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# Polycystic Ovarian Syndrome : Its Impact on Periodontal Disease

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## Abstract

Polycystic ovary syndrome (PCOS) is the common endocrine disorder among women of reproductive age affecting various health systems. This review literature explains pathophysiological mechanisms connecting PCOS and periodontal disease . Furthermore studies are needed to establish a clearer and stronger association between the two disease.

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

## Introduction

Polycystic ovary syndrome (PCOS) is a familiar endocrinopathy in womenmajorly affecting the reproductive systemwith an important collateral negative health effects on metabolic, psychologic, and cardiovascular functions.[1] It is a complex disease involving features of hyperandrogenism and chronic anovulation (CA) with global predominance ranging from 2.2% to 26% in Western countries,[2,3] 2% to 7.5% in China, 6.3% in Sri Lanka, and 9.13% to 36% in India.[4]Patients are at greater risk of cultivating insulin resistance (IR), obesity, dyslipidemia, cardiovascular disease (CVD), and endometrial carcinoma.[5] Periodontitisis caused by the communication between bacterial attack and host inflammatory response which ultimately results in inflammation of surrounding tissues of the teeth causing tissue destruction and tooth loss. It has been proposed as a risk factor for several systemic diseases such as diabetes mellitus, dyslipidemia, obesity, CVDs, rheumatoid arthritis,and respiratory diseases. Persistent low-grade inflammation arise as a conceivable etiologic mechanism connecting periodontal disease and many systemic diseases.[6]

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### CLINICAL FEATURES AND DIAGNOSIS

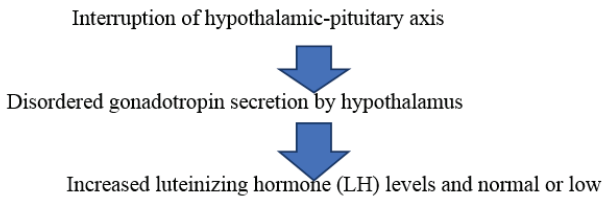
PCOS is characterized by the existence of menstrual deformity (oligomenorrhea or amenorrhea), CA or oligo-ovulation, clinical/biochemical confirmation of hyperandrogenism (hirsutism, acne, or androgenic alopecia), and ultrasound findings.[7]Usually women are affected in their reproductive years.[8]

In 1935, it was first described by Stein and Leventhal , as a variable clinical condition with certain clinical features such as obesity, hirsutism, acne, and amenorrhea related to enlarged bilateral polycystic ovaries. Later in 1990, it was suggested that the diagnostic principles for PCOS should have the collateral anovulation and evidence of hyperandrogenemia – biochemical, clinical (hirsutism/acne), or both – but without reference to ovarian morphology. The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group stated that if any two of these criteria such as CA, hyperandrogenism, and polycystic ovaries on ultrasonographywere present then it can be considered as PCOS. In disparity , Androgen Excess Society suggested that hyperandrogenism (clinical and/or biochemical) is an important criteria and when it is presentalong with ovarian dysfunction (oligo-anovulation and/or polycystic ovaries) it can be considered during the diagnosis of PCOS.For

confirmation of this syndrome, diseases which mimics the clinical features of PCOS such as thyroid disorders, hyperprolactinemia, and nonclassical congenital adrenal hyperplasia should be ruled out [10]

## ETIOLOGY AND PATHOPHYSIOLOGY

The etiology and pathophysiology of PCOS are based on interaction between genetic, metabolic, fetal, and environmental factors. Though research suggests that the disease is originated in the intrauterine atmosphere, indicating the importance of genetic factorsFranks and Berga et al. proposed that genetic factors are partially involved in the etiology of PCOS. Later , Abbott et al. stated that the clinical characteristics of PCOS may emerge as a result of genetically determined hypersecretion of androgens by the ovary. It might even have a relationship with many other factors, such as socioeconomic conditions, ethnic background , diet, physical activity, and lifestyle. King proposed certain pathophysiological mechanisms of PCOS such as modified gonadotropin-releasing hormone secretion, deformity in androgen synthesis, and IR development . One of the excellent theory to explain the pathogenesis of PCOS is :




