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Journal of Parathyroid Disease

Journal of Parathyroid Disease 2026,14, e13318

DOI:10.34172/jpd.2026.13318

Review

Parathyroid hormone dysregulation and oral microbial dysbiosis in primary hyperparathyroidism; interconnected mechanisms

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Abstract

Primary hyperparathyroidism (PHPT), characterized by chronic parathyroid hormone (PTH) excess and sustained hypercalcemia, disrupts the oral environment by intricate systemic-oral interactions. Hypercalcemia alters salivary composition, viscoelasticity, and flow rate, impairing its antimicrobial properties while promoting bacterial adhesion and calcified plaque formation. These changes foster pathogenic microbial colonization and hasten dental calculus deposition. Concurrently, excess PTH directly triggers osteoclastic resorption in alveolar bone, amplifies proinflammatory cytokines, and boosts matrix metalloproteinases, culminating in periodontal destruction and dysbiosis. Clinically, patients experience heightened tooth mobility, accelerated periodontitis, increased caries risk, and oral discomfort. This oral dysbiosis-inflammation axis further elevates systemic inflammatory burden, exacerbating PHPT-related cardiovascular, metabolic, and renal comorbidities. The interplay between PTH-mediated endocrine dysregulation and oral microbiome shifts highlights the imperative for integrated care. Dentists serve as early detectors of subtle oral signs potentially unmasking undetected PHPT, while endocrinologists must incorporate routine dental assessments. Best results arise from collaborative strategies, including intensive preventive dentistry, meticulous oral hygiene, regular surveillance, and parathyroidectomy when warranted, to interrupt this vicious cycle and reestablish oral and systemic equilibrium.

Keywords: Primary hyperparathyroidism, Oral microbiome, Chronic periodontitis, Parathyroid hormone, Oral cavity, Parathormone

Please cite this paper as: Kadhum AAH, Bdair BWH, A. Imeer AT, Algraittee SJR, Nassrullah HAA. Parathyroid hormone dysregulation and oral microbial dysbiosis in primary hyperparathyroidism; interconnected mechanisms. J Parathyr Dis. 2026;14:e13318. doi:10.34172/jpd.2026.13318.

Introduction

Primary hyperparathyroidism (PHPT) arises most commonly from a solitary parathyroid adenoma, less frequently from multi-glandular hyperplasia or, rarely, carcinoma (1). The hallmark biochemical triad is elevated serum parathyroid hormone (PTH), hypercalcemia, and often low or inappropriately normal serum phosphate (2). Previous authors showed that, parathormone exerts its effects primarily through binding to the PTH type 1 receptor (PTH1R), a G-protein coupled receptor widely expressed in bone, kidney, and other tissues (3). In bone, PTH (parathormone) stimulates osteoclast-mediated bone resorption, releasing calcium and phosphate into the bloodstream (4). In the kidney, it enhances calcium reabsorption in the distal tubule while promoting phosphate excretion in the proximal tubule and stimulating the synthesis of active vitamin D, which further increases intestinal calcium absorption (5). The net result is sustained hypercalcemia. However, PTH's influence extends beyond mineral metabolism. It modulates immune cell function, influences vascular tone, and affects cellular proliferation and differentiation in various tissues (6). Importantly, PTH1R expression has been identified in human gingival fibroblasts, periodontal ligament cells, and salivary gland epithelia, indicating direct targets for PTH action within the oral cavity itself (7). Chronic exposure to supra-physiological PTH levels, therefore, has the potential to directly alter the behavior of these cells, impacting tissue integrity, inflammatory responses, and the local microenvironment that shapes microbial colonization and growth (8,9). The oral cavity, a unique and dynamic environment teeming with hundreds of microbial species forming intricate biofilms on teeth, mucosa, and gingival crevices, is exquisitely sensitive to changes in the host's systemic physiology, including mineral homeostasis, immune function, and fluid composition (10). The chronic

Received: 7 Jan. 2026, **Revised:** 28 Jan. 2026, **Accepted:** 29 Jan. 2026, **ePublished:** 7 Feb. 2026

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Implication for health policy/practice/research/medical education

