Journal of the Endocrine Society, 2023, **7**, 1–8
https://doi.org/10.1210/jendso/bvad081
Advance access publication 16 June 2023
Mini-Review

Periostin in Osteoporosis and Cardiovascular Disease

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Abstract

Context: Osteoporosis (OP) and cardiovascular disease (CVD), prevalent disorders worldwide, often coexist and share common risk factors. The identification of common biomarkers could significantly improve patients' preventive care.

Objectives: The objectives are 1, to review periostin (Postn) involvement in osteoporosis and in CVD, and 2, identify if Postn could be a common biomarker.

Design: This is a scoping review on Postn in OP and CVD.

Methods: Databases were searched, in vitro and in vivo, for publications in English on Postn, bone, and the cardiovascular system, with no limit regarding publication date.

Results: Postn appears as a key factor in OP and CVD. Its role as a potential biomarker in both pathologies is described in recent studies, but a number of limitations have been identified.

Conclusions: Current evidence provides fragmented views on Postn in OP and CVD and does not encapsulate Postn as a common pivotal thread linking these comorbidities. A number of gaps impede highlighting Postn as a common biomarker. There is room for future basic and clinical research with Postn as a marker and a target to provide new therapeutic options for aging patients with concomitant OP and CVD.

Key Words: periostin, bone, cardiovascular

Abbreviations: AAC, abdominal arterial calcification; BMD, bone mineral density; CVD, cardiovascular disease; ECM, extracellular matrix; FGF-23, fibroblast growth factor-23; K-Postn, cathepsin K–dependent periostin fragment; miRNA, microRNA; OP, osteoporosis; PLF, Postn-like factor; Postn, periostin; TGF-β, transforming growth factor-β.

Osteoporosis (OP) and cardiovascular disease (CVD) are prevalent disorders worldwide, with a high heritability: It is estimated that 60% to 80% cases of bone mineral density (BMD) [1] and 40% to 60% cases of coronary artery disease [2] are inherited. OP and CVP may be sustained by similar or common pathophysiological mechanisms; they often coexist, especially with aging, and are closely interrelated epidemiologically although causal relationships are not well established. They share environmental risk factors (low physical activity, estrogen deprivation, smoking), and the identification of biological predictive markers for OP and CVD risks could substantially improve and facilitate the phenotyping of patients needing preventive care [3-5].

Clinically, both low BMD and high bone turnover/poor bone microarchitecture are associated with an increased risk of coronary events, cardiovascular morbidity, and mortality. CVD, including ischemic heart disease, vascular calcifications (a surrogate of cardiovascular mortality), and fracture risk are also associated [5-9]. Vascular calcifications correspond to the pathological deposition of calcium-phosphate crystals in the vasculature. Several studies have also focused on the link between abdominal arterial calcifications (AACs) and bone, especially prevalent in patients with chronic kidney disease, and suggest that AAC score increase is linked to an increase in bone resorption in postmenopausal women [10-13]. Likewise, advanced AAC is linked to a 2.3-fold increased risk of proximal femur fracture, as well as to lower BMD and accelerated bone loss in healthy postmenopausal women [13]. This "calcic paradox," in which bone decalcifies while the cardiovascular wall calcifies, remains not fully understood. Vascular calcification and osteogenic differentiation of vascular smooth muscle cells may be associated with the location of the bone and cardiovascular system during embryonic development [14].

Common biomarkers of both osteoporotic fractures and cardiovascular events have been described, like osteoprotegerin, sclerostin, or fibroblast growth factor-23 (FGF-23) levels [3]. Another protein, periostin (Postn), has been suggested to have a potential role in OP [15] and in CVD [16].