Increased luteinizing hormone (LH) levels and normal or low follicle-stimulating hormone (FSH) levels.[11]

According to Qiao and Feng, decreased FSH secretion , raised LH secretion, hyperandrogenemia of ovarian or adrenal origin, and hyperinsulinemia with IR are the extraovarian factors for PCOS pathogenesis. Intraovarian factors are increased androgen levelswhich affect follicular development, ovarian development, and meiotic maturation. Vitamin D deficiency provokes the development of IR and impaired glucose tolerance in obese PCOS patients.[12]

## POLYCYSTIC OVARY SYNDROME AND SYSTEMIC DISEASES

### Metabolic Syndrome, Insulin Resistance, And Type II Diabetes Mellitus

Metabolic syndrome comprises of IR, obesity, hypertension, and hyperlipidemia. Lim et al., conducted a meta-analysis,[13] according to which obesity may aggravate existing clinical, hormonal, and metabolic features in women with PCOS. Nicandri and Hoegerdescribed that the percentage of obesity in PCOS is above 60%. The incidence of IR in PCOS ranges from 50% to 70%.IR associated with abdominal obesity raises the risk of type 2 diabetes in PCOS.

### Cardiovascular Diseases

Patient with PCOS are at higher risk for CVDs, particularly those with, dyslipidemia, hypertension, and hyperinsulinemia at an younger age compared to women without PCOS. According to Wild et al.,women with PCOS have lower high-density lipoprotein cholesterol and higher triglyceride and low-density lipoprotein cholesterol levels than women without PCOS . He then conducted a study [14]suggesting that there is a great chance of hypertension in patients with PCOS. PCOS patients have more extensive coronary artery disease. Greater incidence of coronary artery calcium scores and carotid intima-media thickness in young patients with PCOS proposes an increased susceptibility of subclinical vascular disease than normal women.

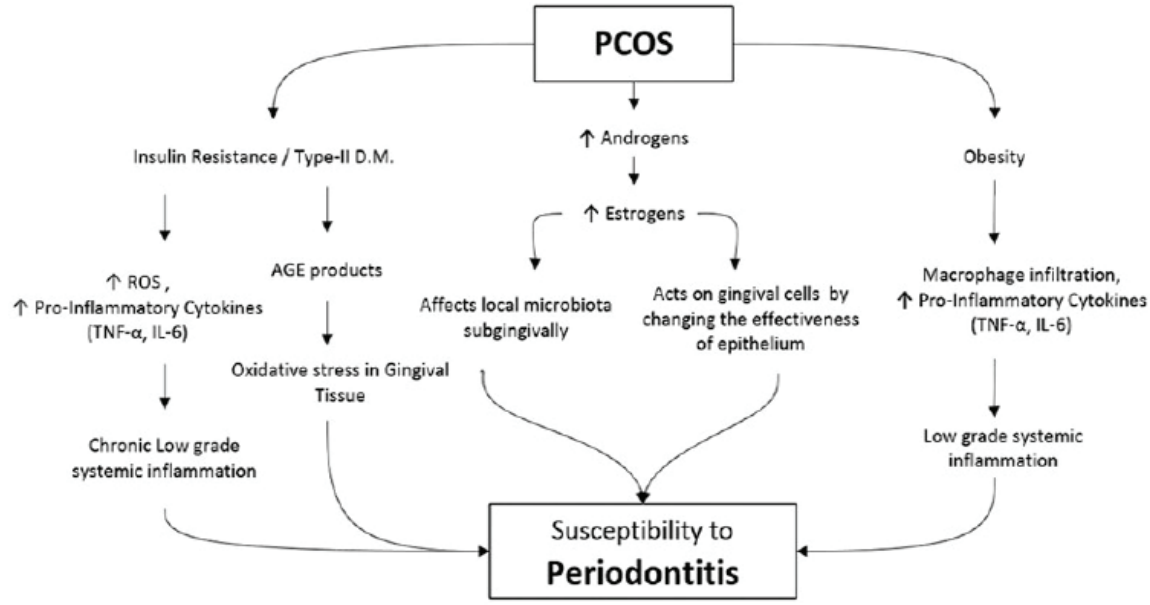
### Other Systemic Disorders

- Endometrial cancer
- Pregnancy complications, including miscarriages, gestational diabetes, and preeclampsia

## POLYCYSTIC OVARY SYNDROME AND PERIODONTAL DISEASES

The mechanisms connecting these two disease entities are not entirely understood but it involvesdifferent aspects of inflammation.

