Novel Biomarkers of Bone Metabolism

Subjects: Physiology

Contributor: Sara Fernández-Villabrille, Beatriz Martín-Carro, Julia Martín-Vírgala, Mª del Mar Rodríguez-Santamaria, Francisco Baena-Huerta, Juan Rafael Muñoz-Castañeda, José Luis Fernández-Martín, Cristina Alonso-Montes, Manuel Naves-Díaz, Natalia Carrillo-López, Sara Panizo

Bone represents a metabolically active tissue subject to continuous remodeling orchestrated by the dynamic interplay between osteoblasts and osteoclasts. These cellular processes are modulated by a complex interplay of biochemical and mechanical factors, which are instrumental in assessing bone remodeling. This comprehensive evaluation aids in detecting disorders arising from imbalances between bone formation and reabsorption. Osteoporosis, characterized by a reduction in bone mass and strength leading to heightened bone fragility and susceptibility to fractures, is one of the more prevalent chronic diseases. Some epidemiological studies, especially in patients with chronic kidney disease (CKD), have identified an association between osteoporosis and vascular calcification. Notably, low bone mineral density has been linked to an increased incidence of aortic calcification, with shared molecules, mechanisms, and pathways between the two processes. Certain molecules emerging from these shared pathways can serve as biomarkers for bone and mineral metabolism. Detecting and evaluating these alterations early is crucial, requiring the identification of biomarkers that are reliable for early intervention. While traditional biomarkers for bone remodeling and vascular calcification exist, they suffer from limitations such as low specificity, low sensitivity, and conflicting results across studies. In response, efforts are underway to explore new, more specific biomarkers that can detect alterations at earlier stages.

Keywords: vascular calcification ; biomarker ; bone mineral density

1. Receptor Activator of Nuclear Factor Kappa B Ligand and Osteoprotegerin

The Receptor Activator of Nuclear Factor kappa B (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG) system, and the more recently discovered member, leucine-rich repeat-containing G protein-coupled receptor 4 (LGR4), play pivotal roles in both bone and vascular mineralization. While the system's involvement in bone maintenance is well-established, recent studies have attributed a significant role to this system in vascular smooth muscle cell (VSMC) calcification. In bone, osteoblasts synthesize and secrete RANKL, which binds to its transmembrane receptor RANK in osteoclast precursors. This binding promotes the maturation, activation, and survival of osteoclasts, thereby increasing bone resorption and loss. Simultaneously, osteoblasts secrete OPG, a soluble receptor of RANKL, which prevents the binding of RANKL to RANK, thereby regulating osteoclastogenesis [1]. The LGR4 extracellular domain competes with RANK for binding to RANKL, resulting in the inhibition of osteoclast differentiation and a subsequent reduction in osteoclastic bone resorption. LGR4 is essential for bone formation by promoting the maturation and mineralization of osteoblasts [2]. Recent findings indicate that LGR4 is expressed in mature osteoclasts, where it inhibits osteoclastogenesis through two distinct mechanisms: (1) by preventing the binding of RANKL to RANK and (2) through the binding of RANKL to LGR4, activating the GSK3-β signaling pathway, suppressing the expression of NFATc1, and inhibiting osteoclast differentiation [2][3].

Some factors, including PTH, facilitate osteoclast differentiation by augmenting RANKL production in osteoblasts and concurrently inhibiting OPG synthesis [1]. The expression of this system is additionally modulated by various cytokines and glucocorticoids [4]. Numerous studies have delved into the impact of diet on BMD. Traditionally, the focus has centered on exploring the influence of the Mediterranean diet on classical biomarkers such as calcium and vitamin D. Nevertheless, a distinct study brought to light that beta-carotene and isoflavones, particularly genistein, exhibited a decelerating effect on bone resorption. This effect manifested through a reduction in serum levels of bone resorption markers, such as RANKL, concomitant with an increase in markers indicative of new bone formation, such as OPG [5][6]. Furthermore, various types of dietary fatty acids can also modulate the RANK/RANKL/OPG system, each with distinct osteogenic potential. The authors suggest that olive oil, in particular, may prevent the development and progression of osteoclast-related diseases [7].