Postn is a ubiquitous 90 kDa protein, originally known as osteoblast-specific factor-2 (OSF-2), and belongs to a group of nonstructural extracellular matrix (ECM) proteins, the matricellular proteins. These have a pivotal role in normal tissue homeostasis and are highly expressed in pathological

Received: 17 April 2023. **Editorial Decision:** 9 June 2023. **Corrected and Typeset:** 22 June 2023

conditions in which trauma, inflammation, or tissue repair are involved [17] (Fig. 1). Postn is expressed in the periosteum (hence its name), is present in the ECM, and also participates in cell-ECM interactions [18]. With its implication in many domains, Postn is often considered as a potential marker of several skeletal and nonskeletal diseases, including lung, asthma, allergy, liver, diabetes, kidney function, or cancer conditions [19-26]. It also influences cell adhesion, proliferation, migration, and angiogenesis via cellular integrin receptors. One particularity is that it contains vitamin K-dependent γ-carboxyglutamic acid residues, involved in many processes including regulation of the coagulation cascade, but it is unknown whether the carboxylation status of Postn affects its action on target tissues [27]. It is upregulated in collagen-rich connective tissues that are submitted to mechanical stress or injury like bone, aorta, heart valves, periodontal ligaments, tendons, lungs, and skin [18]. Postn is a multimodular protein that may interact with or regulate numerous other proteins like osteocalcin, type I collagen, and fibronectin. It plays an important role in collagen assembly, bone turnover, the cardiovascular system, and cross-linking in several tissues [28]. The objective of this scoping review is to review Postn involvement in OP and in CVD and to identify whether it could be a common biomarker for both comorbidities.

Methods, Databases, and Data Treatment

This scoping review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Guidelines [29].

Eligibility Criteria

Peer-reviewed journal articles were included if they involved in vitro and vivo studies on Postn in adult bone and the cardiovascular system. Postn as a marker was followed as a primary or secondary outcome. All available literature including clinical, ex vivo, and in vitro studies and animal studies was included. Nonbone or CVD contexts were excluded. There was no specific requirement regarding the years of publication, and studies had to be available in English.

Information Sources and Search Strategy

To identify potentially relevant articles, the following online databases were searched until April 2023: Medical Subject Headings, Medline database in PubMed, and Cochrane databases with the following key words: (periostin), (periostin AND cardiovascular disease), (periostin AND bone),

