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Polycystic Ovarian Syndrome and Periodontal Disease - A current update on the biologic link

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ABSTRACT

Periodontal disease (PD), one of the most important reason for tooth loss is a chronic inflammatory condition. Multiple systemic conditions such as type 2 Diabetes mellitus, sex hormonal imbalances, nutritional deficiencies are known to impact the periodontal health. One such condition which has garnered reasonable interest is Polycystic ovarian syndrome (PCOS). PCOS also being a chronic inflammatory condition, has increasing global prevalence amongst women under reproductive age group of 18-35 years. The increasing incidence of PCOS is attributed to poor lifestyle habits and stress leading to infertility in women. PCOS women with periodontal disease presented with significantly higher levels gingival and periodontal inflammation presenting as clinical attachment loss when compared to healthy women. Both PCOS and PD share some common risk factors which could increase the risk of developing the disease. Hyperandrogenism and insulin resistance seen in PCOS paves the basis for this biology link. This result increase in alteration in subgingival microbiota and increase in inflammatory burden thereby worsening the periodontal disease. This review aims at understanding the mechanistic pathways underlying the disease based on the current scientific literature.

Keywords: Polycystic ovarian syndrome, Periodontal disease, systemic inflammatory burden, oxidative stress, subgingival microbiota

INTRODUCTION

Amongst the various oral diseases, periodontal disease is the most studied chronic inflammatory condition. Periodontal disease (PD) is termed as the fourth most frequent disease on the Disease Global illness list (Nazir, 2020). Likewise, Global Burden of Disease Study indicates that PD is the 6th most prevalent disease worldwide, with an

overall prevalence of 11.2% (Tonetti *et al.,* 2017). PD is an inflammatory condition in which the periodontal pathogen induce stimulate host immune responses that mediate inflammatory events, leading to tissue destruction in susceptible hosts (Cekici *et al.,* 2014). Periodontal lesions are considered as a major reservoir of gram-negative bacteria, inflammatory mediators such as pro-inflammatory cytokines and microbial toxins which could enter the bloodstream and leads to bacteremia which have been found to be a risk factor for diabetes mellitus, cardiovascular disease, respiratory disease, rheumatoid arthritis and other systemic conditions. Once the bacteraemia occurs, focal infection can occur in the blood stream and organs via spread of pathogens and their toxins (Loktionov *et al.,* 2015).

Page et al had proposed several shared risk factors that commonly link Periodontal disease and Systemic diseases (Page eat al., 2000). The role of subgingival biofilms acting as reservoirs for periodontal pathogens and several pro-inflammatory mediators, which enter the blood stream to bring about adverse effects in other parts of the body. The term periodontal medicine was coined by Offenbacher and highlights the fact that oral cavity as a single unit that is integrated with the whole human body (Beck *et al.,* 2019). Over the last 30 years, several research across the world have assessed the association between PD and systemic conditions/diseases, such as cardiovascular disease, diabetes, preterm birth and low birthweight, chronic lung diseases, and, more recently, Polycystic ovarian syndrome (PCOS), chronic inflammatory bowel disease, colorectal cancer, and Alzheimer's disease are being studied at various levels. In the recent year, translational research has established the link and increased interaction of PD with insulin resistant diseases like Polycystic ovarian syndrome (PCOS), rheumatoid arthritis, Cardiovascular diseases (CVD) and even certain type of cancers. PCOS is a complex endocrine disorder characterized by the presence of anovulation, menstrual dysfunction, infertility, and hirsutism. In its typical form, it is frequently associated with obesity (commonly abdominal phenotype), dyslipidemia, insulin resistance, and hyperinsulinemia, thereby increasing the risk of type 2 diabetes and CVD (Kakoly *et al.,* 2019).

Recently, a significant association has been proposed between PD and PCOS. The stimulation and chronic secretion of proinflammatory cytokines associated with periodontal infection contributes to insulin resistance. This pathognomonic state of systemic inflammation and insulin resistance, present in both PD and PCOS, could be a possible etiologic mechanism linking these two conditions (Martinez-Herrera *et al.,* 2017).

