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Review

Association between periodontal disease and polycystic ovary syndrome: A scoping review.

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Abstract: Background: Polycystic ovary syndrome (PCOS) is one of the most prevalent endocrine disorders in women. It is believed that sex hormones play a role in the maintenance of bone mass and directly or indirectly influence several cell types, including periodontal cells. Objective: To evaluate the association between periodontal disease and PCOS according to the evidence reported in the last decade. Material and Method: A search was made in the biomedical databases: Pubmed, Embase, Scopus, SciELO, Science Direct and SIGLE for the 2007-2017 period. Selection criteria: prospective and retrospective studies reporting the relationship between periodontal disease and PCOS. The methodological quality of the studies was analyzed using the Critical Appraisal Skills Program scale. Results: 10 articles were found: 1 clinical trial and 9 case-control studies. The number of patients ranged from 48 to 196, mean age between 23.3 and 28.1 years, age range between 15 and 45 years. Studies were conducted in Turkey, India and Iran. All the studies presented good methodological quality and a positive association between PCOS and periodontal disease. Conclusion: PCOS shows a positive and significant association with the clinical and molecular parameters of periodontal diseases.

Keywords: Polycystic ovary syndrome; periodontal disease; gingivitis; periodontitis; revision.

INTRODUCTION.

Polycystic ovary syndrome (PCOS) is one of the multiple conditions that affect women, and one of the most frequent endocrine disorders.[1-17] It is characterized by menstrual abnormalities, hyperandrogenism, polycystic ovary and increased risk of developing metabolic and cardiovascular diseases.[2,3,5-18] PCOS is likewise the main cause of infertility,[5,10,11,16,18] and is reciprocally associated with oral health.[11,17]

Periodontal disease consists of a group of conditions that affect the protective (gingiva) and support tissues (periodontal ligament, root cement and alveolar bone) of the teeth. It is caused by persistent infection and inflammation in response to the presence of periodontal pathogens.[10-16,19-21] Currently, more than 500 bacterial species have been identified in periodontal plaque, but there is no agreement on the causative bacterial species.[19,22,23]

The presence of periodontal pathogens is a necessary but not sufficient condition to induce periodontal disease. In a physiological state where there are no disease-modifying risk factors, the host responds appropriately to the growth of bacteria by trying to restrain the infection.

However, disease modifiers, such as smoking and diabetes mellitus, change immunoinflammatory responses putting them outside their normal physiological limits.[9,17,20] In addition, the lipopolysaccharides (LPS) from

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periodontal pathogens stimulate host cells to secrete proinflammatory mediators such as interleukin (IL) -1b, IL-6, IL-11 and IL-17; tumor necrosis factor alpha (TNF-α) and prostaglandin E2 (PGE2).[12,14,16,20,24] These, in turn, stimulate the release of matrix metalloproteinases (MMPs).[6,9-16,25]

It has been recently shown that women with PCOS have high levels of TNF-α due to insulin resistance (IR) and hyperandrogenism (HA);[3,11,26] and high levels of MMPs[6,9] and proinflammatory ILs.[11] Therefore, it is plausible to assert that the severity of periodontal disease may be associated with that of PCOS. In addition, sex hormones (androgens, estrogens and progestins) play a role in the maintenance of bone mass, and directly and indirectly influence several cells through their receptors in target tissues, including periodontal cells.[11,17]

Until now, very few studies have evaluated the relationship between periodontal parameters and PCOS.[6-17] The aim of this scoping review is to evaluate the association between periodontal disease and PCOS according to the evidence reported in the last decade.

MATERIALS AND METHODS.

This review was carried out in accordance with a previously prepared research protocol based on PRISMA statement.[27]

Search

A comprehensive search was carried out in the biomedical databases Pubmed, Embase, Scopus, SciELO, Science Direct, SIGLE (System of Information on Gray Literature in Europe) and a manual search was also conducted from January 2, 2007 to December 1, 2017, in the journals of periodontology with the greatest impact factor, such as: *Periodontology 2000, Journal of Clinical Periodontology, Journal of Periodontology.*

A combination of thematic headings was used including the following keywords: (*"polycystic ovary syndrome"* OR "PCOS" OR *"ovarian cysts"* OR *"síndrome de ovario poliquístico"*) AND (*"periodontal disease"* OR *"gingivitis"* OR *"periodontitis"* OR *"enfermedad periodontal"*).