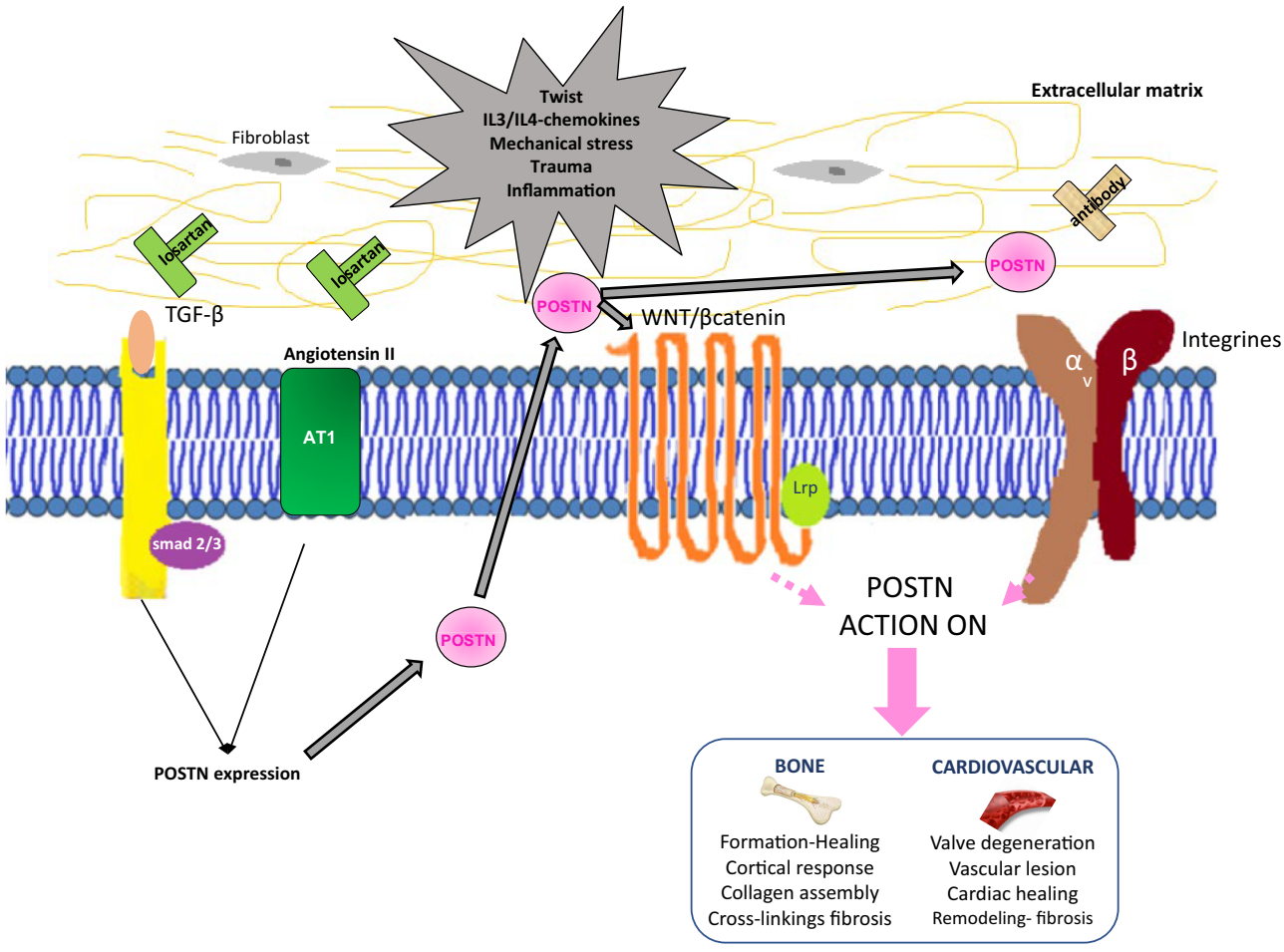

Figure 1. Factors regulating periostin (POSTN) expression. Transcription factors (as Twist), chemokines, mechanical stress, traumatism, or inflammation regulate the expression of POSTN. POSTN acts on bone via its regulation of Wnt/βcatenin pathway. It is also a ligand for integrin αvβ3. Therapeutic strategies involving POSTN include sartans and antibodies. Losartan is an angiotensin II type 1 receptor (AT1) blocker that decreases osteoclast differentiation and activity; the inhibition of POSTN expression could be one explanation. POSTN antibodies have also been developed.

(periostin AND cardiovascular disease AND bone), (circulating periostin). The reference list of all the full-text articles selected after the screening and the list of articles citing these articles were hand-searched for titles not identified by the previous methods.

Study Selection Process

Abstracts were obtained for all the studies identified during the electronic and hand-searches. Two reviewers (M.E.P. and C.O.) screened titles and abstracts or full-text copies independently to eliminate articles that clearly failed to meet the eligibility criteria. Any disagreement was settled through discussion. Full-text copies were obtained for all the selected studies.

Data Charting Process and Synthesis

Predetermined data (including serum Postn, outcomes, …) were extracted from each study independently by 2 reviewers (M.E.P. and C.O.) and discussed between the 2 reviewers, keeping only articles that met the inclusion criteria. Duplicates were identified and excluded.

No quality assessment of the included articles took place, which was in accordance with available guidelines on scoping review [29].

Results and Discussion

A total of 1489 articles were identified (Fig. 2), 1399 articles were discarded (not conforming to the inclusion criteria), and 56 were appropriate for this review, addressing Postn and bone, Postn and CVD, and circulating Postn.