In primary hyperparathyroidism (PHPT), dysregulated parathyroid hormone (PTH) secretion initiates a cascade linking systemic metabolism, immunity, and the oral microbiome. Calcium-phosphate imbalance accelerates bone resorption and modifies saliva, while PTH-driven immune alterations foster a pro-inflammatory oral niche. This environment drives microbial dysbiosis, periodontitis, and tooth loss. These oral pathologies then feed back into systemic circulation, amplifying inflammation and worsening metabolic-endocrine dysfunction. Therefore, this disease creates a vicious cycle; since PTH excess disrupts oral homeostasis, then the ensuing inflammation further dysregulated parathormone secretion. This bidirectional axis involves skeletal turnover, immune activation, and microbial ecology demonstrates the multisystem manifestations of this disease.

elevation of parathormone in PHPT initiates a cascade of alterations that reverberate through the oral ecosystem, potentially fostering dysbiosis as a pathological shift in the microbial community structure away from health-associated symbionts towards pathobionts and overt pathogens (11). This dysbiosis, in turn, can exacerbate local inflammation, tissue destruction, and may even feed back into systemic inflammation, creating a complex, bidirectional relationship that significantly impacts patient well-being (11).

Search strategy

For this narrative review, we conducted a literature search across multiple databases, including PubMed, Google Scholar, the Directory of Open Access Journals (DOAJ), Web of Science, EBSCO, Scopus, and Embase, using a variety of relevant keywords like; primary hyperparathyroidism, oral microbiome, parathormone, chronic periodontitis, parathyroid hormone and oral cavity.

The constituents of oral microbiome

The oral microbiome is a paradigm of a complex, host-adapted ecosystem. In health, it exists in a state of dynamic equilibrium, dominated by commensal bacteria like *Streptococcus sanguinis*, *Streptococcus oralis, Actinomyces* species, and *Veillonella* species, which contribute to colonization resistance against pathogens, aid in nutrient processing, and help maintain mucosal barrier function (12). This balance is maintained by a combination of host factors like saliva flow and composition, epithelial integrity, innate and adaptive immune responses, and microbial factors such as inter-species competition, cooperation and quorum sensing (12). Dysbiosis occurs when this equilibrium is disrupted, often characterized by a decrease in microbial diversity and an increase in the relative abundance of proteolytic, acid-tolerant, and inflammation-associated species, particularly the red complex bacteria, known as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*, which are strongly associated with periodontitis (13). Other key players include *Fusobacterium nucleatum*, which acts as a bridge organism facilitating the integration of late colonizers into biofilms, and pathobionts like *Prevotella intermedia* and *Aggregatibacter actinomycetemcomitans* (14). The transition from symbiosis to dysbiosis is rarely due to a single pathogen but rather a shift in the entire community structure, often triggered by changes in the local environment, such as alterations in pH, oxygen tension, nutrient availability, host immune status, or the composition of the pellicle (15).

Consequences of PHPT on oral ecology

The most direct and profound systemic consequence of PHPT relevant to oral ecology is hypercalcemia (16). Elevated serum calcium levels have several cascading effects on the oral environment. Firstly, calcium is a critical component of saliva (17). Saliva in PHPT patients often exhibits hypercalcemia mirroring the serum levels (18). Calcium ions (Ca^{2+}) play a dual role in the oral cavity. On one hand, they are essential for the structural integrity of tooth enamel and dentin, contributing to remineralization (19). On the other hand, elevated free Ca^{2+} in saliva significantly influences microbial adhesion and biofilm formation (20).

In hypercalcemic saliva may alter the conformation and availability of these pellicle proteins, potentially enhancing the binding sites for certain bacteria while inhibiting others (21). More significantly, elevated Ca^{2+} acts as a potent ionic bridge, facilitating the adhesion of bacterial cells to each other and to the tooth surface. This condition accelerates the initial stages of biofilm formation and increase biofilm biomass and stability (22). Meanwhile, this enhanced adhesion is not selective for beneficial commensals; pathogenic species, including those associated with caries, like *Streptococcus mutans* and Lactobacillus species and periodontitis, such as *P. gingivalis* and *F. nucleatum*, also exploit calcium-mediated adhesion mechanisms (23). Additionally, *S. mutans*, utilizes calcium to strengthen the glucan matrix of its biofilms, making them more resistant to shear forces and antimicrobial agents (24). Periodontal pathogens may use calcium to stabilize their attachment to the altered sub-gingival pellicle or to co-aggregate with other bacteria (25). Thus, hypercalcemic saliva in PHPT creates a physicochemical environment that inherently favors denser, potentially more pathogenic biofilm accumulation on all oral surfaces (18). Beyond adhesion, hypercalcemia directly influences microbial metabolism and virulence (26). Calcium acts as an essential intracellular second messenger in many bacterial species, regulating processes like enzyme secretion, motility, and stress responses (27). Elevated extracellular Ca^{2+} can dysregulate these signaling pathways. For cariogenic bacteria like *S. mutans*, high environmental calcium can enhance aciduricity, as its the

