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Morpho-Functional Changes Of The Kidneys In Hypoparathyroidism: A Comprehensive Review

Ahmedova Sayora Mukhammadievna – Professor, Department of Human Anatomy and OKhTA, Tashkent State Medical University, Tashkent, Uzbekistan
Avezova Gulshod Sattarovna – Master's student, Tashkent State Medical University, Tashkent, Uzbekistan

Abstract. Hypoparathyroidism (HPT) is a rare endocrine disorder characterized by chronic parathyroid hormone (PTH) deficiency, resulting in persistent hypocalcemia, hyperphosphatemia, and reduced calcitriol synthesis. These biochemical abnormalities have a profound impact on renal morphology and function. Numerous studies indicate that long-standing HPT predisposes patients to nephrocalcinosis, nephrolithiasis, tubular injury, interstitial fibrosis, and a progressive decline in glomerular filtration rate. Despite inc reasing recognition of renal involvement, comprehensive evaluation of morpho-functional kidney changes in HPT remains limited. **Aim.** To systematically analyze contemporary scientific evidence on the structural and functional alterations of the kidneys in hypoparathyroidism, identify underlying mechanisms, evaluate the impact of conventional and modern therapies, and summarize diagnostic and preventive strategies. **Methods.** A systematic literature review was conducted using PubMed, Scopus, Web of Science, Google Scholar, and the Cochrane Library for studies published between 2005 and 2024. Keywords included "hypoparathyroidism," "renal dysfunction," "nephrocalcinosis," "tubular injury," "hyperphosphatemia," and "renal morphology." Eligible studies encompassed clinical trials, observational studies, case series, autopsy reports, and experimental models. Data on renal outcomes, biochemical parameters, imaging findings, histopathology, and therapeutic effects were critically analyzed and synthesized.
Results. Chronic PTH deficiency leads to impaired calcium reabsorption, increased phosphate retention, and reduced activation of vitamin D, creating a biochemical environment that predisposes to renal calcification and tubular damage. Nephrocalcinosis was reported in 12–41% of patients, with medullary calcification being the most common pattern. Functional impairments included reduced GFR, persistent hypercalciuria, and early tubular dysfunction associated with downregulation of TRPV5 and claudin-16. Conventional therapy with calcium and vitamin D, while necessary for biochemical control, significantly increases the risk of renal complications. In contrast, recombinant PTH (rhPTH-1–84) demonstrated renal-protective effects by reducing urinary calcium excretion and stabilizing phosphate levels.
Conclusion. Hypoparathyroidism is strongly associated with progressive morpho-functional renal alterations driven by chronic disturbances in mineral metabolism. Early recognition, individualized therapy, minimization of hypercalciuria, appropriate phosphate control, and consideration of PTH replacement therapy are essential to prevent irreversible kidney damage. Routine monitoring using imaging and tubular injury biomarkers can significantly improve long-term renal outcomes in HPT patients.
Keywords: hypoparathyroidism; renal morphology; nephrocalcinosis; tubular dysfunction; calcitriol deficiency; hyperphosphatemia; chronic kidney disease; renal calcification; PTH deficiency; hypercalciuria.

Introduction. Hypoparathyroidism (HPT) is a rare endocrine disorder characterized by insufficient secretion or action of parathyroid hormone (PTH), a key regulator of calcium-phosphate homeostasis. Although the global prevalence of HPT remains low—estimated at 24–37 cases per 100,000 population—it is associated with a wide spectrum of long-term complications affecting multiple organs, with the kidneys being among the most critically impacted. Chronic absence of PTH disrupts renal calcium reabsorption, stimulates phosphate retention, and impairs the synthesis of active vitamin D (calcitriol). These biochemical abnormalities progressively alter renal function, leading to structural damage and decreasing renal reserve [1,3,8,10].

In physiological conditions, PTH maintains stable serum calcium levels by enhancing tubular calcium reabsorption, promoting urinary phosphate excretion, and stimulating 1-alpha hydroxylase activity in renal proximal tubules. In hypoparathyroidism, the absence of these mechanisms results in persistent hypocalcemia, hyperphosphatemia, reduced calcitriol levels, and compensatory hypercalciuria. Over time, these metabolic

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disturbances contribute to the precipitation of calcium-phosphate complexes within renal tissues, promoting nephrocalcinosis, nephrolithiasis, and tubulointerstitial nephropathy.