Periostin and Bone

As an adhesion molecule, Postn binds to cell surface receptors and promotes the differentiation, adhesion, and proliferation of osteoblasts. It is involved in bone formation and cortical bone metabolism, especially because of its preferential localization in periosteal tissues and cortical bone. Postn acts on bone formation via the Wnt-β-catenin pathway [19] indirectly by inhibiting sclerostin expression in bone [30]. Postn expression (see Fig. 1) is regulated by several transcription factors (Twist 1,2), c-Fos/c-Jun, p73, by hormones like parathyroid hormone, estrogens, and angiotensin II, and by growth factors

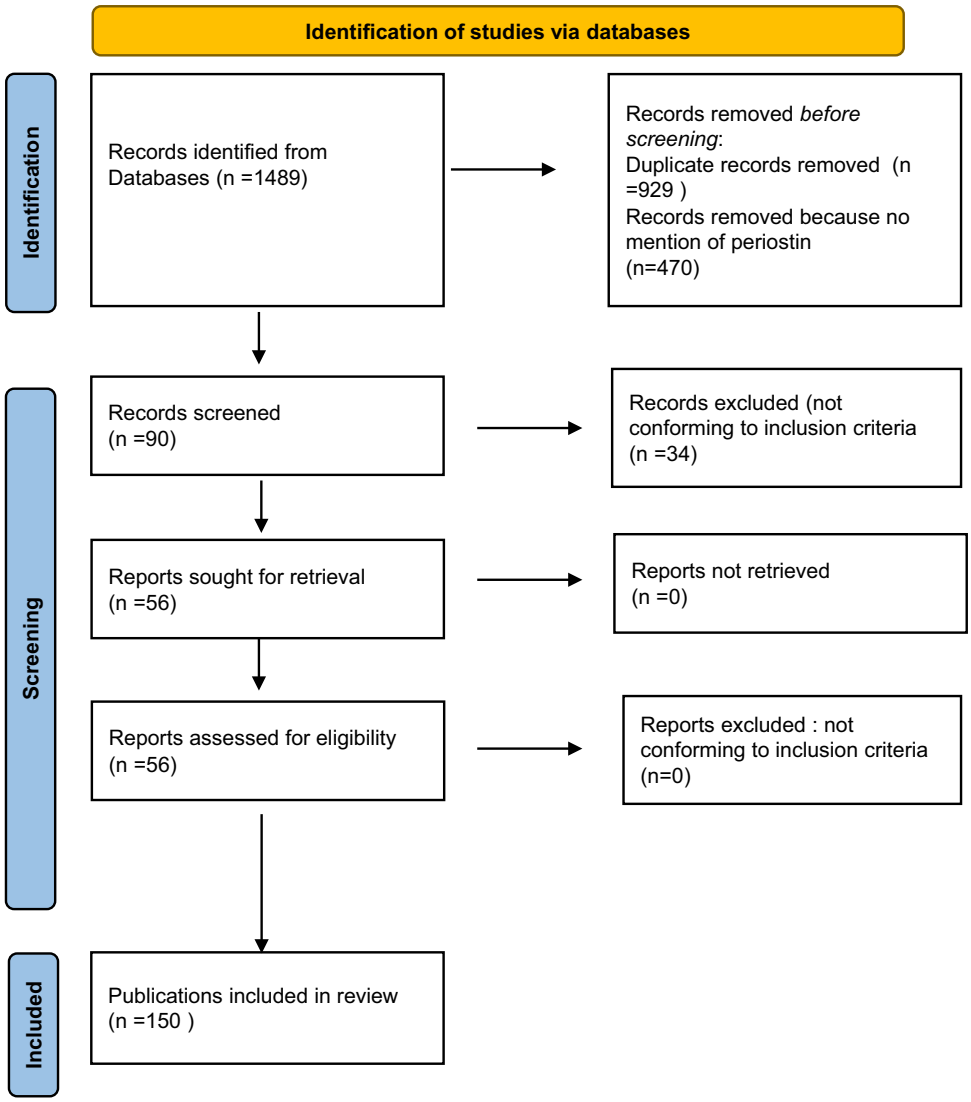

Figure 2. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

and cytokines, including transforming growth factor-β (TGF-β) [28]. The canonical Wnt/β-catenin pathway, with sclerostin as its main antagonist, is fundamental for the maintenance of bone homeostasis. Postn has multiple roles, and studies have focused on its specific properties as an upregulator of Wnt/β-catenin signaling, TGF-β interactions, and ligand to integrin αvβ3 as a receptor [31]. In a cohort of 648 individuals, it was suggested that Postn expression is genetically modulated, particularly by polymorphisms in the Wnt pathway, and is thereby implicated in the genetic variation of bone microstructure [32]. Furthermore, a recent study reported in Chinese women that the genetic variation of serum Postn could be a predicting factor for the risk of vertebral fractures [33]. Postn's major role in dentinogenesis and osteogenesis has been demonstrated in Post-null mice: These are dwarf, with lower BMD, and exhibit reduced cortical bone volume and bone strength [19, 34, 35]. Reduced Postn expression may affect osteoblast differentiation and collagen type I synthesis and predispose to osteoporosis, hence increasing fracture risk. Several studies have shown that Postn contributes directly to bone's adaptive response, and its expression increases with mechanical loading or physical activity [36-38]. Mechanical strain activates calcium signaling and upregulation of COX2 via NO/guanylate cyclase/PKG signaling. COX2 produces PGE2, which activates EP receptors and extracellularly regulated kinase signaling in bone. This strain-induced activation of extracellularly regulated kinase signaling may trigger an upregulation of Postn expression in bone [39]. The mechanisms of downregulation