Parathyroid Hormone: Critical Bridge Between Bone Metabolism and Cardiovascular Disease

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Parathyroid hormone (PTH) is a principal regulator of calcium balance in physiological and pathological conditions associated with cardiovascular disorders and plays a major physiological role in bone homeostasis (Figure 1). PTH systemically controls bone remodeling by modulating the bone marrow microenvironment and regulating osteogenic signaling pathways. PTH and its related peptide can have both anabolic and catabolic effects. Although intermittent administration of PTH is osteoanabolic and antiosteoporotic via stimulation of bone formation, its continuous administration may cause catabolic osteoporotic changes. Experimental studies showed that intermittent injection of full length PTH (PTH 1–84) or its N-terminal fragment (PTH 1–34) increases bone formation with normal microarchitecture by coupling bone remodeling as well as promoting bone vascular structure and function. Clinically, intermittent administration of PTH is an established osteoanabolic therapy that improves quality of life in patients with severe osteoporosis. However, potential adverse effects by long-term use of PTH have not been fully elucidated.

The presence of PTH receptors within the cardiovascular system, including vasculature (smooth muscle cells, endothelial cells) and heart (cardiomyocytes), suggests that secreted PTH may play a role in the pathophysiology of cardiovascular diseases beyond its role in mineral and bone metabolism. Clinically, patients with primary hyperparathyroidism have a higher risk of cardiovascular mortality and have a broad spectrum of adverse cardiovascular disorders such as coronary microvascular dysfunction, subclinical aortic valve calcification, increased aortic stiffness, endothelial dysfunction, and hypertension. Furthermore, secondary hyperparathyroidism, the most significant complication in patients with chronic kidney disease, causes abnormal bone disorders as well as extraskelatal calcification, such as vascular and valvular calcification, and increased risk of cardiovascular mortality. Moreover, recent observational studies indicate that high PTH is an important novel cardiovascular risk factor with powerful predictive value for cardiovascular disease and mortality in individuals even without hyperparathyroidism.

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Hagström et al highlighted PTH as a strong risk predictor for clinical and subclinical atherosclerotic disease using 2 Swedish community-based populations with >1000 70-year-old individuals. The first cohort (PIVUS [Prospective Investigation of the Vasculature in Uppsala Seniors] study) revealed that intact PTH is independently associated with the burden of atherosclerosis, even after adjustment to vascular risk factors and mineral metabolism variables. In a second independent cohort (USLAM [Uppsala Longitudinal Study of Adult Men] study) with a follow-up of 16.7 years, PTH was associated with increased long-term risk of nonfatal atherosclerotic disease in peripheral and large vessels and accounted for 11.6% of the population attributable risk proportion. These findings are consistent with previously published studies. In a prospective study of healthy individuals (n=476), serum PTH levels were positively associated with the number of stenotic coronary arteries. Further, PTH is associated with increased risk of cardiovascular events in patients with stage 3/4 chronic kidney disease independent of calcium-phosphate levels. The Multi-Ethnic Study of Atherosclerosis also demonstrated the association among PTH and hypertension, and a tripartite association among PTH, carotid stiffness, and systolic blood pressure, thus providing new evidence for the role of PTH in cardiovascular diseases.

Recent studies have indicated a protective effect of PTH lowering by cinacalcet on cardiovascular disorders, including the reduction of abdominal aortic calcification and arterial stiffness, whereas reduction in cardiovascular morbidity and mortality in patients on hemodialysis with complications attributable to hyperparathyroidism was not detected. The association between long-term exposure of high PTH and vascular and valvular calcification has been demonstrated mainly in patients with renal dysfunction.