Selection criteria

Articles reporting the relationship between periodontal disease and PCOS, without language restriction, were included in the study. Case reports, case series and systematic reviews were excluded.

Process of selection and extraction of data

The titles and abstracts of each of the studies obtained were reviewed. The full texts of the studies that met these parameters were obtained in order to determine their risk of bias.

To assess the studies, a checklist was made in duplicate, in order to extract the information of interest. Two reviewers (LG and EI) independently carried out the evaluation of the articles regarding name, author, year of publication, type of study, number of patients, age of the patients, country where the study was carried out, groups of study and conclusions. For the resolution of any discrepancy between the reviewers, they met and discussed with a third reviewer (SR) until consensus was reached.

Assessment of methodological quality

The Critical Appraisal Skills Program scale (CASP) was used for the assessment of the methodological quality of each study.[16,28] This tool is based on 11 criteria and there are several versions to be used according to study type, such as randomized controlled trials or case-control studies.

Figure 1. Flowchart of the selection process of articles.

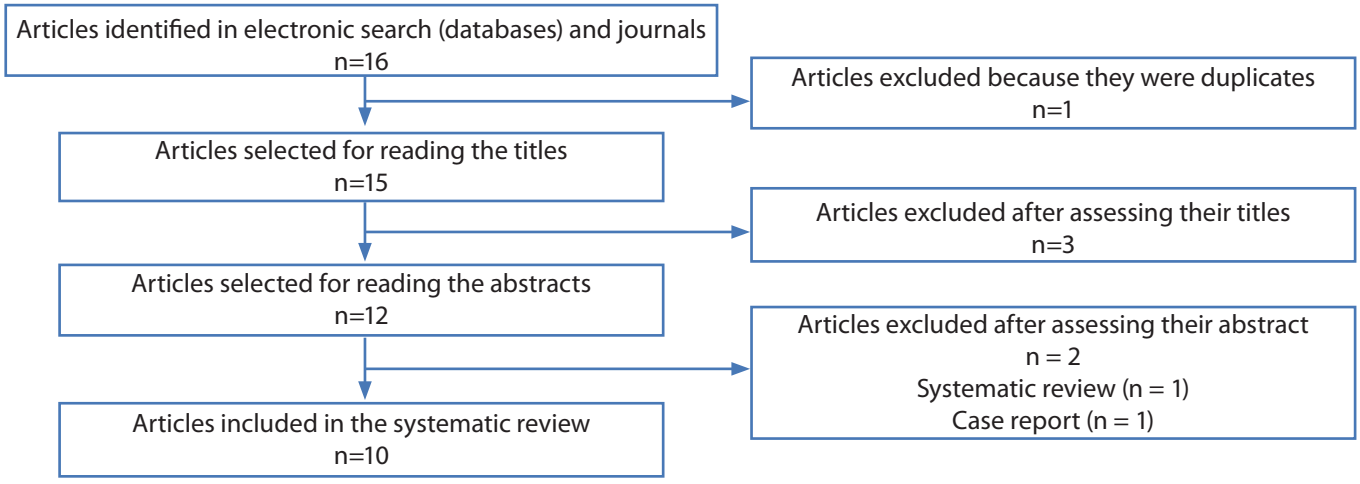

Table 1. Characteristics of analyzed studies.

