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REVIEW

Association between periodontal disease and polycystic ovary syndrome: a systematic review

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The purpose of the present study was to review systematically the association between periodontal diseases (PDs) and polycystic ovary syndrome (PCOS). To address the focused question, 'Is there a relationship between PD and PCOS?' indexed databases were searched up to October 2016 without time or language restrictions using different combinations of the following key words: PCOS, ovarian cysts, PD, periodontitis, gingival diseases and gingivitis. Letters to the Editor, commentaries, historic reviews, case-report, unpublished articles and animal/experimental studies were excluded. Seven case–control studies were included. The number of study participants ranged between 52 and 196 females aged between 15 and 45 years. In three and three studies, proinflammatory cytokines were assessed in gingival crevicular fluid and saliva samples, respectively. In one study, salivary microbes were investigated. All studies reported that a positive association exists between PD and PCOS. In conclusion, there is a positive association between PD and PCOS; however, further well-designed longitudinal controlled clinical trials are needed in this regard. It is recommended that physicians should refer patients with PCOS to oral health-care providers for comprehensive oral evaluation and treatment.

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INTRODUCTION

Periodontal diseases (PDs) (such as gingivitis and periodontitis) are inflammatory disorders (caused by pathogenic microbiota present in the oral biofilm) that trigger innate, inflammatory and adaptive immune responses.[1] PD have been associated with altered vascular response, increased levels of adhesion molecules (such as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1) and higher expression of local and systemic inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6 and monocyte chemoattractant protein-1, resulting in impaired endothelial function.[2–4] In this context, it has been suggested that a bi-directional relationship exists between PD and systemic diseases such as atherosclerosis,[5,6] myocardial infarction,[7] stroke,[8,9] type 2 diabetes mellitus,[10] testosterone insufficiency[11] and erectile dysfunction.[12] Interestingly, Dursun *et al.*[13] reported for the first time an association between PD and polycystic ovary syndrome (PCOS), main cause of anovulatory infertility, and the most common gynecologic and endocrine condition among women in reproductive age, affecting between 5 and 10% of the female population.[14,15] However, only a limited number of studies[16–22] have investigated this association.

PCOS is defined as a syndrome of ovarian dysfunction characterized by hyperandrogenism and polycystic ovary.[23] Other common clinical manifestations of PCOS include reproductive disturbances (such as menstrual irregularities, infertility and hirsutism), metabolic disorders (insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus, adverse cardiovascular risk profiles and obesity) and psychological features (increased anxiety, depression and poor quality of life).[14,24] Although the pathogenesis of PCOS is poorly understood, it has been associated with genetic, metabolic, endocrine and environmental factors.[25,26] Studies[27–29] have suggested that chronic infections associated with increasing levels of reactive oxygen species, myeloperoxidase (MPO), oxidative stress, inflammatory cytokines (such as IL-6 and TNF-α), high-sensitivity C-reactive protein (hsCRP), adhesion molecules and blood lymphocytes and monocytes have a role in the etiology and pathogenesis of PCOS. This cascade of proinflammatory events has also been postulated as a possible link between PD and PCOS. Ozcaka *et al.*[16] analyzed levels of proinflammatory cytokines in the gingival crevicular fluid (GCF), saliva and serum among patients with and without PCOS. The findings suggested that PCOS and gingival inflammation act synergistically, thereby increasing the levels of IL-6 and TNF-α.[16] Similarly, Akcali *et al.*[20] reported increased levels of matrix metalloproteinase-8 (MMP-8) in whole saliva and serum in patients with PD and PCOS compared with healthy controls. Similar results were reported by Porwal *et al.*[18] and Dursun *et al.*[13] These results suggest that a direct and significant relation exists between PD and PCOS. To our knowledge from indexed literature, the association between PD and PCOS has not been systematically reviewed.

The aim of the present study was to assess the association between PD (gingivitis and periodontitis) and PCOS through a systematic review of indexed literature.