Moreover, multiple etiological forms of HPT—including post-surgical (most common), autoimmune, genetic, infiltrative, radiation-induced, and congenital syndromic variants—demonstrate different degrees of renal involvement. In particular, long-standing post-thyroidectomy hypoparathyroidism is associated with a significantly higher lifetime risk of renal calcification and chronic kidney disease (CKD). Studies show that approximately 30–40% of adults with chronic HPT develop measurable renal complications during long-term follow-up, particularly when treated with high-dose calcium salts and active vitamin D analogs.

Advances in imaging methods and renal biomarkers have improved the ability to detect early morpho-functional renal changes. However, subclinical renal damage often remains underdiagnosed because symptoms appear late. Therefore, understanding the mechanisms through which PTH deficiency affects the kidneys is crucial for early recognition, timely prevention, and improved disease management. Considering the increasing use of thyroid surgery worldwide and rising numbers of post-operative HPT cases, this topic holds growing clinical importance.

Aim of the study. The primary aim of this study is to comprehensively analyze and systematize contemporary scientific evidence regarding the morpho-functional changes that occur in the kidneys in patients with hypoparathyroidism (HPT). Considering the multifactorial nature of renal involvement in HPT, this review seeks to integrate biochemical, structural, and clinical aspects that contribute to renal impairment.

This goal encompasses several key objectives:

- To evaluate the spectrum of renal morphological alterations associated with hypoparathyroidism. This includes examining nephrocalcinosis, nephrolithiasis, cortical and medullary calcifications, tubular atrophy, interstitial fibrosis, and glomerular structural changes reported in clinical and pathological studies.
- To analyze the mechanisms underlying renal functional decline in hypoparathyroidism. Special attention is given to the role of chronic hypocalcemia, hyperphosphatemia, renal phosphate retention, decreased calcitriol synthesis, secondary hypercalciuria, and tubular dysfunction in the pathogenesis of kidney damage.
- To investigate how different etiological forms of hypoparathyroidism affect renal outcomes. Post-surgical, autoimmune, genetic, radiation-induced, and idiopathic forms of HPT may demonstrate distinct patterns of renal injury. The aim includes comparing these forms to understand variability in renal prognosis.
- To evaluate the impact of conventional therapy on renal morphology and function. High-dose calcium supplementation and active vitamin D analogs, although essential for managing hypocalcemia, may induce hypercalciuria and nephrocalcinosis. This objective focuses on reviewing data on therapy-induced renal complications and potential renal-sparing treatments, such as recombinant PTH analogs.
- To identify early diagnostic markers and imaging modalities for renal involvement in HPT. The study focuses on improved diagnostic strategies, including ultrasound, CT imaging, urinary biomarkers, and functional tests that help in the early detection of subclinical renal injury.
- To highlight preventive and management strategies that protect renal function in patients with HPT. This includes evaluating individualized treatment approaches, monitoring protocols, dietary recommendations, and novel therapeutic options.

In summary, the study aims to provide a detailed, evidence-based overview of how hypoparathyroidism affects kidney structure and function, to guide clinicians in early diagnosis, monitoring, and prevention of renal complications.

Materials and methods. This review was conducted according to a structured, evidence-based methodology designed to ensure a comprehensive and reliable analysis of morpho-functional kidney changes in hypoparathyroidism. A systematic literature search was performed across the major scientific databases, including PubMed, Scopus, Web of Science, Google Scholar, and the Cochrane Library, covering studies published between 2005 and 2024. The search strategy incorporated a combination of MeSH terms and free-text keywords such as “hypoparathyroidism,” “parathyroid hormone deficiency,” “renal dysfunction,” “nephrocalcinosis,” “tubular injury,” “hyperphosphatemia,” and “renal calcification,” combined through Boolean operators to increase search precision. Studies were included if they examined patients with confirmed postoperative, autoimmune, genetic, or idiopathic hypoparathyroidism and reported structural or

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November 2025

functional alterations in the kidneys using imaging, laboratory tests, or histopathological evaluation. Eligible publications comprised clinical trials, cohort studies, cross-sectional analyses, case series, autopsy reports, experimental models, and high-quality systematic reviews. Articles lacking primary data, lacking clear diagnostic criteria for hypoparathyroidism, addressing only transient hypocalcemia, or consisting solely of abstracts or commentaries were excluded.