Author(s)	Year	Type of study	Country	Number of patients	Mean age (range)	Groups under study	Mean age by group	Results	Conclusions
Akcali *et al.*[6]	2017	Case-control	Turkey	125	25.7 (17 – 43)	45 with PCOS and healthy periodontium (Ph) 25 systemically and periodontally healthy (Hh) 35 with PCOS and gingivitis (Pg) 20 systemically healthy, with gingivitis (Hg)	NR NR NR NR	Salivary levels of MMP-9 and NE, aswell as the MMP-9/TIMP-1 ratio were higher in the Hg group compared to the Ph group, respectively <0.001, $p<0.01$, $p<0.0001$. Serum levels of MMP-9 and MPO were higher in the Pg group compared to the Ph group ($p<0.05$). The serum levels of MMP-9 were lower in the Hg group than in the Hh and Pg groups ($p<0.05$). The groups with PCOS exhibited a positive correlation between clinical periodontal parameters and serum levels of MMP-9 or salivary MPO, levels of NE and the MMP-9/MMP-1 ratio. The correlation was negative between the clinical periodontal parameters and the serum levels of MMP-9 and the MMP-9/TIMP-1 ratio exhibited by the systemically healthy groups ($p<0.05$).	Findings emphasize that PCOS and gingival inflammation are associated with each other, as demonstrated by salivary and serum levels of neutrophilic enzymes. This interaction may contribute to the disturbance of ovarian remodeling that characterizes PCOS.
Deepti *et al.*[7]	2017	Randomized and controlled clinical trial	India	60	23.3 (15 – 35)	26 with PCOS and periodontitis treated with non-surgical periodontal treatment+Myo-inositol supplements (Test) 25 with PCOS and periodontitis treated with Myo-inositol supplements (Control)	24 22.6	Periodontal parameters improved significantly in the test group compared to the control group at 3 and 6 months of follow-up ($p<0.001$). A statistically significant reduction in hsCRP and HOMA was observed in both groups at 3 and 6 months of follow-up ($p<0.05$). However, a significant improvement was observed in hsCRP ($p<0.05$) and a statistically comparable reduction in HOMA ($p<0.05$) in the test group compared to the control group at 3 and 6 months. Both the test and the control groups showed a significant and constant improvement of the metabolic parameters at 3 and 6 months of follow-up, which was also comparable to a systemically and periodontally healthy group.	Root planning along with medical treatment results in a greater reduction of the systemic inflammatory load in the treatment of women with PCOS and periodontitis compared to medical treatment alone.
Saglam *et al.*[10]	2017	Case-control	Turkey	48	28.1 (19 – 40)	22 with PCOS and chronic periodontitis (PCOSCP) 22 systemically healthy, with chronic periodontitis (SHCP) 22 with PCOS and periodontally healthy (PCOSPH) 22 systemically and periodontally healthy (SPH)	28.23 28.61 27.64 27.78	Salivary levels of 8-OHdG in the groups with PCOSCP and SHCP were statistically higher than those in the groups with PCOSPH and SPH ($p<0.05$). There were no statistical differences in saliva levels of MDA and TAS between the PCOSCP, SHCP and PCOSPH groups ($p>0.05$). The highest serum levels of 8-OHdG and MDA and the lowest serum levels of TAS were observed in the PCOSCP group ($p<0.05$). Serum levels of 8-OHdG and MDA in the PCOSPH group were higher than those in both systemically healthy groups ($p<0.05$). Salivary TAS levels were higher ($p<0.05$) in the SPH group. There were no statistical differences between the SHCP and PCOSPH groups, but the serum levels of SAD were lower than those in the SPH group ($p<0.05$).	Chronic periodontitis leads to an increase in serum and salivary levels of 8-OHdG and MDA and a decrease in serum levels of TAS in patients with PCOS, thus contributing to an increase in oxidative stress. This effect was more prominent in serum levels than in salivary levels.
Akcali *et al.*[9]	2015	Case-control	Turkey	125	25.9	45 with PCOS and healthy periodontium 35 with PCOS and gingivitis 25 systemically and periodontally healthy 20 systemically healthy and with gingivitis	25.02 26.4 25.84 26.4	Salivary levels of MMP-8 and the MMP-8/TIMP-1 ratio were significantly higher in women with PCOS, who also exhibited more gingivitis than systemically healthy women. No significant changes were observed in salivary TIMP-1 levels with respect to PCOS. The serum levels of MMP-8 and the MMP-8/TIMP-1 ratio were significantly higher in women with PCOS, regardless of the presence of gingivitis, while there were no differences in TIMP-1 levels. A positive correlation was indicated between probing depth, bleeding on probing, plaque index and salivary or serum MMP-8 levels or the MMP-8/TIMP-1 ratio in the case of PCOS, while a negative correlation for TIMP-1 was found in systemically healthy women.	The increase in MMP-8 levels in saliva and serum seems to be more pronounced in women with PCOS and is potentiated in the presence of gingival inflammation. Alterations in the MPM/TIMP system triggered by local and systemic inflammation may be involved in the pathogenesis of PCOS or in the worsening of its clinical presentation.

