

Evaluation of Levels of Advanced Oxidative Protein Products in Patients with Polycystic Ovary Syndrome with and without Chronic Periodontitis: A Cross-Sectional Study

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Abstract

Polycystic ovary syndrome (PCOS) is a common condition with a multifactorial aetiology. Chronic periodontitis (CP) is an immunoinflammatory disease that is linked to PCOS via the excessive production of reactive oxygen species (ROS), which leads to an imbalance in the antioxidant system. However, limited studies have evaluated the relationship between these diseases. The current study aims to evaluate the levels of advanced oxidation protein products (AOPP) in patients with periodontitis and PCOS. Four groups, each consisting of 12 patients, with both PCOS and CP (PCOSCP), systemically healthy women with CP, periodontally healthy women with PCOS (PCOSPH), and periodontally and systemically healthy women (PH) were included in the study. Clinical parameters such as clinical attachment loss, bleeding on probing (BOP), and periodontal inflamed surface area (PISA) index were noted. AOPP were evaluated in the saliva and serum samples by spectrophotometric detection. Salivary and serum AOPP levels were highest in the PCOSCP group ($75.16 \pm 7.50 \mu\text{mol/l}$, $97.92 \pm 6.50 \mu\text{mol/l}$, respectively). Statistical significance ($P < 0.05$) was noted between the salivary AOPP levels of the PCOSCP group and PCOS group. PISA was greatest in the PCOSCP group ($1338.40 \pm 285.96 \text{ mm}^2$) followed by the PCOS group ($680.33 \pm 79.49 \text{ mm}^2$), which showed the impact of PCOS on gingival inflammation. According to the results of this study, increased levels of advanced oxidative protein products appeared to show the effect of CP on worsening PCOS.

Keywords: Gingivitis, Oxidative Stress, Reactive Oxygen Species

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Polycystic ovary syndrome (PCOS), first described by Stein and Leventhal (1), is a complex endocrine disorder and a common cause of anovulatory infertility, dysmenorrhea, and hirsutism. Although the aetiology of PCOS is not completely understood, mounting evidence suggests the presence of a low-grade systemic inflammation. Multiple markers of oxidative stress (OS) and inflammation, such as C-reactive protein, monocyte chemoattractant protein 1, and endothelial dysfunction are highly correlated with the levels of circulating androgens, and inflammation is likely to be associated with other features of PCOS, such as insulin resistance and cardiovascular risk factors.

Periodontitis is a microbially-associated, host mediated inflammation that results in loss of tooth supporting structures (2). Periodontal tissue destruction is the result of an inappropriate host response to periodontal pathogens and its products. Neutrophils

are recruited to the site of infection and encounter bacterial challenge through a non-oxidative killing mechanism by producing proteolytic enzymes or through an oxidative killing mechanism by producing superoxide anions, which results in oxidative burst. Periodontal inflammation presents with excessive reactive oxygen species (ROS) production, which are deleterious to host tissues and result in tissue damage and clinical attachment loss. OS affects periodontal tissues by targeting biologic molecules such as lipids, proteins, and DNA (3). Recruitment of neutrophils at the gingival site and release of proteolytic enzymes and ROS are considered the two main aspects of the host response upon bacterial antigen stimulation in periodontitis-susceptible individuals. This process might result in a systemic inflammatory response. An important factor that determines the extent and severity of periodontal disease is the host response. Changes in circulating hormone levels, reduction in polymorphonuclear neutrophils, nutritional

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deficiencies, and psychosomatic conditions result in an increased rate and severity of periodontal disease. Growing evidence suggests that periodontal disease is an independent risk-factor several significant systemic diseases, and they brought a shift in the rationale about causality and directionality of oral and systemic associations. This paradigm shift is encapsulated by the term 'periodontal medicine', which is a branch of periodontology that focuses on establishing a relationship between periodontal disease and systemic health. Periodontal infection may contribute to cardiovascular diseases (CVD) (4), rheumatoid arthritis (5), and diabetes mellitus (6).

Advanced oxidative protein products are involved in several systemic disorders such as diabetes mellitus (7), renal and liver diseases (8), coronary artery disease (9) and periodontitis (10). The link between PCOS and periodontal inflammation is unclear, despite numerous studies of both diseases. Therefore, the aim of the present study is to evaluate the levels of advanced oxidative protein products (AOPP) in patients with PCOS and periodontal disease.

