Narrative Review Article

Elucidating the Overlapping Immunometabolic Etiologies of Polyendocrine Metabolic Ovarian Syndrome and Periodontal Disease

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ABSTRACT

Polyendocrine Metabolic Ovarian Syndrome (PMOS) and periodontal disease are among the most prevalent chronic inflammatory conditions worldwide, yet their clinical intersection remains underrecognized. PMOS is increasingly understood as a systemic inflammatory disorder, while periodontal disease is a leading cause of tooth loss. Clinical, biomarker, and epidemiological studies consistently show that women with PMOS demonstrate greater periodontal susceptibility than healthy controls, including elevated probing depths, clinical attachment loss, and gingival inflammation, even when oral hygiene is statistically controlled. Meta-analytic evidence supports a bidirectional association, with PMOS raising the odds of periodontitis by 28 percent and periodontitis raising the odds of PMOS by 46 percent. These findings support integrating routine periodontal assessment into PMOS management and call for interdisciplinary collaboration among dentistry, gynecology, and endocrinology. This literature review synthesizes current evidence on the relationship between these two conditions, focusing on shared immunometabolic mechanisms and the modifying roles of age, metabolic severity, and oral hygiene.

Keywords: Polyendocrine Metabolic Ovarian Syndrome; Periodontal Disease; Periodontitis; Systemic Inflammation; Insulin Resistance; Oral-Systemic Health; Cytokines; Oxidative Stress

INTRODUCTION

Polyendocrine Metabolic Ovarian Syndrome (PMOS), previously known as Polycystic Ovary Syndrome (PCOS), and periodontal disease represent two of the most prevalent chronic inflammatory conditions affecting the global population, yet their potential interconnection has received limited attention. This review adopts the term PMOS in place of the more widely used PCOS to reflect a growing clinical view that the condition is fundamentally a systemic polyendocrine and metabolic disorder rather than one defined by ovarian morphology; polycystic ovaries are neither required for diagnosis nor present in all affected women. Because the large majority of the literature cited in this review, including the diagnostic guidelines and primary studies discussed below, was published using PCOS terminology, PMOS and PCOS are treated as synonymous throughout this manuscript. Original PCOS terminology is preserved in reference titles as published, consistent with standard citation practice. Global Burden of Disease analyses confirm that

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global PMOS prevalence reached approximately 65.8 to 69.4 million cases by 2021, with incidence increasing by 26 percent since 1990, a trajectory projected to continue rising. The economic burden of PMOS in the United States is estimated to exceed $15 billion annually, encompassing fertility treatment, metabolic disease management, and associated mental health comorbidities (1). Together, these figures underscore the growing public health impact of PMOS.

Periodontal disease occupies an equally prominent position in the global chronic disease burden. As a leading cause of tooth loss in adults, periodontal disease imposes considerable public health consequences through functional impairment, reduced quality of life, and elevated systemic inflammatory burden. The annual global economic costs number in the tens of billions of dollars (2). Although these conditions have traditionally been approached as distinct clinical entities, growing evidence situates PMOS and periodontal disease as potentially related through shared immunometabolic pathways (3). The oral-systemic medicine framework has established that the mouth is not isolated from systemic health. Periodontal inflammation interacts bidirectionally with conditions such as type 2 diabetes, cardiovascular disease, and adverse pregnancy outcomes (4, 5).

The possibility that PMOS, a condition characterized by chronic low-grade systemic inflammation, insulin resistance, and oxidative stress, could similarly influence periodontal immune responses represents a clinically important and scientifically compelling question. This convergence positions PMOS within the broader oral-systemic framework. The objective of this review is to critically synthesize the clinical, biomarker, and epidemiological evidence linking PMOS and periodontal disease and to evaluate the strength and specificity of the immunometabolic mechanisms proposed to explain this association. Specifically, this review addresses three questions: (1) Is the association between PMOS and periodontal disease independent of shared confounders such as obesity, insulin resistance, and oral hygiene behavior, or can it be substantially explained by them? (2) What is the quality and directness of evidence supporting each proposed mechanistic pathway, cytokine-mediated, hormonal, oxidative, and microbial, linking the two conditions? (3) What modifiable targets, particularly oral hygiene support and metabolic management, could reduce the combined disease burden, and what gaps in longitudinal and mechanistic evidence must be resolved before periodontal care can be formally integrated into routine PMOS management?

POLYENDOCRINE METABOLIC OVARIAN SYNDROME

Incidence, Economic Burden, and Reproductive Impact

Polyendocrine Metabolic Ovarian Syndrome is the most prevalent endocrine disorder affecting women of reproductive age globally, affecting 6 to 20 percent of this population and imposing a substantial healthcare burden estimated at $4.36 billion annually in the United States, a figure that exceeds $15 billion once associated depression, anxiety, and eating disorders are included (6-8). Beyond its metabolic and reproductive consequences, PMOS is associated with elevated rates of depression, anxiety, and reduced quality of life (9), and its incidence among adolescents and young adults has risen sharply over the past three decades (10). This adolescent trend is directly relevant to the periodontal literature discussed later in this review, which similarly points to early, subclinical inflammatory changes that may precede overt clinical disease.