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Rahiminejad *et al.*[10]	2015	Case-control	Iran	196	28.85 (18 – 45)	98 with PCOS 98 systemically healthy	29.1 28.6	The number of sites with loss of clinical insertion and with bleeding on probing were significantly higher in women with PCOS (p<0.05). However, no significant difference was observed in the rate of tooth loss among women with and without PCOS (p=0.384). In the PCOS group, 92 women (93.9%) were affected by mild periodontitis and 6 (6.1%) were diagnosed with moderate periodontitis. Mild periodontitis was observed in 97 women (99%) in the control group, while only one (1%) had moderate periodontitis. There was no significant difference between these groups in terms of periodontitis severity (p=0.118).	The prevalence of periodontal disease is higher in women with PCOS. This is related to the role of chronic systemic inflammation in the pathophysiology of both PCOS and periodontal diseases.
Akcali *et al.*[11]	2014	Case-control	Turkey	125	25.9	45 with PCOS and healthy periodontium 35 with PCOS and gingivitis 25 systemically and periodontally healthy 20 systemically healthy and with gingivitis	25.02 26.4 25.84 26.4	In women with PCOS, the salivary levels of *Porphyromonas gingivalis*, *Fusobacterium nucleatum, Streptococcus oralis* and *Tannerella forsythia* were higher than in systemically healthy women, particularly in the case of gingivitis. The levels of Aggregatibacter *actinomycetemcomitans* and *Treponema denticola* were similar between the of groups under study. The presence PCOS also increased serum antibody levels against *P. gingivalis, Prevotella intermedia* and *S. oralis,* when gingivitis was also present. Gingival inflammation correlated positively with the levels of the taxa studied in saliva, particularly in women with PCOS. The presence of *P. gingivalis* and *F. nucleatum* in saliva also showed a strong positive correlation with the corresponding serum antibody levels.	PCOS quantitatively affects the composition of the oral microbiota and the elevated systemic response to the selective members of this microbial community, playing a role in the resultin gingival inflammation and in periodontal health. The most consistent effect is exerted on Pg.
Porwal *et al.*[12]	2014	Case-control	India	126	24.2 (15 – 36)	41 with PCOS 45 with PCOS in treatment 40 systemically healthy	26.3 22.7 23.5	Women with recently diagnosed PCOS had increased bleeding on probing (BP), probing depth (PD), loss of clinical insertion level (LCIL), waist circumference (WC), hsCRP, and prevalence of periodontitis compared with control and PCOS groups in treatment (p≤0.05) In the partial correlation analysis after controlling for confounding factors, it was observed that BP and LCIL correlated positively and significantly with hsCRP (p=0.01 and p=0.005). The multivariate linear regression analysis revealed that BP and LCIL (dependent variable) (p=0.009/R2=0.05 and p=0.005/R2=0.07, respectively) had a significant association with hsCRP. In addition, when hsCRP is considered as a result, it also showed association with LCIL and WC (p=0.002/R2=0.07 and p=0.04/R2=0.106). The logistic regression analysis showed that the group with PCOS was 2.88 times more likely to suffer from moderate periodontitis (adjusted odds ratio 2.88, 95% confidence interval = 1.18 to 6.98).	Women with recently diagnosed PCOS have a higher prevalence and probability of periodontitis, with greater measurements of inflammation than those who receive medical treatment for PCOS and those who are systemically healthy.
Özcaka *et al.*[13]	2013	Case-control	Turkey	73	24.3 (15 – 42)	30 with PCOS and gingivitis 31 with PCOS and healthy periodontium 12 systemically and periodontally healthy	23.5 21 28.5	The multivariate analysis of the general linear model, adjusted for age or plaque index, showed that the two groups with PCOS had higher concentrations of IL-17A, IL-17F and IL-17A/F in serum and higher levels of IL- 17A and IL-17F in crevicular fluid and saliva, but lower IL-17E in serum than systemically healthy women. IL-17E levels were lower in women with PCOS and gingivitis who also had the highest FGS. Serum levels of IL-17A and IL-17F correlated positively with FGS and depth of periodontal probing (all r> 0.33, p<0.005). The IL-17E serum showed an inverse relationship and was also negatively correlated with IL-17A (r> -0.28, p<0.05).	IL-17 levels are altered in non-obese women with PCOS and may influence gingival inflammation.

