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Aggravation of atherosclerosis by parathyroid hormone access

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Abstract
Parathyroid hormone (PTH), primarily known for its role in calcium and phosphate metabolism, has increasingly been implicated in the development and progression of atherosclerosis. Elevated PTH levels, whether due to primary or secondary hyperparathyroidism, are linked to a higher risk of cardiovascular disease, including both subclinical and overt atherosclerotic vascular disease. Evidence shows that, PTH impairs endothelial function by increasing the production of reactive oxygen species (ROS), particularly mitochondrial ROS, which leads to oxidative stress and impaired vascular relaxation. This dysfunction is a key early event in atherogenesis. Moreover, PTH stimulates endothelial cells to upregulate the expression of inflammatory markers such as interleukin-6 (IL-6) and the receptor for advanced glycation end products (RAGE), both of which are involved in vascular inflammation and plaque formation. These effects are mediated via protein kinase A (PKA) and protein kinase C (PKC) pathways and are nitric oxide (NO) dependent. Chronic elevation of PTH also promotes apoptosis of vascular smooth muscle cells (VSMCs), which precedes and contributes to vascular calcification as a hallmark of advanced atherosclerosis, since PTH-induced calcification is associated with endoplasmic reticulum (ER) stress in VSMCs. Additionally, chronic hypercalcemia driven by high PTH levels accelerates calcification of vessel walls and atherosclerotic plaques. Finally, Elevated PTH is associated with metabolic disturbances such as hyperlipidemia and impaired glucose tolerance, both of which exacerbate the atherosclerotic process.

Keywords: Parathyroid hormone, Atherosclerosis, Parathormone, Endothelial cell, Nitric oxide, Reactive oxygen species
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Introduction

Parathyroid hormone (PTH) contributes to the progression of atherosclerosis through several specific mechanisms affecting vascular structure and function (1). This hormone stimulates endothelial cells to increase the expression of the receptor for advanced glycation end products (RAGE) and interleukin-6 (IL-6) mRNA, which are involved in vascular inflammation and atherosclerosis development (2). This stimulation occurs by protein kinase C (PKC) and protein kinase A (PKA) pathways which depends on nitric oxide (NO) synthase activity. Elevated RAGE and IL-6 promote vascular calcification and arteriosclerosis, key processes in atherosclerosis progression (3). Elevated PTH (parathormone) levels are also associated with increased vascular stiffness and hypertension, both of which contribute to the development and worsening of atherosclerotic disease (4). Additionally, PTH, is a regulator of calcium and phosphate metabolism, which influences vascular calcification, as a hallmark of atherosclerosis, that especially notable in conditions like chronic kidney disease where secondary hyperparathyroidism is present (5). Finally, elevated PTH is linked to hyperlipidemia and impaired glucose tolerance, metabolic disturbances that exacerbate atherosclerosis progression Community-based cohort studies have demonstrated that higher circulating PTH levels are associated with greater atherosclerotic burden and an increased risk of clinically overt atherosclerotic disease, independent of traditional cardiovascular risk factors (6). Both primary and secondary hyperparathyroidism are linked to increased risks of endothelial dysfunction, vascular stiffness, hypertension, coronary artery disease, and peripheral arterial disease. These associations persist even after adjusting for classical risk factors for atherosclerosis (7). Elevated PTH levels in patients with cardiovascular disease, such as heart failure, are associated with worse outcomes, including higher rates of stroke and mortality (8). Epidemiological studies in community cohorts show that higher circulating PTH levels correlate with greater atherosclerotic burden assessed by whole-body magnetic resonance angiography and predict increased risk of clinically overt atherosclerotic disease independent of traditional cardiovascular risk factors (9).

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Implication for health policy/practice/research/ medical education

Elevated parathyroid hormone levels aggravate atherosclerosis through various mechanisms, including endothelial dysfunction, inflammation, vascular calcification, and metabolic disturbances. These effects contribute to an increased risk of cardiovascular morbidity and mortality in individuals with hyperparathyroidism or chronically elevated PTH, highlighting the importance of monitoring and managing PTH levels in at-risk populations.

Search strategy

For this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ) and Embase, using different keywords such as parathyroid hormone, atherosclerosis, parathormone, endothelial cell, nitric oxide and reactive oxygen species.