The identification that OPG knockout mice develop osteoporosis and severe arterial calcification [8], along with the observation that RANKL expression increases in calcified arterial tissue [9], and evidence that RANKL induces VSMC

calcification in vitro, with OPG preventing this process [10][11], suggests that the RANK/RANKL/OPG/LGR4 axis may serve as a crucial autocrine/paracrine system involved in both bone loss and vascular calcification. Consequently, it was anticipated that Denosumab, a human monoclonal antibody against RANKL used for osteoporosis treatment, could prevent or delay the progression of vascular calcification. Indeed, Helas et al. demonstrated that Denosumab reduced vascular calcium deposition in glucocorticoid-induced osteoporosis in mice, affirming the existence of a connection between the bone and vascular systems [12]. However, the FREEDOM study involving osteoporotic patients revealed that the frequency of aortic calcification progression and adverse cardiovascular events was similar between women in the placebo and Denosumab groups, despite the improvement in BMD and reduction in fracture risk due to the treatment [13]. These findings highlight the necessity for studies investigating the regulatory mechanisms of this pathway in both bone and vessels, ensuring that strategies aimed at bone protection do not inadvertently result in counterproductive effects on vascular calcification.

The role of OPG and RANKL as serum biomarkers has been reported by several authors. The RANKL/OPG ratio is crucial in determining the degree of bone remodeling and bone mass [9]. Postmenopausal women with low BMD demonstrated lower serum OPG levels and a higher RANKL/OPG ratio compared to women with normal BMD [14]. Similarly, in a study involving rheumatoid arthritis patients, those with osteoporosis exhibited lower serum OPG levels and higher RANKL levels compared to patients with normal BMD [15][16].

Although consensus is lacking regarding their relation with vascular calcifications, several studies in CKD patients have associated vascular calcification with elevated OPG serum levels [17][18]. However, in another study involving patients with ischemic coronary disease [19], circulating OPG levels exhibited a negative correlation with total coronary artery calcification, no correlation with serum RANKL concentration, and a positive correlation between the RANKL/OPG ratio and total coronary artery calcification. These variations in results may be attributed to the timing of disease progression during biomarker determinations and the challenge of discerning whether the biomarker is being produced by the bone undergoing mineralization, the vessel undergoing calcification, or a vessel protected from calcification. Another possible cause that explains these differences is the different populations used, which is commonly called selection bias.

A study proposed the feasibility of detecting LGR4 in serum [20], positing that it may sequester RANKL, thereby preventing its binding to RANK in bone. However, the biological significance of this discovery remains undetermined. In an unpublished preliminary study conducted by the group, rats with chronic renal failure, manifesting vascular calcification and bone demineralization, revealed elevated serum RANK/OPG ratios, with no concurrent alterations in the serum levels of LGR4. Further investigations are essential to elucidate the potential role of LGR4 as a serum biomarker for bone loss or vascular calcification.

2. Sclerostin and Dickkopf1

The Wnt/β-catenin pathway constitutes an intracellular signaling pathway that serves as a primary regulator of bone formation and it is involved in the progression of vascular calcification. Wnt/β-catenin governs osteoblast activity [21]. Endogenous antagonists of the Wnt/β-catenin pathway include, among others, sclerostin (also known as Sost) and dickkopf1 (Dkk1). In bone, PTH acts as a key modulator of this pathway: PTH inhibits sclerostin, thereby enhancing bone formation. Similarly, PTH inhibition leads to increased expression of sclerostin, underlining the close relationship between sclerostin and PTH [22]. However, there is a lack of consensus regarding the effects of PTH on Dkk1 [23][24].

Sclerostin and Dkk1 are predominantly secreted by osteocytes into the circulation, and their serum levels are indicative of inhibited bone formation. Circulating sclerostin levels are influenced by gender, increase with age, and exhibit higher concentrations in elderly subjects compared to younger counterparts with similar BMD [25]. Moreover, exercise downregulates sclerostin [26][27]. Notably, postmenopausal women demonstrate increased sclerostin levels [28]. Although it might be expected that sclerostin and Dkk1 are inversely correlated with BMD in postmenopausal women, several studies have revealeda positive association between BMD and sclerostin and Dkk1 [29][30][31]. For instance, a recent study found a positive correlation between sclerostin and Dkk1 expression in bone from postmenopausal women with osteoporosis and BMD, with their serum levels reflecting their bone levels [29]. This discrepancy may be explained by the fact that bone sclerostin and Dkk1 are primarily produced by live osteocytes, and their levels may reflect osteocyte numbers (associated with higher BMD). The number of live osteocytes typically decreases with age, leading to lower levels of bone sclerostin and Dkk1. Conversely, other studies suggest a negative association between serum sclerostin levels and BMD [32][33], with elevated circulating sclerostin levels identified as a strong and independent risk factor for osteoporosis-related fractures in postmenopausal women [34]. The age-dependent decline in glomerular filtration rate should be considered when interpreting circulating sclerostin levels, necessitating further studies to ascertain its value as a bone biomarker. A recent

