

Peripheral artery disease and osteoporosis: Not only age-related (Review)

AGOSTINO GAUDIO, ANASTASIA XOURAFA, ROSARIO RAPISARDA,
PIETRO CASTELLINO and SALVATORE SANTO SIGNORELLI

Department of Clinical and Experimental Medicine, University of Catania,
University Hospital 'G. Rodolico', I-95123 Catania, Italy

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Abstract. Osteoporosis and atherosclerosis are two chronic degenerative diseases that share several biochemical pathways and risk factors. Previous studies have associated osteoporosis with carotid atherosclerosis, cardiovascular mortality and stroke, but data on the relationship with peripheral artery disease are few and conflicting. The OPG/RANK/RANKL system and Wnt/beta catenin signaling seem to be deeply involved in the pathogenesis of bone alterations and atherosclerotic processes also affect arteries of the lower extremities. Hypovitaminosis D could also play a role in the relationship of these two diseases. New and larger studies are necessary to shed light on this association and to design new drugs able to act in both these chronic degenerative diseases.

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1. Introduction

Occlusive atherothrombotic diseases occur in different vascular territories such as in coronary, carotid and peripheral arteries.

Correspondence to: Professor Salvatore Santo Signorelli, Department of Clinical and Experimental Medicine, University of Catania, University Hospital 'G. Rodolico', Via S. Sofia 78, I-95123 Catania, Italy
E-mail: ssignore@unict.it

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The consequent diseases such as coronary heart diseases (CHD), carotid disease (CD) and peripheral artery disease (PAD) may be considered cardiovascular killers. In general, cardiovascular diseases have mostly been investigated for prevalence, frequency, pathophysiology, outcome and prevention, but PAD is not sufficiently considered compared to other diseases (1-3). There are discordant results on PAD epidemiology but they derive from different study populations (hospitalized, general) or from different diagnostic methods (clinical, instrumental, discharge code). However, effective epidemiological data are derived from the use of the ankle-brachial index (ABI) to diagnose PAD (4-7). To the best of our knowledge, the prevalence of PAD in advanced countries ranges from 3 to 10% in individuals aged 40-70 years, and 10-20% in individuals over 70 years of age (8-14) (Table I). The prevalence of PAD is the same in men and women, whereas ABI is higher in women (10.6 vs. 4.3%) (15). Similarly, both diabetics and regular smokers show a higher prevalence of PAD (1,3,10-15). The number of elderly people has tripled during the last 50 years and therefore the number of patients with PAD has increased. Secondly, PAD patients have been diagnosed more frequently in hospital where there is greater awareness about managing them according to guidelines for the secondary prevention of cardiovascular events, improvement in physical performance, clinical symptoms and improvement in the quality of life. Data provided following a global estimation of PAD prevalence show that, 202 million individuals are affected by this occlusive artery disease, but it is very interesting to note an increase of 23.5% in PAD diagnoses from 2000 to 2010 (7). PAD has become a serious medical and social issue. However, PAD is underrecognized although it may easily be diagnosed by using a handheld Doppler to measure ABI. PAD is also undertreated because its clinical signals (i.e., intermittent claudication) often do not appear in older individuals or those leading a sedentary lifestyle (16-20).

2. Atherosclerosis and osteoporosis

Osteoporosis and atherosclerosis are two chronic degenerative diseases whose incidence increases with age. At present, mounting evidence indicates a relationship between cardiovascular disease and osteoporosis, regardless of age. These seem to have many common biochemical pathways and risk factors.

In addition, the mechanism of arterial calcification is similar to the process of osteogenesis, involving various cells, proteins and cytokines, which lead to tissue mineralization (21). Due to these strict interconnections, the drugs used for osteoporosis treatment (vitamin D, estradiol, and bisphosphonates) may interfere with vessel wall processes. On the other hand, several of the drugs used to treat cardiovascular diseases (statins, anti-hypertensives, warfarin, and heparins) may affect bone tissue metabolism (22).

Previous studies have associated osteoporosis with cardiovascular mortality (23,24), aortic and coronary calcification (25,26), carotid atherosclerosis (27), and stroke (28) in men and women, particularly the latter. There are little data available on the relationship between osteoporosis and PAD.

3. Methods

A literature search was conducted to identify studies published in English language journals since 1990 concerning the relationship between osteoporosis and PAD. The MEDLINE electronic database was used to identify potential studies. The MEDLINE search terms included peripheral artery disease and osteoporosis or bone turnover markers, osteoprotegerin and sclerostin.

4. Peripheral artery disease and osteoporosis: Epidemiological data

The data associating PAD and osteoporosis are conflicting. The osteodensitometric evaluation by Fehérvári *et al* (29) found 37% of patients with lower limb ischemia had osteopenia and 31% had osteoporosis, with significantly more females than males having osteoporosis. Most recently, Baldwin *et al* (30) found that osteopenia and osteoporosis are independent risk factors for PAD in both males and female. The data agree with previous results showing an increased prevalence of PAD in osteoporotic postmenopausal women (31).