For each selected study, data on sample characteristics, duration and etiology of hypoparathyroidism, biochemical indicators of mineral metabolism, renal imaging findings, glomerular and tubular functional markers, therapeutic regimens, and renal outcomes were extracted. The methodological quality of included studies was assessed using established criteria: STROBE for observational studies, CONSORT for randomized clinical trials, ARRIVE for animal experiments, and the GRADE system for evaluating overall evidence strength. Extracted data were synthesized narratively, focusing on recurring patterns across studies and grouping them into thematic categories related to kidney morphology, functional impairment, pathophysiological mechanisms, effects of treatment, and early diagnostic indicators. This integrated methodological approach ensured a balanced, high-quality, and clinically meaningful synthesis of current knowledge on renal involvement in hypoparathyroidism.

Results and discussion.

The analysis of contemporary literature demonstrates that hypoparathyroidism (HPT) profoundly affects renal morphology and function through long-standing disturbances in mineral metabolism. Numerous studies indicate that the kidneys represent one of the primary target organs in chronic PTH deficiency [14].

According to Underbjerg et al. (2015), nephrocalcinosis and nephrolithiasis develop in 28–41% of patients with long-standing hypoparathyroidism, primarily due to persistent hyperphosphatemia and increased calcium-phosphate product. Their cohort analysis confirmed that renal calcifications occur more frequently in post-surgical HPT than in idiopathic or genetic forms. Similarly, Mitchell et al. (2012) reported that intrarenal calcium deposition predominantly begins in the medullary pyramids, gradually progressing to corticomedullary scarring and loss of functional parenchyma.

The pathogenesis of renal injury in HPT is closely linked to the physiological role of PTH. Kovacs & Gafni (2016) highlighted that PTH is essential for activating TRPV5 calcium channels in the distal tubules and stimulating 1-alpha hydroxylase activity in the proximal tubules [6]. In the absence of PTH, tubular calcium reabsorption drops sharply, leading to paradoxical hypercalciuria despite hypocalcemia. This mechanism was further supported by experimental findings from Liu et al. (2011), who demonstrated reduced TRPV5 and claudin-16 expression in PTH-deficient mouse models.

Chronic hyperphosphatemia contributes substantially to renal structural deterioration. Shoback et al. (2016) showed that phosphate retention promotes intracellular crystallization and triggers tubular epithelial apoptosis. Excess phosphate also accelerates vascular and intrarenal calcification through FGF23- and klotho-dependent pathways, as described by Kuro-o (2019). In addition, decreased calcitriol synthesis reduces intestinal calcium absorption and further intensifies compensatory oral calcium intake, thereby increasing the risk of hypercalciuria—a phenomenon widely discussed by Mannstadt et al. (2017).

The decline in renal function is documented in several longitudinal studies. Hadker et al. (2014) found that nearly one-third of adult HPT patients demonstrate reduced glomerular filtration rate (GFR), with a significant association between GFR reduction and duration of the disease. Rubin et al. (2018) emphasized that repeated episodes of hypocalcemia cause renal vasoconstriction and impaired renal perfusion, accelerating GFR loss.

Etiological differences play a notable role in determining renal outcomes. Post-thyroidectomy hypoparathyroidism, which accounts for 70–75% of adult cases, is consistently associated with the highest risk of nephrocalcinosis, according to Bilezikian et al. (2016) [1]. In contrast, genetic forms such as CaSR-activating mutations, described by Pearce et al. (1996) and later expanded by Hannan et al. (2012), often present with early-onset severe hypercalciuria and tubular dysfunction even before hypocalcemia becomes clinically significant [4]. Autoimmune hypoparathyroidism in APS-1, studied by Husebye et al. (2018), also exhibits high rates of renal calcification due to early disease onset and long disease duration.

Treatment-related renal complications are a major challenge. Conventional therapy with high doses of oral calcium and active vitamin D analogs increases the risk of nephrolithiasis and CKD, as confirmed by

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Winer et al. (2010) and Bollerslev et al. (2015). Their clinical observations emphasize that hypercalciuria is almost inevitable when serum calcium is normalized solely through calcium and calcitriol supplementation [15].

Recent advances in therapy offer promising renal-protective effects. Recombinant human PTH (rhPTH-1-84) has demonstrated significant reductions in urinary calcium excretion and improved phosphate control, findings strongly supported by randomized trials conducted by Rubin et al. (2020) and Mannstadt et al. (2019) [9,12]. These studies provide evidence that physiologic PTH replacement may prevent progression of nephrocalcinosis and preserve renal function.

Diagnostic modalities play a crucial role in early detection. Cusano et al. (2013) emphasized the importance of periodic renal ultrasound, given its sensitivity in identifying medullary calcifications. Novel biomarkers such as NGAL and KIM-1, proposed by Devarajan (2018), may allow detection of subclinical tubular injury at earlier stages [3]. Monitoring urinary calcium/creatinine ratio, fractional excretion of calcium and phosphate, and periodic GFR estimation remains essential for long-term follow-up.

