Review Article

Polycystic Ovary Syndrome and Periodontal disease: Underlying Links- A Review

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Abstract

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women of reproductive age, which negatively affects various health systems. There is an extensive literature regarding the association of PCOS and other systemic conditions such as diabetes mellitus, cardiovascular disease, and psychological disorders. However, there is a lack of literature in associating PCOS and periodontal disease. Hence, PubMed search was done for various articles related to PCOS and its association with other comorbidities, including periodontal diseases. Analysis was done and data were synthesized and compiled in a sequential and presentable paradigm. This literature review of the pathophysiological mechanisms linking the two diseases suggests a positive relation between the two comorbidities. However, multicenter studies, with larger sample sizes, are to be conducted to establish a clearer and stronger association.

Keywords: Insulin resistance, obesity, periodontal disease, polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women, primarily affecting the reproductive system, with substantial collateral negative health effects on metabolic, psychologic, and cardiovascular functions.[1] It is a complex disease with characteristics of hyperandrogenism and chronic anovulation (CA) with global prevalence ranging from 2.2% to 26% in Western countries,[2,3] 2% to 7.5% in China,[4] 6.3% in Sri Lanka,[5] and 9.13% to 36% in India.[6,7] Patients with this syndrome are at higher risk of developing insulin resistance (IR), obesity, dyslipidemia, cardiovascular disease (CVD), and endometrial carcinoma.[8-11] IR and hyperinsulinemia are responsible for the low-grade chronic systemic inflammation.[12]

Periodontitis, an immunoinflammatory disease, is a result of interaction between bacterial attack and host inflammatory response, causing inflammation of supporting tissues of the teeth leading to tissue destruction and tooth loss. It has been suggested as a risk factor for many systemic diseases such as diabetes mellitus,[13] dyslipidemia,[14] obesity,[15] CVDs,[16] rheumatoid arthritis,[17] and respiratory diseases.[18] Chronic low-grade inflammation is emerging as a plausible etiologic mechanism linking periodontal disease and many systemic diseases.[19]

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Methods

A thorough PubMed search was conducted using the keywords "Insulin resistance," "Obesity," "Periodontal disease," and "Polycystic ovary syndrome" to identify articles published until May 2017. After further reading the full-text of the articles, analysis was done and data were compiled in a sequential way to give a brief introduction of PCOS and its relation to other comorbidities and discuss elaborately the plausible association between PCOS and periodontal disease.

Clinical features and diagnosis of polycystic ovary syndrome

PCOS is a complex, heterogeneous endocrine disorder, characterized by the presence of menstrual abnormalities (oligomenorrhea or amenorrhea), CA or oligo-ovulation, clinical/biochemical evidence of hyperandrogenism (hirsutism, acne, or androgenic alopecia), and ultrasound findings.[20] It usually affects women in their reproductive years.[21]

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It was first reported in the modern medical literature by Stein and Leventhal, in 1935,[22] who in their original report described PCOS as a variable clinical condition with characteristics such as obesity, hirsutism, acne, and amenorrhea associated with enlarged bilateral polycystic ovaries. Later in 1990, at an international meeting which was held at the U. S. National Institutes of Health, it was recommended that the diagnostic criteria for PCOS should comprise the concomitant presence of anovulation and evidence of hyperandrogenemia – biochemical, clinical (hirsutism/acne), or both – but without reference to ovarian morphology.[23] The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group suggested that if two of the three criteria (CA, hyperandrogenism, and polycystic ovaries on ultrasonography) were present, it can be considered as PCOS.[20] In contrast, the Androgen Excess Society states that hyperandrogenism (clinical and/or biochemical) is the key feature and its presence in combination with ovarian dysfunction (oligo-anovulation and/or polycystic ovaries) is considered during the diagnosis of PCOS.[24]

The criteria mentioned in Table 1 are considered in the diagnosis of PCOS, and to confirm this syndrome, diseases with similar clinical characteristics of PCOS must be excluded, such as thyroid disorders, hyperprolactinemia, and nonclassical congenital adrenal hyperplasia.[25]