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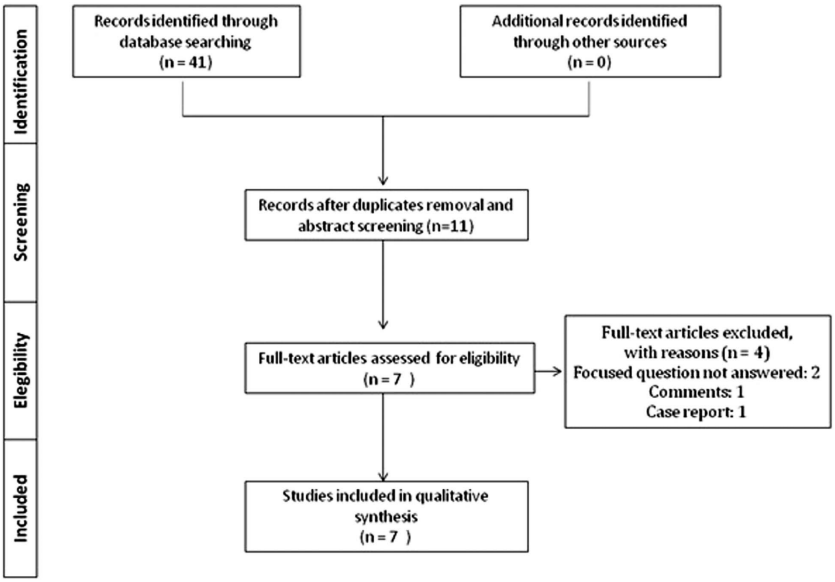

Figure 1. Article selection flow chart for the systematic review according to PRISMA guidelines.

MATERIALS AND METHODS

Focused question

Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a specific question was constructed according to the Participants, Interventions, Control, and Outcomes (PICO) principle.[30] The focused question was 'Is there a relationship between PD and PCOS?' (P) *Participants*: Non-obese females in reproductive age undergoing medical and periodontal evaluation. (I) *Types of interventions*: Evaluation of periodontal status in females diagnosed with PCOS. (C) *Control Intervention*: Evaluation of periodontal status in healthy females (without PCOS). (O) *Outcome Measures*: Periodontal clinical parameters, immunoinflammatory and/or microbiological parameters in women with and without PCOS.

Literature search protocol and eligibility criteria

To identify the pertinent studies, an electronic search without time or language restrictions was conducted up to October 2016 using PubMed (National Library of Medicine, Washington, DC, USA), Google-Scholar, Scopus, EMBASE, MEDLINE (OVID) and Web of Knowledge databases. The following Medical subject headings (MeSH) were used: (1) PCOS, (2) ovarian cysts, (3) PD, (4) periodontitis, (5) gingival diseases, (6) gingivitis, and the combinations 1 or 2 and 3; 1 or 2 and 4; 1 or 2 and 5; and 1 or 2 and 6. Other relevant non-MeSH words were used in the search process to identify articles discussing periodontal inflammatory parameters in patients with PCOS. These included 'inflammation', 'plaque index', 'bleeding index', 'clinical attachment loss' and 'bleeding on probing'.

The eligibility criteria were as follows: (a) clinical studies; (b) prospective and retrospective studies; and (c) studies assessing the relationship between PD and PCOS. Articles available online in electronic form ahead of print were considered eligible for inclusion. Letters to the Editor, commentaries, historic reviews, case-report, unpublished articles and animal/experimental studies were excluded. Titles and abstracts of studies identified using the above-described protocol were screened by two authors (SVK and VRM) and checked for agreement. Full-texts of studies judged by title and abstract to be relevant were read and independently evaluated for the stated eligibility criteria. Reference lists of potentially relevant original and review articles were hand-searched to identify studies that have remained unidentified in the previous step. Once again, the articles were checked for disagreement via discussion among the authors. κ-Scores (Cohen κ-coefficient) were used to determine the level of agreement between the two reviewers (κ-score = 0.9).[31] Figure 1 summarizes the literature search strategies.

Quality assessment

Critical Appraisal Skills Program Cohort Study Checklist[32] was performed to grade the methodological quality of each study included in the present systematic review. This tool is based on 12 criteria that are as follows: (1) study issue is clearly focused (relationship between PD and PCOS); (2) cohort is recruited in an acceptable way; (3) exposure is accurately measured; (4) outcome is accurately measured; (5) confounding factors are addressed; (6) follow-up is long and complete; (7) results are clear; (8) results are precise; (9) results are credible; (10) results can be applied to the local population; (11) results fit with available evidence; and (12) there are important clinical implications. According to the Critical Appraisal Skills Program scale, each criterion is given a response of either 'Yes', 'No' or 'cannot tell' and the maximum score a study could have was 12.