Clinical Manifestations, Diagnosis, and Treatment

The clinical presentation of PMOS is heterogeneous, manifesting in four recognized phenotypes defined by the presence of hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology; phenotype A, in which all three features co-occur, carries the greatest degree of insulin resistance and systemic inflammation (9, 11). This phenotypic heterogeneity is critical for interpreting variability in PMOS-periodontal research findings, since studies that do not report phenotype distribution may be pooling biologically distinct inflammatory profiles under a single diagnostic label. First-line management centers on weight loss and insulin-sensitizing agents such as metformin, alongside combined oral contraceptives and, increasingly, GLP-1 receptor agonists (9, 11); whether these metabolic interventions confer a secondary periodontal benefit, beyond their intended reproductive and metabolic effects, is a question this review returns to in the Conclusion.

Genetic and Inflammatory Etiology

Genome-wide association studies have identified multiple PMOS susceptibility loci implicating insulin signaling, gonadotropin regulation, and steroidogenesis, and twin studies support an additional heritable component that interacts with environmental exposures such as diet and endocrine-disrupting chemicals (10, 12). This gene-environment interplay establishes PMOS as

a condition shaped by both inherited vulnerability and modifiable lifestyle factors, factors that, as discussed below, also independently affect periodontal risk and therefore complicate attribution of periodontal findings to PMOS-specific biology.

Central to understanding PMOS pathophysiology is the recognition that chronic low-grade systemic inflammation functions as a core feature of the disorder. Women with PMOS consistently demonstrate elevated circulating levels of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), IL-1beta, IL-17, IL-18, and C-reactive protein (CRP) (13,14). CRP levels in women with PMOS are, on average, 96 percent higher than in controls (15). The mechanisms driving inflammation are tightly linked to insulin resistance and hyperandrogenism. Visceral adipose tissue in PMOS undergoes polarization of macrophages from an anti-inflammatory M2 phenotype toward a pro-inflammatory M1 phenotype associated with elevated TNF-alpha and IL-6 levels that further impair insulin signaling. TNF-alpha directly inhibits insulin receptor tyrosine kinase activity in muscle and adipose tissue, while IL-6 activates hepatic CRP synthesis and promotes atherogenesis (14). Peripheral T-cell dysregulation, including T helper type 1 (Th1) and Th17 bias, reduced regulatory T-cell populations, and elevated natural killer cell activity, further contribute to the systemic inflammatory phenotype of PMOS and create the immune milieu upon which periodontal susceptibility may be superimposed (14, 16). Together, these mechanisms establish a self-reinforcing cycle of metabolic and immune dysfunction that underlies many of the systemic manifestations of PMOS. Although each of these inflammatory abnormalities is well documented within PMOS itself, their direct causal contribution to periodontal tissue destruction has not been demonstrated in human PMOS-periodontal cohorts; the connection is inferred by analogy to systemic inflammatory disease more generally, and the periodontal biomarker studies discussed later in this review provide the more direct, though still limited, evidence on this specific point.

PERIODONTAL DISEASE

Incidence, Economic Burden, and Societal Impact

Periodontal disease encompasses a spectrum of chronic inflammatory conditions affecting the tooth-supporting structures. Modifiable risk factors include oral hygiene practices, smoking, diet, and obesity, while non-modifiable factors include genetic predisposition, age, and sex; systemic conditions marked by immune or metabolic dysregulation, such as diabetes, rheumatoid arthritis, and chronic kidney disease, are well-established risk modifiers (4, 17-19). Mild-to-moderate periodontitis affects 45 to 50 percent of adults worldwide, severe periodontitis affects 10 to 15 percent, and management costs reach billions of dollars annually (2, 17, 20, 21). This is the established framework of systemic risk modifiers within which PMOS should be situated, and the sections below evaluate how well the current evidence supports that placement.

Clinical Manifestations, Staging, Grading, and Treatment

Periodontal diseases range from the reversible inflammation of gingivitis to the irreversible tissue destruction of periodontitis. Gingivitis is characterized by gingival redness, edema, bleeding on probing, and plaque accumulation in the absence of clinical attachment loss or radiographic bone loss (18). Untreated gingivitis may progress to periodontitis in susceptible individuals, as host immune factors, microbial virulence, and modifying risk factors collectively determine disease progression (17). Host-dependent susceptibility is particularly relevant in the context of PMOS, where systemic immune dysregulation may lower the threshold for progression from gingivitis to periodontitis.

The classification framework for periodontitis integrates clinical, radiographic, and systemic dimensions of disease in a way that is directly applicable to PMOS-related research. Periodontal and Peri-Implant diseases are staged (I-IV) and graded (A-C) based on clinical attachment loss, radiographic bone loss, tooth loss, probing depths, and the rate of progression, associated risk factors, and systemic disease impact, respectively (17). Notably, the inclusion of systemic risk modifiers within the grading criteria creates explicit space for conditions like PMOS to be recognized as clinical risk factors in periodontal staging. Treatment follows a stepwise approach, from non-surgical scaling and root planning to surgical intervention in advanced stages, with adjunctive antimicrobial and host-modulation therapies reducing local and systemic inflammatory markers including CRP, IL-6, and TNF-alpha (4, 5). This systemic anti-inflammatory effect is particularly pertinent to PMOS, where reducing periodontal inflammatory burden could theoretically attenuate the broader systemic inflammatory load; however, this has not been directly tested in PMOS-specific populations and is identified in the Conclusion as a priority for future interventional research.