ability to survive and metabolize at low pH by stabilizing cell membranes and modulating F1F0-ATPase activity, the enzyme complex crucial for expelling protons and maintaining intracellular pH during acid production (28). This makes them more resilient in the acidic environments they create during sugar metabolism, accelerating enamel demineralization (28). For periodontal pathogens, calcium signaling is intricately linked to the expression of virulence factors (29). Moreover, *P. gingivalis*, as a master manipulator of the host environment, requires calcium for the activity of its potent proteases, the gingipains (30). In fact, gingipains are essential for nutrient acquisition named degrading host proteins, evasion of host immunity as cleaving antibodies and complement factors, and disruption of host cell signaling (30). Elevated calcium levels can enhance gingipain activity and stability, amplifying the bacterium's destructive potential within the periodontal pocket (30). Similarly, calcium can modulate the expression of fimbriae and other adhesion molecules in periodontal pathogens, further enhancing their colonization and invasion capabilities (29).

Direct effects of parathormone on oral cavity

The impact of PHPT on the oral cavity extends far beyond calcium's direct effects on microbes (8). Parathormone itself, acting locally by PTH1R expressed on gingival and periodontal cells, can modulate the host response through dysbiosis (7,31). Chronic PTH elevation has been shown to stimulate gingival fibroblasts to produce higher levels of pro-inflammatory cytokines like interleukin-6 (IL-6) and interleukin-8 (IL-8), and matrix metalloproteinases (MMPs), particularly MMP-1, MMP-2, and MMP-9 (32). In fact, MMPs are enzymes responsible for degrading the extracellular matrix components of the periodontal ligament and gingival connective tissue (33). While essential for normal tissue remodeling, their chronic overexpression leads to pathological tissue breakdown, a hallmark of periodontitis (33). PTH can also influence the RANKL/RANK/OPG pathway within the periodontium (34). Meanwhile, RANKL (receptor activator of nuclear factor kappa-B ligand), expressed by osteoblasts and stromal cells, binds to RANK on osteoclast precursors, stimulating osteoclastogenesis and bone resorption (35). Osteoprotegerin (OPG) acts as a decoy receptor, inhibiting this process (35). Furthermore, PTH potently upregulates RANKL expression and downregulates OPG production in bone cells (36). Recent studies suggested a similar PTH-mediated dysregulation in periodontal tissues, shifting the balance towards increased osteoclast formation and alveolar bone resorption (34). This local bone loss creates deeper periodontal pockets, which provide an anaerobic, nutrient-rich environment ideal for the proliferation of proteolytic, anaerobic periodontal pathogens like *P. gingivalis* and *T. denticola*, which further driving dysbiosis and inflammation in a vicious cycle (30). Likewise, PTH can impair the function of immune cells within the oral mucosa (6). It may suppress neutrophil chemotaxis and phagocytic activity, reducing the first line of defense against bacterial invasion (34). It can also modulate macrophage polarization towards a more pro-inflammatory (M1) phenotype, perpetuating tissue-damaging inflammation rather than promoting resolution and repair (37). In fact, PTH alters the host's immune-inflammatory response, creating a permissive environment for pathogenic bacteria by impairing clearance (6). Saliva, as the lifeblood of oral health, undergoes significant alterations in PHPT beyond just calcium concentration (8). Hyposalivation is a major risk factor for oral dysbiosis (38); since, saliva provides essential protective functions, consisting of mechanical cleansing like washing away microbes and food debris, buffering capacity, containing neutralizing acids produced by bacteria, antimicrobial activity by lysozyme, lactoferrin, peroxidase systems, secretory IgA, and re-mineralization by calcium, phosphate, and fluoride ions. Reduced flow diminishes all these functions (39). The buffering capacity is particularly crucial; without adequate saliva to neutralize acids, the oral pH drops more readily and remains low for longer periods after carbohydrate intake, favoring the selection and proliferation of acidogenic and aciduric bacteria like *S. mutans* and lactobacilli, the primary drivers of dental caries (23). Furthermore, hypercalcemia alters the protein and electrolyte composition of saliva. Elevated levels of calcium and phosphate can lead to increased precipitation of calcium phosphate salts, contributing to calculus formation (40). Calculus provides a rough, retentive surface that is difficult to clean and serves as a reservoir for bacterial biofilms, particularly subgingivally where it acts as a constant irritant to the gingiva, perpetuating inflammation and creating a protected niche for periodontal pathogens (25). Changes in salivary protein profiles, including potential alterations in the concentration or glycosylation of protective proteins like histatins, statherin, and mucins, can further impair innate immune defense and microbial adhesion control, tipping the balance towards dysbiosis (41).