of sclerostin following mechanical strain remain unclear, but in vitro studies in mechanical-loading conditions showed that Postn is required for sclerostin inhibition and therefore is one of the key factors of the bone adaptive response [35]. An age-related decrease of Postn expression has also been shown in the fracture callus of old mice compared to young [40], and the unique role of Postn in regulating periosteal bone formation at different ages has been demonstrated with the potential for vitronectin to compensate in the absence of Postn [41].

Periostin and Cardiovascular Disease

Postn is expressed in the cardiovascular system and in other extraskeletal tissues. It is involved in cardiac mesenchymal tissue development, highly expressed in structures of the developing heart (outflow tract endocardial cushions) that will lead in particular to aortic valves, and in postnatal cardiomyocyte maturation and innervation. Postn advances atherosclerotic and rheumatic cardiac valve degeneration by inducing angiogenesis and matrix metalloproteinase production in humans and rodents. Postn mediates vascular smooth muscle cell migration through the integrins αvβ3 and αvβ5 and focal adhesion kinase pathway [42, 43]. Other in vitro studies report that trauma to the aorta promotes the expression of Postn, and that Postn leads to the calcification of the smooth muscle of the aortic wall. So far, only local Postn (not circulating) has been shown to be increased in animals with atherosclerotic cardiac valve degeneration [22]. Postn is also associated with fibroproliferative diseases in the myocardium, and a higher expression of Postn after cardiovascular events has been shown in preclinical and clinical studies [16, 44, 45]. In a recent study [46], Postn caused arterial calcification, overactivated glycolysis, and damaged normal oxidative phosphorylation. PPARγ agonists alleviated Postn-promoted arterial calcification and corrected abnormal glycolysis and unbalanced mitochondrial homeostasis. Furthermore, a relationship between Postn and lactate in patients with arterial calcification has been observed [46]. Increased Postn expression in cardiac remodeling has also been shown to nurture tumor growth and metastasis, and therefore promotes cancer progression [6]. In a cohort of home-dwelling men, higher levels of Postn were associated with higher all-cause mortality, but not specifically with cardiovascular mortality [47].