Özçaka *et al.*[14]	2012	Case-control	Turkey	73	24. 3 (20 – 32)	30 with PCOS and gingivitis 31 with PCOS and healthy periodontium 12 systemically and periodontally healthy	23.5 21 28.5	The PCOS+gingivitis group showed significantly higher concentrations of IL-6 in crevicular fluid, saliva and serum than those in the PCOS+healthy periodontium group (p<0.0001). The two groups of PCOS exhibited significantly higher concentrations of TNF-α in saliva than the control group (p=0.024 and p=0.013, respectively). The FGS index was significantly higher in the PCOS + gingivitis group than in the PCOS+healthy periodontium group (p=0.030). The PCOS+gingivitis group showed a significantly higher insulin concentration than the PCOS + healthy periodontium and control groups (p=0.014 and p<0.0001, respectively). Serum levels of TNF-α, TNF-αRs and serum, crevicular fluid and salivary IL-6 were correlated with clinical periodontal measurements.	PCOS and gingival inflammation act synergistically on the proinflammatory cytokines IL-6 and TNF-α. Thus, PCOS may have an impact on gingival inflammation or *vice versa*.
Dursun *et al.*[15]	2011	Case-control	Turkey	52	23.5	25 with PCOS 27 systemically healthy	22.7 24.2	The average BMI was higher in the PCOS group (p=0.01). The PCOS group had a higher tT, a lower SHBG and higher levels of FAI (p<0.001 for all). The evaluation of the homeostasis model of IR and glucose-120 were higher in women with PCOS (p=0.003, p=0.009, respectively). The levels of TC and HDL-C were not different between the groups, while TG levels were higher among women with PCOS (p=0.02). In women with PCOS, the clinical periodontal parameters and the volume of crevicular fluid (subclinical sign of gingival inflammation) were higher than in the control group. There were no significant differences between the groups with respect to gingival index (p=0.14) and plaque index (p=0.86). MPO and NO levels were higher in the PCOS group (p=0.019 and p=0.02, respectively), while the difference in NO levels between the groups was not significant (p=0.71). There were significant positive correlations between clinical periodontal parameters, MPO and NO levels and serum parameters. Fasting insulin and glucose-120 levels correlated with the parameters of gingival inflammation: fasting gingival-insulin index (r=0.29, p=0.04), gingival-glucose-120 index (r=0.29, p=0.04), bleeding on probing-glucose-120 (r=0.36, p=0.009) and volume of crevicular fluid-glucose-120 (r=0.37, p=0.007). The volume of crevicular fluid was correlated with tT (r=0.28, p=0.04) and FAI (r=0.30, p=0.03).	In conclusion, susceptibility to periodontitis can increase significantly in patients with PCOS, and gingivitis is a common finding; the local/periodontal oxidation state seems to be affected in PCOS.

PCOS: Polycystic ovary syndrome. **NR:** Not reported. **MMP:** Matrix metalloproteinases. **TIMP:** Metalloproteinase inhibitor. **IL:** Interleukin. **TNF-α:** Tumor necrosis factor α; **NE:** Neutrophil elastase. **MPO:** Myeloperoxidase. **hsCRP:** Serological marker of inflammation (high sensitivity C-reactive protein). **HOMA:** Serological marker of insulin resistance (homeostatic model assessment). **8-OHdG:** 8-hydroxy-2'-deoxyguanosine. **MDA:** Malondialdehyde. **TAS:** total antioxidant status. **Pg:** *Porphyromona gingivalis*. **FGS:** Ferriman-Gallwey scale; **BMI:** Body mass index; tT: Total testosterone; SHBG; Sex hormone binding globulin. **FAI:** Free androgen index. **IR:** insulin resistance. **TC:** Total cholesterol. **HDL-C:** High density lipoprotein cholesterol.**TG:** Triglycerides. **NO:** Nitric oxide

Table 2. Diagnostic methods, confounding factors, and altered clinical parameters of the analyzed studies.