Etiology and pathophysiology of polycystic ovary syndrome

The etiology and pathophysiology of PCOS are complex and are the results of interaction between genetic, metabolic, fetal, and environmental factors. Research suggests that the disease is originated in the intrauterine environment, indicating the importance of genetic factors.[26] However, Franks and Berga *et al*.[27] indicated that genetic factors play only a partial role in the etiology of PCOS. Abbott *et al*.[28] suggested that the clinical features of PCOS may develop as a consequence of genetically determined hypersecretion of androgens by the ovary. It might also have an association with many other factors, such as socioeconomic conditions, ethnic factors, diet, physical activity, and lifestyle.[29] The following are some of the pathophysiological mechanisms of PCOS, suggested by King:[30] altered secretion of the gonadotropin-releasing hormone, defect in androgen synthesis, and development of IR [Figure 1]. One of the best-described theories to explain the pathogenesis of PCOS is the disturbance of the hypothalamic-pituitary axis, resulting in disordered secretion of gonadotropin by the hypothalamus leading to raised luteinizing hormone (LH) levels and normal and/or low follicle-stimulating hormone (FSH) levels.[29]

Table 1: Criteria for the diagnosis of polycystic ovary syndrome

NIH/NICHD, 1992[23]	Rotterdam criteria, 2004[20]	Androgen Excess Society, 2006[24]
Includes all the following	Includes two of the following	Includes all the following
Hyperandrogenism and/or hyperandrogenemia	Clinical and/or biochemical hyperandrogenism	Clinical and/or biochemical hyperandrogenism
Oligo-ovulation/anovulation	Oligo-ovulation or anovulation	Ovarian dysfunction and/or polycystic ovaries
	Polycystic ovaries	

NIH: National Institutes of Health, NICHD: National Institute of Child Health and Human Disease

According to Qiao and Feng,[31] deficient FSH, excess secretion of LH, hyperandrogenemia of ovarian or adrenal origin, and hyperinsulinemia with IR are the extraovarian factors for PCOS pathogenesis, and the intraovarian factors could be raised levels of androgens that adversely affect follicular development, ovarian development, and meiotic maturation. Vitamin D deficiency plays an important role in the development of IR and impaired glucose tolerance in obese PCOS patients.[32]

Association of polycystic ovary syndrome with other systemic diseases

Metabolic syndrome, insulin resistance, and type II diabetes mellitus

Metabolic syndrome is composed of many diseases, such as IR, obesity, hypertension, and hyperlipidemia. According to a meta-analysis conducted by Lim *et al*.,[33] obesity can exacerbate preexisting clinical, hormonal, and metabolic features in women with PCOS. Nicandri and Hoeger[34] showed the prevalence of obesity in PCOS to be above 60%. The prevalence of IR in PCOS ranges from 50% to 70%.[35] The compensatory hyperinsulinemia, in women with PCOS, contributes to hyperandrogenism[36] by direct stimulation of ovarian production of androgens. IR combined with abdominal obesity increases the risk of type 2 diabetes in PCOS.[37] Legro *et al*.[38] put forward the prevalence of impaired glucose tolerance and type 2 diabetes in women with PCOS to be approximately 30%–40% and 7.5%–10%, respectively.

Cardiovascular diseases

Women with PCOS are at risk for CVDs, especially those with, dyslipidemia, hypertension, and hyperinsulinemia at an younger age than women without PCOS.[39] In a recent meta-analysis, conducted by Wild *et al*.,[40] women with the PCOS have lower high-density lipoprotein cholesterol and higher triglyceride and low-density lipoprotein cholesterol levels than women without the syndrome. A study conducted by Wild *et al*.[41] suggested that there might be a risk of hypertension in patients with PCOS. Women with PCOS have more extensive coronary artery disease.[42] Higher prevalence of coronary artery calcium scores and carotid intima-media thickness in young women with PCOS suggests the increased susceptibility of subclinical vascular disease than normal women.[43]

Other comorbidities

According to the data from a recent meta-analysis, women of all ages with PCOS are at an increased risk of endometrial cancer, but there is no significant association of PCOS and