RESULTS

Study selection

Forty-one potential articles were initially identified. Thirty publications that were either duplicates or did not answer the focused question were excluded. In the next step, four more articles were excluded, because it did not answer the focused question, were comments and/or presented a case-report design (Appendix A). A total of seven studies[13,16–21] were included in the present systematic review and processed for data extraction.

Characteristics and participants

All studies[13,16–21] were clinical and were performed on humans in accordance of ethical principles at universities or health-care settings. The studies[13,16–21] had a case–control design and were conducted in the following countries: India, Iran and Turkey. The number of study participants ranged between 52 and 196 females with mean ages ranging between 15 and 45 years. The median ages of patients with PCOS and controls (regularly menstruating females with no clinical or biochemical signs of hyperandrogenism and ultrasound exclusion of PCOS) ranged between 22.68 and

Table 1. General characteristics of the studies included in the present review

Authors (region of study, year)	*Study design*	*Population*	*Mean age in years (range)*	*Periodontal status diagnostic methods*	*PCOS diagnostic methods*	*Confounders variables assessed*
Dursun *et al.*[13] (Turkey, 2011)	Case–control	Total: 52 Group 1: 25 PCOS Group 2: 27 SH	Group 1: 22.7 ± 3.6 Group 2: 24.2 ± 2.5	Oral examination PPD, CAL, GI, BOP, PI Radiographs GCF sampling Spectrophometric MPO assay	Medical history Rotterdam criteria Ultrasound Serum levels	BMI > 30 kg/m^2, Cushing's syndrome, congenital adrenal hyperplasia, hyperprolactinemia, thyroid disorders, androgen-secreting tumors, smoking, oral contraceptives
Ozcaka *et al.*[16] (Turkey, 2012)	Case–control	Total: 73 Group 1: 30 PCOS +gingivitis Group 2: 31 PCOS +HP Group 3: 12 SH+HP	Group 1: 23.5 (20–28.8) Group 2: 21 (20–26.5) Group 3: 28.5 (24.8–32.3)	Oral examination BOP, PPD, CAL, PI Radiographs GCF sampling Saliva sampling ELISA TNF-α, TNF-αR1, TNF-αR2, IL-6	Medical history Rotterdam criteria Ultrasound Serum levels FGS	BMI > 30 kg/m^2, androgen-secreting tumors, congenital adrenal hyperplasia, thyroid disorders, DM, hyperprolactinemia, Cushing's syndrome, HBP, hepatic and renal dysfunction, oral contraceptives, steroid hormone, insulin-sensitizing drugs, alcohol, smoking
Ozcaka *et al.*[17] (Turkey, 2013)	Case–control	Total: 73 Group 1: 30 PCOS +gingivitis Group 2: 31 PCOS +HP Group 3: 12 SH+HP	Group 1: 23.5 (20–28.8) Group 2: 21 (20–26.5) Group 3: 28.5 (24.8–32.3)	Oral examination BOP, PPD, PI, CAL GCF sampling Saliva sampling ELISA IL-17	Medical history Rotterdam criteria Ultrasound Serum levels FGS	BMI > 30 kg/m^2, hyperandrogenism, thyroid disorders, hyperprolactinemia, CVD, DM, HBP, oral contraceptive, steroid hormones, insulin-sensitizing drugs
Porwal *et al.*[18] (India, 2014)	Case–control	Total: 126 Group 1: 41 Newly PCOS Group 2: 45 PCOS on treatment Group 3: 40 SH	Group 1: 26.28 (15–36) Group 2: 22.68 (16–31) Group 3: 23.50 (17–32)	Oral examination GI, BOP, PPD, CAL, PI	Medical history Rotterdam criteria Ultrasound WC and WHR hsCRP Serum level	BMI > 30 kg/m^2, thyroid disorders, hyperprolactinemia, androgen-secreting tumors, chronic inflammatory diseases, DM, CVD, cancer, smoking, alcohol, antibiotics, periodontal treatment, aggressive periodontitis
Akcali *et al.*[19] (Turkey, 2014)	Case–control	Total: 125 Group 1: 45 PCOS +HP Group 2: 35 PCOS +gingivitis Group 3: 25 SH+HP Group 4: 20 SH +gingivitis	Group 1: 25.02 ± 5.86 Group 2: 26.40 ± 5.77 Group 3: 25.84 ± 4.07 Group 4: 26.40 ± 5.42	Oral examination PPD, PI, BOP qPCR for salivary bacteria quantification	Medical history Rotterdam criteria Ultrasound Serum antibody levels with ELISA	BMI > 30 kg/m^2, hyperandrogenism, DM, hyperprolactemia, congenital adrenal hyperplasia, thyroid disorders, Cushing's syndrome, HBP, CVD, hepatic or renal dysfunction, oral contraceptives, steroid hormones, insulin-sensitizing medications
Akcali *et al.*[20] (Turkey, 2015)	Case–control	Total: 125 Group 1: 45 PCOS +HP Group 2: 35 PCOS +gingivitis Group 3: 25 SH+HP Group 4: 20 SH +gingivitis	Group 1: 25.02 ± 5.86 Group 2: 26.40 ± 5.77 Group 3: 25.84 ± 4.07 Group 4: 26.40 ± 5.42	Oral examination PPD, PI, BOP MMP-8 Saliva analysis with IFA TIMP-I with ELISA	Medical history Rotterdam criteria Ultrasound MMP-8 Serum levels with IFA TIMP-I with ELISA	BMI > 30 kg/m^2, hyperandrogenism, DM, hyperprolactemia, congenital adrenal hyperplasia, thyroid disorders, Cushing's syndrome, HBP, CVD, hepatic or renal dysfunction, oral contraceptives, steroid hormones, insulin-sensitizing medications
Rahiminejad *et al.*[21] (Iran, 2015)	Case–control	Total: 196 Group 1: 98 PCOS Group 2: 98 healthy controls	(19–45) Group 1: 29.1 ± 6.6 Group 2: 28.6 ± 6.4	Oral examination BOP, PPD, CAL, PI, tooth loss	Medical history Rotterdam criteria Ultrasound Serum levels	Pregnancy, smoking, malignancies, osteoporosis, antibiotics, periodontal treatment, BMI > 25 kg/m^2, IGT