Epidemiologic link between pcos and periodontal disease

The association between periodontal disease and PCOS was first studied by Dursun *et al.,* (2011). Following which multiple studies have been reported to assess the same (Rahiminejad *et al.,* 2015; Kellesarian *et al.,* 2017). Till date 16 published papers on the association between PCOS and PDD, including 15 cross-sectional studies and 1 randomized controlled trial. In a systematic review by Farooq et al it was reported that women with PCOS presented with statistically higher clinical attachment loss and probing depth when compared to healthy women (Fathima *et al.,* 2019). PCOS had been consistently associated with obesity and all the studies included in this study have excluded obese PCOS women with a BMI> 30. It was interesting to note that with medical management of PCOS improved periodontal clinical parameters in PCOS women (Porwal *et al.,* 2014).

Pathogenesis underlying the link

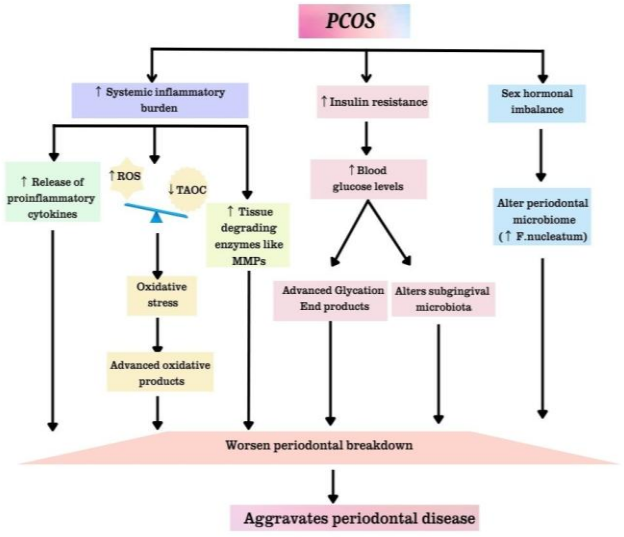

Figure 1: Mechanistic Link Between PCOS and PD

The research conducted over the years have tried to understand the biologic link between PCOS and PD. Reason behind the worsening of periodontal attachment in PCOS women has been attributed to various factors as explained in Figure 1, predominantly by the influence of exaggerated systemic inflammatory response due to PCOS.

Changes in microflora

An otherwise reversible gingivitis progresses into an irreversible periodontitis due to the irrevocable presence of dysbiotic microflora. This dysbiotic ecosystem constantly triggers the immune system resulting in a cascade of proinflammatory mediators leading to chronic inflammatory state that occurs in periodontitis. Considerable number of studies have been reported that suggests that PCOS exaggerates the local dysbiotic microbiome which could possibly resulting worsening of clinical attachment loss (Lindheim *et al.,* 2016). In a study by Li et al in 2020, increased salivary levels of Fusobacterium along with reduction of Actinobacteria were observed in the PCOS women (Li *et al.,* 2021). Higher levels of Fusobacterium nucleatum and Tannerella forsythia in gingival crevicular fluid was also noted Akcali *et al.,* 2014).

Actinobacteria are usually seen in abundance in a healthy state than a diseased state, thereby playing a prudent role in maintaining the homeostasis of oral microbiome. Reduction of Actinobacteria were also reported in few other studies (Lindheim *et al.,* 2016; Gao *et al.,* 2018). Suprisingly a similar pattern was observed in Diabetic patients with periodontal disease (Barutta *et al.,* 2022) [18]. This could possibly be attributed to the insulin resistance seen in both PCOS and diabetes. The above results in concordance with our study where we reported higher levels of Fusobacterium nucleatum from subgingival plaque samples in patient with PCOS and Periodontitis (Achu *et al.,* 2023). Subgingival plaque sample microbiota is a better representation of microbial changes as periodontal disease is a site-specific disease. Fusobacterium nucleatum, an anerobic bacteria is known as the bridging organism that helps in aggregating periodontal pathogens such as Porphyromonas gingivalis and Tannerella forsythia. This bridging organism plays a crucial role in etiopathogenesis of Periodontal disease. Increase in their number in PCOS with Periodontitis is a notable finding. This is possibly attributed to the sex hormonal imbalance seen in PCOS. Changes in microbial profile correlating with sex hormonal changes has been previously reported. Hyperandrogenism and Insulin resistance seen in PCOS can influence oral microbiota changes (Dou et al. 2023). Infact a PCOS specific universal microbiome-derived signature reflecting a gut oral microbiome dysbiosis which could predict PCOS was also identified Huang *et al.,* 2024).