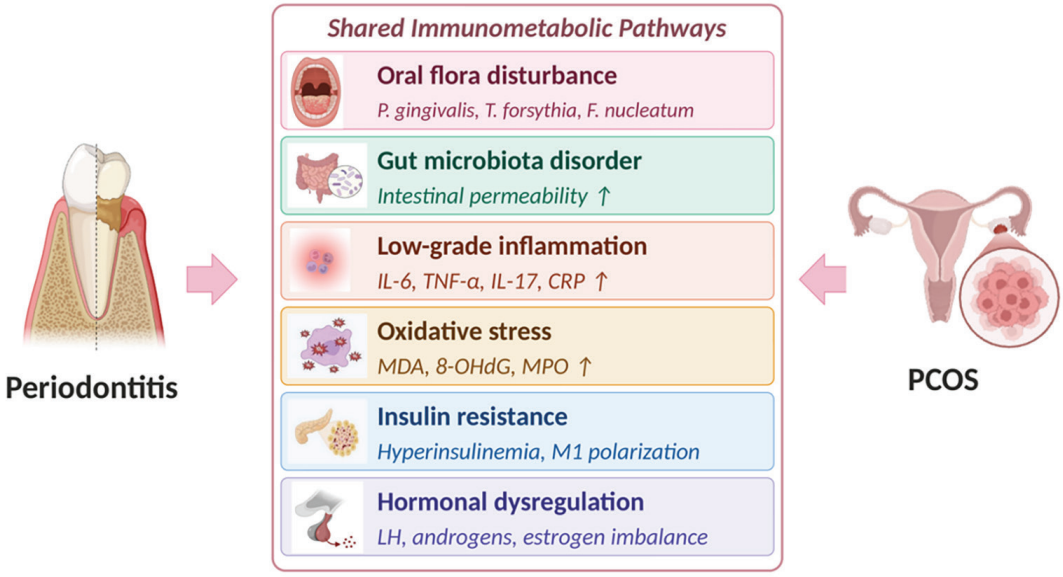

***Figure 1.* Shared Immunometabolic Pathways Linking PMOS and Periodontal Disease.** *PMOS and periodontal disease share overlapping mechanisms, including microbial dysbiosis, gut microbiota disruption, chronic low-grade inflammation, oxidative stress, insulin resistance, and hormonal dysregulation. Elevated inflammatory mediators (e.g., IL-6, TNF-α, IL-17, CRP) and altered immune responses create a pro-inflammatory environment that promotes periodontal tissue destruction and reinforces systemic metabolic dysfunction, supporting a bidirectional relationship between the two conditions.*

Genetic and Inflammatory Etiology

The pathogenesis of periodontal disease is driven by the dynamic interaction between dysbiotic subgingival microbial biofilms and host immune responses, an immune-inflammatory framework that is central to understanding its relationship with PMOS. Low abundance pathobionts such as Porphyromonas gingivalis can subvert host immune surveillance and orchestrate an oral microbial dysbiosis that amplifies inflammatory responses disproportionate to bacterial load (22, 23). Inflammatory mediators in periodontal disease overlap substantially with those dysregulated in PMOS. IL-1beta, IL-6, TNF-alpha, IL-17, prostaglandin E2, and matrix metalloproteinases collectively orchestrate immune cell recruitment, cytokine amplification, and osteoclast activity in periodontal tissues (18). Notably, IL-6 and TNF-alpha are consistently elevated in PMOS. IL-17, produced by Th17 cells, is dysregulated in both PMOS and periodontal disease (23). This cytokine overlap positions the PMOS immune phenotype as one that may directly amplify periodontal tissue destruction (Figure 1). It is important to note, however, that this overlap is inferred from parallel elevations reported in two largely separate disease literatures rather than from studies measuring both cytokine panels within the same PMOS-and-periodontitis patients; the biomarker studies reviewed in the Immunological and Mechanistic Pathways section below provide more direct, though still limited, evidence on this specific point.

ORAL SYSTEMIC RELATIONSHIPS

Oral-Systemic Associations

The concept of oral-systemic health has recently garnered substantial scientific validation. Among the strongest is the bidirectional relationship between periodontitis and type 2 diabetes mellitus. Diabetes impairs periodontal immune defenses, accelerating gingival inflammation and bone loss, while periodontitis worsens glycemic control by amplifying systemic insulin resistance (5,18). Scaling and root planing reduce Hemoglobin A1c (HbA1c) levels in diabetic patients (24). Moreover, periodontitis is linked to increased risk of coronary artery disease, myocardial infarction, stroke, and peripheral vascular disease through systemic dissemination of oral bacteria, elevation of circulating inflammatory cytokines, and endothelial dysfunction (25). The 2023 consensus report by the European Federation of Periodontology and WONCA Europe formally recognized these associations and

called for integrated care pathways between dental and medical professionals for patients with both conditions (5). Periodontal inflammation has similarly been implicated in preterm birth, rheumatoid arthritis, and several other systemic conditions through shared inflammatory mechanisms (4, 17). Elevated circulating IL-6, TNF-alpha, and CRP from periodontal lesions is a common driver of remote organ effects. It is within this established oral-systemic health framework that the PMOS-periodontal relationship must be understood as a clinically coherent extension of a well-validated biological principle.