Molecular and cellular mechanisms

Parathyroid hormone acts on vascular smooth muscle cells and endothelial cells via its receptor, which is expressed in these cell types (10). Several experimental evidence indicates that PTH may alter vascular tone and remodeling, possibly promoting hypertension and vascular stiffness as the risk factors to exacerbate the atherosclerosis (11). Although acute PTH exposure can stimulate endothelial vasodilation, chronic elevated PTH correlates with endothelial dysfunction in clinical studies, indicating more complex, possibly detrimental long-term effects on the vasculature (12). Elevated PTH is also linked to increased intracellular calcium in arterial walls, leading to vascular smooth muscle contraction and hypertrophy, contributing to arterial stiffness and plaque development (13). Furthermore, high parathormone concentration have been implicated in promoting vascular calcification, regarded as a hallmark of advanced atherosclerosis and arterial stiffness, particularly in contexts of hyperparathyroidism and kidney disease (4). Meanwhile, elevated PTH induces high bone turnover and medial arterial calcification resembling Mönckeberg's sclerosis, thus aggravating vascular pathology. Importantly, calcimimetic treatments lowering PTH levels can reduce vascular calcification in experimental models, supporting the causative role of PTH in this process (14).

Focus on endothelial cell function and structure by PTH excess

Parathormone influences endothelial cell function by inducing endothelial dysfunction through multiple interconnected molecular and cellular mechanisms involving calcium signaling, oxidative stress, metabolic alterations, and modulation of gene expression (15). PTH receptors (PTH1R), which are G protein-coupled receptors, are expressed in endothelial cells of various vascular beds including human valvular endothelial cells (VEC) and human umbilical vein endothelial cells (HUVECs) (10). Binding of this hormone to these receptors initiates downstream signaling pathways that affect endothelial cell behavior (16). Meanwhile PTH exposure leads to a reduction in endothelial nitric oxide synthase (eNOS) expression and nitric oxide (NO) production, critical mediators of vascular homeostasis and vasodilation (17). This reduction in NO bioavailability contributes to endothelial dysfunction. Concurrently, PTH induces elevated reactive oxygen species (ROS) production and decreases antioxidant enzyme activities such as catalase, exacerbating oxidative stress in endothelial cells (18). Prior studies found that, this hormone impairs mitochondrial respiration and shifts endothelial cellular metabolism towards a glycolytic phenotype (12). If fact, following prolonged exposure, endothelial cells show decreased mitochondrial oxygen consumption and ATP production, accompanied by increased glycolysis, which is associated with vascular inflammation and dysfunction. Likewise, PTH activates mitogen-activated protein kinases (MAPKs), specifically p38MAPK and ERK1/2, in endothelial cells (19). These kinases modulate the expression of osteogenic and inflammatory molecules, including BMP-2, osteopontin, bone sialoprotein, and transcription factors Runx-2 and Sox9, contributing to a pro-calcific endothelial phenotype (20). Recent studies show, in human umbilical vein endothelial cells, PTH enhances store-operated Ca2+ entry (SOCE) by upregulation of the Orai1 channel (21). This calcium influx triggers activation of the calmodulin/calcineurin/nuclear factor of activated T cells (NFATC1) signaling pathway leading to NFATC1 nuclear translocation (21). NFATC1 in the nucleus promotes expression of collagen type I alpha 1 (COL1A1), a key extracellular matrix protein, which mediates increased endothelial cell migration and proliferation—a hallmark of endothelial dysfunction (22). Parathyroid hormone excess can induce endothelial-mesenchymal transition as a process where endothelial cells acquire mesenchymal characteristics contributing to calcification, at physiologically relevant concentrations, PTH does not significantly trigger this transition in valvular endothelial cells, suggesting dose-dependent effects (23). Since, PTH-induced endothelial dysfunction leads to secretion of mediators from endothelial cells that promote osteogenic differentiation of adjacent valvular interstitial cells (VIC) (24). This is characterized by increased expression of osteogenic molecules (BMP-2/4, osteocalcin, TGF-β1) by VIC and decreased collagen I/III production, favoring valvular calcification and dysfunction (25).

Conclusion

Parathyroid hormone promotes atherosclerosis by inducing endothelial inflammation and dysfunction, increasing vascular stiffness, enhancing vascular calcification, and contributing to adverse metabolic profiles, thereby accelerating the development and

clinical manifestation of atherosclerotic vascular disease across with cardiovascular morbidity and mortality. The observed associations are independent of confounding factors such as calcium and vitamin D levels, highlighting this hormone as a potential target for interventions aimed at reducing vascular disease risk.

Conflicts of interest

The author declares that she has no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

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