Abbreviations: BMI, body mass index; BOP, bleeding on probing; CAL, clinical attachment loss; CVD, cardiovascular diseases; DM, diabetes mellitus; ELISA, enzyme-linked immunosorbent assay; FGS, Ferriman–Gallwey score; GCF, gingival crevicular fluid; GI, gingival index; HBP, high blood pressure; HP, healthy periodontum; hsCRP, high-sensitivity C-reactive protein; IFA, immunofluorometric assay; IGT, impaired glucose tolerance; IL, interleukin; MMP, matrix metalloproteinase; MPO, myeloperoxidase; PCOS, polycystic ovary syndrome; PI, plaque index; PPD, periodontal probing depth; qPCR, quantitative real-time polymerase chain reaction; SH, systemically healthy; TIMP, tissue inhibitors of MMP-I; TNF-α, tumor necrosis factor-α; TNF-αR1, TNF-α receptor-1; TNF-αR2, tumor necrosis factor-α receptor-2; WC, waist circumference; WHR, waist-to-hip ratio.

29.1 ± 6.6 and 23.5 and 28.6 ± 6.4 years, respectively. In all studies[13,16–21] PCOS was diagnosed according to the 2003 criteria of Rotterdam with the presence of at least two of the following: (1) polycystic ovaries (presence of >12 follicles in each ovary measuring 2–9 mm in diameter and/or increased ovarian volume >10 ml), (2) oligomenorrhea and/or anovulation and (3) hyperandrogenism (clinical and/or biochemical).[23]

Confounding factors

In all studies[13,16–21] confounding factors were assessed, including medical conditions associated with hyperandrogenism, such as androgen-secreting tumors and congenital adrenal hyperplasia (tested by levels of 17-α-hydroxyprogesterone), hyperprolactinemia, congenital adrenal hyperplasia, thyroid disorders, Cushing's syndrome, hypertension, hepatic or renal dysfunction and cardiovascular diseases. All studies[13,16–21] assessed confounding medications that could affect periodontal status within the past 3 to 6 months prior inclusion, such as oral contraceptive agents, steroids hormones, antihypertensive medications, antibiotics and anti-inflammatory drugs. In all the studies,[13,16–21] obese females (body mass index (BMI) >30 kg/m^2), smokers and alcohol consumers were excluded.