PMOS and Periodontal Disease: Clinical Evidence

Early clinical investigations found significantly elevated probing depths, bleeding on probing, and clinical attachment loss alongside higher serum malondialdehyde and 8-OHdG levels in women with PMOS, suggesting that oxidative stress mediates the exacerbated periodontal response (26). Subsequent research has replicated these findings while extending them to encompass additional populations and clinical parameters. Comparison of 60 women with PMOS to 60 healthy controls found significantly higher plaque and gingival indexes, bleeding on probing and probing depth in the PMOS group, supporting a systemic explanation that extends beyond oral hygiene disparities alone (27). Neither of these early studies reported whether groups were matched for BMI, insulin resistance, or socioeconomic status, which, as discussed below, limits how confidently the periodontal differences can be attributed to PMOS itself rather than to these correlated factors.

Cross-sectional data from 196 women aged 17 to 45 further showed that PMOS participants had significantly higher gingival index and loss of attachment scores despite similar oral hygiene index scores (28). A particularly important strand of evidence concerns adolescent PMOS populations, where subclinical inflammatory priming may precede overt clinical periodontal disease. In 31 adolescents with PMOS compared to 28 healthy controls, no significant differences in clinical periodontal parameters were found; however, the PMOS group showed significantly elevated salivary IL-6, TNF-alpha, and IL-1beta (29). This pattern of inflammatory elevation without commensurate clinical tissue destruction supports an inflammation-first model in which PMOS creates a pro-inflammatory oral environment that may predispose to periodontal breakdown over time. Clinically, this suggests that adolescents with PMOS may be in a subclinical inflammatory stage that warrants monitoring even in the absence of overt periodontal disease. Age-stratified comparisons further illuminate the temporal trajectory through which subclinical inflammatory priming in PMOS converts into measurable periodontal tissue damage. Adults, compared to adolescents, had more sites with probing pocket depth of 3 to 4 mm, higher mean clinical attachment level, and rates of Stage I periodontitis, despite similar PMOS phenotype distribution between age groups (28). Collectively, these studies strengthen the case for a PMOS-specific systemic inflammatory contribution to periodontal disease beyond what oral hygiene differences can explain and emphasize the impact of cumulative PMOS-related inflammatory exposure on measurable periodontal damage (Figure 2).

Meta-analytic evidence has strengthened the case for a bidirectional association between PMOS and periodontal disease. PMOS patients have a 28 percent higher chance of having periodontitis, while periodontitis was associated with a 46 percent higher chance of PMOS (30). This meta-analysis pooled studies that varied considerably in how, or whether, they adjusted for BMI, smoking, and socioeconomic status, meaning the pooled risk ratios likely reflect a mixture of PMOS-specific and shared-risk-factor effects rather than an isolated PMOS contribution. This bidirectionality is mechanistically plausible; if periodontitis elevates systemic inflammatory and insulin-resistant burden, it could exacerbate metabolic features of PMOS in susceptible women. Nationwide population-based retrospective cohort data from Taiwan lend further epidemiological support to this reverse direction of effect, finding significantly increased risk of PMOS in women with chronic periodontitis (31). Beyond clinical periodontal parameters, emerging evidence highlights that PMOS combined with periodontitis produces compounded negative effects on bone metabolism and the subgingival microbiome. For example, women with PMOS and chronic periodontitis present with lower bone mineral density, increased bone resorption, and decreased bone formation (32). Microbial profiling of PMOS patients with periodontitis found increased abundance of periodontal pathogens, including Porphyromonas gingivalis and Fusobacterium nucleatum, compared to non-PMOS controls with periodontitis, suggesting that the PMOS endocrine environment may foster a more pathogenic subgingival microbiome (33). Collectively, PMOS may function as a systemic modifier that amplifies gingival inflammation and worsens bone and microbial outcomes in ways that compound the burden of concurrent periodontal disease.

