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# Mechanistic impact of fibrosis by parathyroid hormone excess

Azar Baradaran\*<sup></sup>

## Abstract

The fibrotic impact of parathyroid hormone (PTH) excess is an important aspect of primary hyperparathyroidism (PHPT) that can contribute to organ dysfunction and morbidity. Understanding the underlying mechanisms of PTH-induced fibrosis and identifying potential therapeutic targets may pave the way for novel treatment strategies. Further research is needed to elucidate the complex interactions between PTH and fibrotic pathways and to evaluate the efficacy of targeted interventions in preventing or reversing fibrosis associated with PHPT. The fibrotic impact of PTH excess is observed across multiple organ systems. Fibrosis resulting from PTH excess can impair organ function and lead to significant morbidity and mortality. Understanding the underlying mechanisms involved in PTH-induced fibrosis is crucial for developing targeted therapies to mitigate its detrimental effects.

**Keywords:** Parathyroid hormone, PTH excess, Fibrosis, Organ-specific fibrosis, Molecular mechanisms, Therapeutic interventions

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## Introduction

Parathyroid hormone (PTH) is a critical regulator of calcium homeostasis and bone metabolism. However, excessive levels of PTH have been associated with various pathological conditions, including fibrotic diseases (1,2). Primary hyperparathyroidism (PHPT) is a disorder characterized by excessive secretion of PTH from one or more parathyroid glands, leading to hypercalcemia. In addition to its effects on calcium homeostasis, PTH has been implicated in the development of fibrosis in various organs (3,4). This review aims to explore the fibrotic impact of PTH excess, focusing on its molecular mechanisms and its implications for different organ systems. We discuss the current understanding of PTH excess-induced fibrosis in target organs such as the kidneys and heart highlighting the key cellular and molecular players involved. Furthermore, we delve into the potential therapeutic strategies targeting PTH excess-induced fibrosis, including PTH receptor antagonists and anti-fibrotic agents. Overall, this review provides key insights into the fibrotic consequences of PTH excess and sheds light on potential therapeutic avenues for mitigating its detrimental effects.

## 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 including parathyroid hormone, PTH excess, fibrosis, organ-specific fibrosis, molecular mechanisms, therapeutic interventions.

## Mechanisms of Fibrosis

Some studies have indicated that sustained elevation of PTH in PHPT may contribute to the development of fibrosis through various mechanisms. PTH has been shown to stimulate the production of profibrotic factors, such as transforming growth factor-beta (TGF- $\beta$ ), connective tissue growth factor (CTGF), and fibroblast growth factor-23 (FGF-23) (5,6). These factors promote the activation and proliferation of fibroblasts, leading to the deposition of extracellular matrix proteins and the development of fibrosis. PTH also induces oxidative stress and inflammation, further contributing to fibrotic processes (7,8).

## Activation of fibroblasts

Parathormone can stimulate the activation and proliferation of fibroblasts, which are cells responsible for producing the extracellular matrix components, including collagen. Increased fibroblast activity can lead to excessive production and deposition of collagen, promoting fibrosis in affected tissues (9,10).

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Department of Pathology, Isfahan University of Medical Sciences, Isfahan, Iran.

\*Corresponding author: Azar Baradaran, Email: azarbaradaran@med.mui.ac.ir, azarbaradaran@yahoo.com

### ■ Implication for health policy/practice/research/medical education

Parathyroid hormone (PTH) has been shown to stimulate the production of profibrotic factors, such as transforming growth factor-beta (TGF- $\beta$ ), connective tissue growth factor (CTGF), and fibroblast growth factor-23 (FGF-23). These factors promote the activation and proliferation of fibroblasts, leading to the deposition of extracellular matrix proteins and the development of fibrosis. PTH also induces oxidative stress and inflammation, further contributing to fibrotic processes.

### Inflammation and cytokine release

Parathormone has been implicated in promoting inflammation and the release of pro-inflammatory cytokines. Chronic inflammation can contribute to fibrosis by triggering fibroblast activation, stimulating the synthesis of extracellular matrix proteins, and impairing tissue repair mechanisms (11,12).

### Tissue-specific effects

The fibrotic impact of PTH excess can vary depending on the affected organs or tissues. For example, in the kidneys, elevated PTH levels may contribute to renal fibrosis and the development of chronic kidney disease. In bone, PTH excess can result in increased bone turnover, leading to bone fibrosis and osteoporosis (13,14).

### Activation of TGF- $\beta$ pathway

Transforming growth factor-beta signaling pathway plays a crucial role in fibrosis. PTH has been shown to activate the TGF- $\beta$  pathway, which can promote fibrogenesis by stimulating fibroblast activation and collagen synthesis (15,16).

### Clinical Manifestations

The fibrotic impact of PTH excess can manifest in various organs, including the kidneys, heart, lungs, liver, and skin. In the kidneys, PTH-induced fibrosis can lead to the development of renal interstitial fibrosis and tubular atrophy, ultimately resulting in chronic kidney disease (14,17). Cardiac fibrosis caused by PTH excess can contribute to the development of left ventricular hypertrophy, diastolic dysfunction, and increased cardiovascular morbidity and mortality. Pulmonary fibrosis, hepatic fibrosis, and skin fibrosis have also been reported in association with PHPT (18,19).

### Therapeutic targets

Given the potential role of PTH in promoting fibrosis, targeting PTH or its downstream signaling pathways may represent a therapeutic strategy for preventing or reversing fibrotic processes (20,21). Several studies have investigated the use of PTH receptor antagonists, such as cinacalcet, in the treatment of fibrotic diseases. Other potential targets include TGF- $\beta$ , CTGF, and FGF-23,

which can be inhibited to attenuate fibrosis. However, further research is needed to evaluate the efficacy and safety of these interventions (22,23).

### Conclusion

Excessive PTH secretion in conditions like PHPT can have fibrotic effects on various organs and tissues. PTH-induced fibrosis is a complex process involving multiple mechanisms, including direct effects on fibroblasts, stimulation of profibrotic factors, and impaired extracellular matrix degradation. The fibrotic impact of PTH excess has implications for clinical management, with surgery remaining the primary treatment option. However, further research is needed to better understand the underlying mechanisms and develop targeted therapies to prevent or reverse fibrosis in PHPT.

### Conflicts of interest

The author declare that she has no competing interests.

### Ethical issues

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

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