

Polycystic Ovarian Syndrome and Periodontal Diseases: The Link Demystified

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ABSTRACT

Polycystic Ovarian Syndrome (PCOS) is one of the most commonly diagnosed endocrine disorders, affecting 7-20% of women of reproductive age. In the case of PCOS, the ovaries have a large number of cystic follicles linked to persistent anovulation and androgen overproduction. PCOS is also linked to other systemic disorders, such as diabetes mellitus, cardiovascular disorders, and psychological conditions. Research studies indicate that PCOS may increase susceptibility to periodontal disease. The mechanisms underpinning the links between these two conditions are not completely understood. There is emerging evidence to support the existence of a two-way relationship between PCOS and periodontitis, with PCOS increasing the risk for periodontitis and periodontal inflammation worsening the PCOS status. This narrative review of the various pathophysiological mechanisms linking the two diseases depicts a positive correlation between the two conditions.

Keywords: Ovarian degeneration, Periodontitis, Sclerocystic

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS), also known as Stein-Leventhal syndrome, is an endocrine disorder of unknown aetiology that is common among women of reproductive age [1]. PCOS is clinically characterised by chronic anovulation, clinical and/or biochemical hyperandrogenism, and a polycystic appearance in the ovaries [2]. PCOS is noted to have a global prevalence ranging from 2.2 to 26% in Western countries [3,4], 2 to 7.5% in China [5], 6.3% in Sri Lanka [6], and 9.13 to 36% in India [7,8]. PCOS is known to affect several systems and is presented by menstrual irregularities (oligomenorrhoea, dysfunctional uterine bleeding), signs of hyperandrogenism (hirsutism, acne, sebaceous skin), obesity, and metabolic syndrome [9].

The pathogenesis of PCOS remains obscure due to its multifactorial profile [10]. Studies have suggested that the aetiology and pathogenesis of PCOS may be influenced by chronic infections linked to rising levels of reactive oxygen species, Myeloperoxidase (MPO), Oxidative Stress (OS), inflammatory cytokines {such as Interleukin (IL)-6 and Tumour Necrosis Factor- α (TNF- α)}, high-sensitivity C-Reactive Protein (hsCRP), adhesion molecules, blood lymphocytes, and monocytes. This cascade of a proinflammatory state has been one of the most investigated for the link between PCOS and periodontitis [11].

Periodontitis is an immunoinflammatory disease that occurs as a result of interaction between bacterial attack and host inflammatory response, thereby causing inflammation of the supporting tissues of the teeth leading to tissue destruction and tooth loss. Periodontitis is considered a risk factor for many systemic diseases such as diabetes mellitus, dyslipidemia, obesity, Cardiovascular Diseases (CVDs), rheumatoid arthritis, and respiratory diseases [12-17]. Chronic low-grade inflammation is the plausible etiologic pathway connecting periodontal disease and systemic disorders [18].

Evidence over the past decade suggests that patients with PCOS are more prone to develop periodontitis [19]. With PCOS, there will be an increased amount of androgens and oestrogens, which affect the subgingival microbiota locally and invariably act on the gingival cells to alter the efficiency of the epithelium, resulting in gingivitis and periodontitis [20]. Therefore, the current review attempts to update the evidence and provide further insight into the relationship between periodontal disease and PCOS.

DISCUSSION

Periodontal diseases include gingivitis and periodontitis, which are two types of chronic, microbially caused, inflammatory illnesses that damage the bone and soft tissue supporting the teeth. A localised, treatable gum irritation is known as gingivitis [21]. The extension of inflammation and destruction of tooth-supporting structures is known as periodontitis. Tissue destruction in periodontitis leads to the breakdown of collagen fibers in the periodontal ligament, resulting in the formation of a periodontal pocket between the gingiva and tooth [22].

Periodontitis is a slowly progressing disease that is largely irreversible. In the majority of populations evaluated, the illness is extremely prevalent, with severe periodontitis jeopardising tooth retention affecting 10-15% of adults [23]. Periodontitis is a chronic inflammatory disease that also causes systemic inflammation. Periodontitis can activate the host immune response both locally and systemically, which is detectable through increased serum levels of inflammatory markers such as C-reactive protein and IL-6. Hence, it is seen that periodontitis plays a vital role in the pathogenesis of systemic diseases and may thereby increase their presentation [24].

