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Systematic Review

Bidirectional Relationship Between Periodontal Disease and Reproductive Disorders: Focus on Polycystic Ovary Syndrome

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Abstract

Background: Polycystic ovary syndrome (PCOS) is an endocrine disorder characterized by hyperandrogenism, irregular ovulation, and polycystic ovarian morphology. The severity of periodontal inflammation in PCOS may be linked to elevated levels of inflammatory mediators, like interleukins (IL-6, IL-17), and matrix metalloproteinase-8 (MMP-8), found in both serum and saliva samples. This systematic review aims to assess the presence, nature, and variations in salivary inflammatory biomarkers in individuals with PCOS and their potential connection to periodontal disease (PD). **Materials and Methods:** Selected databases were PubMed, Scopus, Google Scholar, and Web of Science. The search strategy included the following terms: "oral inflammatory biomarkers", "Salivary mediators," "metabolic indicators," "periodontal diseases," "periodontitis," "polycystic ovary syndrome," "PCOS," and "ovulatory dysfunction." Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used. **Results:** Several salivary inflammatory biomarkers are present in women with PCOS, including cytokines, C-reactive protein (CRP), reactive oxygen species (ROS), MMPs, and microbial diversity alterations. Additionally, the reviewed studies suggest a correlation between PCOS and PD, as patients with PCOS exhibit greater periodontal alterations compared to healthy women. The heightened periodontal response in PCOS appears to be associated with a systemic inflammatory state, probably increasing the susceptibility to PD. **Conclusions:** Salivary inflammatory biomarkers in PCOS patients are a useful diagnostic tool for evaluating the heightened risk of periodontal disease. Further research with stricter protocols is necessary to better define the diagnostic potential of these biomarkers for PCOS patients and determine their role in the early detection of periodontal disease.

Keywords: polycystic ovary syndrome; periodontal disease; gender dentistry; inflammatory biomarkers; salivary biomarkers

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1. Introduction

Polycystic ovary syndrome (PCOS) is a common metabolic and endocrine disorder affecting women of childbearing age. It is characterized by oligo/anovulation, hyperandrogenism, and polycystic ovarian morphology [1]. Depending on diagnostic criteria such as

the Rotterdam criteria, which require at least two of these features, its global prevalence ranges between 5% and 20% [2,3]. Nevertheless, 70% of women remain undiagnosed. PCOS is often associated with insulin resistance, diabetes, cardiovascular disease, obesity, and infertility, affecting 8–13% of women worldwide. Recent studies suggest that it is a systemic disorder similar to periodontal disease, as both are linked to systemic inflammation and hormonal imbalances [1]. Periodontal disease (PD), including gingivitis and periodontitis, comprises inflammatory conditions affecting the supporting structures of teeth such as gingiva, bone, and periodontal ligament. If untreated, PD can lead to tooth loss and contribute to systemic inflammation. Severe periodontitis affects about 10–15% of adults in industrialized countries, especially those aged 50–60 [4]. Studies show that periodontal treatment reduces systemic inflammatory markers, supporting the role of periodontitis alongside chronic conditions like diabetes and cardiovascular diseases in systemic inflammation [5–7]. Women with PCOS are more susceptible to gingivitis and periodontal disease, with greater severity reported in this group, highlighting the need for regular periodontal care [8–12]. Clinical and laboratory data suggest PCOS patients are more prone to periodontitis than unaffected individuals [13,14]. A possible bidirectional relationship exists between PCOS and PD, though its exact nature is unclear [15]. Women with PCOS have a 28% increased risk of PD, and those with PD have a 46% higher risk of PCOS [12]. This link may involve oxidative stress, hormonal imbalances, and altered bacterial flora, as PCOS-related metabolic and hormonal disorders increase susceptibility to PD [15–20]. PCOS may influence periodontal inflammation via inflammatory mediators such as interleukins (IL-6, IL-17 induced by IL-36), CRP, TN, and MMP-8 found in serum and saliva [21–23]. Altered MMP levels correlate with ovulatory dysfunction in PCOS, affecting the follicular development stages [24,25]. However, the exact role of sex hormones in proinflammatory cytokine release is still unknown. Although some reviews exist, conclusive evidence on the PCOS–PD association is lacking [15]. Moreover, preventive aspects of PCOS in this context have not been thoroughly researched, and PCOS is not yet recognized as a key to early diagnosis in the literature. Exploring the potential bidirectional relationship between PCOS and PD could open new insights into early PCOS diagnosis, with periodontitis serving as a possible clinical marker. If confirmed as a risk factor, patients with periodontal disease could be monitored for endocrine-metabolic symptoms, and dentists could assist in early detection by referring patients to specialists. Early screening would clarify whether periodontitis is a predictive factor for PCOS, as both share low-grade chronic inflammation [15–18]. Investigating shared inflammatory biomarkers could help define this connection. If PCOS contributes to periodontal disease progression through hormonal and metabolic changes, more intensive periodontal care may be required. Early PCOS diagnosis could support new prevention strategies and screening tools, improving management and reducing metabolic, reproductive, and cardiovascular risks [9–13]. This systematic review aims to assess the extent of the literature concerning the type, presence, and differences in salivary biomarkers of inflammation in patients suffering from PCOS and the risk of periodontal disease, with the ultimate goal of protecting women's health by implementing the knowledge of oral medicine and gender dentistry, in line with Goals 3 (health and well-being) and 5 (gender equality) of the UN 2030 Agenda for Sustainable Development [26].