Given its elevated expression in chronic kidney disease patients, these findings suggest that cardiovascular calcification might be the key link between PTH and atherosclerosis. Nevertheless, there have been several experimental studies challenging this hypothesis. PTH 1–34 has been shown to reduce vascular calcification in vitro and in vivo by suppressing vascular BMP2-Msx2-Wnt signaling. Like PTH 1–34, PTH-related peptide suppresses the expression of osteogenic markers and calcium deposition in smooth muscle cells. Conversely, the PTH1R antagonist PTH-related peptide, enhances alkaline phosphatase expression and calcium deposition in vitro.
It is important to mention that most of these experimental studies were performed using the N-terminal fragment of PTH, whereas clinical studies measure intact PTH, indicating that mechanistic studies may not reflect the clinical situation. Moreover, emerging evidence indicates that modifications of PTH alter its biological function. The carboxyl-terminal PTH fragment, which represents 70% to 95% of circulating PTH, exerts specific effects on calcium homeostasis and bone metabolism, opposite to those of the synthetic agonist of PTH/PTH-related peptide receptor, suggesting that carboxyl-terminal PTH may promote vascular calcification. Also, in patients requiring dialysis, a certain proportion of circulating PTH is oxidized and thus loses its PTH receptor–stimulating properties but remains detectable by immunoassay. Therefore, current PTH assay systems may inadequately reflect PTH-related cardiovascular abnormalities in patients on chronic hemodialysis. Indeed, in a diabetic rat model with metabolic disorder and elevated oxidative stress, the positive bone anabolic effects of PTH were blunted, suggesting that conditions with high oxidative stress modify PTH. Indeed, a recent clinical study revealed that the mortality in hemodialysis patients was associated with oxidized PTH but not with nonoxidized PTH levels. It is intriguing to speculate that oxidative stress, a well-established risk factor for cardiovascular diseases, might be an important missing link for the association between PTH and atherosclerotic disease. Oxidized PTH is likely to be increased with age, which in turn associates with accelerated oxidative stress. For the evaluation of PTH as a cardiovascular risk factor, it is necessary to assess the biological function and importance of PTH subtypes (eg, oxidized PTH, carboxyl-terminal PTH) that may differ from the most studied PTH forms (PTH1–34, PTH1–84) and thereby introduce different clinical implications, including cardiovascular calcification.

Changes in mineral metabolism as well as interactive cross talk between the skeletal system and cardiovascular system play a crucial role in vascular disorders such as atherosclerosis or vascular calcification. Although the relationship between osteoporosis and vascular calcification has long been known as the calcification paradox, the key players in this process still remain unclear. Many studies have highlighted an important role for the RANK/RANKL/OPG (receptor activator of nuclear factor kappa B/receptor activator of nuclear factor kappa B ligand/osteoprotegerin) axis in skeletal and extraskeletal calcification. PTH could be a potential candidate to add to the list of mediators of the bone–vascular interaction.

The ultimate clinical goal in the field is to establish a therapy for preventing bone loss without increasing the risk for cardiovascular disorders. In the present study, Hagström et al showed that the highest quartile of PTH (>5.27 pmol/L) in the cohort was associated with the degree of atherosclerosis and increased risk of nonfatal atherosclerotic disorders. Considering the causal role of PTH in atherosclerosis as suggested above, a possible cardiovascular intervention for patients might be the lowering of specific subtypes of PTH that do not affect bone metabolism. In addition, visualizing of extraskeletal calcification and correlation of calcium scores with PTH levels in the future clinical trials would help answering many key questions. Taken together, PTH may provide not only critical information about bone disease but also offer novel preventive measures and therapeutic insights into patients’ cardiovascular health.

Acknowledgements

We thank Joshua D. Hutcheson, PhD, for editorial assistance.

Sources of Funding

Dr Aikawa is supported by grants from the National Institutes of Health (R01HL114805; R01HL109506).

Disclosures

None.
References


Key Words: atherosclerosis ■ bone ■ calcification ■ cardiovascular ■ inflammation
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Arterioscler Thromb Vasc Biol. 2014;34:1333-1335
doi: 10.1161/ATVBAHA.114.303637
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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