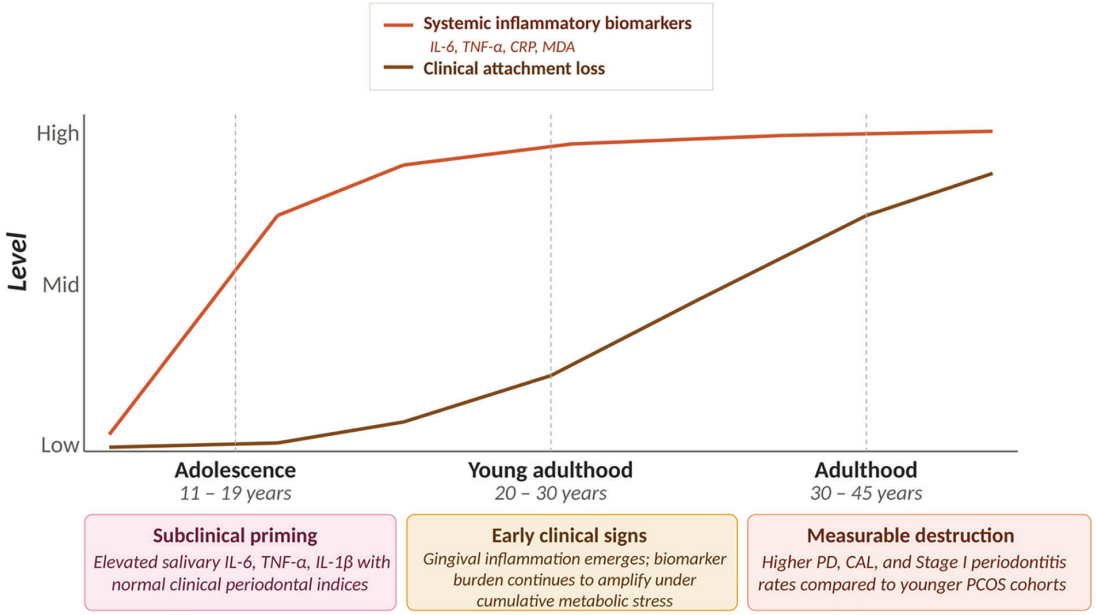

Figure 2. ***Inflammation-first susceptibility model in PMOS.*** *Systemic inflammatory biomarkers (e.g., IL-6, TNF-α, CRP) increase early in PMOS, preceding measurable periodontal tissue destruction. While inflammatory burden rises rapidly during adolescence and remains elevated, clinical attachment loss develops more gradually, becoming pronounced in adulthood. This temporal separation reflects a subclinical priming phase, followed by early clinical signs and eventual periodontal damage, supporting a model in which chronic inflammation in PMOS predisposes to later periodontal disease.*

Confounding and Alternative Explanations

The consistency of the PMOS-periodontal association across multiple study designs is compelling, but shared risk factors complicate causal interpretation and warrant discussion. Obesity and insulin resistance are common to both conditions independent of any PMOS-specific hormonal mechanism: adiposity itself drives cytokine release in periodontal tissue regardless of ovarian pathology, so studies comparing PMOS to healthy controls without matching for BMI or HOMA-IR risk attribute to PMOS an effect that is substantially attributable to adiposity. Several of the case-control studies discussed above did not report BMI-matched or insulin-resistance-matched control groups (26, 27), and the Chinese subgroup analysis discussed later in this review found that BMI-related obesity, rather than PMOS phenotype itself, was the stronger determinant of periodontal severity (34), directly illustrating this confounding concern.

Oral hygiene behavior is more consistently addressed in this literature: several studies statistically controlled for, or reported comparable, oral hygiene index scores between PMOS and control groups (27, 28), which strengthens the case that the association is not purely behavioral. However, oral hygiene indices capture plaque and calculus at a single examination and do not capture longitudinal brushing frequency, dental care-seeking behavior, or access to professional cleanings, any of which could differ systematically between women with and without a chronic endocrine diagnosis that requires more frequent medical contact.

Socioeconomic status and healthcare access represent the least examined potential confounders in this literature. Women with PMOS often experience delayed diagnosis and disproportionate psychological and financial burden (9), both of which plausibly correlate with dental care access independent of any biological mechanism; none of the primary studies reviewed here reported socioeconomic status, insurance status, or dental care utilization as covariates. Dietary patterns are similarly unexamined: high-glycemic diets are implicated in both PMOS pathophysiology and periodontal inflammation, raising the possibility that diet functions as an unmeasured common cause rather than PMOS acting through a distinct hormonal or immune pathway. Until studies systematically adjust for BMI, insulin resistance, socioeconomic status, and dietary intake, the independent contribution of PMOS-specific

biology to periodontal risk, beyond what these shared factors would predict on their own, cannot be considered fully established.

Table 1 consolidates the primary clinical, epidemiological, and biomarker studies discussed above, including their design, population, principal findings, and the limitations that bear most directly on the confounding concerns raised in the preceding section.