2. Materials and Methods

The research question was built according to the PICOS criteria, [27] defining the following parameters:

- Population: reproductive age women
- Intervention: key to diagnosing PCOS via inflammatory biomarkers in the saliva and serum sample
- Comparison: biomarker levels in PCOS patients in the presence or absence of periodontal disease
- Outcomes: association between Periodontal Disease and PCOS
- Study: type, presence, and differences in salivary biomarkers of inflammation in patients suffering from PCOS

2.1. Search Strategy

Four different academic search engines were used to develop a search strategy, including the following: Pubmed (https://pubmed.ncbi.nlm.nih.gov/ accessed on 29 September 2024), Google Scholar (https://scholar.google.com, accessed on 29 September 2024), Scopus (https://www.scopus.com/search/form.uri?display=basic&zone=header&origin=searchbasic#basic, accessed on 29 September 2024), and Web of Science (https://www.google.com/url?sa=t&source=web&rct=j&opi=89978449&url=https://www.webofscience.com/wos&ved=2ahUKEwisnpmblLOIAxUMgP0HHUR7OcAQFnoECBMQAQ&usg=AOVaw1M2P0aoNpNftfJkVHUyGuM, accessed on 29 September 2024), to identify articles on the topic, published from 1 January 2014 to 1 January 2024 in the last 10 years. Authors adhered to the PRISMA for systematic Review PRISMA Flow Diagram (https://www.prisma-statement.org/prisma-2020-flow-diagram, accessed on 29 September 2024).

We adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [28,29]. The protocol of the systematic review was registered in PROSPERO 2025, the International Prospective Register of Systematic Reviews, under the number CRD420250542393.

2.2. Search Terms

This search used controlled vocabulary in both English and Italian and the Boolean operators AND and OR to increase the precision of the search. The keywords were combined using Boolean operators (AND, OR) to link the different relevant topics.

An electronic search was executed using the following keywords:

"Oral inflammatory biomarkers" OR "salivary mediators" OR "Metabolic indicators" AND "Periodontal diseases" OR "Periodontitis" AND "Polycystic ovary syndrome" AND "PCOS" OR "Ovulatory Dysfunction".

In PubMed, the following MeSH terms were also applied to increase the accuracy of the search: "Periodontal diseases", "Periodontitis", and "Polycystic ovary syndrome".

See Table 1 for the adapted search strategies used for each included database.

Table 1. Table definition—search strategy for systematic review.