This cross-sectional study was approved by the Institutional Review Board and ethical clearance was obtained from the Ethics Committee of Sri Ramachandra Institute of Higher Education and Research, Chennai (CSP/18/NOV/74/319). From January 2019 to April 2019, a total of 48 out of 65 initially assessed South Indian patients were chosen from the Outpatient Department of the Department of Periodontology and the Department of Gynaecology and Obstetrics and all the patients signed an approved informed consent for participation in the study.

All individuals who met the following criteria were included in the study: i. Non-smokers, ii. Not pregnant at the time of the study, iii. No history of systemic disease other than PCOS, iv. Consumed no medications within the past three months, and v. Had no periodontal therapy. Patients were classified into the following four groups - group 1: patients with PCOS and chronic periodontitis (PCOSCP, n=12); group 2: patients with PCOS (PCOS, n=12); group 3: patients with (CP, n=12); and group 4: healthy control subjects (PH, n=12).

PCOS was diagnosed by a single gynaecologist (U.V.) based on the 2003 Rotterdam Criteria (11), according to the presence of at least two of the following symptoms: i. Oligomenorrhea and/or anovulation, ii. Hyperandrogenism (clinical and biochemical), or iii. Polycystic ovaries detected on ultrasound examination. Individuals who had no systemic diseases or periodontal problems comprised the control group.

Periodontitis patients were screened by a single trained examiner (S.D.) using a standardized probing force of 0.75 N. The patients were classified according

to the following 2012 definition by Eke et al. (12): mild periodontitis (≥ 2 interproximal sites with clinical attachment loss (CAL) ≥ 3 mm and ≥ 2 interproximal sites with probing depth (PD) ≥ 4 mm [not on the same tooth] or one site with PD ≥ 5 mm); moderate periodontitis (≥ 2 interproximal sites with CAL ≥ 4 mm [not on the same tooth] or ≥ 2 interproximal sites with PD ≥ 5 mm [not on the same tooth]); and severe periodontitis (≥ 2 interproximal sites with CAL ≥ 6 mm [not on the same tooth] and ≥ 1 interproximal site with PD ≥ 5 mm).

Periodontal probing was manually performed by a single trained examiner who used a UNC 15 probe at the mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual and distolingual sites of each tooth. The number of bleeding sites per tooth were noted.

The probing depth values and bleeding on the probing values were used to calculate the periodontal inflamed surface area (PISA) scores for each patient by entering them into a previously obtained spreadsheet (<http://www.parsprototo.info/docs/PISA-CAL.Xls>) (13). The periodontal epithelial surface area (PESA) for that specific tooth was calculated and subsequently multiplied by the proportion of sites around that tooth, which was affected by bleeding on probing (BOP) in order to obtain the PISA of that specific tooth.

For biochemical analysis, we collected 2 ml of venous blood from the antecubital vein and 2 ml of unstimulated saliva prior to the periodontal measurement. The samples were centrifuged at 1500 rpm for 10 minutes and subsequently stored at -80° until analyses. Determination of AOPP was based on spectrophotometric detection by Witko-Sarsat et al. (14), which was modified by Kalousová et al. (15). Based on this technique, 200 μ l of the sample was diluted with 1:5 phosphate-buffered saline (PBS). A total of 200 μ l of chloramine T was used for calibration and 200 μ l of PBS was the blank, which was placed on the microtiter plate. Next, 10 μ l of 1.16 M potassium iodide (PI) and 20 μ l of acetic acid were added and absorbance was measured at 340 nm. All statistical analyses were performed using SPSS version 13.0. One way analysis of Variance (ANOVA) and the post hoc test were used for data analysis. $P < 0.05$ was considered statistically significant.

Out of the 65 patients examined for the study, 48 met the inclusion criteria. Therefore, there were 12 women in the PCOSCP group, 12 in the PCOS group, 12 in the CP group, and 12 healthy controls. Table 1 lists the participants' mean values for age, probing pocket depth, BOP, and PISA values.