Plausible Two-way Link between Polycystic Ovarian Syndrome (PCOS) and Periodontitis

The link between periodontal disease and PCOS is based on the "chronic subclinical inflammatory states" caused by the disease [25,26]. A long period of subclinical inflammatory state causes the production of a cascade of proinflammatory markers, which includes CRP, TNF- α , interleukins IL-6, IL-17, and Matrix Metalloproteinase (MMP)-9 [27,28], resulting in an oxidative stress (OS) environment by increasing the local oxidant status, such as MPO and nitric oxide [29].

Pathogenic Mechanisms Linking Polycystic Ovarian Syndrome (PCOS) and Periodontal Disease

- Polycystic Ovarian Syndrome (PCOS) and gingival inflammation:** PCOS is known to cause low-grade systemic inflammation, as indicated by an increase in CRP, proinflammatory cytokines, white blood cell count, as well as chemokines such as IL18, monocyte chemoattractant protein 1, and macrophage inflammatory protein 1. Additionally, there is an

increase in OS markers, suggesting PCOS as an inflammatory condition [30]. One of the major factors contributing to PCOS is Insulin Resistance (IR) [31].

Inflammatory cytokines such as TNF- α , IL-1 β , IL-6, leptin, adiponectin, and resistin, along with signaling pathways like (IKK β /NF- κ B) Inhibitor of Nuclear Factor kappa-B kinase subunit beta/Nuclear Transcription factor kappa-B pathway, c-Jun N-terminal kinase (JNK) pathway, and inflammasome pathway, contribute to low-grade systemic inflammation, thereby leading to IR [32].

Periodontitis is also a chronic inflammatory disease, and it is inflammation that links periodontitis with PCOS [18]. Some studies have shown an increase in CRP levels in patients with PCOS, which is connected to low-grade systemic inflammation leading to IR. IR plays a major role in the pathogenesis of PCOS with associated hyperinsulinemia [30]. It is also noteworthy that patients with periodontitis are associated with an increase in CRP levels and pro-inflammatory cytokines such as TNF- α and IL-1 in Gingival Crevicular Fluid (GCF) and serum. The elevation of CRP in chronic infections such as periodontitis might lead to systemic inflammation, an OS, thereby leading to IR, which is an important factor in the pathogenesis of PCOS [33].

During times of inflammatory stress, the hormone-regulated proinflammatory cytokine IL-6 promotes the hypothalamic-pituitary-adrenal axis. Obesity and IR, two characteristics of PCOS, are associated with higher levels of IL-6 [34]. Similarly, increased concentrations of the inflammatory biomarker IL-6 are found in gingival tissue, as well as in the serum of patients with gingival inflammation and periodontitis [33].

Many studies support the fact that systemic inflammation is the underlying link connecting PCOS and Periodontal disease [35-38]. A study by Rahiminejad M et al., showed that there is a higher prevalence of periodontal disease parameters in non-obese women with PCOS compared to systemically healthy controls and proposed that systemic inflammation could be the underlying factor [35].

In a study by Porwal S et al., patients with newly diagnosed PCOS have a higher prevalence of periodontitis than those receiving medicinal therapy for females with PCOS and healthy systems [36]. hsCRP was used in present study as a marker for systemic inflammation. It was discovered that serum hsCRP levels were higher in females with newly diagnosed PCOS compared to controls with systemically healthy bodies and females receiving medical treatment for PCOS, which led to the assumption that systemic inflammation and periodontal breakdown might be related. A study by Akcalı A et al., found that women with PCOS had raised serum and salivary Matrix Metalloproteinase (MMP)-8 concentrations, particularly in the presence of gingivitis and an elevated MMP-8/Tissue Inhibitors of Metalloproteinase (TIMP)-1 ratio in women with PCOS, irrespective of the presence of gingivitis [37].

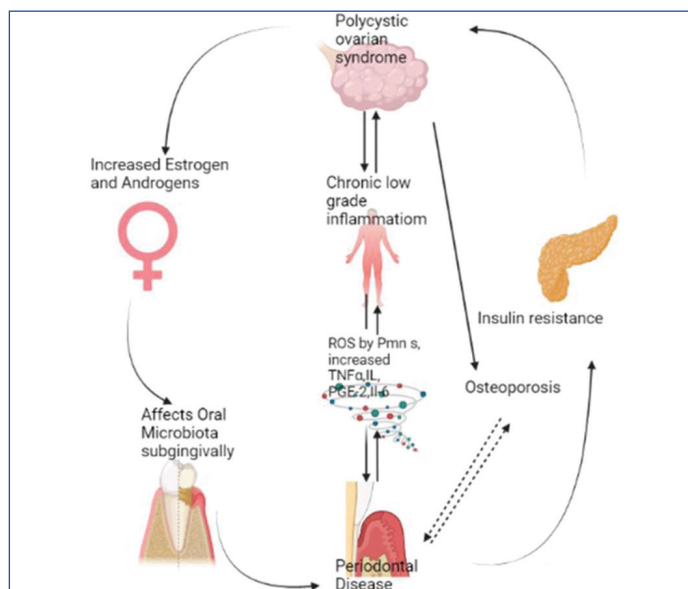
It is also interesting to note that the White Blood Cell (WBC) count, which is linked to many chronic inflammatory diseases, is a sign of low-grade inflammation. In a case-control research, Orio F et al., found that, compared to controls of the same age and Body Mass Index (BMI), women with PCOS had increased leukocyte counts, a sign of low-grade inflammation and cardiovascular risk [38]. Similarly, people with persistent periodontitis may also have an elevated white blood cell count [39].