Database	Search Terms	MeSH Terms
PubMed	oral inflammatory biomarkers OR salivary mediators OR Metabolic indicators AND Periodontal diseases OR Periodontitis AND Polycystic ovary syndrome AND PCOS OR Ovulatory Dysfunction	Periodontal diseases Periodontitis Polycystic ovary syndrome

Table 1. *Cont.*

Database	Search Terms	MeSH Terms
Scopus	ALL (oral AND inflammatory AND biomarkers OR salivary AND mediators OR metabolic AND indicators AND periodontal AND diseases OR periodontitis AND polycystic AND ovary AND syndrome AND pcos OR ovulatory AND dysfunction)	
Web of Science	ALL = (oral inflammatory biomarkers) OR ALL = (salivary mediators) OR ALL = (Metabolic indicators) AND ALL = (Periodontal diseases) OR ALL = (Periodontitis) AND ALL = (Polycystic ovary syndrome) AND ALL = (PCOS) OR ALL = (Ovulatory Dysfunction)	
Google Scholar	oral inflammatory biomarkers OR salivary mediators OR Metabolic indicators AND Periodontal diseases OR Periodontitis AND Polycystic ovary syndrome AND PCOS OR Ovulatory Dysfunction	

2.3. Inclusion and Exclusion Criteria

Articles were incorporated into the review if they satisfied the following inclusion criteria: human studies (RCTs, observational studies, cross-sectional studies) evaluating the presence and differences in salivary biomarkers of inflammation in patients affected by PCOS. Studies analyzing saliva samples with or without serum. Articles were excluded if they met the following exclusion criteria: case reports and case series with a small sample size (<30 participants); no peer review; abstracts only; conference procedure; book chapters; literature reviews; systematic, meta-analysis, and scoping review. Only original studies presenting primary data were included. Case reports and small case series were initially considered but ultimately excluded, as they do not provide sufficient evidence to support the objectives of this systematic review. Only studies with larger sample sizes and robust study designs were included, ensuring the reliability and comparability of the results. Reviews and meta-analyses were excluded to avoid duplication of data and enable direct assessment of the quality of individual studies, to ensure the inclusion of scientifically verified primary data, since the data from these studies cannot be directly compared with that from original studies. However, reviews and meta-analyses remain essential for interpreting the results and are referenced in the discussion section.

2.4. Study Selection

The preliminary literature search was conducted by two independent investigators (F.A. and D.G.). Subsequently, the selected titles were reassessed by the researchers, with any studies not aligning with the predefined eligibility and inclusion criteria being excluded. The remaining articles were then subjected to a rigorous full-text review to assess their relevance. In instances of disagreement between authors following independent evaluations, consensus was reached through re-examination and discussion. In instances where data inconsistencies were identified, the authors of the respective studies were contacted via email for further clarification, when possible. Cohen's Kappa coefficient (κ) was calculated to assess inter-rater reliability during the study selection process. The final set of articles was then subjected to qualitative synthesis. Duplicates among studies identified across the different databases were removed through manual review to verify any remaining duplicate entries. See Figure 1, the PRISMA flow diagram, for a clear indication of the number of duplicates removed during the initial screening.