The mean probing depth was the highest in the PCOSCP group (2.96 ± 0.76 mm), followed by the CP (2.42 ± 0.421 mm) and PCOS (1.82 ± 0.146 mm) groups. Table 2 shows the mean AOPP values for serum and saliva for all the study participants.

Table 1: Participants' mean values per group

| Groups | PCOSCP group 1 | PCOS group 2 | CP group 3 | Control group 4 | P value |
|-------------------------|------------------|----------------|-----------------|-----------------|---------|
| Age (Y) | 23.17 ± 3.070 | 23.17 ± 2.855 | 25.58 ± 3.232 | 24.08 ± 3.088 | 0.189 |
| Probing depth (mm) | 2.96 ± 0.76 | 1.82 ± 0.146 | 2.42 ± 0.421 | 1.73 ± 0.763 | 0.000 |
| BOP (no. of sites) | 3.81 ± 0.89 | 4.20 ± 0.27 | 2.37 ± 0.80 | 1.30 ± 0.408 | 0.000 |
| PISA (mm ²) | 1338.40 ± 285.96 | 680.33 ± 79.49 | 621.85 ± 180.34 | 193.05 ± 56.33 | 0.000 |

Data are presented as mean ± SD. PCOSCP; Polycystic ovary syndrome and chronic periodontitis, PISA; Periodontal inflamed surface area, and BOP; Bleeding on probing.

Table 2: AOPP values for the study groups

| Groups | PCOSCP | PCOS | CP | Control | P value |
|----------------------|--------------|---------------|---------------|--------------|---------|
| AOPP serum (µmol/l) | 97.92 ± 6.50 | 72.00 ± 9.323 | 78.83 ± 9.14 | 44.25 ± 7.79 | 0.000 |
| AOPP saliva (µmol/l) | 75.16 ± 7.50 | 52.75 ± 11.69 | 72.83 ± 8.088 | 33.33 ± 4.97 | 0.000 |

Data are presented as mean ± SD. PCOSCP; Polycystic ovary syndrome and chronic periodontitis, PISA; Periodontal inflamed surface area, and AOPP; Advanced oxidation protein products.

Figure 1 lists the PISA values for all of the groups. The PCOSCP group had the highest PISA value compared to the other groups, which could be attributed to the inflammatory burden.

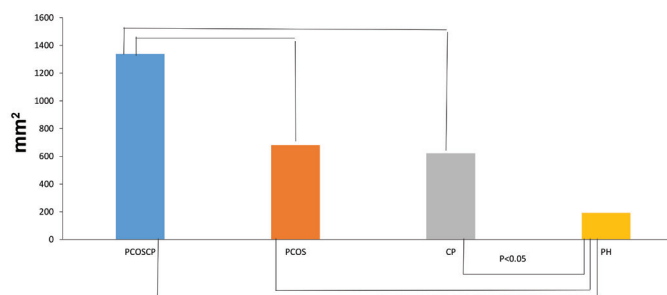


Fig.1: Graph showing the PISA scores. Lines connecting the bars indicate a statistical significant difference P<0.05. PISA; Periodontal inflamed surface area and PCOSCP; Polycystic ovary syndrome and chronic periodontitis.

The PCOSCP group had statistically higher AOPP levels than the other groups (P<0.05). The difference between the PCOS and CP groups was not statistically significant (P>0.05, Fig.2).

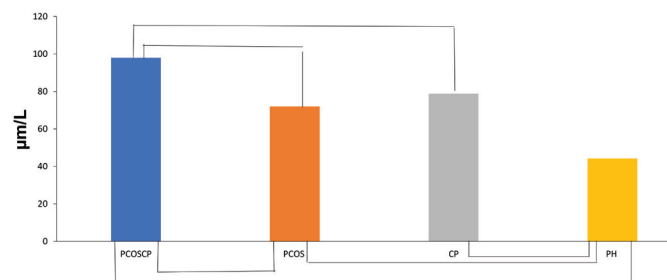


Fig.2: Graph showing the AOPP serum levels. Lines connecting the bars indicate a statistical significant difference P<0.05. PISA; Periodontal inflamed surface area and PCOSCP; Polycystic ovary syndrome and chronic periodontitis.

Salivary AOPP levels were increased in all of the CP patients. The highest value was in the PCOSCP group, followed by the CP group. The salivary AOPP values were statistically significant among the groups compared to the healthy controls (P<0.05, Fig.3).