Thus, inflammation might be thought of as a pathophysiological process in light of the components of inflammation outlined above as potential linkages between PCOS and periodontal disease [Table/Fig-1,2] [35,36,40].

- Oxidative Stress (OS) as a linking mechanism in PCOS and periodontal disease:** OS results from an imbalance between oxidants and antioxidants, which favours oxidants [29]. OS and inflammation are pathophysiological processes that are closely interrelated. Obesity, diabetes mellitus, metabolic syndrome,

Author	Place of study	Parameters studied	Type of study	Study result
Rahiminejad M et al., 2015 [35]	Iran	Parameters assessed include Periodontal parameters (Bleeding On Probing (BOP), probing depth, Clinical Attachment Loss (CAL), plaque index, and tooth loss)	Case -control Which included 98 with PCOS and 98 systemically healthy	Study showed higher prevalence of periodontal disease parameters in women with PCOS comparing to systemically healthy controls
Porwal S et al., (2014) [36]	India	Parameters assessed include Periodontal parameters (Plaque Index (PI), Gingival Index (GI), BOP, probing depth PD, and Clinical Attachment Level CAL)	Case-control 41 newly diagnosed patients with PCOS (PCOS-N), 45 patients with PCOS on medical treatment (PCOS-MT), and 40 systemically healthy controls	Study results showed that In comparison to those receiving medical therapy for PCOS and systemically healthy females, women with newly diagnosed PCOS may have a higher prevalence and chance of developing periodontitis, as well as higher measurements of periodontal inflammation and breakdown. Additionally, systemic inflammation and periodontal disease may be related to one another.
Özçaka O et al., 2012 [40]	Turkey	Parameters assessed include Clinical periodontal measurements, body mass index, and Ferriman Galloway Score (FGS) (a measure of hirsutism in females) were recorded. Circulating levels of sex hormones, cortisol, insulin and levels of IL-17 were also determined.	Case-control 31 females with PCOS, 30 females with PCOS and gingivitis, and 12 systemically and periodontally healthy females participated in the study	Study results indicated a positive correlation between IL-6 and TNF alpha. Thus, PCOS may have an impact on gingival inflammation or vice versa.

[Table/Fig-1]: Studies showing inflammation as the pathogenic link [35,36,40].



[Table/Fig-2]: Link between PCOS, periodontitis and low-grade systemic inflammation.

and atherosclerosis are some conditions connected with increased OS [26]. It is also noteworthy that OS biomarkers were found in the peripheral blood of chronic periodontitis and PCOS patients [41]. OS is also found to be higher in patients with PCOS, which was evaluated by circulating markers such as Malondialdehyde (MDA), Superoxide Dismutase (SOD), Glutathione Peroxidase (GPx), and advanced oxidative protein products [42]. In a study done by Dursun E et al., study results showed that patients with PCOS had higher levels of MPO and Nitric Oxide (NO) levels in GCF with unaltered serum NO levels [19]. From the study, it is seen that periodontal NO metabolism is more influenced. This study shows an increased susceptibility for periodontitis and a local/periodontal pro-oxidative state in lean and normal glucose-tolerant women with PCOS compared with healthy women. A study by Saglam E et al., also showed that in the group with periodontal disease along with PCOS, there is an increase in serum and salivary 8-hydroxy-2'-deoxyguanosine (8-OHdG) and MDA levels and a decrease in serum Total Antioxidant Status (TAS) levels [29].