In a large prospective cohort of 3,998 Chinese men and women (65-92 years of age) in Hong Kong, the ABI correlated positively with hip BMD (correlation coefficient=0.27; $P<0.001$). However, after adjustment for confounding factors, the correlation became much weaker (correlation coefficient=0.03; $P<0.05$) (32).

The Rotterdam Study (3,053 women and 2,215 men) associated low femoral neck BMD and PAD in women only. By contrast, lumbar spine BMD and PAD were not associated in either men or women (33).

Pasqualini *et al* (34), reported that hypovitaminosis D and increased bone turnover were risk factors for PAD and its severity. However, the presence of PAD even if asymptomatic and diagnosed by a lowered ABI could identify a population at risk of osteoporosis.

Fehérvári *et al* (35) found a connection between the severity of atherosclerosis and osteoporosis in patients with PAD, specific to the site of the lesion. In patients with iliac disease, a Bollinger angiographic score (BS, a method of PAD classification according to the occlusive pattern) was associated with lumbar-BMD and with femoral-BMD. These findings support the hypothesis that reduced blood flow is the key factor in the inverse association of BMD with atherosclerosis.

During an average 4-year follow-up, women with PAD had a significantly higher rate of bone loss than women without PAD ($P=0.05$). By contrast, PAD was not associated in men with osteoporosis, but men with PAD had lower BMD at the femoral neck than men without PAD ($P=0.03$). PAD was not associated with osteoporotic fractures in either males or females (36).

5. Peripheral artery disease and osteoporosis: Possible common pathogenic factors

Osteoprotegerin (OPG), a member of the tumor necrosis factor receptor family, is involved in the process of bone turnover and in the pathogenesis of osteoporosis and premature calcification of the vascular system (37).

Few data are available associating serum OPG plasma levels with PAD or its severity. Ziegler *et al* (38), reported that plasma OPG concentrations were significantly higher in subjects with PAD undergoing percutaneous transluminal angioplasty (PTA) because of advanced clinical stages III-IV than in patients without ischemic ulcerations. In addition, OPG correlated positively with BS of disease, age and creatinine values and correlated negatively with ABI.

Those data conflict with our results, which found similar serum OPG and RANKL levels in PAD patients and controls. We concluded there was no increased activation of the OPG-RANKL system (39).

Recently, Demková *et al* (40), confirmed that OPG levels were significantly higher in patients with PAD than patients without PAD. Additionally, serum OPG levels were associated significantly with PAD and its severity in patients with T2DM. Those data suggest that OPG may be a biomarker for atherosclerosis in patients with T2DM.

The role of OPG as a marker of arterial consequences in diabetic patients particularly in PAD subjects has been previously reported. Esteghamati *et al* (41) reported that in patients with T2DM for >5 years without apparent diabetic foot ulcer, one standard deviation increase in log-osteoprotegerin was associated with a >2-fold increase in the risk of having PAD (odds ratio 2.26, 95% confidence interval 1.50-3.40). In addition, in type 1 diabetes, OPG levels were associated with the development of foot ulcer, even after comprehensive adjustment (42).

OPG is not only important in diabetic patients. In fact, O'Sullivan observed that PAD is associated with higher serum OPG, regardless of the co-existence of DM (43).

In a systematic review, it was found that OPG is a marker of atherosclerosis. OPG concentrations were associated with stable coronary artery disease and its severity, acute coronary syndrome, and cerebrovascular disease but no association was found between PAD and OPG concentrations (44).

However, another recent review reported eight studies showing correlations between OPG levels and PAD, its progression and severity, whereas just one study did not find OPG levels significantly higher. The authors concluded that the results from clinical and experimental research on the role of vascular calcification markers in PAD are controversial, although most studies suggest a positive correlation (45).

Further studies are required to analyze the role of OPG as a diagnostic marker for the severity of atherosclerosis particularly in PAD patients.

Table I. Number of studies on the prevalence of PAD in general and in hospitalized populations.

Author	Prevalence (%)	Subjects	Study population	(Refs.)
Murabito <i>et al</i> , 2002	3.9 (male) 3.3 (female)	3,313	Population-based	(3)
Selvin <i>et al</i> , 2004	4.3	2,174	From National Survey (NHANES)	(8)
Mostaza <i>et al</i> , 2008	a) 33.8 b) 32.4 c) 53.9	1,203	Internal medicine outpatients with: a) previous coronary event, b) cerebrovascular disease c) disease in both territories	(11)
Ramos <i>et al</i> , 2009	4.5	6,262	Population-based cross-sectional survey	(12)
Alzamora <i>et al</i> , 2010	7.6	3,786	Population-based	(13)
Santo Signorelli <i>et al</i> , 2010	2.3	3,412	Population-based from general physicians files	(19)