study suggests that the sclerostin/PTH ratio best defines bone status since the ratio can integrate both PTH-dependent bone formation and a lower rate of bone formation associated with high levels of sclerostin [35].

In the vasculature, the role of sclerostin and Dkk1 remains controversial. Some studies in CKD patients report increased serum sclerostin levels positively correlated with aortic calcification [36]. However, another CKD study indicates that higher sclerostin levels are associated with lower aortic calcification and a better survival rate [33]. In a mouse model of adenine diet-induced vascular calcification, sclerostin knockout mice exhibited more extensive vascular calcification than wild-type mice [37]. Conversely, in another mouse model of vascular calcification induced by warfarin, anti-sclerostin treatment increased aortic and vascular calcification, suggesting a protective role for sclerostin against vascular calcification [37]. These results are in agreement with studies that have shown an association between the presence of vascular calcification in the aorta of rats with chronic renal failure with a decrease in aortic Sost gene expression levels [10]. However, a study in diabetic rats with chronic renal failure demonstrated that monoclonal antibodies against Dkk1 prevented both bone and vascular damage [38]. More research is imperative to resolve these conflicting findings.

Romosozumab, an anti-sclerostin treatment, presents a promising avenue for preventing and treating fractures in osteoporosis among postmenopausal women; however, potential negative cardiovascular effects need careful consideration [10][37][39][40].

3. Periostin

Periostin, also known as a specific osteoblastic factor, is a non-collagenous protein predominantly expressed in the periosteum, a fibrous membrane covering the bone surface and connected to the muscles. The periosteum consists of two layers, with the outer layer primarily composed of fibroblasts and the inner layer housing bone progenitor cells, osteoblasts, nerves, and blood vessels. Periostin is also expressed in other connective tissues, including the periodontal ligament, muscle fascia, aorta, heart valves, and tendons, contributing to their structural integrity and participating in reparative processes. In bone, periostin regulates collagen crosslinking that contributes to bone strength [41]. Periostin-deficient mice exhibit low BMD, impaired microarchitecture and decreased bone strength [42].

In addition, periostin may serve as a crucial mediator of the effects of PTH on the Wnt/β-catenin pathway. Intermittent PTH administration stimulates periostin and inhibits sclerostin synthesis in bone and osteoblasts in vitro. Moreover, the addition of recombinant periostin also suppresses the expression of sclerostin [42][43]. Teriparatide (PTH 1–34) therapy increases periostin secretion in postmenopausal women [44]. In animal models, hypocaloric diets diminished serum periostin [45].

Periostin is a soluble factor detectable in serum and plasma. Studies examining its role as a biomarker of bone metabolism present conflicting results. The OFELY (Os des Femmes de Lyon) study positively associated serum periostin levels with fracture risk in postmenopausal women [46]. This unexpected finding is explained as an adaptive metabolic response of periosteal cells to maintain bone. Similar results were observed in another study, where plasma periostin levels were higher in postmenopausal women with non-vertebral fractures, suggesting that plasma periostin may be a potential biomarker for osteoporotic fracture risk, particularly in non-spinal skeletal sites [47]. However, another study found no differences in periostin levels between postmenopausal women with normal and low BMD [48].