Clinical periodontal parameters investigated

In all the studies,[13,16–21] a comprehensive clinical periodontal examination was performed to assess the periodontal probing depth (PPD), plaque index (PI) and bleeding on probing (BOP). Clinical attachment loss (CAL) and gingival index (GI) were reported in five studies[13,16–18,21] and two studies,[13,18] respectively. One study[21] reported the rate of tooth loss among patients with and without PCOS. Intraoral radiographs were used in three studies[13,16,17] to assess bone loss.

Oral immunoinflammatory and microbiological parameters investigated

GCF samples were collected in three studies[13,16,17] to assess inflammatory cytokines levels with specific enzyme-linked immunosorbent assay (ELISA) and/or MPO activity using spectrophometric MPO assay. In three studies,[16,17,19] saliva samples were collected to quantify salivary levels of cytokines, MMPs and/or tissue inhibitors of MMPs (TIMPs) using ELISA, and/or immunofluorometric assay. Akcali *et al.*[19] used quantitative real-time polymerase chain reaction to assess salivary microbes among patients with PCOS and controls.

Systemic immunoinflammatory and microbiological parameters investigated

In all studies,[13,16–21] venous blood samples were collected from patients with PCOS and controls. In three studies,[16,17,20] ELISA was used to assess inflammatory cytokines, MMP-8 and/or TIMP-1 levels in serum. Porwal *et al*.[18] measured serum levels of hsCRP. Dursun *et al*.[13] determined nitric oxide serum levels with and without PCOS to reflect the strength of oxidative stress. Akcali *et al*.[19] used ELISA to assess the systemic antibody response to seven specific periodontal pathogens in serum (Table 1).

Main outcomes

In all studies[13,16–21] a positive relationship between PD and PCOS was reported.

Microbiological outcomes

In the study by Akcali *et al*.[19] higher salivary levels of *Porphyromonas gingivalis* and *Fusobacterium nucleatum* in patients with PCOS and gingivitis, compared with healthy controls and patients with PCOS without gingivitis was reported. The presence of PCOS also raised *P. gingivalis*, *Prevotella intermedia* and *Streptococcus oralis* serum antibody levels, when gingivitis was also present. *Aggregatibacter actinomycetemcomitans* and *Treponema denticola* levels were similar among study groups.[19]

Clinical and immunoinflamatory outcomes

Rahiminejad *et al*.[21] reported higher CAL, PI and BOP in patients with PCOS compared with healthy controls; however, no significant difference in tooth loss between the groups was identified. Similar findings were reported in the study by Dursun *et al*.[13] where patients with PCOS presented significantly higher PPD, GI, BOP and PI compared with healthy controls. Furthermore, in other study Ozcaka *et al*.[17] reported a positive relation between PPD and IL-17A and IL-17F serum levels in females with PCOS.

Akcali *et al*.[20] identified a positive correlation between salivary and serum MMP-8 and MMP-8/TIMP-I ratio levels and periodontal parameters (PPD, BOP and PI) in women with PCOS. Ozcaka *et al.*[16] reported a positive correlation between PPD, BOP and PI and serum TNF-α, TNF-α receptors, GCF and salivary IL-6 levels in women with PCOS and gingivitis. In the study by Porwal *et al.*[18]

Table 2. Primary outcomes of the studies included

Authors	*Altered parameters in patients with PCOS and periodontal disease*		
	Clinical	*Immunoinflammatory*	*Microbiological*
Dursun *et al.*[13]	PPD, GI, BOP, PI	MPO and NO in GCF	NA
Ozcaka *et al.*[16]	PPD, BOP, PI	IL-6 in GCF, saliva and serum TNF-α in saliva	NA
Ozcaka *et al.*[17]	PPD, BOP, PI	IL-17A, IL-17F and IL-17A/F in serum IL-17A and IL-17F in GCF and saliva	NA
Porwal *et al.*[18]	BOP, PPD, CAL	hsCRP	NA
Akcali *et al.*[19]	PI, BOP, PPD	NA	Saliva: *P. gingivalis F. nucleatum* Serum antibodies: *P. intermedia*, *P. gingivalis*, *S. oralis*
Akcali *et al.*[20]	PI, BOP, PPD	MMP-8 MMP-8/TIMP-1 ratio	NA
Rahiminejad *et al.*[21]	BOP, CAL, PI	NA	NA

Abbreviations: BOP, bleeding on probing; CAL, clinical attachment loss; GCF, gingival crevicular fluid; GI, gingival index; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; MMP, matrix metalloproteinase; MPO, myeloperoxidase; NA, not applicable; NO, nitric oxide; PCOS, polycystic ovary syndrome; PI, plaque index; PPD, periodontal probing depth; TIMP, tissue inhibitors of MMP-I; TNF-α, tumor necrosis factor-α.

women with newly diagnosed PCOS presented increased BOP, PD and CAL compared with healthy controls and women with PCOS under medical treatment. Logistic regression analysis demonstrated that women with newly diagnosed PCOS had 2.88 times increased likelihood of having moderate periodontitis (odds ratio = 2.88, 95% confidence interval = 1.18–6.98) compared with healthy controls and women with PCOS under treatment.