### PathogenesisRelating Polycystic Ovary Syndrome and Periodontitis




PCOS is correlated with low-grade systemic inflammation and is marked by elevation of certain markers of inflammation such as C-reactive protein (CRP), proinflammatory cytokines and chemokines such as interleukin 18 (IL-18), monocyte chemoattractant protein-1 and macrophage inflammatory protein-1, and white blood count. Moreover higher oxidative stress and its biomarkers proposes PCOS as an inflammatory disease. Periodontitis is a chronic inflammatory disease , since inflammation is the key factor it is associated with various systemic diseases. Certain inflammatory cytokines including tumor necrosis factor α (TNF-α), IL-1 β, IL-6, leptin, adiponectin, and resistin and signalling pathways such as (IKKβ/NF--B) 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. IL-1β triggers IR by impairing insulin signalling in peripheral tissues and macrophages, causing reduced insulin sensitivity of β-cells and possible impaired insulin secretion. IL-6 induces IR by producing glucose transporter-4 (GLUT-4) and insulin receptor substrate-1 (IRS-1) and by blocking the phosphoinositide 3-kinase (PI3K) pathway.CRP is an important marker of inflammation secreted under the stimulatory control of proinflammatory cytokines such as IL-6 and TNF-α. Higher CRP levels are found in many systemic diseases such as PCOS, which is related to low-grade chronic inflammation, linked to IR, that plays a role in syndrome pathogenesis involving hyperinsulinemia. Periodontitis patients have increased serum CRP levels and proinflammatory cytokines such as TNF-α and IL-1 in serum and/or gingival crevicular fluid (GCF).[48] The elevated serum levels of CRP and other proinflammatory conditions, in chronic infections such as periodontitis may provoke systemic inflammation and oxidative stress causing IR, which are the features of PCOS. Proinflammatory cytokine IL-6 (hormonally regulated) stimulates the hypothalamic– pituitary–adrenal axis during inflammatory stress, and higher levels of IL-6 are correlated with obesity and IR, which is associated to PCOS. Rahiminejad etal. conducted a case–control study [18]proposing a greater incidence of periodontitis in nonobese women with PCOS compared to systemically healthy women and also stated that systemic inflammation can be a attributing factor.

Porwal et al., conducted a cross-sectional study [19]where a higher prevalence of periodontitis is noted in patients who are recently diagnosed with PCOS than individual under treatment for PCOS and systemically healthy females. Furthermore , serum levels of high-sensitivity C-reactive protein (hsCRP) , a marker for systemic inflammation were higher in females with

recently diagnosed PCOS compared to systemically healthy women and females on medical treatment for PCOS. IL-17 cytokines causes atherosclerosis as a complication related to PCOS.WBC count , a marker of low-grade inflammation is related to several chronic inflammatory conditions. Likewise increased white blood cell count can be seen in chronic periodontitis patients.From the above collected data, it can be noticed that components of inflammation plays a vital role in association of PCOS and periodontal disease.

**Oxidative Stress**

Oxidative stress and inflammationare closely related pathophysiological processes. Higher oxidative stress is linkedwithobesity,diabetesmellitus,metabolicsyndrome, and atherosclerosis. Oxidative stress biomarkers were detected in peripheral blood of chronic periodontitis and PCOS patients. Two meta-analyses[20]indicateshigher levels of oxidative stress biomarkers in both the diseases, particularly malondialdehyde and lower levels of antioxidants. Moreover women with PCOS had raised myeloperoxidase and nitric oxide (NO) levels in GCF including unaltered serum NO levels. This suggests a local/periodontal oxidative stress and therefore it was decided that gingivitis is a common observation in patients with PCOS and that local/periodontal oxidant status appears to be affected in PCOS.