The impact of periostin on vascular calcification is less explored, although it is considered a promotor of vascular calcifcation. A recent study demonstrated that recombinant periostin in vitro promoted the phenotypic transdifferentiation of VSMCs to a calcifying phenotype. Ex vivo, recombinant periostin accelerated aortic calcification, partly through excessive activation of glycolysis and imbalanced mitochondrial homeostasis [49]. Furthermore, the study observed a positive association between plasma periostin levels and the calcification score (Agatston score) in patients with angina pectoris or suspected coronary artery disease [49]. Another recent study noted increased periostin expression in calcified VSMCs and calcified arteries of diabetic rats. It was further described that periostin acts on calcification by blocking autophagic flow [50]. Additionally, periostin increases human VSMC calcification via activation of β-Catenin, and serum periostin levels were higher in hemodialysis patients compared with healthy controls [51]. Therefore, periostin appears to regulate various processes influencing vascular calcification.

4. Sphingosine-1-Phosphate

Sphingosine-1-phosphate (S1P) is a lipid mediator that acts through G protein-coupled receptors, controlling various cell functions. In bone, S1P regulates osteoblast survival and migration, while also stimulating RANKL synthesis and promoting osteoclast differentiation [52]. Additionally, S1P controls the dynamic migration of osteoclast precursors between

blood and bone through its receptors S1PR1 and S1PR2, which exert opposing actions. S1PR1 mediates positive chemotaxis toward S1P in osteoclast precursors, while S1PR2 directs negative chemotaxis (or chemorepulsion) by generating gradients [53].

Some recent articles show that increased serum levels of S1P are responsible for reduced levels of BMD and increased levels of bone resorption markers, which are associated with an increased risk of osteoporosis [54][55]. In human studies, circulating levels of S1P are increased in postmenopausal women compared to premenopausal women and men. Furthermore, elevated serum levels are associated with lower BMD in postmenopausal and premenopausal women, as well as in men [56]. Additionally, serum levels of S1P are positively correlated with bone resorption markers [56]. Other studies suggest that S1P may be a potential predictor of fracture risk in postmenopausal women [54][55][57].

The effects of S1P in vascular calcification are less well evaluated. A recent study observed that S1P is increased in phosphate-induced VSMC calcification [58], and the exogenous addition of S1P to VSMCs accelerated their calcification [58]. In the interstitial cells of the valve, S1P caused increases in bone morphogenetic protein 2 (BMP2), alkaline phosphatase (ALP), and calcification, as well as proinflammatory effects [59]. Currently, its potential role as a serum biomarker of vascular calcification is still unknown.