Table 1. *Summary of Key Studies Examining the PMOS-Periodontal Relationship.*

Study (Ref #)	Design & Sample	Population	Major Findings	Principal Limitations
Dursun *et al*. (26)	Case-control	PMOS vs. healthy controls	↑ probing depth, bleeding on probing, and clinical attachment loss; ↑ serum MDA and 8-OHdG in PMOS, suggesting oxidative mediation.	Early/small study; cross-sectional; BMI and insulin-resistance matching not reported.
Rahiminejad *et al*. (27)	Case-control, n=98 PMOS / n=98 controls	Reproductive-age women	↑ plaque and gingival indices, bleeding on probing, and probing depth in PMOS group.	Single-center; BMI, insulin-resistance, and socioeconomic matching not reported.
Pavankumar *et al*. (28)	Cross-sectional, n=196	Women aged 17–45, age-stratified	↑ gingival index and loss of attachment in PMOS despite similar OHI-S; adults showed more PD 3–4mm sites and Stage I periodontitis than adolescents.	Cross-sectional design precludes causal or temporal inference; metabolic phenotype not detailed.
Wendland *et al*. (29)	Case-control, n=31 PMOS / n=28 controls	Adolescents	No difference in clinical periodontal indices; PMOS group had ↑ salivary IL-6, TNF-α, and IL-1β.	Salivary (not serum/GCF) cytokines only; adolescent-only sample limits generalizability.
Machado *et al*. (30)	Systematic review & meta-analysis	Pooled across primary studies	PMOS associated with 28% higher risk of periodontitis; periodontitis associated with 46% higher odds of PMOS.	Substantial heterogeneity in how primary studies adjusted for BMI, smoking, and socioeconomic status.
Tong *et al*. (31)	Nationwide retrospective cohort	Taiwanese population-based registry	Chronic periodontitis associated with significantly increased subsequent risk of PMOS diagnosis.	Claims-based diagnosis coding; residual confounding by unmeasured lifestyle/SES factors likely.
Zia *et al*. (32)	Case-control	PMOS with vs. without chronic periodontitis	PMOS + periodontitis associated with lower bone mineral density, ↑ bone resorption, ↓ bone formation markers.	Cross-sectional; cannot establish whether periodontitis or PMOS severity drives the bone changes.
Joseph *et al*. (33)	Case-control, microbial profiling	PMOS + periodontitis vs. non-PMOS periodontitis	↑ abundance of P. gingivalis and F. nucleatumin the PMOS group.	Small sample typical of microbiome case-control work; directionality not established.
Özçaka *et al*. (35)	Case-control biomarker study	PMOS with and without gingival inflammation	↑ serum IL-6/TNF-α in PMOS + gingival inflammation vs. either condition alone; lowered IL-17 signaling in non-obese PMOS.	Single study; cross-sectional; non-obese-subgroup IL-17 finding not yet replicated.

Continued Table 1. *Summary of Key Studies Examining the PMOS-Periodontal Relationship.*

Study (Ref #)	Design & Sample	Population	Major Findings	Principal Limitations
Saljoughi *et al*. (36)	Case-control, GCF biomarker study	PMOS with periodontitis	Elevated gingival crevicular fluid visfatin in PMOS patients with periodontitis.	Single small study; proposed signaling mechanism not tested directly in this cohort.
Saglam *et al*. (37)	Cross-sectional, serum & GCF markers	PMOS with and without periodontitis	Oxidative markers (MDA, myeloperoxidase, nitric oxide) most elevated in combined PMOS-plus-periodontitis group.	Single cross-sectional study; cannot establish temporal sequence or causality.
Min *et al*. (10)	Bidirectional Mendelian randomization	Genetic-instrument analysis	Genetically elevated LH causally associated with increased risk of oral ulcers.	Outcome studied was oral ulcers, not periodontitis; extrapolation to periodontal disease is unverified.
Liu *et al*. (34)	Subgroup analysis by BMI/ phenotype	Chinese women with PMOS + periodontitis	BMI-related obesity was a stronger determinant of periodontal severity than PMOS phenotype; PMOS + obesity combined carried the greatest risk.	Single-population study; may not generalize across ethnic or phenotypic groups.

PMOS and Periodontal Disease: Immunological and Mechanistic Pathways

The mechanistic pathways discussed in this section vary considerably in evidentiary strength, and that hierarchy is made explicit here rather than left implicit. Serum cytokine differences between PMOS and control populations rest on multiple case-control studies and are the most directly documented finding. Gingival crevicular fluid adipokine and oxidative stress findings derive from single or few studies and require replication before they can be considered established. The broader narrative connecting hormonal signaling, microbiome shifts, and periodontal tissue destruction is, at several points, inferential, built by analogy to better-established disease models such as diabetes-associated periodontitis rather than demonstrated directly in PMOS. The following mechanisms should be weighed accordingly.

The mechanistic basis for the PMOS-periodontal relationship centers on overlapping immunometabolic pathways, with cytokine synergy among the most directly documented. Women with PMOS and concurrent gingival inflammation have significantly higher serum IL-6 and TNF-alpha levels than women with either condition alone (35,36). Non-obese women with PMOS had significantly lowered IL-17 signaling, suggesting dysregulation of the Th17 immune axis resulting in impaired resolution of periodontal inflammation, though this finding comes from a single cross-sectional study and awaits replication (37). Gingival crevicular fluid (GCF) biomarker analyses have provided complementary insight into the local periodontal immune environment in PMOS, identifying adipokine-mediated mechanisms. Significantly elevated visfatin concentrations have been found in the GCF of PMOS patients with periodontitis in one small case-control study (36). Visfatin, an adipokine with pro-inflammatory and insulin-mimetic properties, promotes secretion of IL-1beta, TNF-alpha, and IL-6 and activates NF-kappaB signaling in periodontal fibroblasts, suggesting it may serve as a biochemical bridge between adipose-derived PMOS inflammation and local periodontal tissue destruction. Quantification of oxidative stress markers, including malondialdehyde, myeloperoxidase, and nitric oxide in serum and gingival crevicular fluid, has further revealed elevations particularly pronounced in the combined PMOS-plus-periodontitis group, consistent with synergistic oxidative damage (37). As with the visfatin findings, this evidence derives from a single cross-sectional study and describes an association at one point in time rather than establishing a causal or temporal sequence. These local biomarker profiles reinforce the conclusion that PMOS creates a biochemically hostile environment within

the periodontal tissues themselves, not merely in the systemic circulation.