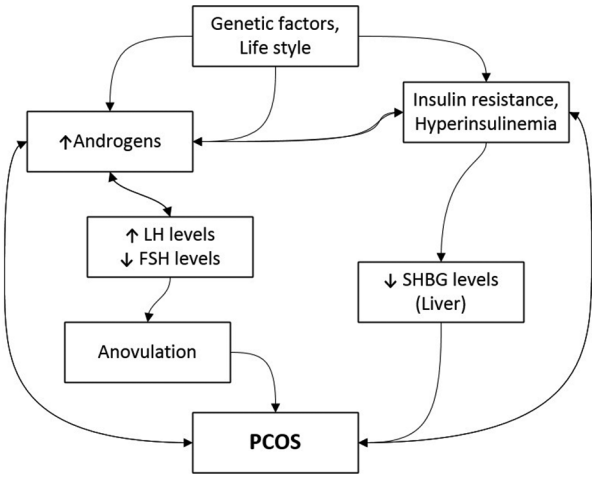

Figure 1: SHBG: Sex Hormone-Binding Globulin. LH- Luteinizing hormone. FSH- Follicle-stimulating hormone

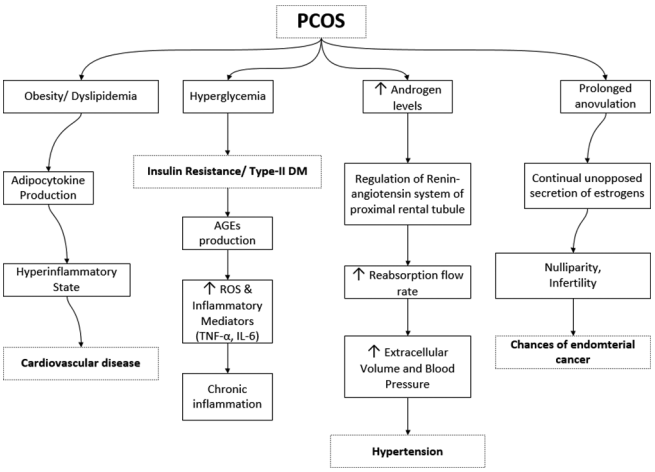

Figure 2: Type-II D.M. - Type-II Diabetes Mellitus. ROS - Reactive Oxygen Species. AGE - Advanced Glycation End products. TNF-α - Tumor Necrosis Factor – α.IL-6 - Interleukin-6

ovarian and breast cancer.[44] In a meta-analysis conducted by Dokras *et al*.,[45] specified anxiety is more common in women with PCOS compared to controls. Women with the PCOS are at higher risk for pregnancy complications, including miscarriages, gestational diabetes, and preeclampsia.[46] This association between PCOS and other systemic diseases with the linking mechanisms is represented in Figure 2.

Association of polycystic ovary syndrome with periodontal diseases

More recent studies showed significant associations between periodontal health and PCOS. The mechanisms that link these two disease entities are not completely and clearly understood but involve various aspects of inflammation. Hence, the authors considered reviewing various mechanisms that link PCOS and periodontal disease.

Pathogenic mechanisms linking polycystic ovary syndrome and periodontitis [Figure 3]

Inflammation: A key factor in the pathogenesis of polycystic ovary syndrome and periodontitis

PCOS is associated with low-grade systemic inflammation and is indicated by elevation of multiple markers of inflammation such as C-reactive protein (CRP), proinflammatory cytokines and chemokines including interleukin 18 (IL-18), monocyte chemoattractant protein-1 and macrophage inflammatory protein-1, and white blood count. Furthermore, increased oxidative stress and its biomarkers suggest PCOS as an inflammatory disease.[47] It is a deep-rooted fact that periodontitis is a chronic inflammatory disease and it is the inflammation that links periodontitis with various systemic diseases.[19]