References

1. Boyce, B.F.; Xing, L. Biology of RANK, RANKL, and osteoprotegerin. Arthritis Res. Ther. 2007, 9 (Suppl. S1), S1.
2. Luo, J.; Yang, Z.; Ma, Y.; Yue, Z.; Lin, H.; Qu, G.; Huang, J.; Dai, W.; Li, C.; Zheng, C.; et al. LGR4 is a receptor for RANKL and negatively regulates osteoclast differentiation and bone resorption. Nat. Med. 2016, 22, 539–546.
3. Takegahara, N.; Kim, H.; Choi, Y. RANKL biology. Bone 2022, 159, 116353.
4. Schulz, E.; Arfai, K.; Liu, X.; Sayre, J.; Gilsanz, V. Aortic calcification and the risk of osteoporosis and fractures. J. Clin. Endocrinol. Metab. 2004, 89, 4246–4253.
5. Andreo-López, M.C.; Contreras-Bolívar, V.; García-Fontana, B.; García-Fontana, C.; Muñoz-Torres, M. The Influence of the Mediterranean Dietary Pattern on Osteoporosis and Sarcopenia. Nutrients 2023, 15, 3224.
6. Marini, H.; Bitto, A.; Altavilla, D.; Burnett, B.P.; Polito, F.; Di Stefano, V.; Minutoli, L.; Atteritano, M.; Levy, R.M.; D'Anna, R.; et al. Breast safety and efficacy of genistein aglycone for postmenopausal bone loss: A follow-up study. J. Clin. Endocrinol. Metab. 2008, 93, 4787–4796.
7. Carmen Naranjo, M.; Garcia, I.; Bermudez, B.; Lopez, S.; Cardelo, M.P.; Abia, R.; Muriana, F.J.G.; Montserrat-de la Paz, S. Acute effects of dietary fatty acids on osteclastogenesis via RANKL/RANK/OPG system. Mol. Nutr. Food Res. 2016, 60, 2505–2513.
8. Bucay, N.; Sarosi, I.; Dunstan, C.R.; Morony, S.; Tarpley, J.; Capparelli, C.; Scully, S.; Tan, H.L.; Xu, W.; Lacey, D.L.; et al. Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. Genes. Dev. 1998, 12, 1260–1268.
9. Hofbauer, L.C.; Schoppet, M. Clinical implications of the osteoprotegerin/RANKL/RANK system for bone and vascular diseases. JAMA 2004, 292, 490–495.
10. Carrillo-López, N.; Panizo, S.; Alonso-Montes, C.; Martínez-Arias, L.; Avello, N.; Sosa, P.; Dusso, A.S.; Cannata-Andía, J.B.; Naves-Díaz, M. High-serum phosphate and parathyroid hormone distinctly regulate bone loss and vascular calcification in experimental chronic kidney disease. Nephrol. Dial. Transplant. 2019, 34, 934–941.
11. Panizo, S.; Cardus, A.; Encinas, M.; Parisi, E.; Valcheva, P.; López-Ongil, S.; Coll, B.; Fernandez, E.; Valdivielso, J.M. RANKL increases vascular smooth muscle cell calcification through a RANK-BMP4-dependent pathway. Circ. Res. 2009, 104, 1041–1048.
12. Helas, S.; Goettsch, C.; Schoppet, M.; Zeitz, U.; Hempel, U.; Morawietz, H.; Hofbauer, L.C. Inhibition of receptor activator of NF-kappaB ligand by denosumab attenuates vascular calcium deposition in mice. Am. J. Pathol. 2009, 175, 473–478.
13. Samelson, E.J.; Miller, P.D.; Christiansen, C.; Daizadeh, N.S.; Grazette, L.; Anthony, M.S.; Egbuna, O.; Wang, A.; Siddhanti, S.R.; Cheung, A.M.; et al. RANKL inhibition with denosumab does not influence 3-year progression of aortic calcification or incidence of adverse cardiovascular events in postmenopausal women with osteoporosis and high cardiovascular risk. J. Bone Miner. Res. 2014, 29, 450–457.
14. Azizieh, F.Y.; Shehab, D.; Al Jarallah, K.; Gupta, R.; Raghupathy, R. Circulatory Levels of RANKL, OPG, and Oxidative Stress Markers in Postmenopausal Women With Normal or Low Bone Mineral Density. Biomark. Insights 2019, 14,

1177271919843825.