Author(s)	Diagnostic methods of periodontal state	Diagnostic methods of PCOS	Confounding factors evaluated and periodontal disease	Altered clinical parameters in patients with PCOS		
				Periodontal	Immunoinflammatory	Microbiological
Akcali *et al.*[6]	Oral examination, PD, BP, PI, X-rays, and serum and salivary levels of MMP-9, TIMP-1, MPO and NE with ELISA	Medical history, Rotterdam criteria, ultrasound and serum and salivary levels of MMP-9, TIMP-1, MPO and NE with ELISA	BMI>30 kg/m^2, hyperandrogenism, diabetes mellitus, hyperprolactemia, congenital adrenal hyperplasia, thyroid disorders, Cushing's syndrome, hypertension, hepatic or renal dysfunction, cardiovascular disease, oral contraceptives, steroid hormones, insulin-sensitizing medications, antibiotics or anti-inflammatory drugs and smoking	PD, BP and PI	Serum and salivary levels of MMP-9, ratio MMP-9/ TIMP-1, MPO and NE	NR
Deepti *et al.*[7]	Oral examination, PD, CAL, BP, GI and PI	Medical history, criteria of the Androgen Excess and PCOS Society, ultrasound, waist circumference, waist-hip ratio, MFG and serum levels of hsCRP and HOMA	Androgen-secreting tumors, congenital adrenal hyperplasia and thyroid dysfunction, nephrotic syndrome, chronic renal failure, cardiovascular disease, diabetes mellitus type 1 or type 2, cancer, smoking, alcohol consumption, systemic antibiotics, oral contraceptives, periapical pathology or other oral inflammatory conditions, and periodontal treatment.	PD, CIL, BP,	hsCRP and HOMA GI and PI	NR
Saglam *et al.*[8]	Oral examination, PD, CAL, BP, GI, PI, serum and salivary levels of 8-OHdG with ELISA and serum and salivary levels of photometry	Medical history, Rotterdam criteria, ultrasound, waist circumference, waist-hip ratio, serum and salivary levels of 8-OHdG with ELISA and serum and salivary levels of MDA and TAS with spectrophotometry	BMI>25 kg/m^2, pregnancy, smoking, Cushing's syndrome, non-classical congenital adrenal hyperplasia, hyperprolactinemia, thyroid dysfunction, androgen-secreting tumors, antibiotics, oral contraceptives, steroid hormones or associated preparations, medications for hypertension and insulin-sensitizing medications	PD, BP, GI and PI	8-OHdG in serum and saliva, MDA in serum	22 with PCOS and chronic periodontitis (PCOSCP)
Akcali *et al.*[9]	Oral examination, PD, BP, PI, MMP-8 in saliva with IFMA and TIMP-1 with ELISA	Medical history, Rotterdam criteria, ultrasound, serum levels of MMP-8 with IFMA and TIMP-1 with ELISA	BMI>30 kg/m^2, hyperandrogenism, diabetes mellitus, hyperprolactemia, congenital adrenal hyperplasia, thyroid disorders, Cushing's syndrome, hypertension, cerebrovascular disease, hepatic or renal dysfunction, oral contraceptives, steroid hormones and insulin-sensitizing medications	PD, BP and PI	MMP-8 and MMP-8/ TIMP-1 ratio	NR
Rahiminejad *et al.*[10]	Oral examination, PD, BP, PI, CAL and loss of teeth	Medical history, Rotterdam criteria, ultrasound, and serum levels	Pregnancy, smoking, malignant neoplasms, osteoporosis, antibiotics, periodontal treatment, BMI>25kg/m^2 and glucose intolerance	BP, CIL and PI	NR	NR
Akcali *et al.*[11]	Oral examination, PD, BP, PI, and qPCR for the quantification of salivary bacteria	Medical history, Rotterdam criteria, ultrasound, and serum antibody levels with ELISA	BMI>30 kg/m^2, hyperandrogenism, diabetes mellitus, hyperprolactemia, congenital adrenal hyperplasia, thyroid disorders, Cushing's syndrome, hypertension, cerebrovascular disease, hepatic or renal dysfunction, oral contraceptives, steroid hormones and insulin-sensitizing medications	PD, BP and PI	NR	Pg and Fn in saliva; Pi, Pg and So in serum
Porwal *et al.*[12]	Oral examination, PD, CAL, BP, PI and GI	Medical history, Rotterdam criteria, ultrasound, waist circumference, waist-hip ratio, hsCRP serum levels	BMI>30kg/m^2, thyroid disorders, and insulin-sensitizing hyperprolactinemia,androgen-secreting tumors, chronic inflammatory diseases, diabetes mellitus, cerebrovascular disease, cancer, smoking, alcohol consumption, antibiotics, periodontal treatment and aggressive periodontitis	PD, BP and CIL	hsCRP	NR
Özcaka *et al.*[13]	Oral examination, PD, CAL, BP, PI, X-rays, crevicular fluid samples, saliva samples, ELISA and IL-17	Medical history, Rotterdam criteria, ultrasound, serum levels and FGS	BMI>30 kg/m^2, hyperandrogenism, thyroid disorders, hyperprolactinemia, cerebrovascular disease, diabetes mellitus, hypertension, oral contraceptives, steroid hormones and insulin sensitizing medications	PD, BP and PI	IL-17A, IL-17F and IL-17A/F in serum; IL-17A and IL-17F in crevicular fluid and saliva	NR
Özçaka *et al.*[14]	Oral examination, PD, CAL, BP, PI, X-rays, crevicular fluid samples, saliva samples, ELISA, TNF-α, TNF-αR1, TNF-αR2 and IL-6	Medical history, Rotterdam criteria, ultrasound, serum levels and FGS	BMI>30 kg/m^2, androgen-secreting tumors, congenital adrenal hyperplasia, thyroid disorders, diabetes mellitus,hyperprolactinemia, Cushing's syndrome, hypertension, hepatic and renal dysfunction, oral contraceptives, steroid hormone, insulin-sensitizingmedications, alcohol consumption, and smoking	PD, BP and PI	IL-6 in crevicular fluid, saliva and serum; TNF-α in saliva	NR
Dursun *et al.*[15]	Oral examination, PD, CAL, GI, BP, PI, X-rays, crevicular fluid samples and MPO spectrophotometric assay	Medical history, Rotterdam criteria, ultrasound and serum levels	BMI>30kg/m^2, Cushing's syndrome, congenital adrenal hyperplasia, hyperprolactinemia, thyroid disorders, androgen-secreting tumors, smoking and oral contraceptives	PD, GI, BP and PI	MPO and NO	NR