Some inflammatory cytokines such as tumor necrosis factor α (TNF-α), IL-1 β, IL-6, leptin, adiponectin, and resistin and signaling pathways such as (IKKβ/NF-κB) Inhibitor of nuclear factor kappa-B kinase sub unit beta/Nuclear Transcription factor kappa-B pathway, c-Jun N-terminal kinase (JNK) pathway, and inflammasome pathway, link low-grade inflammation to IR, an important feature of PCOS. TNF-α triggers IR in visceral adipocytes by activating JNK1/2.[48] IL-1β contributes to IR by impairing insulin signaling in peripheral tissues and macrophages, which leads to the reduced insulin sensitivity of β-cells and possible impaired insulin secretion.[49] IL-6 causes IR by reducing the expression of glucose transporter-4 (GLUT-4) and insulin receptor substrate-1 (IRS-1) and by blocking the phosphoinositide 3-kinase (PI3K) pathway.[50]

For this reason, the author has hypothesized inflammation as a primary element, in associating PCOS and periodontitis and reviewed various manifestations of inflammation as pathogenic links.

CRP is one of the important markers of inflammation, produced under the stimulatory control of proinflammatory cytokines such as IL-6 and TNF-α. The raised CRP levels are observed in many systemic diseases, including PCOS, which is connected to low-grade chronic inflammation, linked to IR, that plays a critical role in syndrome pathogenesis along with hyperinsulinemia.[10,47] Patients with periodontitis have a higher serum CRP levels and proinflammatory cytokines such as TNF-α and IL-1 in serum and/or gingival crevicular fluid (GCF).[51] The elevated serum levels of CRP and other proinflammatory conditions, in chronic infections such as periodontitis, might induce systemic inflammation and oxidative stress leading to IR, which are characteristics of PCOS. Another proinflammatory cytokine IL-6 is considered as hormonally regulated, that stimulates the hypothalamic–pituitary–adrenal axis during inflammatory stress, and increased levels of IL-6 are correlated with obesity and IR, which are attributes of PCOS.[52] Similarly, increased concentrations of inflammatory biomarkers such as CRP and IL-6 in both gingival tissue and serum have been found in patients with periodontitis.[51] According to Nicklas *et al*.,[53] in patients with PCOS, long-term lifestyle modification reduced CRP, IL-6, IL-8, and TNF-α levels, which in turn reduced the

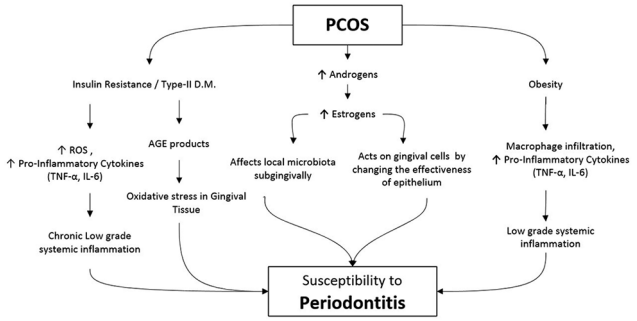

Figure 3: Type-II D.M. - Type-II Diabetes Mellitus. ROS - Reactive Oxygen Species. AGE - Advanced Glycation End products. TNF-α - Tumor Necrosis Factor – α.IL-6 - Interleukin-6

systemic inflammatory burden that cutbacks periodontitis, as systemic inflammation and periodontitis are interrelated.[51] The argument that systemic inflammation is a pathophysiologic link between PCOS and periodontitis is reinforced by many epidemiological studies. A recent case–control study conducted by Rahiminejad *et al*.[54] showed a higher prevalence of periodontal disease parameters in nonobese women with PCOS compared to systemically healthy controls and proposed that systemic inflammation could be the attributing factor.