Insulin resistance, a core feature of PMOS affecting approximately 50 to 70 percent of patients, represents an additional mechanistic pathway that may amplify periodontal susceptibility through direct effects on periodontal tissue biology. Elevated insulin and IGF-1 signaling can alter gingival fibroblast and periodontal ligament cell biology, impair tissue repair, and enhance susceptibility to microbial invasion (38). The parallel to diabetes-associated periodontitis is noteworthy: just as hyperglycemia promotes advanced glycation end-product accumulation in gingival tissues and impairs neutrophil function, insulin resistance in PMOS may similarly dysregulate the local immune microenvironment, although this parallel is drawn by analogy to the diabetes literature and has not been directly tested in PMOS cohorts (18,39). Studies that control for Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and Body Mass Index (BMI) are particularly valuable in distinguishing the independent contributions of metabolic severity from other PMOS features, and identifying insulin resistance as a direct mediator would have therapeutic implications for managing periodontal risk in PMOS.

Hormonal mechanisms constitute a further layer of the PMOS-periodontal relationship, as sex steroids directly modulate periodontal tissue biology. Estrogen receptors are expressed on gingival fibroblasts and osteoblasts, and estrogen modulates periodontal ligament cell proliferation and bone homeostasis; progesterone can suppress immune responses, which may compromise periodontal defense under certain hormonal conditions (17). In PMOS, the altered estrogen-to-progesterone ratio combined with androgen excess creates an atypical hormonal environment for the periodontium. Bidirectional Mendelian randomization analysis specifically examining the role of PMOS-related sex hormones in oral inflammatory diseases found that elevated LH levels were causally associated with increased risk of oral ulcers, providing genetic epidemiological evidence that hormonal dysregulation in PMOS contributes to oral mucosal and periodontal inflammation through mechanisms distinct from inflammation alone (13). This Mendelian randomization design is methodologically stronger than the observational studies elsewhere in this review, since genetic instruments are less susceptible to confounding and reverse causation; however, its outcome, oral ulcers, is clinically distinct from periodontitis, and the extension of this finding to periodontal disease specifically has not yet been tested and should be treated as a hypothesis rather than established evidence. This hormonal axis thus adds a molecularly distinct but clinically interconnected dimension to the PMOS-periodontal relationship.

Metabolic severity appears to function as a key amplifier of the PMOS-periodontal inflammatory relationship and may partly account for the heterogeneity observed across studies. Metabolic severity correlates with elevated IL-6 levels in PMOS patients who demonstrate insulin resistance (14,40). Studies examining PMOS subgroups by BMI or metabolic phenotype report divergent periodontal findings that underscore the role of metabolic severity as a modifier. PMOS-periodontal associations include participants with higher BMI or more pronounced metabolic dysfunction, while lean PMOS patients often present fewer periodontal differences (41). Subgroup analysis by BMI and PMOS phenotype among Chinese women with both PMOS and periodontitis found that BMI-related obesity, rather than PMOS phenotype alone, was the stronger determinant of periodontal severity, though the combination of PMOS plus obesity carried the greatest periodontal risk (34). These findings collectively suggest that metabolic severity is a critical effect modifier that clinicians should systematically assess when evaluating periodontal risk in PMOS patients.

This modifying effect follows directly from the visceral-adiposity-driven macrophage and cytokine pathway already described in the PMOS section above, rather than a separate mechanism: the same M1 macrophage polarization and cytokine release that impair systemic insulin signaling plausibly worsen periodontal tissue destruction locally. The related concept of metabolic inflammaging, chronic low-grade inflammation driven by cumulative metabolic burden, offers one framework for why PMOS patients with greater metabolic severity exhibit progressively worse periodontal outcomes (38,42), though, consistent with the Confounding and Alternative Explanations section above, this effect cannot yet be cleanly separated from obesity's independent effect on periodontal tissue. Interventions that reduce metabolic dysfunction in PMOS may therefore confer periodontal benefit, a hypothesis returned to in the Conclusion (Figure 3).