PCOS: polycystic ovary syndrome.**PD:** probing depth. **CAL:** Clinical attachment level. **GI:** gingival index.**BP:** bleeding on probing. **PI:** plaque index. **NR:** Not reported. **MMP:** Matrix metalloproteinases; **TIMP:** Metalloproteinase inhibitor. **IL:** Interleukin. **TNF-α:** Tumor necrosis factor α. **NE:** Neutrophil elastase. **MPO:** Myeloperoxidase. **hsCRP:** Serological marker of inflammation (high sensitivity C-reactive protein). **HOMA:** Insulin resistance serological marker (homeostatic model assessment). **8-OHdG:** 8-hydroxy-2'-deoxyguanosine. **MDA:** Malondialdehyde. **TAS:** total antioxidant status. **Pg:** *Porphyromona gingivalis*. **Fn:** Fusobacterium nucleatum. **Pi:** Prevotella intermedia. **So:** *Streptococcus oralis*. **FGS:** Ferriman-Gallwey scale. **BMI:** Body mass index. **ELISA:** Enzyme-linked immunosorbent assay. **IFMA:** Analysis by immunofluorometric assay. **qPCR:** Quantitative polymerase chain reaction. **NO:** Nitric oxide; MFG: Modified scale of Ferriman-Gallwey.

RESULTS.

The selection process of the articles is shown in Figure 1. After that, ten articles were selected for a thorough review of their content.

The number of patients ranged from 48 to 196 in the included studies,[6-15] mean age ranged from 23.3 to 28.85 years, and the age range was between 15 and 45 years. The 10 selected studies were conducted in: Turkey,[6,8,9,11,13-15] India,[7,12] and Iran.[10] Nine studies[6,8-15] were cases-controls and one study[7] was a randomized controlled trial. Characteristics, results and conclusions of the included studies are shown in Table 1.