In a cross-sectional study conducted by Porwal *et al*.,[55] a higher prevalence of periodontitis is found in patients who are newly diagnosed with PCOS than those on medical treatment for PCOS and systemically healthy females. In this study, serum levels of high-sensitivity C-reactive protein (hsCRP) were measured as a marker for systemic inflammation and found that serum hsCRP levels were higher in females with newly diagnosed PCOS compared to systemically healthy controls and females on medical treatment for PCOS, which established the presumption that periodontal breakdown might depend on systemic inflammation and vice versa. Interestingly, family members of a less widely studied cytokine IL-17, namely IL-17 A and IL-17F levels, were found to be higher in GCF and serum of chronic periodontitis and aggressive periodontitis patients, respectively, compared to healthy individuals.[56,57] Similarly, IL-17 cytokines play an important role in complications associated with PCOS such as atherosclerosis.[58] Correspondingly, Özçaka *et al*.[59,60] indicated a positive correlation between GCF IL-17A and serum IL-17A and IL-17A/F with clinical periodontal parameters in females with PCOS; similarly, higher serum, saliva, and GCF IL-6 levels were reported in patients with PCOS and gingivitis compared with PCOS without gingivitis. Akcalı *et al*.[61] found that women with PCOS had raised serum and salivary MMP-8 concentrations, particularly in the presence of gingivitis and elevated MMP-8/TIMP-1 ratio in women with PCOS, irrespective of the presence of gingivitis.

WBC count is also a marker of low-grade inflammation and it is associated with many chronic inflammatory conditions. Orio *et al*.[62] in a case–control study suggested that women with PCOS showed higher leukocyte count, a marker of low-grade inflammation and cardiovascular risk, than age- and body mass index-matched controls. Similarly, raised white blood cell count can be observed in chronic periodontitis patients.[63] In the light of above-mentioned components of inflammation, as potential links between PCOS and periodontal disease, inflammation can be contemplated as a pathophysiologic mechanism operating behind the association between these two disorders.

Oxidative stress

Inflammation and oxidative stress are closely related and tightly linked pathophysiological processes. Increased oxidative stress is associated with obesity, diabetes mellitus, metabolic syndrome, and atherosclerosis. Oxidative stress biomarkers were found in peripheral blood of chronic periodontitis and PCOS patients. This agrees with two meta-analyses[64,65] which indicated increased levels of oxidative stress biomarkers in both the diseases, especially malondialdehyde and decreased levels of antioxidants. A case–control study conducted by Dursun *et al*.[66] showed higher scores of periodontal indices and GCF volume in PCOS patients compared with age- and weight-matched healthy control women. Furthermore, women with PCOS had increased myeloperoxidase and nitric oxide (NO) levels in GCF along with unaltered serum NO levels, suggesting a local/periodontal oxidative stress and hence it was concluded that gingivitis is a common finding in patients with PCOS and that local/periodontal oxidant status appears to be affected in PCOS.

Advanced Glycation End Products

Reactive oxygen species cause systemic oxidative stress in PCOS patients, inducing the development of IR and Advanced Glycation End Products(AGE).[67] AGE products are detrimental to the development and severity of periodontal disease. Through their RAGE (Receptor-AGE) mediational effect, AGE products induce oxidant stress in the gingiva, which accelerates tissue injury.[68] High RAGE expression in periodontal tissues makes these tissues sensitive to products derived from oxidative damage.[69]

Oral microbiota

The hormonal changes in PCOS might influence the salivary levels of putative periodontal pathogens and/or their systemic antibody responses, especially in the presence of gingival inflammation. This could be explained by the accumulation of active progesterone and estrogen in the periodontal tissues, which provides the essential nutrients required for the bacterial growth.[70] The lipopolysaccharides from periodontal organisms in subgingival plaque have the ability to induce the production of significant amounts of IL-1 and TNF-α,[71] and such a chronic upregulation of cytokines aggravates the state of IR, which is characteristic of PCOS. Akcalı *et al*.[72] reported higher salivary levels of *Porphyromonas gingivalis* and *Fusobacterium nucleatum* in patients with PCOS and gingivitis, compared with healthy controls and patients with PCOS and without gingivitis, which indicates that PCOS might have an augmented effect on the levels of

P. gingivalis and *F. nucleatum* and their association with gingival inflammation. Serum antibody levels to *P. gingivalis, Prevotella intermedia*, and *Streptococcus oralis* were raised in patients with PCOS. However, *Aggregatibacter actinomycetemcomitans* and *Treponema denticola* levels were similar among study groups.