**Oral Microbiota**

The hormonal changes in PCOS controls the salivary levels of putative periodontal pathogens and/or their systemic antibody responses, particularly in gingivitis. This is due to the accumulation of active progesterone and estrogen in the periodontium , which supplies the essential nutrients necessary for the bacterial growth. The lipopolysaccharides from periodontal organisms in subgingival plaque produces significant amounts of IL-1 and TNF-α, and chronic upregulation of cytokines triggers the state of IR, which is a feature of PCOS. Akcalı et al. [21]proposed that comparatively increased salivary levels of Porphyromonas gingivalis and Fusobacterium nucleatum are seen in patients with PCOS and gingivitis than healthy controls and patients with PCOS and without gingivitis. This signify that PCOS may have an improved effect on the levels of P. gingivalis and F. nucleatum and their association with gingivitis. Serum antibody levels to P. gingivalis, Prevotella intermedia, and Streptococcus oralis are higher in patients with PCOS.

**Role of Hormones**

Modification of various hormone levels in the body can be observed in PCOS females. Female sex steroid hormones plays a vital role in progression of periodontal disease and periodontal and implant wound healing. Gingiva is capable of metabolizing hormones such as estrogen and progesterone. Furthermore, gingival tissue exhibits receptors for such hormones and it is decided as a target organ for their direct action.These hormones acts on gingival cells by altering the effectiveness of the epithelial barrier to bacterial injury or by affecting the collagen maintenance and repair.

**Obesity**

Obesity is the chief risk factor for diabetes, CVD, and periodontal disease. Similarly , its predominance in PCOS is raising and it is above 60%.Studies have stated that a raise in the abdominal fat in patients with PCOS is in charge for hyperinsulinemia and IR compared with weight-matched controls.[23]Data from a systematic review denotes that increase in waist circumference, serum lipid levels, and incidence of subcutaneous fat might increase the risk for periodontitis.[23]

**Vitamin D Deficiency**

Vitamin D plays a major role in modulation of skeletal and mineral homeostasis and has anti-inflammatory and immunomodulatory effects. Many scientists suggest that Vitamin D supplementation is necessary in maintenance of periodontal health.[24] This is due to the direct effects on bone metabolism, antibacterial effects on periodontopathogens, and elimination of inflammatory mediators that donate to the periodontal destruction. Vitamin D is observed in patients with PCOS and it may be attributed to the polymorphisms in Vitamin D receptor (VDR) gene, such as Cdx 2, Taq1, Bsm1, Apa1, and Fok1, which play a crucial role in insulin secretion and sensitivity in PCOS women. Similarly, VDR gene polymorphisms are related to chronic periodontitis, and VDR genotype is recommended as a risk factor for chronic periodontitis.[25]

**Treatment**

· Medications involving metformin, clomifene, letrozole, and gonadotropins.

· Recent research is done to detect the efficiency of certain anti-inflammatory supplements such as omega 3 fatty acids,

· Vitamin D, and curcuminand antimicrobials such a doxycycline[26]to reduce the androgen levels, modify the IR index, to reduce the inflammatory burden causing periodontal diseases. But there is no evidence to ensure their benefits

## Conclusion

We can derive a conclusion that PCOS might aggrevate the periodontal condition through plaque, various pathophysiological links, namely, low-grade systemic inflammation, oxidative stress, IRand systemic hormonal levels. According to the suggestions , periodontal disease induces chronic subclinical inflammation causing IR, initiating the development of type 2 diabetes, which acts as an important feature in PCOS. Therefore ,we can consider that there is a two-way relationship between PCOS and periodontal disease. Furthermore studies are needed to establish a powerful relation between two diseases which will be useful in early diagnosis, treatment, and prevention of long-term sequelae. Especially, health-care professionals, gynaecologists, and endocrinologists should cheer up the patients with PCOS in maintaininghealthy oral hygiene and a visit to dentist for eradicating periodontal problems since hormonal imbalance affects the susceptibility to plaque-induced periodontal disease.

**Ethical Clearance –** Not required since it is a review article

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**Conflict of Interest –** Nil

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