



Cardiovascular disease and bone loss—new research in identifying common disease pathophysiologies and predictors

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Cardiovascular diseases (CVDs) including coronary heart disease, with associated outcomes such as heart attack and stroke, are the number one cause of death worldwide (1). The World Health Organization estimates that >17 million people die annually due to CVD (1). Osteoporosis, or bone disease, is another common disease resulting in almost 9 million bone fractures globally per year (2); 1 in 3 women, and 1 in 5 men over the age of 50 will experience an osteoporotic fracture in their lifetime (3,4). Fractures are associated with significant morbidity and mortality (5-7), and are a major health concern. As highlighted by the global statistics, both CVD and osteoporosis each contribute independently to a large disease burden worldwide.

Research demonstrates that CVD and osteoporosis often present concurrently. Shared risk factors, such as aging, smoking, low physical activity, and elevated body mass index (BMI), suggest that these disease states may have a shared pathophysiology. For example, women with osteoporosis have a 3.9-fold increased risk for experiencing a cardiovascular event (8). Reduced bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) is also associated with increased CVD risk in postmenopausal women and in older men (9,10). Some evidence indicates a stronger inverse association between bone health and CVD in women compared with men (11,12), with estrogen deficiency suggested as a major contributing factor (11,12). However, a recent systematic review and meta-analysis reported that after adjusting for sex (among other parameters), decreased BMD remained significantly

associated with an increased incidence of atherosclerotic vascular abnormalities (13). These findings suggest that BMD is a strong independent predictor of CVD risk, and that this association is evident in both men and women.

The exact shared pathophysiology between CVD and bone loss is unclear. Circulating cytokines that help regulate both cardiovascular and bone health have been suggested as one mechanism (14,15). Osteoprotegerin (OPG), for example, regulates both bone and vascular metabolism (i.e., vascular calcification) (16-18). OPG is a soluble glycoprotein that is distributed in tissues throughout the body (18) including bone-building cells (osteoblasts) (19), and regulates bone resorption by preventing the formation and survival of bone resorption cells (osteoclasts) via inhibition of receptor activator of NF- κ B ligand (RANKL) (20). OPG knockout mice have increased osteoclast activity resulting in decreased total BMD, trabecular and cortical porosity, an increased number of osteoclasts, and develop spontaneous fractures (21). In clinical studies, increased OPG is associated with fractures (22-24); for example, in a case-control study of 69 postmenopausal women post hip fragility fracture, there were a higher number of women with fracture at increasing OPG concentrations (22). Increased serum OPG is also independently associated with increased risk of hip fracture in postmenopausal women (25).

In addition to its bone specific effects, OPG is released from vascular smooth muscle cells in response to inflammatory stimuli, playing a protective role in reducing vascular inflammation and atherosclerosis (15). OPG is

thought to inhibit vascular calcification through RANKL inhibition (RANKL has pro-calcific actions) (26). Studies in knockout OPG mice demonstrate an increase in vascular calcification, and that OPG inhibits vascular calcification by regulating RANKL (26). In contrast, clinical studies report that high OPG levels are associated with vascular calcification and arterial stiffness. In one study OPG was an independent predictor of pulse wave velocity (and indication of arterial stiffness) in postmenopausal women with osteoporosis (27). In a large prospective trial, OPG levels were measured at baseline in patients with coronary artery disease, who were then followed for up to 6 years for cardiovascular events and all-cause mortality. OPG was statistically higher in non-survivors compared to survivors, and was an independent predictor of mortality after adjusting for clinical and conventional cardiovascular risk markers (28).

Research supports that OPG has a role in both regulating bone and cardiovascular health; high OPG levels are evident in both diseases. However, most of the published literature linking OPG to bone and cardiovascular health has focused on women, or has been conducted in cohorts of both women and men (23,28-35). Although men have a lower incidence of osteoporosis and fracture (3,4), following hip fracture they less often receive treatment for osteoporosis, and have higher mortality compared to women (36). Men also have a higher rate of CVD, and CVD related mortality when compared to women (1). Research supports a sex-mediated difference in OPG with men tending to have overall lower levels of OPG than women (34,37). Despite the inherent sex related OPG differences in men *vs.* women, to our knowledge, there are no studies published to date that focus on OPG, bone and cardiovascular risk prediction in only men.

This research gap was addressed in a recent publication in the *Journal of Bone and Mineral Research* titled “Prediction of fractures and major cardiovascular events in men using serum osteoprotegerin levels: the prospective STRAMBO study” (38). Szulc and colleagues (38) evaluated the associations of OPG with CVD and fracture risk prospectively, in 819 men (60 years of age and older), from The Structure of Aging Men’s Bones (STRAMBO) cohort. OPG, BMD by DXA (at the spine and hip), abdominal aortic calcification on lateral DXA, and other serum measures (such as testosterone) were measured at baseline. Men were then followed up prospectively for 8 years, and completed a yearly questionnaire that collected information about incident fractures and cardiovascular events.

Additional study visits were completed at year 4 and 8 (38).