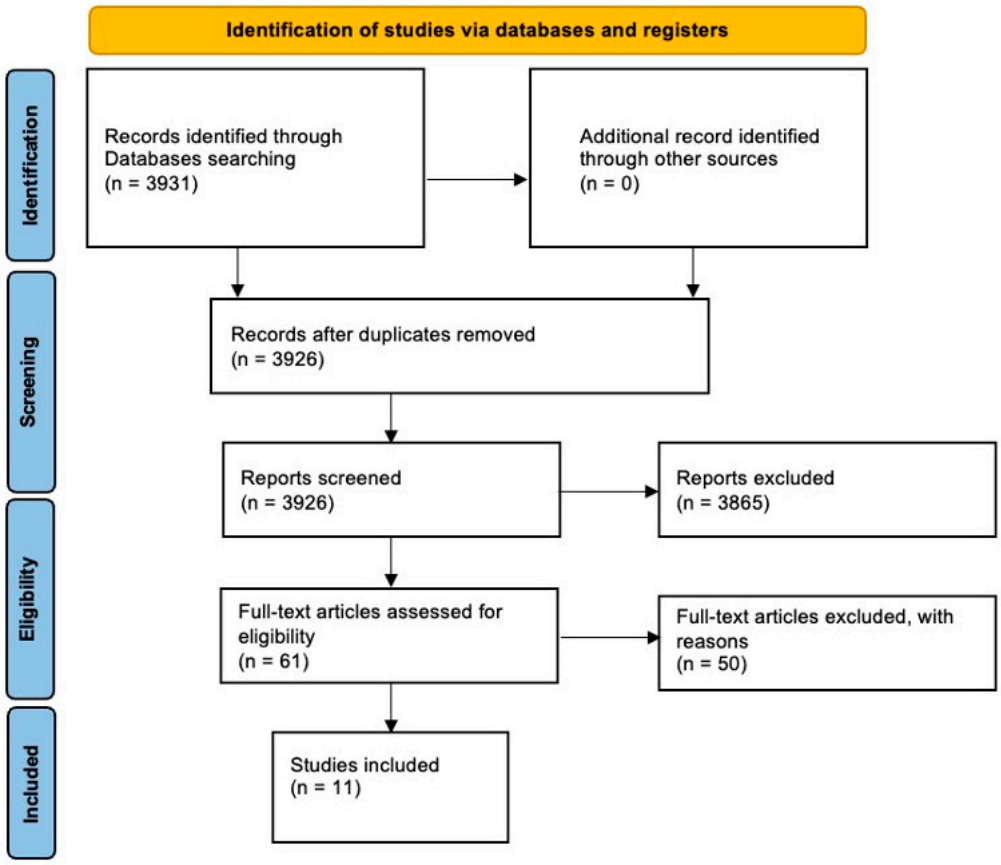

Figure 1. PRISMA flowchart illustrating the experimental study search and selection process.

2.5. Data Collection

A table was prepared to facilitate the analysis of the 11 selected articles. The analysis included the following study features: (a) author identifiers and year, (b) title, (c) periodontal index, (d) salivary index, (e) methodological design of the study, (f) meaning (Table 2). In a summary table, data were extracted, including (a) authors and (b) results (Table 3).

Table 2. Selected studies.

Authors Year	Type of Study	Periodontal Indices	Other Indices	Sample	Group	Aim
Wendland et al. (2021) [20]	Case–control	PI GI PPD BOP%	TT salivar IL-6 IL-1β TNF-α	Saliva (Salivette) serum	PCOS:31 HC:28	The influence of hormonal and metabolic imbalances on gingival health and salivary concentrations of TNF-α, IL-1β, and IL-6 in adolescent girls with PCOS.
Akcali et al. (2014) [23]	Case–control	PI BOP PPD	MMP-8 TIMP-1	Saliva serum	PCOS + HP:45 PCOS + GG:35 HC + GG:20 HC + HP:25	Relationship between MMP-8 and TIMP-1 in saliva and serum samples in female patients with PCOS.
Maboudi et al. (2023) [30]	Case–control	GI BOP PI	MMP-9	saliva	PCOS + GG:26 PCOS:26 HC:26	Relationship between the gingival inflammation indices and MMP-9 in saliva sample in patients with PCOS.
HU et al. (2024) [31]	Case–control	FMPS BOP PD CAL	IL-6 IL-17 MMP-8	Saliva serum	HC:15 PCOS:28 PDD:5 PCOS + PDD:12	Relationship between the interaction and disease progression of cytokine levels, sex hormone levels and metabolism-related indicators with PCOS and periodontitis.