Dursun *et al.*[13] reported higher GCF volume (subclinical sign of gingival inflammation) and a significant positive correlation among clinical periodontal parameters, GCF MPO and nitric oxide levels and serum parameters in PCOS. Akcali *et al.*[20] reported higher GCF volume, MMP-8 and MMP-8/TIMP-I ratio salivary levels in women with PCOS and gingivitis, compared with systemically healthy women. Ozcaka *et al.*[16,17] reported higher serum, saliva and GCF IL-6 levels in patients with PCOS and gingivitis compared with PCOS without gingival inflammation; similarly, higher concentrations of IL-17A, IL-17F and IL-A/F in serum and higher levels of IL-17A and IL-17F in GCF in patients with PCOS compared with systemically healthy controls were reported. Porwal *et al.*[18] reported higher hsCRP serum levels in newly diagnosed PCOS compared with healthy controls and women under PCOS treatment (Table 2).

Quality assessment of included studies

Through the quality assessment was identified that all studies[13,16–21] presented a quality score of 10. The most common shortcoming among all studies[13,16–21] was the short-term, non-follow-up of the groups, and inability to extrapolate the results to general population. Thus, on average, the quality of included studies assessing the relationship between PD and PCOS was good; however, short-term and non-follow-up limit the application of these study outcomes. Quality assessment of the individual papers is summarized in Table 3.

DISCUSSION

From the literature reviewed, seven studies[13,16–21] fulfilled the eligibility criteria and were systematically reviewed. Interestingly, results from all the studies[13,16–21] showed a positive association between PCOS and PD. Therefore, it is tempting to speculate that patients with PCOS are at increased risk on developing PD compared with controls. However, upon a vigilant review of the studies,[13,16–21] it was observed that a variety of factors may have influenced the reported results. First, PCOS complexity and heterogeneity are demonstrated by the difficulty to reach a definition of the disease by itself.[33] PCOS is associated with common metabolic disorders, including type 2 diabetes mellitus, dyslipidemia and cardiovascular diseases, resulting in insulin resistance, hyperinsulinemia and obesity.[34,35] Currently, the diagnosis of PCOS follows the Rotterdam criteria, which comprises of a combination of clinical, biological and ultrasound evaluations.[23,36] Since the clinical presentation of PCOS varies between continents, it is difficult to establish a universal diagnosis of PCOS using merely European or North American guidelines.[36] Moreover, because of the commonness of ultrasound features of polycystic ovaries in healthy women, the inclusion of this sign to the diagnostic criteria of PCOS is still debatable.[37] It is therefore hypothesized that besides PD other risk factors inherent to a misdiagnosed PCOS, such as chronic hyperglycemia, raised systemic levels of proinflammatory cytokines and cardiovascular disorders, may have significantly contributed in aggravating the local and systemic inflammation. For instance, in the study by Dursun *et al.*[13] the plasma glucose level values at 120 min during oral glucose tolerance test were significantly higher in the PCOS group compared with the control group. Further studies are warranted in this regard.

It is noteworthy that all the included studies[13,16–21] designed a stringent inclusion and exclusion criteria to restrain confounders. For example, females who had BMI > 30 kg/m^2 were defined as obese and excluded from all the studies.[13,16–21] In addition, Porwal *et al.*[18] measured waist circumference and waist-to-hip ratio. However, selection of BMI as an indicator of obesity has its limitations because it frequently fails to measure adiposity.[38] Moreover, a recent study[39] reported that Asian young adult women (all the studies included in the review were conducted in Asia) tends to have lower BMI and higher body fat percentage than other ethnic groups, and suggested to combine BMI and biometrical impedance analysis for obesity and overweight screening in Asian young adults. It is therefore hypothesized that periodontal clinical parameters and the local and systemic inflammatory profile in the PCOS groups could be associated with undiagnosed higher central fat levels leading to a chronic low-grade inflammation. In this regard, the conclusions of the studies included in the present systematic review should be interpreted with caution.