- **Oral microbiota/microbiome and PCOS:** The clinical presentation and incidence of plaque-induced gingivitis are affected by increased sex steroid hormone levels [43]. The hormonal alterations in PCOS may affect the salivary levels of potential periodontal pathogens and/or their systemic immune responses, particularly in the presence of gingival inflammation. This could be attributed to the fact that there is an accumulation of active progesterone and oestrogen in periodontal tissue, thereby providing the essential nutrients for bacterial growth [44]. In the subgingival plaque, Lipopolysaccharides from periodontal organisms have been shown to have the capacity to significantly increase IL-1 and TNF production, and this ongoing cytokine overexpression exacerbates the IR that is a defining feature of PCOS [45]. Thus, the composition of oral microflora will be quantitatively affected by PCOS, which may have a confounding role in gingival inflammation and periodontal health.

A study by Akcali A et al., evaluated the levels of putative periodontal pathogens in saliva and their antibody response in serum in PCOS patients compared with healthy subjects using real-time polymerase chain reaction and analysing serum antibody levels via Enzyme Linked Immunosorbent Assay (ELISA) [27]. The study results showed that PCOS may quantitatively affect the composition of oral microbiota and the raised systemic response to selective members of this microbial community, exerting a confounding role in resultant gingival inflammation and periodontal health. The most consistent effect appeared to be exerted on *P. gingivalis*. A study by Li N et al., found significant differences in the composition of the salivary microbiota between PCOS and healthy women at different points in time [46]. For the first time, it was noticed in the study that the diurnal rhythm of some salivary bacteria was disrupted in PCOS patients, potentially leading to oral and metabolic disorders in PCOS patients.

- **Sex hormones serve as a link between PCOS and periodontal disease:** Steroid sex hormones are crucial for maintaining bone mass. Through their receptors in target tissues, including the gingiva, they have both direct and indirect influence over a variety of cells [47]. These hormones also influence collagen maintenance and repair, as well as how well the epithelium functions as a defense against bacterial injury [48]. In females with PCOS, there is an alteration of various hormone levels. Females with PCOS have excess androgens in combination with insulin resistance. Their oestrogen levels can vary greatly, ranging from low to abnormally high. Oestrogen plays a significant role in maintaining bone mass by influencing bone mineral metabolism and inducing fibroblast and keratinocyte proliferation. It also increases the synthesis of fibrous collagen [47].

The human gingiva is capable of metabolising hormones like progesterone and oestrogen. Furthermore, gingival tissue has such hormone receptors and is thought to be a target organ for their direct action [49]. These hormones may affect the maintenance and repair of collagen or alter the efficiency of the epithelial barrier against bacterial damage to affect gingival cells [50].

CLINICAL IMPLICATIONS

Here are the corrected clinical implications of the link between PCOS and periodontitis:

- **Increased susceptibility to periodontitis:** Women with PCOS may have an increased susceptibility to periodontitis compared to women without the condition. PCOS is associated with systemic inflammation and hormonal imbalances, which may contribute to the development and progression of periodontal disease. Individuals with PCOS may exhibit compromised immune responses and altered inflammatory pathways, making them more prone to periodontal infections.
- **Aggravation of PCOS symptoms:** Periodontitis is a chronic inflammatory condition that can exacerbate systemic inflammation in the body. Inflammation is a key feature of PCOS and is believed to contribute to various aspects of the condition, including hormonal imbalances, insulin resistance, and metabolic dysfunction. The presence of periodontitis may further exacerbate inflammation in individuals with PCOS, potentially worsening their symptoms and increasing the risk of associated complications [37].
- **Implications for fertility and pregnancy:** Both PCOS and periodontitis have been independently associated with adverse pregnancy outcomes, including infertility, miscarriage, preterm birth, and low birth weight. The combination of these two conditions may have compounding effects on reproductive health. Periodontitis-related inflammation and oral bacteria may potentially affect the reproductive organs and interfere with normal hormonal and physiological processes, further compromising fertility and pregnancy outcomes in women with PCOS [31].
- **Shared underlying factors:** PCOS and periodontitis share common underlying risk factors such as obesity, insulin resistance, and chronic inflammation. These factors may contribute to the development and progression of both conditions. Managing these shared risk factors, such as through weight management, improving insulin sensitivity, and controlling systemic inflammation, may have positive effects on both PCOS and periodontitis [10].
- **Interdisciplinary care:** Given the potential association between PCOS and periodontitis, interdisciplinary collaboration between gynecologists, endocrinologists, and dental professionals is crucial. Women with PCOS should receive regular dental check-ups, and dental professionals should be aware of the potential systemic implications of periodontitis in individuals with PCOS [22].

CONCLUSION(S)

It is important to note that while there is evidence suggesting a link between PCOS and periodontitis, further research is needed to establish the exact mechanisms and causal relationship between the two conditions. Nevertheless, addressing oral health and managing periodontitis can be an important aspect of comprehensive care for individuals with PCOS.

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