PCOS driven systemic inflammation

Chronic low-grade inflammation seen in PCOS can be an important factor worsening periodontal inflammation (Kelly *et al.,* 2001). Many studies have revealed that multiple proinflammatory cytokines such as IL-6, IL-17, and TNF-a have led to the interaction between PCOS and PDD, including IL-6, IL-17, and TNF-a. Reduced estrogen levels in PCOS can predispose to higher levels of proinflammatory cytokines like IL-1, IL-6, IL-8, IL-10, TNFa, and granulocyte colony-stimulating factor (GCSF), which contributes to proinflammatory subgingival environment that further leads to increased attachment loss in Patients with PCOS (Jafri *et al.,* 2015; Massler , 1951. Systemic inflammatory markers HsCRP were higher in serum and saliva of PCOS patients (Porwal *et al.,* 2014; Deepti *et al.,* 2017) Proinflammatory cytokines alter the host immune response by stimulating the enzymatic function of neutrophils. These neutrophils trigger the release of collagenases such as MMP-9 which breakdown the periodontal connective tissue. Higher levels of MMP-9 have been observed in saliva of PCOS women signifying periodontal breakdown (Akcali *et al.,* 2017).

Oxidative stress

The otherwise protective reactive oxygen species which help in elimination of offending microbes, can result in oxidative stress (OS) when they outweigh the system's antioxidant system in disease. Chronic inflammation and OS are pathophysiological processes that are intimately related to each other. The constant accumulation of ROS under results in the oxidation of lipids, glucose, protein and DNA resulting in various advanced oxidative products of the same. These advanced oxidative products can trigger downstream pathways leading to secretion of cytokines. Serum and GCF malonodialdehyde levels positively corelated with gingival inflammation in PCOS women (Salam *et al.,* 2018). Furthermore, women presenting with PCOS

and PDD showed higher serum levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG), Myeloperoxide and lower total antioxidant status (TAS) than women with PCOS alone (Akcali *et al.,* 2017). Higher levels of myeloperoxidase indicate exaggerated oxidative killing mechanism of neutrophils, thus leading to more periodontal breakdown. In our previous study, we also found out that higher levels of serum and salivary advanced oxidative products were presented in women with PCOS and periodontitis when compared to women with only PCOS (Daruman *et al.,* 2022). Our unpublished data from our research also indicates higher levels of both Advanced glycated end products (AGE) in patients with PCOS and periodontitis. Interestingly it can be noted that these advanced oxidative products positively corelated with Periodontal inflammatory surface index score signifying that as the severity of inflammation increases as oxidative stress increases.

Common risk factors associated with both conditions

Both conditions being chronic inflammatory in nature, share some common environmental and lifestyle related risk factors between them. Obesity and chronic stress being the most predominant factors. Systemic and local inflammatory burden seems to increase significantly with the presence of obesity and stress predisposing them to higher risk of developing chronic inflammatory diseases such as PCOS and periodontal disease. These risk factors also cause sex hormonal imbalance thereby worsening the condition. Insulin resistance is another pathognomonic feature commonly seen associated with PCOS and Periodontal disease.

CONCLUSION

Literature suggests that PCOS is significantly associated with Periodontal disease. Even though a bidirectional link has been studied previously the impact of Periodontal disease on PCOS still seems unclear and vague due to paucity of studies with strong association and interventional studies. This narrative review focused on the impact of PCOS on worsening of Periodontal disease and the biologic plausibility behind the same. Multiple pathways have been identified and studied to have a better understanding of this association. More randomized control interventional studies are required in the future to strengthen this link. It is important that female patients who suffer from PCOS are educated about the deleterious effects of PCOS on their oral health, particularly periodontal health. This can be ensured only both the gynecologist and periodontist come together to improve the overall quality of life of the patients.

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