Considering the effect of mechanical loading in vessels, aortic aneurysm in which vascular cells are exposed to permanent distension and pulsatile stretch is an interesting model for understanding its process. In vitro studies focused on abdominal aortic aneurysm show that Postn mediates the maintained inflammatory response to mechanical loading in human tissue specimens, cultured vascular smooth muscle cells, and in vivo mouse models, via focal adhesion kinase activation [36]. Endothelial cells may also contribute to vascular calcification in conditions of mechanical stress, via the upregulation of pro-osteogenic factor BMP-2mRNA, and also by regulating the expression of other osteogenic factors in vascular interstitial cells, including a decrease in Postn expression. The latter's reduction is usually found in ectopic calcification and calcified aortic valves [48]. Some studies have also focused on a specific isoform of Postn, referred to as Postn-like factor (PLF) [3], expressed in the cardiac myocytes of human myocardium [49, 50]. Each isoform of the Postn family represents a splice variant from a single gene and may have a unique function. In animals (rat), heart failure and volume overload hypertrophy were associated with increases in PLF expression, and inversely, mechanical or surgical unloading was linked to a decrease in PLF expression, supporting the idea that PLF expression is responsive to changes in cardiac loading conditions [49].

Noncoding microRNAs (miRNAs), powerful regulators of gene expression [51], have been identified as increasing Postn expression. For example, miR-1468-3p promotes cardiac fibrosis by inducing collagen deposition and cell metabolic activity and enhancing Postn expression. Anti-miR-1468-3p antagonizes TGF-b1–induced collagen deposition and metabolic activity: Targeting miR-1468-3p in the older population may be of therapeutic interest to reduce cardiac fibrosis [52].

Postn as a Biomarker but not a Common Biomarker of Osteoporosis and Cardiovascular Disease

In healthy individuals, circulating Postn levels are stable from age 32 past 70 [53], and Postn levels, specific to each assay, range from 36.1 to 133.3 ng/mL [54]. Serum Postn levels in healthy people do not need to be adjusted to take into account a patient's age or sex, although levels are lower in current smokers [54] and sex differences have not been described. Postn is stable in serum and suitable for use in routine clinical practice [55]. Salivary and urinary Postn may be interesting noninvasive alternatives [56, 57]. Circulating Postn levels must always be considered in the context of other bone turnover markers.

Postn has been suggested as a biomarker of numerous bone conditions including cortical bone metabolism [19], chondrosarcoma [58], arthritis [38], fibrous dysplasia of bone severity [59], and a surrogate marker for osteolytic lesions in breast cancer [60]. Postn is a good marker of cortical porosity [61], as its serum concentration increases with cortical porosity in conditions of mechanical stress under gravity. Postn has been shown to be a substrate of cathepsin K; levels of this

cathepsin K–dependent periostin fragment (K-Postn) reflect cathepsin K activity, particularly in the cortical compartment. The level of K-Postn has been shown to be a predictor of incident low-trauma fractures, independently of BMD, the fracture risk assessment tool (FRAX), and bone turnover markers such as P1NP and CTX [62]. However, serum Postn measures do not always correlate with spine and hip area BMD, nor with standard bone turnover markers. Paradoxical findings have been observed [63], with high circulating levels of Postn being associated with a higher risk of fracture in women, more specifically nonvertebral fractures, independently of BMD [19]. No clear correlations between circulating Postn and circulating traditional bone markers have been shown in OP [64]. With osteocyte factors, such as sclerostin and serum FGF-23, studies in OP comorbidities or in different pathologies have shown a negative correlation between Postn and sclerostin in spinal cord injury with OP [65], but no correlation was found between Postn and FGF-23 levels in the ossification of the posterior longitudinal ligament [66]. Correlations between Post and all bone markers, traditional and new ones, need to be sought in OP [67].

Among several hypotheses, the authors suggest this finding may be related to Postn measurement, as while the assay is believed to detect all isoforms of circulating Postn, the most relevant isoform to assess bone metabolism is not known. A similar observation was made in individuals affected by primary hyperparathyroidism, where the bone isoform was measured and serum K-Postn was significantly associated with fracture in primary hyperparathyroidism, independently of BMD [68]. Furthermore, the proportion of circulating Postn from skeletal origin is unknown, and comorbidities might also have interfered as inflammation increases Postn. Of note, plasma and synovial fluid Postn levels are correlated with the radiographic severity and progression of knee osteoarthritis [69]. Postn has been shown to be reduced under high glucose levels and reverses high-glucose–inhibited osteogenesis of periodontal ligament stem cells via the protein kinase B pathway [70]. Finally, it is not well known how OP therapy can modify serum Postn levels except for a few papers that showed that teriparatide therapy increased Postn secretion, without knowing if this increase mediates the effect of the drug on bone [71], while zoledronic acid treatment has no effect on serum Postn levels [72].