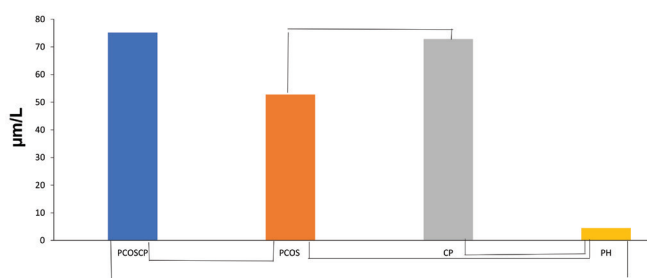


Fig.3: Graph showing the AOPP levels in saliva. Lines connecting the bars indicate a statistical significant difference P<0.05. PISA; Periodontal inflamed surface area and PCOSCP; Polycystic ovary syndrome and chronic periodontitis.

PCOS primarily affects the reproductive system, with substantial systemic collateral negative health effects on metabolic and psychologic functions. The interaction between genetic, metabolic, foetal, and environmental factors results in the complex aetiology and pathophysiology of PCOS. These patients often present with low-grade chronic inflammation due to insulin resistance (IR) and hyperinsulinemia, and therefore are predisposed to an increased risk for development of obesity, dyslipidaemia, CVD, and endometrial carcinoma. Its prevalence ranges from 9.13% to 36% in India (16).

OS is an imbalance between oxidants and antioxidants, which favours oxidants. It is higher in patients with PCOS (17) when oxidative status is evaluated by circulating markers such as malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GPx), and AOPP. Increased OS is also positively associated with other complications of PCOS such as obesity, insulin resistance, hyperandrogenaemia, and increased risk for cancers of the reproductive system (18).

There is a loss of homeostatic balance between exaggerated ROS production and the antioxidant defence system in chronic periodontitis. Thus, we sought to study the effect of PCOS on periodontal health in an Indian population by analysing AOPP levels.

AOPP was first described by Witko-Sarsat et al. (14) and it is a serologic marker of systemic inflammation. AOPP is formed during OS by the action of chlorinated oxidants, mainly hypochlorous acid and chloramines on albumin; they are closely correlated with dityrosine, a hallmark of oxidized proteins, and pentosidine, a marker of enzymatic protein glycation that is tightly related to OS. AOPP thus reflects the intensity, availability, degree of inflammation, and activation of monocytes and neutrophils.

AOPP is implicated in the mechanistic link between CP and other diseases. Although the implication of OS in the pathophysiology of PCOS and CP has been suggested, little is known about the underlying mechanisms. It is hypothesized that chronic periodontitis and PCOS may have a possible role in AOPP.

The mean age of our study population was 24 years and there was no statistical difference in the mean age values between the groups. In this study, we enrolled age-matched controls. Although the mean probing depth in the PCOSCP group was higher, there was no statistical significance observed between the PCOSCP and CP groups. This could be attributed to the younger age group, which had an increased prevalence of mild periodontitis.

Gingival inflammation can be elicited by change in colour, consistency, and bleeding on probing (BOP) from the gingival sulcus. BOP indicates an active stage of periodontitis at a specific site. Özçaka et al. (19), reported a synergistic effect on IL-6 and tumor necrosis factor- α (TNF- α) in patients with PCOS and gingival inflammation and that a relationship exists between both the conditions. In line with this, the mean BOP values of our PCOSCP and PCOS groups were comparable. A statistical difference existed between the PCOS and CP groups, which showed the impact of PCOS on gingival inflammation.

PISA gives an estimate of inflammation in periodontal tissue and helps to quantify the inflammatory status of the gingival epithelium (20). This is important because fluctuating levels of sex hormones during puberty, pregnancy, and menopause have direct effects on oral health and influence susceptibility to periodontal disease. There was no statistical significance observed between the PISA values of the PCOS and CP groups. Higher PISA values were seen in the PCOS group (680.33 ± 79.49 mm²) compared to the CP group (621.85 ± 180.34 mm²), which could be attributed to variations in the severity of PCOS in the study population.