Table 2. *Cont.*

Authors Year	Type of Study	Periodontal Indices	Other Indices	Sample	Group	Aim
Abbas et al. (2014) [32]	Case–control	PI GI	PCR	Saliva (Salimetric ELISA)	PCOS:19 HC:26	Salivary CRP levels, gingival index (GI), and periodontal pocket depth (PPD) indices along with the correlation between these indices and salivary CRP levels.
Hilaloğlu et al. (2022) [33]	Case–control	DMFT	s.mutans, (primer forward: 5′-CCGGTGACGGCAAG CTAA-3′, reverse; 5′ TCATGGAGGCG AGTTGCA-3′) salivary Ph	saliva	PCOSID (+): 25 PCOSID (−):25 ControlID (+):25 ControlID (−):25	The bacteria responsible for dental caries in young adults diagnosed with PCOS during the early reproductive phase, when metabolic disorders are less pronounced.
Ghosh et al. (2023) [34]	Case–control	NA	16S rDNA (primer 27 F primer AGAGTTTGAT CMTGGCTCAG e 1492 R primer GGTTACCTTGT-TACGACTT)	saliva	PCOS:100 HC:110	The association of salivary microbial diversity between PCOS and non-PCOS individuals.
Lindheim et al. (2016) [16]	Case–control	NA	rRNA 16S F27 (AGAGTTGATCCTG-GCTCAG) e R357 (CTGCTGCCTYCCGTA)	saliva	PCOS:24 HC:20	The salivary microbiome in individuals with PCOS and its association with parameters related to the condition.
Saglam et al. (2017) [35]	Case–control	PPD BOP GI PI CAL	MDA 8-OHdG TAS	Serum saliva	PCOSHP:22 PCOSCP:22 CP:22 HPCP:22	Saliva and serum levels of 8-hydroxy-2ó-deoxyguanosine (8-OHdG), malondialdehyde (MDA) and total antioxidant status (TAS) in women with chronic periodontitis (CP) and PCOS compared to healthy women.
Hu et al. (2023) [36]	Case–control	FMPS BOP CAL PPD	IL-6 IL-17 MMP-8	Saliva serum	PCOS:66 HC:22	Hormonal, metabolic, and inflammatory profiles in PCOS and non-PCOS individuals with various periodontal conditions analyzed using Raman spectroscopy on serum and saliva samples.
Varghese et al. (2019) [37]	Case–control	BOP PPD CAL	IL-6	saliva	PCOS + PDD:42 PCOS:42	IL-6 levels in the saliva of PCOS patients with and without chronic periodontitis

Alu I: restriction enzyme digestion. HC: healthy control women. TT: total testosterone. PI: plaque index. DMFT: Decayed, Missing, Filled Teeth. FAI: free androgen index. GI: gingival index. GLP-1: glucagonlike peptide-1. BOP%: bleeding on probing score. BMI: body mass index. PD: probing depth. TT: total testosterone. TNF-α: tumor necrosis factor α; IL-6: interleukin 6; IL-1β: interleukin 1β. N.A.: not applicable. hsCRP: high-sensitivity C-reactive protein. HOMA: Homeostatic Model Assessment. MI: Myo-inositol. OHI: oral hygiene instructions. MDA: malondialdehyde. MPO: myeloperoxidase. NA: not applicable. NE: neutrophil elastase. TIMP: tissue inhibitors of MMP-1. TAS: total antioxidant status. 5-HT: 5-hydroxytryptamine. WHR: waist–hip ratio. PISA: Periodontal inflammatory surface area. PESA: Periodontal Epithelial surface area calculation. 8-OHdG: 8-hydroxy-2′-deoxyguanosine. CP: Chronic periodontitis.

Table 3. Summary results of the articles.

Authors Year	Results
Wendland et al. (2021) [20]	TT salivar significantly higher in the PCOS group ($p = 0.0007$). Test group and control group do not differ significantly with periodontal parameters. Test group higher levels of salivary cytokines ($p < 0.0001$). GI and BOP% positively correlated with PI in both groups (rs ≥ 0.60, $p < 0.001$), and negatively correlated with salivary testosterone level in the PCOS group (rs = −0.44, $p = 0.0138$ and rs = −0.37, $p = 0.0424$, respectively). TT salivar positively correlated with TNF-α in the control group (rs = 0.41, $p = 0.0321$).
Akali et al. (2014) [23]	Salivary MMP-8 and the MMP-8/TIMP-1 significantly elevated in women with PCOS, with GG and HCHP. No major changes in salivary TIMP-1 levels with regard to PCOS. PD, BOP, PPD positive correlation with salivary or serum MMP-8 levels or MMP-8/TIMP-1 ratio in PCOS groups. negative correlation for TIMP-1 in systemically HC