In nine studies,[6,8-15] PCOS was diagnosed according to the Rotterdam 2003 criteria, requiring having 2 out of 3 of the following factors: 1) clinical or biochemical HA, 2) chronic oligo-anovulation (OA), 3) polycystic ovaries (PO) (12 follicles in each ovary measuring 2-9mm in diameter and/or ovarian volume >10ml), excluding other etiologies.[1-3,29,30] In one study,[7] PCOS was diagnosed according to the criteria of the Androgen Excess and PCOS Society (AES-PCOS) published in 2006, which include the presence of HA (necessary condition) in combination with ovarian dysfunction (*i.e.* OA or ultrasound with PO), with the exclusion of other causes.[1,3,6,18] Diagnostic methods, confounding factors and altered clinical parameters of the analyzed studies are shown in Table 2.

All the studies reached 10 out of a maximum of 11 points on the CASP scale.

DISCUSSION.

All the analyzed studies showed a positive association between PCOS and periodontal diseases (gingivitis and/or periodontitis). Therefore, it is possible to assert that patients with PCOS have a higher risk of developing periodontal disease. However, there are factors in all the studies that may have influenced the reported results.

First, there is the complexity and heterogeneity of PCOS, with different definitions. Nevertheless, PCOS is one of the most prevalent endocrinopathies and the main cause of HA.[9-17,31] Second, the pathophysiology of PCOS is multifactorial,[1-3,32-35] involving a metabolic and endocrine component related to IR,[11-15,31-34] a polygenic component,[1-3,33-42] intrauterine environmental influences,[1,3,9,16,18] alterations in ovarian and adrenal steroidogenesis,[1,3,16,18,43] neuroendocrine dysfunction,[2,3,11,31,34] and environmental factors (dietary pattern, physical activity, smoking and stress).[3,16,18,29] None of these factors alone can explain the spectrum of alterations that characterize the syndrome.[1,3,14,16,29] Third, the diagnosis of PCOS is based on the Rotterdam criteria, consisting of a combination of clinical, biological and ultrasound evaluations.[1-3,29,30] Fourth, heterogeneity in the clinical expression of the condition makes diagnosis difficult, even more so with metabolic comorbidities and reproductive disorders that are frequently associated with this syndrome (obesity, type 2 diabetes, cardiovascular disease, venous thromboembolism, infertility, endometrial hyperplasia, sleep apnea, endometrial cancer, ovarian cancer, mood disorders, etc.).[1-3,9-18,44-46]

Given that the clinical presentation of PCOS varies between continents, it is difficult to establish a universal diagnosis using only European or North American guidelines.[16,47] Because of the common ultrasound finding of polycystic ovaries in healthy women, the inclusion of this sign in the diagnostic criteria of PCOS is still debatable.[16,48]

A relevant aspect of this review was the finding of a clinical trial[7] that showed that the integral treatment of periodontal disease could also contribute to the treatment of patients with PCOS by reducing the levels of proinflammatory mediators, reactive oxygen species and oxidative stress. Therefore, future evaluation of periodontal disease in patients with PCOS should explore in greater depth the effect of non-surgical periodontal therapy on the improvement of inflammatory parameters and the severity of PCOS.

It should also be noted that eight studies[6,9-15] included strict inclusion and exclusion criteria in order to restrict confounding factors. For example, women with a BMI>25 kg/m^2 were defined as obese and excluded from a study. In addition, Deepti *et al.*,[7] Saglam *et al.*,[8] and Porwal *et al.*,[12] measured the waist circumference and waist-hip ratio of the subjects. However, the selection of BMI as an indicator of obesity has its limitations because it often does not measure adiposity.[16,49] In addition, one study[50] reported that Asian young adult women (all studies included in the review were conducted in Asia) tend to have lower BMI and higher percentage of body fat than other ethnic groups, so it was suggested to combine the BMI and the analysis of biometric impedance for the detection of obesity and overweight in young Asian adults. Therefore, it is hypothesized that periodontal clinical parameters

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and the local and systemic inflammatory profile in the PCOS groups could be associated with higher levels of undiagnosed central adiposity, which lead to chronic low-grade inflammation.[16]

From a statistical perspective, emphasis should be placed on the use of an adequate sample size together with the extraction and collection of high quality data. In addition, all studies were observational and conducted only in three Asian countries. Longitudinal, multicenter, well-designed prospective clinical studies conducted in patients of different ethnicities are suggested.

This will make it possible to generalize these findings to the global population. Nevertheless, the conclusions of the studies included in the present scoping review should be interpreted with caution.

CONCLUSION.

PCOS shows a positive and significant association with the clinical and molecular parameters of periodontal diseases.

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