It has been reported that increased female sex hormones may modulate the function of immune cells (21). Preshaw and Bissett (6) observed that an increase in circulating levels of oestrogen and progesterone appeared to have a dramatic effect on the periodontium throughout pregnancy and this can be owed to the localization of the oestrogen and progesterone receptors in the human periodontium (22). This finding could be applied to PCOS, which is an endocrine disorder characterized by a hormonal imbalance.

The link between PCOS and periodontitis is not completely understood, but many authors have postulated the involvement of various aspects of inflammation, OS, and formation of advanced glycation end products (AGEs). The role of insulin resistance and hyperinsulinemia in the development of PCOS has been explored, and it is generally accepted to play an important role in the implicated molecular mechanisms. Similar to AGEs, AOPP also signals via the receptor for AGE (RAGE) thereby causing detrimental effects in the tissues (23).

Previous studies have estimated AOPP levels in periodontitis and PCOS patients independently, but not in PCOS patients with periodontitis. To the best of our knowledge, the present study is the first to evaluate AOPP in patients with both PCOS and chronic periodontitis. The majority of published data about oxidative protein damage reported higher AOPP levels in the saliva of patients with periodontitis (10). In the present study, on a comparative scale, the two periodontitis groups (PCOSCP and CP) had higher salivary AOPP levels compared to the other groups, which clearly demonstrated the contribution of gingival inflammation to PCOS. The highest serum AOPP levels were observed in the PCOSCP group, and were statistically significant with the PCOS and CP groups. AOPP, a marker for OS, was increased in the presence of both PCOS and CP. This was in line with the trend for increased susceptibility for periodontitis and a local/periodontal prooxidative state in women with PCOS. Periodontitis presents in two stages - an exaggerated inflammatory phase and a quiescent phase. In this study, the AOPP values in the periodontitis group were higher than the PCOS group; this could be attributed to the exacerbated inflammatory phase in periodontitis patients. OS levels in PCOS patients vary with the severity of the condition. Serum AOPP levels were lower in PCOS patients, which could be due to the fact that the patients were identified as PCOS patients but were not graded according to their severity of their symptoms. Kaya et al. (24) reported significantly higher AOPP levels in women with PCOS compared to healthy controls (79.4 ± 12.0 vs. 45.8 ± 6.1 μ mol/l) and suggested that hyperinsulinemia, IR, elevated homocystine (Hcy), and C reactive protein (CRP) might be associated with the formation of AOPP in PCOS patients. In line with this, the results of the present study show that both PCOS and CP can generate an increase in OS, as shown by an increase in the modification of proteins and subsequent formation of AOPPs.

Interestingly, our findings indicated a direct relationship between periodontal health and PCOS, according to the increase in PISA values. These findings concurred with a case-control study conducted by Dursun et al. (25), who reported increased levels of myeloperoxidase (MPO), nitric oxide (NO), and periodontal indices in PCOS patients compared to healthy control women. The PCOS women had higher gingival crevicular fluid (GCF) NO levels and unchanged serum NO levels, which showed the contribution of PCOS and periodontal disease on local oxidant status.

The limitations of this study included the small sample size and multifactorial nature of both diseases, which made it difficult to control other confounding factors. The use of GCF would be a better biomarker because it would have been site specific. Longitudinal, prospective studies conducted in larger populations should be undertaken to more clearly determine the relationship between PCOS and chronic periodontitis. The changes in oral microbiota in patients with PCOS may give significant information regarding the association between PCOS and chronic periodontitis. The effect of periodontal therapy on PCOS should be assessed by well-controlled randomised control trials (RCTs). More objective criteria to grade the severity of PCOS should be developed.

We can derive the following conclusions given the limitations of our study: i. CP contributes to increasing the severity of PCOS by increasing AOPP levels in patients with PCOS, ii. Eliminating gingival inflammation with periodontal therapy and periodic evaluation of oral hygiene status may help reduce OS in PCOS patients.

Authors' Contributions

S.D.; Patient data acquisition and drafted the manuscript. S.A.K.; Designed the study and drafted the manuscript. S.K.B.; Screened the periodontitis patients. U.V.; Screened and diagnosed the PCOS patients. M.S.; Conceptual framework, interpretation of the data, and drafted and revised the manuscript. R.P.P.; Biochemical analysis. All authors read and approved the final manuscript.

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