative correlation of OPG serum concentrations with BMD in postmenopausal women (15). In a recent study, Szulc and colleagues (16) evaluated OPG serum levels in an age-stratified male cohort, and observed positive correlations of OPG serum levels with bioavailable testosterone and estrogen levels, negative correlations with parathyroid hormone (PTH) serum levels and urinary excretion of total deoxypyridinoline, but no correlation with BMD at any site (16). The finding that PTH serum levels and gene expression of OPG by bone cells are inversely correlated was also reported in postmenopausal women (17), and systemic administration of human PTH(1–34) to postmenopausal women with osteoporosis inhibited circulating OPG serum levels (18). Finally, a study of patients with renal diseases showed a decline of serum OPG levels following initiation of systemic glucocorticoid therapy (19). The regulation pattern of OPG by systemic hormones has been described *in vitro*, and has led to the hypothesis that most hormones and cytokines regulate bone resorption by modulating either RANKL, OPG, or both (9). Interestingly, several studies showed that serum OPG levels increased with ageing and were higher in postmenopausal women (who have an increased rate of bone loss) as compared with men, thus supporting the hypothesis of a counter-regulatory function of OPG in order to prevent further bone loss (13–16).

In this issue of the *Journal*, Ueland and associates (20) add another important piece to the picture of OPG regulation in humans *in vivo*. By studying well-characterized patient cohorts with endocrine and immune diseases such as Cushing's syndrome, acromegaly, growth hormone deficiency, HIV infection, and common variable immunodeficiency (CVI), the investigators reported

increased OPG serum levels in both groups with persistent immune activation (HIV, CVI) which were positively correlated with serum levels of tumor necrosis factor (TNF)- α . TNF- α is a known stimulator of OPG production *in vitro* (9) and, especially in advanced HIV infection, is considered to be an important contributor to chronic wasting and other HIV-associated diseases. Of note, patients with Cushing's syndrome had increased OPG serum levels. This latter finding is in contrast to a study in which systemic glucocorticoid therapy led to decreased OPG serum levels (19), and was thought to represent a compensatory mechanism in response to enhanced bone resorption and bone loss observed in Cushing's syndrome. In summary, these data provide further evidence that the immune system and bone metabolism may be linked through the RANKL/OPG system, but do not allow us to attribute OPG a role as cause or consequence of bone loss.

The clinical significance of OPG serum levels has just recently started to emerge, and ongoing studies are currently designed to evaluate the role of this parameter as a biochemical marker for risk stratification, assessment of disease activity, and drug monitoring in metabolic bone diseases. One recent study even suggests that serum levels of OPG may serve as a cardiovascular risk factor (21). Postmenopausal women within the highest quintile of OPG serum levels had a fourfold higher relative risk of cardiovascular mortality which indicates a potential involvement of OPG in the pathogenesis of vascular diseases such as arterial calcification and atherosclerosis (21). These results may reflect the ubiquitous production of OPG which, in addition to the skeleton and the vascular system, is also produced by a variety of other tissues and cell types. Therefore, OPG production by tissues other than bone and the vascular system may contribute to the serum pool of OPG. Other important caveats that need to be considered when interpreting serum OPG measurement studies include the comparability of the OPG protein measurement systems in terms of specificity, sensitivity, and the ability to discern between the free and the RANKL-bound OPG form. Assessment of local and systemic levels of OPG, development and evaluation of sensitive RANKL protein assays, and correlation of RANKL, OPG, and the RANKL-to-OPG ratio with other markers of bone formation and resorption, disease activity, or response to therapy may help to determine whether RANKL and OPG measurement in the serum can live up to the great expectations.

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