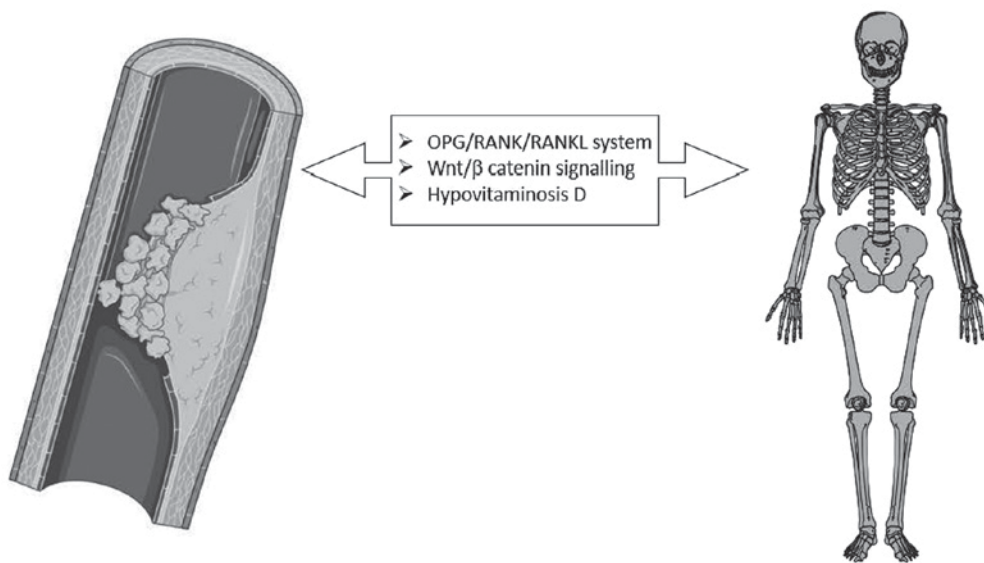


Figure 1. Figure summarizes the possible pathogenetic links between PAD and osteoporosis.

Ye *et al* (46), suggested that a multi-marker approach may improve the inter-individual prediction of variation in ABI and it may be useful in predicting PAD. In particular, those authors evaluated biomarkers including C-reactive protein, interleukin-6, tumor necrosis factor receptor-II, lipoprotein(a), N-terminal pro-brain natriuretic peptide, pro-atrial natriuretic peptide, C-terminal pro-arginine vasopressin, osteoprotegerin, and fibrinogen in African-Americans and non-Hispanic whites. It was suggested that different factors could play a pathogenetic role for osteoporosis and PAD, particularly data on hypovitaminosis D.

Hypovitaminosis D is frequent in patients with PAD. Secondary hyperparathyroidism and osteomalacia as consequences may contribute to bone pain and myalgias, and worsen clinical symptoms of PAD such as intermittent claudication (47).

In the last decade, canonical Wnt/beta signaling has been shown to play a significant role in the control of osteoblastogenesis and bone formation. This signaling is finely controlled via several soluble inhibitors such as sclerostin and DKK-1. There

is some evidence of a possible role for Wnt/beta signaling in atherosclerosis, but data on PAD patients are insufficient (48).

Sclerostin and Dkk-1 are two soluble inhibitors of Wnt/beta signaling associated with acute ischemic stroke (49).

In an animal model, upregulating SOST (gene coding for sclerostin) inhibits aortic aneurism and atherosclerosis development with potentially important implications for treating these vascular diseases (50).

In subjects with coronary artery disease who underwent CABG (coronary artery bypass graft), serum sclerostin levels were higher compared to controls (51).

In a previous study, we showed that, following adjustment for confounders, sclerostin is an independent predictor of arterial stiffness in the outpatient population (52). Sclerostin may serve as a useful biomarker for early atherosclerosis in obese individuals without a previous history of cardiometabolic disorders but this requires further testing (53).

Morales-Santana *et al* (54) produced some interesting results on sclerostin circulating levels in T2DM patients with atherosclerotic lesions. Authors of that study found higher

circulating sclerostin levels, and a significant negative correlation between sclerostin and other bone markers such as DKK-1 with intima-media thickness of the carotid artery (CIMT) (55). Based on those data, sclerostin may protect against arterial consequences in T2DM, possibly by attenuating the upregulation of β -catenin activity in vascular cells. Romosozumab is a monoclonal antibody that binds to and inhibits sclerostin, increasing bone formation and decreasing bone resorption. In a recent trial conducted on post-menopausal women, serious adverse cardiovascular events were observed more often with romosozumab than with alendronate (56). The findings support our hypothesis of a protective role for sclerostin in atherosclerosis.

6. Conclusion

A large amount of data support, over an age-related association between PAD and atherosclerosis, a possible sharing of common pathogenetic links. In particular, the OPG/RANK/RANKL system and Wnt/beta catenin signaling seem to be deeply involved in the pathogenesis of bone alterations and atherosclerotic processes also affecting the arteries of the lower extremities (Fig. 1). The complete comprehension of these common pathways, through future studies, could be extremely important in the designing of future innovative drugs able to protect both arterial walls and bone.

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Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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