15. Xu, S.; Wang, Y.; Lu, J.; Xu, J. Osteoprotegerin and RANKL in the pathogenesis of rheumatoid arthritis-induced osteoporosis. Rheumatol. Int. 2012, 32, 3397–3403.
16. Fadda, S.; Hamdy, A.; Abulkhair, E.; Elsify, H.M.; Mostafa, A. Serum levels of osteoprotegerin and RANKL in patients with rheumatoid arthritis and their relation to bone mineral density and disease activity. Egypt. Rheumatol. 2015, 37, 1–6.
17. Nitta, K.; Akiba, T.; Uchida, K.; Otsubo, S.; Takei, T.; Yumura, W.; Kabaya, T.; Nihei, H. Serum osteoprotegerin levels and the extent of vascular calcification in haemodialysis patients. Nephrol. Dial. Transplant. 2004, 19, 1886–1889.
18. Osorio, A.; Ortega, E.; Torres, J.M.; Sanchez, P.; Ruiz-Requena, E. Biochemical markers of vascular calcification in elderly hemodialysis patients. Mol. Cell Biochem. 2013, 374, 21–27.
19. Mohammadpour, A.H.; Shamsara, J.; Nazemi, S.; Ghadirzadeh, S.; Shahsavand, S.; Ramezani, M. Evaluation of RANKL/OPG Serum Concentration Ratio as a New Biomarker for Coronary Artery Calcification: A Pilot Study. Thrombosis 2012, 2012, 306263.
20. Li, B.; Yao, Q.; Guo, S.; Ma, S.; Dong, Y.; Xin, H.; Wang, H.; Liu, L.; Chang, W.; Zhang, Y. Type 2 diabetes with hypertensive patients results in changes to features of adipocytokines: Leptin, Irisin, LGR4, and Sfrp5. Clin. Exp. Hypertens 2019, 41, 645–650.
21. Westendorf, J.J.; Kahler, R.A.; Schroeder, T.M. Wnt signaling in osteoblasts and bone diseases. Gene 2004, 341, 19–39.
22. Pereira, L.A.L.; Meng, C.; Amoedo, M.A.G.; Pinto, M.T.D.S.C.; Mendes, F.; Marques, M.A.M.P.; Weigert, A.L.L. Etelcalcetide controls secondary hyperparathyroidism and raises sclerostin levels in hemodialysis patients previously uncontrolled with cinacalcet. Nefrología 2023, 43, 197–203.
23. Kulkarni, N.; Halladay, D.; Miles, R.; Gilbert, L.; Frolik, C.; Galvin, R.; Martin, T.; Gillespie, M.; Onyia, J. Effects of parathyroid hormone on Wnt signaling pathway in bone. J. Cell Biochem. 2005, 95, 1178–1190.
24. Silva, B.C.; Bilezikian, J.P. Parathyroid hormone: Anabolic and catabolic actions on the skeleton. Curr. Opin. Pharmacol. 2015, 22, 41–50.
25. Mödder, U.I.; Hoey, K.A.; Amin, S.; McCready, L.K.; Achenbach, S.J.; Riggs, B.L.; Khosla, S. Relation of Age, Gender, and Bone Mass to Circulating Sclerostin Levels in Women and Men. J. Bone Miner. Res. Off. J. Am. Soc. Bone Miner. Res. 2011, 26, 373–379.
26. Asadipooya, K.; Abdalbary, M.; Ahmad, Y.; Kakani, E.; Monier-Faugere, M.-C.; El-Husseini, A. Bone Quality in CKD Patients: Current Concepts and Future Directions—Part I. Kidney Dis. 2021, 7, 268–277.
27. Gomes, T.S.; Aoike, D.T.; Baria, F.; Graciolli, F.G.; Moyses, R.M.; Cuppari, L. Effect of Aerobic Exercise on Markers of Bone Metabolism of Overweight and Obese Patients with Chronic Kidney Disease. J. Ren. Nutr. 2017, 27, 364–371.
28. Ardawi, M.-S.M.; Al-Kadi, H.; Rouzi, A.; Qari, M.H. Determinants of serum sclerostin in healthy pre- and postmenopausal women. J. Bone Miner. Res. 2011, 26, 2812–2822.
29. Peng, J.; Dong, Z.; Hui, Z.; Aifei, W.; Lianfu, D.; Youjia, X. Bone Sclerostin and Dickkopf-related protein-1 are positively correlated with bone mineral density, bone microarchitecture, and bone strength in postmenopausal osteoporosis. BMC Musculoskelet. Disord. 2021, 22, 480.
30. Kuo, T.-H.; Lin, W.-H.; Chao, J.-Y.; Wu, A.-B.; Tseng, C.-C.; Chang, Y.-T.; Liou, H.-H.; Wang, M.-C. Serum sclerostin levels are positively related to bone mineral density in peritoneal dialysis patients: A cross-sectional study. BMC Nephrol. 2019, 20, 266.
31. Gorter, E.A.; Reinders, C.R.; Krijnen, P.; Appelman-Dijkstra, N.M.; Schipper, I.B. Serum sclerostin levels in osteoporotic fracture patients. Eur. J. Trauma. Emerg. Surg. 2022, 48, 4857–4865.
32. Lu, J.-W.; Syu, R.-J.; Wang, C.-H.; Hsu, B.-G.; Tsai, J.-P. Serum Sclerostin Level Is Negatively Associated with Bone Mineral Density in Hemodialysis Patients. Medicina 2022, 58, 385.
33. Jean, G.; Chazot, C.; Bresson, E.; Zaoui, E.; Cavalier, E. High Serum Sclerostin Levels Are Associated with a Better Outcome in Haemodialysis Patients. Nephron 2016, 132, 181–190.
34. Ardawi, M.-S.M.; Rouzi, A.; Al-Sibiani, S.; Al-Senani, N.S.; Qari, M.H.; Mousa, S. High serum sclerostin predicts the occurrence of osteoporotic fractures in postmenopausal women: The Center of Excellence for Osteoporosis Research Study. J. Bone Miner. Res. 2012, 27, 2592–2602.
35. Pereira, L.; Magalhaes, J.; Mendonca, L.; Neto, R.; Santos, J.; Carvalho, C.G.; Oliveira, A.; Beco, A.; Frazao, J. Evaluation of Renal Osteodystrophy and Serum Bone-Related Biomarkers in a Peritoneal Dialysis Population. J. Bone Miner. Res. 2022, 37, 1689–1699.