It is well known that progression of PD is associated with multiple factors including mechanical removal of plaque, glycemic levels, and frequency and duration of smoking.[40–43] It is therefore plausible that the severity of PD may also be associated with the aggravation of PCOS. Upon a vigilant evaluation of all the studies[13,16–21] included in the present systematic review, it was observed that only one study[18] evaluated the progression of PD associated with PCOS. Further well-designed studies assessing the association between PD and PCOS focusing in the progression of both diseases are needed. Furthermore, it is noteworthy that all the studies[13,16–21] were observational investigations, conducted in only three Asian countries with a reduced number of participants. It is therefore demanding to generalize these findings to the global population. Additional well-designed prospective longitudinal, multicenter clinical studies on patients from varying ethnicities are needed in this regard.

Table 3. CASP quality assessment of the reviewed papers

Authors	*Item 1*	*Item 2*	*Item 3*	*Item 4*	*Item 5*	*Item 6*	*Item 7*	*Item 8*	*Item 9*	*Item 10*	*Item 11*	*Item 12*	*Total quality score (0–12)*
Dursun *et al.*[13]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Ozcaka *et al.*[16]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Ozcaka *et al.*[17]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Porwal *et al.*[18]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Akcali *et al.*[19]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Akcali *et al.*[20]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Rahiminejad *et al.*[21]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10

Abbreviation: CASP, Critical Appraisal Skills Program. Item 1: study issue is clearly focused; item 2: cohort is recruited in an acceptable way; item 3: exposure is accurately measured; item 4: outcome is accurately measured; item 5: confounding factors are addressed; item 6: follow-up is long and complete; item 7: results are clear; item 8: results are precise; item 9: results are credible; item 10: results can be applied to the local population; item 11: results fit with available evidence; item 12: there are important clinical implications.

From a statistical perspective, power analysis is an important aspect of experimental design to establish the sample size required to detect an effect of a given size with a given degree of confidence. It is pertinent to mention that from the literature reviewed, power analysis was reported only in three studies.[16–18] Therefore, it is feasible that a wrong interpretation of results due to either very low or very high power, and/or to inappropriate selection of a statistic to test the hypotheses altered the reported results. It is emphasized that using an adequate sample size along with high-quality data collection will result in more reliable and valid results.

Non-surgical periodontal therapy has been reported as an effective tool reducing glycemic levels in patients with DM.[40,44,45] Javed *et al.*[46] reported that non-surgical periodontal therapy combined with adjunct laser therapy is effective in reducing serum proinflamatory cytokines levels in patients with coronary heart disease. Therefore, it is hypothesized that comprehensive dental treatment of PD may also contribute in the treatment of patients with PCOS by reducing levels of proinflammatory mediators, reactive oxygen species and oxidative stress. Hence, the future assessment of PD in patients with PCOS should explore the effect of non-surgical periodontal therapy in the improvement of inflammatory parameters and PCOS severity.

Within the limits of the evidence available, there seems to be a positive relationship between PD and PCOS. However, further studies implementing accurate diagnostic tools for PCOS assessment are needed to establish if there is a causal or occasional relationship.

CONCLUSIONS

From the literature reviewed, there seems to be a positive association between PD and PCOS; however, further well-designed controlled clinical trials and longitudinal prospective studies are needed in this regard. Physicians should refer patients with PCOS to oral health-care providers for a comprehensive oral evaluation and treatment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDIX A
List of excluded articles

a Asnani KP, Hingorani D, Kheur S, Deshmukh V, Romanos GE. Expression of nuclear receptors of gingiva in polycystic ovarian syndrome: a preliminary case study. *Aust Dent J* 2014; **59**: 252–257 (case-report design).
b Greenhill C. Reproductive endocrinology: PCOS raises risk of periodontitis. *Nat Rev Endocrinol* 2010; **6**: 656 (comment).
c Mattout P, Pelissier H, Codaccioni M. Histological study of dental and periodontal inclusions in a dermoid cyst of the ovary. *J Parodontol* 1985; **4**: 55–62 (focus question was not answered).
d Levin HL. Some dental aspects of endocrine diseases. *Oral Surg Oral Med Oral Pathol Oral Radiol* 1965; **19**: 466–477.