A short look at the dental manifestations of PHPT

Dental manifestations reported in PHPT include bone resorption of the jaws, tooth mobility, loss of lamina dura, and in some cases brown tumors or osteitis fibrosa cystica of the jaws in severe, prolonged disease (42). These morphological changes are not only markers of systemic bone disease but also create ecological consequences for microbial colonization (43). Areas of exposed cementum and root surfaces provide attachment sites for plaque accumulation, and tooth mobility alters mechanical self-cleansing during mastication (44). Moreover, gingival bleeding influenced by mucosal vascular fragility or inflammatory states increases heme availability in pockets, a nutrient that supports the growth of key periodontopathic anaerobes (45).

Clinical manifestations of PTH-oral microbiome interactions

The clinical manifestations of this PTH-oral microbiome interplay are increasingly recognized, though often underappreciated in routine PHPT management (8). Dental professionals may be the first to observe subtle signs. Accelerated dental caries is a frequently reported, though not universal, finding in PHPT patients (46).

Treatment modalities

Therapeutic interventions for PHPT, as surgical parathyroidectomy or medical management when surgery is not indicated, offer further insight into the interplay between endocrine control and oral ecology (47). Clinical reports suggest that normalization of PTH and serum calcium levels after successful parathyroidectomy may lead to stabilization or improvement of some oral manifestations (42-44). In addition, combined dental interventions like mechanical debridement, improved oral hygiene, and anti-inflammatory measures are likely necessary to reshape the microbial community back toward health (15,44).

Conclusion

Excess PTH, as seen in PHPT, profoundly perturbs oral and periodontal homeostasis through interconnected metabolic, immunologic, and microbial mechanisms. Persistent PTH elevation enhances osteoclastic bone resorption and disturbs systemic calcium–phosphate equilibrium, resulting in elevated mineral concentrations in saliva and gingival crevicular fluid. These biochemical shifts alter salivary viscosity, buffering capacity, and microbial nutrient availability, fostering rapid biofilm maturation, calculus deposition, and colonization by proteolytic and anaerobic species such as *P. gingivalis* and *T. forsythia*. Simultaneously, PTH-mediated immune modulation compromises neutrophil function, skews cytokine profiles toward a proinflammatory phenotype, and impairs local resolution pathways, thereby diminishing the host's ability to constrain dysbiosis. Pathogenic microbes exploit the disrupted epithelial barrier and nutrient-enriched gingival crevicular fluid to establish a chronic inflammatory state that further activates osteoclastogenesis and connective tissue degradation. This self-reinforcing cycle accelerates periodontal attachment loss and bone destruction. Clinically, PHPT is frequently associated with severe periodontitis, increased tooth mobility, characteristic radiographic bone loss, and delayed post-extraction healing. Beyond localized damage, chronic oral inflammation contributes to the systemic inflammatory milieu, potentially exacerbating cardiovascular and metabolic complications linked to PHPT. Recognizing oral manifestations as extensions of endocrine dysfunction reframes PHPT as a condition with important dental implications. Integrated dental-endocrine collaboration, including routine periodontal evaluation, early recognition of oral signs, and timely parathyroid intervention, is therefore critical for preventing irreversible tissue damage and restoring systemic and oral equilibrium.

Authors' contribution

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Writing–original draft: All authors.
Writing–review and editing: All authors.

Ethical issues

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

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.

Conflicts of interest

The authors declare that they have no competing interests.

Funding/Support

None.

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