Hormones as pathophysiologic link

In PCOS females, there is an alteration of various hormone levels in the body. Female sex steroid hormones play a key role in periodontal disease progression and periodontal and implant wound healing.[73] Human gingiva has the capacity to metabolize hormones such as estrogen and progesterone. Moreover, gingival tissue exhibits receptors for such hormones and it is considered as a target organ for their direct action.[74] These hormones might act on gingival cells by changing the effectiveness of the epithelial barrier to bacterial injury or by affecting the collagen maintenance and repair.[75]

Does obesity play a vital role?

Obesity is one of the important risk factors for diabetes, CVD, and periodontal disease. Likewise, its prevalence in PCOS is increasing and it is above 60%.[34] Studies have shown that an increase in the abdominal fat in patients with PCOS is responsible for hyperinsulinemia and IR compared with weight-matched controls.[76] Similarly, data from a systematic review indicate that increase in waist circumference, serum lipid levels, and percentage of subcutaneous fat might give rise to increased risk for periodontitis.[77]

Is Vitamin D deficiency a potential link?

Vitamin D plays a key role in modulation of skeletal and mineral homeostasis and has anti-inflammatory and immunomodulatory effects. Data from many scientific studies suggest that Vitamin D supplementation helps in maintenance of periodontal health.[78] This could be explained by direct effects on bone metabolism, antibacterial effects on periodontopathogens, and suppression of inflammatory mediators that contribute to the periodontal destruction. Vitamin D deficiency has also been found in patients with PCOS and it could be attributed to the polymorphisms in Vitamin D receptor (VDR) gene, such as Cdx 2, Taq1, Bsm1, Apa1, and Fok1, which play a pivotal role in insulin secretion and sensitivity in PCOS women.[79] Similarly, VDR gene polymorphisms are associated with chronic periodontitis, and VDR genotype is considered as a risk indicator for chronic periodontitis.[80]

Thus, there is an emerging evidence to support the complex association between PCOS and periodontal disease. Our view and argument in the current literature review is reinforced by the findings of a recent systematic review conducted by Kellesarian *et al*.[81]

The classic treatment approach for PCOS includes metformin, clomifene, letrozole, and gonadotropins.[82] However, the latest research is into determining the efficacy of certain anti-inflammatory supplements such as omega 3 fatty acids,[83] Vitamin D,[84] and curcumin[85] and antimicrobials such as doxycycline[86] to reduce the androgen levels, alter the IR index, and in turn reduce the inflammatory burden that causes periodontal diseases. However, there is lack of evidence to confirm their usefulness.

Conclusion

Considering above-discussed literature, we can excogitate that PCOS might exacerbate the periodontal condition that is caused by plaque, through various pathophysiological links, namely, low-grade systemic inflammation, oxidative stress, IR, AGE products, and systemic hormonal levels. Evidence has suggested that periodontal disease causes chronic subclinical inflammation leading to IR, initiating the development of type 2 diabetes, which is a prominent feature in PCOS. Hence, we can contemplate that there exists a two-way relationship between PCOS and periodontal disease. However, evidence linking the two is in its nascent stage and warrants further research. Multicenter studies with larger sample sizes and long terms are to be conducted to establish a clear and stronger association between the two disease entities and help in early diagnosis, treatment, and prevention of long-term sequelae. Health-care professionals, gynecologists, and endocrinologists in particular would need to proactively motivate patients diagnosed with PCOS to maintain good oral hygiene at all times and refer to dentist to avoid periodontal implications as this hormonal disorder can worsen the vulnerability to plaque-induced periodontal disease.

The following are some of the actions that can be taken by the research community for further strengthening the validity of the association between PCOS and periodontal disease.

1. Studies to be conducted on estrogen and progesterone receptors in periodontitis patients with and without PCOS
2. Assessing various biomarkers of inflammation and oxidative stress in GCF, saliva, and serum that can help in linking the two diseases
3. Conducting long-term studies in females with PCOS and periodontitis at different age groups
4. Determine the influence of PCOS treatment on periodontal condition and periodontal treatment on ovulation

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Conflicts of interest

There are no conflicts of interest.

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