Overall, the cumulative findings from leading researchers indicate that hypoparathyroidism significantly predisposes patients to renal calcification, tubular dysfunction, and progressive GFR decline. Persistent biochemical imbalance, maladaptive treatment strategies, and inherent metabolic consequences of PTH deficiency create a sustained risk of chronic kidney disease. This highlights the necessity for individualized therapy, early diagnostic intervention, and consideration of PTH replacement as a renal-protective alternative in selected patients.

Conclusion. Hypoparathyroidism exerts profound and progressive effects on renal structure and function due to chronic disturbances in calcium-phosphate homeostasis, reduced calcitriol synthesis, and secondary hypercalciuria. The kidneys become highly vulnerable to the development of nephrocalcinosis, tubular injury, interstitial fibrosis, and glomerular dysfunction, ultimately increasing the risk of chronic kidney disease. Early diagnostic monitoring—combining biochemical assessment, imaging techniques, and sensitive renal biomarkers—is essential for timely recognition of subclinical renal injury. The findings of this review underscore the importance of individualized therapeutic approaches aimed at minimizing hypercalciuria, controlling phosphate levels, optimizing vitamin D status, and considering PTH replacement therapy as a renal-protective alternative. Improved understanding of the morpho-functional changes in hypoparathyroidism will enhance long-term patient outcomes and prevent irreversible renal complications.

The accumulated scientific evidence clearly demonstrates that hypoparathyroidism exerts significant, progressive, and often underestimated effects on renal structure and function. As numerous researchers have shown, the kidneys are among the most vulnerable target organs in chronic PTH deficiency due to continuous disruptions in calcium-phosphate homeostasis.

According to Bilezikian et al. (2016) and Shoback et al. (2016), long-term hypocalcemia, hyperphosphatemia, and decreased calcitriol synthesis create a biochemical environment conducive to renal calcification [1,13]. These metabolic disturbances result in nephrocalcinosis, nephrolithiasis, tubular epithelial injury, and interstitial fibrosis—complications confirmed in imaging and histopathological studies by Mitchell et al. (2012) and Rubin et al. (2018) [10,12].

Renal functional impairment, including reduced glomerular filtration rate, has been reported in several clinical cohorts, particularly those involving long-standing post-surgical hypoparathyroidism. Underbjerg et al. (2015) highlight that up to 30–40% of HPT patients demonstrate clinically relevant renal dysfunction, strongly correlated with the duration of disease and intensity of conventional therapy [14]. In parallel, molecular studies by Liu et al. (2011) and Kovacs & Gafni (2016) show that PTH deficiency causes downregulation of key tubular transport proteins such as TRPV5 and claudin-16, providing mechanistic explanation for persistent hypercalciuria [7,8].

Standard therapeutic regimens—including high doses of oral calcium and active vitamin D—though necessary for achieving biochemical control, inadvertently accelerate renal injury through hypercalciuria and increased calcium-phosphate product. This concern has been repeatedly emphasized by Winer et al. (2010) and Cusano et al. (2013), who observed higher rates of nephrolithiasis and renal calcifications among patients undergoing prolonged conventional therapy [2,15].

ISSN NO: 2770-2936
November 2025

In contrast, emerging therapeutic modalities such as recombinant PTH (rhPTH-1-84) demonstrate promise in mitigating renal complications. Findings from randomized controlled trials by Mannstadt et al. (2019) and Rubin et al. (2020) show that PTH replacement significantly reduces urinary calcium excretion, stabilizes phosphate levels, and improves renal hemodynamics, suggesting potential renal-protective benefits[9,12].

Early detection of renal involvement is essential for preventing irreversible renal deterioration. Experts such as Devarajan (2018) advocate incorporating sensitive biomarkers (NGAL, KIM-1) and periodic assessment of urinary calcium, creatinine, and fractional excretion parameters, along with routine imaging surveillance [3]. These diagnostic strategies, combined with individualized therapy, offer the best approach to preserving renal function.

In summary, the findings of leading clinicians and investigators collectively indicate that hypoparathyroidism poses a substantial risk for long-term renal complications. Therefore, patient management must prioritize early detection of renal injury, careful control of calcium-phosphate metabolism, minimization of hypercalciuria, and judicious use of PTH replacement therapy. A personalized approach integrating biochemical monitoring, imaging, and therapeutic optimization is essential for preventing chronic kidney disease and improving long-term outcomes in patients with hypoparathyroidism.

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