Serum OPG positively correlated with age ($r=0.45$, $P<0.001$). BMI did not differ by OPG status. The presence of ischemic heart disease increased with higher OPG ($P<0.001$), as did diabetes mellitus ($P<0.001$) (38). Over the 8-year follow-up period, 106 men reported a fragility fracture. When OPG was grouped by quartile, fragility fracture incidence was similar among the lowest three quartiles (percentage of men with fracture in Q1 =11%, Q2 =12%, and Q3 =12%), but was higher in the highest quartile (Q4 =18%). Vertebral fracture incidence also increased across the OPG quartiles. The odds ratio (OR; 95% CI) for incident vertebral fractures (when adjusted for FRAX score calculated by the FRAX tool) in the highest OPG quartile was 2.47 (1.00–6.17); 2-fold higher in OPG Q4 *vs.* OPG Q1. Cardiovascular events (including heart attack, and sudden death), were reported in 53 men over the 8 years. The risk of major adverse cardiovascular events increased as OPG increased. The highest quartile of OPG was associated with an almost 4-fold increase in CV events compared to the lowest quartile (OR =3.93; 95% CI =1.54–10.04; when adjusted for age, weight, alcohol intake, presence of co-morbidities, treatment, and blood work measures) (38).

Szulc and colleagues (38) concluded that in older men, higher OPG levels were associated with a higher risk of both fracture and cardiovascular outcomes. These findings are not surprising based on previous reports of both increased fracture and CVD risk in studies that include women (23,28,30,34,35,39), but the current study is the first to report these associations in a large cohort of men. This study contributes to an important area of research, and highlights the potential role of OPG in the pathophysiologies of both bone and cardiovascular health in men. The authors did a commendable job at presenting extensive data and analyses (unadjusted, and then adjusted for multiple factors), and they supported their findings with a well-articulated discussion (38).

One important area that the authors of this article discuss is that although consistent with previously published data, higher OPG and its association with fracture risk in men is contrary to its reported physiological role. As discussed earlier in this Editorial, *in vivo* studies in mice demonstrate that increased OPG is beneficial for bone—as it blocks the bone resorption action initiated by RANKL. Similarly, increased OPG in the cardiovascular system is beneficial physiologically (it slows arterial calcification). This paradoxical finding of increased OPG with fractures/

CVD has been suggested to reflect a responsive increase in OPG secretion when extensive bone loss or cardiovascular changes are present. Szulc *et al.* (38) also note in their study, that while their findings are interesting and warrant further investigation, it is not determined whether high OPG plays the role of a biomarker, determinant (i.e., pathophysiological), intermediary, or bystander in bone fractures; or whether it might be indicative of inflammatory status, or proatherogenic pathways in CVD.

Nevertheless, the finding that OPG is associated with both increased fracture and cardiovascular risk has interesting clinical implications. For example, serum OPG might be a useful predictive marker for physicians to assess the risk of bone and CV disease in their patients. That said, the availability of OPG assay kits, ease of running these kits (i.e., timing of samples etc.), and potential high cost per sample, may be prohibiting factors. For example, Szulc and colleagues (38) used non-fasting serum samples that were stored at -80°C . They do not mention when samples were processed (centrifugation and plasma separation is recommended as soon as possible, within 20 minutes, by the kit manufacturer Biomedica) (40), or how long the samples were stored before analysis, which may be of importance because a previous report indicated that storage of the sample for over 6 months at -70°C might reduce serum OPG measures (41). That said, the Biomedica brand assay used in the Szulc's study (38) has been successfully used in many clinical studies, and their assay insert supports that serum samples properly stored at -80°C with minimal freeze-thaw cycles can be used after up to 2 years of storage (40). The utility of OPG as a predictive tool needs to be weighed against some of the limitations of measuring serum OPG; however, in our opinion, the data presented by Szulc (38) is convincing to support a role for measuring OPG as a clinical prediction tool for fractures and CVD.

Manipulating the OPG/RANKL pathway has also been examined as a treatment approach, primarily for bone health, but also for vascular calcification. Denosumab is a monoclonal antibody against RANKL, and is a pharmaceutical agent that acts much like OPG does. Improved BMD by DXA, improved bone turnover markers, and reduced fracture risk was reported in participants randomized to the denosumab group in the FREEDOM trial (42), which targeted postmenopausal women. Denosumab's therapeutic role in vascular calcification is unclear, and not well supported. One *in vitro* study reported that in porcine valve interstitial cells, denosumab inhibited induced calcium deposition to basal cells (43). A reduction

in calcium deposition in the aorta of mice with denosumab has also been described (44). However, a study (subset from the FREEDOM trial) of over 2,300 postmenopausal women with osteoporosis at high risk of CV events, found that aortic calcification progression over 3 years did not differ between women taking placebo *vs.* denosumab. As well, frequency of CV adverse events did not differ between the placebo and denosumab group (45). Therefore, current published research doesn't support a role for the use of denosumab in treating both fractures and CVD; and pharmaceutical therapies in general for osteoporosis are not well defined in men (46). Advances in treating bone and CVD concurrently, in men, remains an interesting area for future research.

In conclusion, Szulc and colleagues offer an important contribution to the literature with their prospective study on the association of OPG with bone and cardiovascular health in older men (38). Future research may benefit from the inclusion of OPG as a widespread clinical marker for the prediction of these two diseases. Subsequent studies to investigate the role of increased OPG (e.g., biomarker *vs.* pathophysiological), and the potential for targeting OPG as an intervention in ameliorating both CVD and osteoporosis will be of interest.

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