36. Lv, W.; Guan, L.; Zhang, Y.; Yu, S.; Cao, B.; Ji, Y. Sclerostin as a new key factor in vascular calcification in chronic kidney disease stages 3 and 4. Int. Urol. Nephrol. 2016, 48, 2043–2050.

37. De Maré, A.; Opdebeeck, B.; Neven, E.; D'Haese, P.C.; Verhulst, A. Sclerostin Protects Against Vascular Calcification Development in Mice. J. Bone Miner. Res. 2022, 37, 687–699.

38. Fang, Y.; Ginsberg, C.; Seifert, M.; Agapova, O.; Sugatani, T.; Register, T.C.; Freedman, B.I.; Monier-Faugere, M.-C.; Malluche, H.; Hruska, K.A. CKD-induced wingless/integration1 inhibitors and phosphorus cause the CKD-mineral and bone disorder. J. Am. Soc. Nephrol. 2014, 25, 1760–1773.

39. Carrillo-López, N.; Martínez-Arias, L.; Fernández-Villabrille, S.; Ruiz-Torres, M.P.; Dusso, A.; Cannata-Andía, J.B.; European Renal Osteodystrophy (EUROD) Workgroup. Role of the RANK/RANKL/OPG and Wnt/β-Catenin Systems in CKD Bone and Cardiovascular Disorders. Calcif. Tissue Int. 2021, 108, 439–451.

40. Saag, K.G.; Petersen, J.; Brandi, M.L.; Karaplis, A.C.; Lorentzon, M.; Thomas, T.; Maddox, J.; Fan, M.; Meisner, P.D.; Grauer, A. Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis. N. Engl. J. Med. 2017, 377, 1417–1427.

41. Hwang, E.Y.; Jeong, M.S.; Park, E.-K.; Kim, J.H.; Jang, S.B. Structural characterization and interaction of periostin and bone morphogenetic protein for regulation of collagen cross-linking. Biochem. Biophys. Res. Commun. 2014, 449, 425–431.

42. Bonnet, N.; Standley, K.N.; Bianchi, E.N.; Stadelmann, V.; Foti, M.; Conway, S.J.; Ferrari, S.L. The matricellular protein periostin is required for sost inhibition and the anabolic response to mechanical loading and physical activity. J. Biol. Chem. 2009, 284, 35939–35950.

43. Bonnet, N.; Conway, S.J.; Ferrari, S.L. Regulation of beta catenin signaling and parathyroid hormone anabolic effects in bone by the matricellular protein periostin. Proc. Natl. Acad. Sci. USA 2012, 109, 15048–15053.

44. Gossiel, F.; Scott, J.R.; Paggiosi, M.; Naylor, K.; McCloskey, E.V.; Peel, N.F.; Walsh, J.S.; Eastell, R. Effect of Teriparatide Treatment on Circulating Periostin and Its Relationship to Regulators of Bone Formation and BMD in Postmenopausal Women with Osteoporosis. J. Clin. Endocrinol. Metab. 2018, 103, 1302–1309.

45. Khan, R.A.; Bhandari, U.; Kapur, P.; Jain, A.; Farah, F. Effects of rosuvastatin (added to hypocaloric diet) on serum periostin, adiponectin, proinflammtory cytokines levels and hepatic steatosis in non-alcoholic fatty liver disease patients with dyslipidemia. Clin. Epidemiol. Glob. Health 2019, 7, 53–59.

46. Rousseau, J.C.; Sornay-Rendu, E.; Bertholon, C.; Chapurlat, R.; Garnero, P. Serum periostin is associated with fracture risk in postmenopausal women: A 7-year prospective analysis of the OFELY study. J. Clin. Endocrinol. Metab. 2014, 99, 2533–2539.

47. Kim, B.-J.; Rhee, Y.; Kim, C.H.; Baek, K.H.; Min, Y.-K.; Kim, D.-Y.; Ahn, S.H.; Kim, H.; Lee, S.H.; Lee, S.-Y.; et al. Plasma periostin associates significantly with non-vertebral but not vertebral fractures in postmenopausal women: Clinical evidence for the different effects of periostin depending on the skeletal site. Bone 2015, 81, 435–441.