CONCLUSION

Taken together, the evidence reviewed here, and summarized comparatively in Table 1, shifts the central

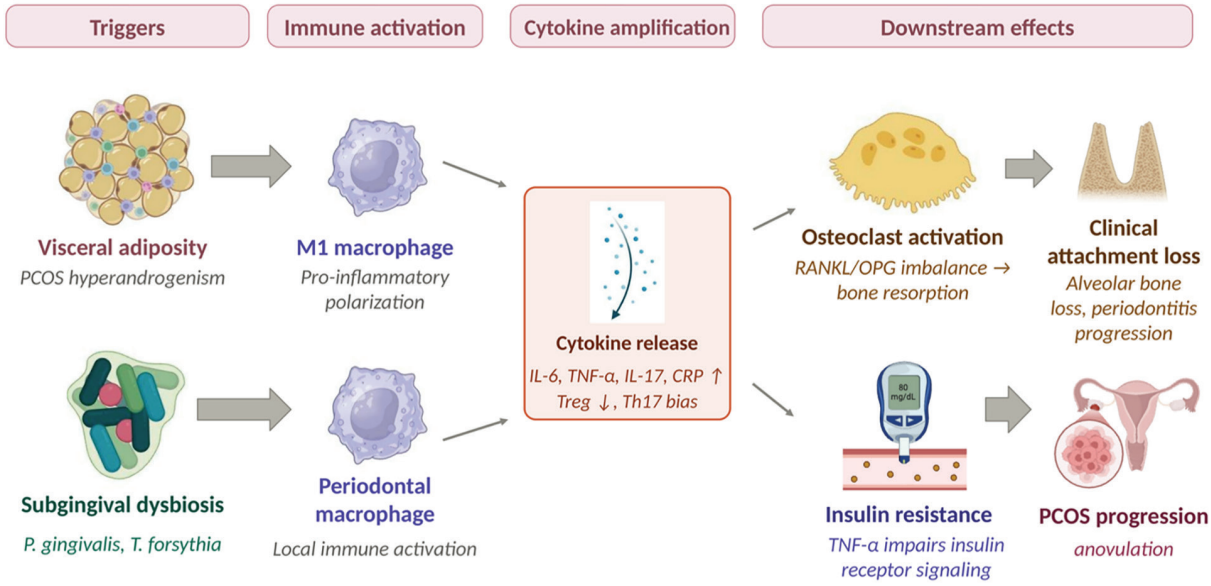

Figure 3. ***Shared Inflammatory Cascade linking PMOS and Periodontal Disease.*** *Common triggers, including visceral adiposity and subgingival dysbiosis, drive immune activation and pro-inflammatory macrophage polarization, leading to cytokine release (e.g., IL-6, TNF-α, IL-17, CRP). This amplified inflammatory response promotes osteoclast activation and clinical attachment loss in periodontal tissues, while simultaneously contributing to insulin resistance and progression of PMOS, supporting a bidirectional inflammatory relationship.*

question from whether PMOS and periodontal disease are associated, which is now well established across multiple study designs, to how much of that association reflects PMOS-specific biology as opposed to the shared metabolic and behavioral risk factors discussed above. Women with PMOS demonstrate heightened periodontal susceptibility that exceeds what local plaque burden alone can explain, with age and metabolic severity functioning as key amplifiers of this risk over time. This susceptibility, however, has not yet been convincingly separated from the contribution of shared risk factors, chiefly obesity, insulin resistance, and possibly socioeconomic status, that the studies reviewed here have inconsistently controlled for. The bidirectionality of the association, where periodontitis may itself worsen PMOS-related metabolic burden, adds further urgency to integrating periodontal assessment into routine PMOS care across gynecology and endocrinology settings. Importantly, oral hygiene functions as a modifiable risk factor that may meaningfully alter this trajectory. Because PMOS-related systemic inflammation appears to amplify the periodontal response to a given plaque burden, targeted oral hygiene support and more frequent professional maintenance intervals could partially offset this elevated susceptibility and, by reducing chronic periodontal inflammation, may also confer indirect benefit on PMOS-related metabolic and inflammatory severity.

Several important gaps in the current evidence base warrant attention. Longitudinal studies are needed to confirm the temporal sequence from subclinical inflammatory priming in adolescent PMOS populations to clinical periodontal destruction in adulthood, moving beyond the cross-sectional designs that dominate the existing literature. Future research should incorporate standardized metabolic phenotyping, including HOMA-IR, BMI subgrouping, and Rotterdam phenotype classification, to clarify which patients carry the greatest periodontal risk and at what threshold metabolic burden becomes clinically decisive. Future studies should also systematically adjust for BMI, insulin resistance, socioeconomic status, and dietary intake, and should explicitly distinguish correlational cytokine and biomarker findings from mechanistically validated causal pathways, in order to determine which components of the PMOS-periodontal association reflect PMOS-specific biology rather than shared upstream risk factors. The emerging oral-gut microbiome axis and its hormonal modulation by estrogen and LH represent a particularly underexplored mechanistic territory, warranting

dedicated longitudinal microbiome studies that track dysbiosis alongside clinical periodontal outcomes.

From a therapeutic standpoint, intervention trials examining whether periodontal treatment reduces systemic inflammatory markers in PMOS, paralleling the well-established diabetes-periodontitis treatment literature, represent a high-priority research direction. Whether PMOS-targeted metabolic interventions such as metformin or GLP-1 receptor agonists confer secondary periodontal benefit through reduction of shared inflammatory mediators similarly merits prospective investigation. Antioxidant-targeted strategies may also warrant exploration, given the documented synergistic oxidative burden observed in women carrying both diagnoses. Establishing interdisciplinary screening protocols that bridge dental, gynecological, and endocrinological care will ultimately require clinical trials powered to detect meaningful periodontal endpoints in well-characterized PMOS populations.

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CONFLICT OF INTEREST

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