Postn has been suggested as a biomarker of CVD. It has been shown to be associated with myocardial fibrosis in human heart failure [73] and to decrease together with a reduction in myocardial fibrosis in hearts unloaded in mice and in humans [74]. Postn is increased in hypertrophic mice hearts together with interstitial fibrosis [75], and Klotho null mice have been described as a new model for calcific aortic valve disease, with premature aging and calcific nodules in the aortic valve hinge region [76].

It is also, with interleukin-13 and TGF-1, a potential biomarker for coronary artery disease with acute heart failure, and patients with higher coronary artery disease had higher Postn levels than age-matched (aged 63 years) controls [77]. A recent study [78] investigated 6 biomarkers in degenerative aortic stenosis in the tissue of stenotic aortic valves excised at surgery for aortic valve replacement and compared this to normal aortic valves obtained at cardiac transplantation, and in the serum of patients and controls. Postn serum levels correlated significantly with immunohistochemistry and messenger RNA tissue levels in patients with aortic stenosis [78].

Therapeutic strategies involving Postn have been published, such as Postn antibodies against the development of pathologies like chronic kidney disease [79] but have not been shown in OP or CVD, where this targeting would imply excessive Postn production at the tissue level with unknown possible detrimental effect. Another approach involves angiotensin II, a major stress hormone acting through AT1 receptor stimulation (see Fig. 1). Sartans are angiotensin II type 1 receptor blockers used largely for hypertension as they do not produce cough as a side effect, which is commonly seen with angiotensin-converting inhibitors. They are commonly prescribed, especially in older individuals, because of their excellent tolerance profile, as well as in patients suffering from diabetes for the prevention of diabetic nephropathy. Losartan binds strongly to AT1 receptor: This decreases osteoclast differentiation and activity, Postn levels, and strain-induced bone remodeling in orthodontic tooth movement [80]. Further prospective investigations of losartan's potential ability in other patients are now needed to confirm these findings.

There are, however, a number of limitations identified in this review, and Postn is not a common biomarker of OP and CVD. The role of Postn in the paradoxical phenomenon of impaired bone mineralization accompanied by vascular calcification, the calcification paradox, [81] is not defined; the place of Postn in the concept of endothelial progenitor cells and circulating calcifying cells in the bone-vascular axis [82, 83] has not been studied; and the hypothesis of Postn acting like osteocalcin as a circulating hormone [84], regulating both bone and cardiovascular systems, in the context of biological mechanisms currently known on the intercommunications between bone and the cardiovascular system, must be ascertained.

Furthermore, Postn is involved in OP and in CVD, but no longitudinal study in a large sample has specifically followed a population with concomitant comorbidities and circulating Postn measurements. A translational approach is warranted to provide more information on the link that occurs between vascular calcification and OP, and on the role of Postn in both domains. There are also inconsistencies between studies correlating circulating Postn with one or the other pathology, controverted results in OP, OP-related fracture risk, and CVD [16], and an overall scarcity of clinical data. Finally, technical issues with serum Postn measurement, different isoforms of Postn, specificities in bioassays, duration, and conditions of conservation of samples, often obtained in long-term cohorts, analysis in the context of other markers like sclerostin, have been underlined.

Conclusion

Current evidence provides fragmented views on Postn in OP and CVD, and does not encapsulate Postn as a common pivotal thread linking these comorbidities. A number of gaps impede highlighting Postn as a universal marker in each pathology, and consequently clear interconnections between OP and CVD are absent. There is room for future basic and clinical research with Postn as a substantial marker and a target to provide new therapeutic options for aging patients with comorbid OP and CVD, and in preventive care.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Disclosures

The authors have nothing to disclose.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study. This is a scoping review and all articles used in this review have been included.

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