48. Anastasilakis, A.D.; Polyzos, S.A.; Makras, P.; Savvides, M.; Sakellariou, G.T.; Gkiomisi, A.; Papatheodorou, A.; Terpos, E. Circulating periostin levels do not differ between postmenopausal women with normal and low bone mass and are not affected by zoledronic acid treatment. Horm. Metab. Res. 2014, 46, 145–149.

49. Zhu, Y.; Ji, J.-J.; Wang, X.-D.; Sun, X.-J.; Li, M.; Wei, Q.; Ren, L.-Q.; Liu, N.-F. Periostin promotes arterial calcification through PPARγ-related glucose metabolism reprogramming. Am. J. Physiol. Heart Circ. Physiol. 2021, 320, H2222–H2239.

50. Sun, X.-J.; Ma, W.-Q.; Zhu, Y.; Liu, N.-F. POSTN promotes diabetic vascular calcification by interfering with autophagic flux. Cell Signal 2021, 83, 109983.

51. Alesutan, I.; Henze, L.A.; Boehme, B.; Luong, T.T.D.; Zickler, D.; Pieske, B.; Eckardt, K.-U.; Pasch, A.; Voelkl, J. Periostin Augments Vascular Smooth Muscle Cell Calcification via β-Catenin Signaling. Biomolecules 2022, 12, 1157.

52. Ryu, J.; Kim, H.J.; Chang, E.-J.; Huang, H.; Banno, Y.; Kim, H.-H. Sphingosine 1-phosphate as a regulator of osteoclast differentiation and osteoclast-osteoblast coupling. EMBO J. 2006, 25, 5840–5851.

53. Ishii, M.; Kikuta, J.; Shimazu, Y.; Meier-Schellersheim, M.; Germain, R.N. Chemorepulsion by blood S1P regulates osteoclast precursor mobilization and bone remodeling in vivo. J. Exp. Med. 2010, 207, 2793–2798.

54. Bae, S.J.; Lee, S.H.; Ahn, S.H.; Kim, H.-M.; Kim, B.-J.; Koh, J.-M. The circulating sphingosine-1-phosphate level predicts incident fracture in postmenopausal women: A 3.5-year follow-up observation study. Osteoporos. Int. 2016, 27, 2533–2541.

55. Ardawi, M.-S.M.; Rouzi, A.A.; Al-Senani, N.S.; Qari, M.H.; Elsamanoudy, A.Z.; Mousa, S.A. High Plasma Sphingosine 1-phosphate Levels Predict Osteoporotic Fractures in Postmenopausal Women: The Center of Excellence for

Osteoporosis Research Study. J. Bone Metab. 2018, 25, 87–98.

56. Lee, S.H.; Lee, S.Y.; Lee, Y.S.; Kim, B.J.; Lim, K.H.; Cho, E.H.; Kim, G.S. Higher circulating sphingosine 1-phosphate levels are associated with lower bone mineral density and higher bone resorption marker in humans. J. Clin. Endocrinol. Metab. 2012, 97, E1421–E1428.
57. Alam, M.S.; Getz, M.; Safeukui, I.; Yi, S.; Tamez, P.; Shin, J.; Haldar, K. Genomic expression analyses reveal lysosomal, innate immunity proteins, as disease correlates in murine models of a lysosomal storage disorder. PLoS ONE 2012, 7, e48273.
58. Morris, T.G.; Borland, S.J.; Clarke, C.J.; Wilson, C.; Hannun, Y.A.; Ohanian, V.; Canfield, A.E.; Ohanian, J. Sphingosine 1-phosphate activation of ERM contributes to vascular calcification. J. Lipid Res. 2018, 59, 69–78.
59. Fernández-Pisonero, I.; López, J.; Onecha, E.; Dueñas, A.I.; Maeso, P.; Crespo, M.S.; Román, J.A.S.; García-Rodríguez, C. Synergy between sphingosine 1-phosphate and lipopolysaccharide signaling promotes an inflammatory, angiogenic and osteogenic response in human aortic valve interstitial cells. PLoS ONE 2014, 9, e109081.