Table 3. *Cont.*

Authors Year	Results
Maboudi et al. (2023) [30]	PCOS + PDD women (388/37 ± 75.05) higher salivary MMP-9 levels than HC (166/25 ± 35/43). PCOS women without PDD (233.00 ± 47.76) higher levels of salivary MMP-9 than HC ($p < 0.05$).
HU et al. (2024) [31]	Salivary MMP-8 significantly higher in PCOS but without periodontitis group (Group B) than in non-PCOS and non-periodontitis group (Group A) ($p < 0.05$). Salivary MMP-8 significantly higher in disease group (Group D) than in Group B ($p < 0.05$), Salivary IL-6 and MMP-8 differed significantly between Group A and B and the periodontitis group (Group C) and Group D ($p < 0.05$). Spearman correlation analysis: positive correlations of LH and LH/FSH with PD ($p < 0.05$) PD, BOP, and FMPS positively correlated with salivary MMP-8 levels ($p < 0.01$).
Abbas et al (2014) [32]	GI, PI in PCOS (Group Test): (2.5 ± 0.4, and 2.4 ± 0.4) GI, PI in HC (Group Control): (1.4 ± 0.3, and 1.2 ± 0.2) Salivary CRP in Test Group: (226.8 ± 34 SD) Salivary CRP in Control group: (173.8 ± 22.5). Positive correlation between GI and salivary PCR (R = 0.8) Positive correlation between PI and salivary PCR (R = 0.7)
Hilaloğlu et al. (2022) [33]	PCOSID(+) group: the highest DMFT index, *S. mutans* values ControlID(−) group: the lowest DMFT index, *S. mutans* values PCOSID(+) group: lowest saliva pH value
Ghosh et al. (2023) [34]	DNA PCOS fragments after being digested with Alu I: length 200–225 bp DNA NON-PCOS fragments after being digested with Alu I: length 100 bp and 200 bp
Lindheim et al. (2016) [16]	Saliva microbiome: phylum Bacteroidetes (±45%), Firmicutes (26%), Proteobacteria, Fusobacteria, Actinobacteria, and TM7 < 10%. Prevotella single most abundant genus (±31%), Streptococcus (11%), other genera contributing (<10%). Saliva samples from PCOS patients showed a significant reduction in the relative abundance of bacteria from the Actinobacteria phylum (FDR $p = 0.024$). However, no significant differences were found between the test group and controls at the class, order, family, genus or OTU level. In addition, the phylogenetic diversity and the number of OTUs observed were comparable between PCOS patients and healthy controls.
Saglam et al. (2017) [35]	Salivary 8-OHdG in PCOSCP + SHCP statistically higher than 8-OHdG in PCOSPH and SPH ($p < 0.05$). No statistical differences in saliva levels of MDA and TAS between the PCOSCP, SHCP, and PCOSPH groups ($p > 0.05$). Salivary MDA in HPCP is statistically significantly lower than MDA in the other groups ($p < 0.05$). No statistical difference in the salivary MDA levels between the PCOSCP, CP, and PCOSPH groups ($p > 0.05$). Salivary TAS higher ($p < 0.05$) in SPH. no statistical differences between the SHCP and PCOSPH groups for saliva parameters.

Table 3. *Cont.*

Authors Year	Results
Hu et al. (2023) [36]	PD value higher in PCOS group than in non-PCOS group salivary MMP-8 level significantly higher in periodontitis group than that in non-periodontitis group ($p < 0.001$). **The mean salivary Raman spectral intensity—proteins in the H-Perio group:** positively correlated with LH/FSH (value = 0.314, $p < 0.05$) and negatively correlated with the level of IL-17A in saliva (value = −0.373, $p < 0.05$). **The mean salivary Raman spectral intensity—lipids:** positively correlated with LH/FSH (value = 0.357, $p < 0.05$) in H-Perio group **The mean salivary Raman intensity of the attributed proteins:** (value = 0.450, $p < 0.01$) in PC-Perio groups. negatively correlated with IL-17A (value = −0.374, $p < 0.05$) and BOP (value = −0.363, $p < 0.05$) in H-Perio group. The mean salivary Raman spectral intensities of the attributed lipids: negatively correlated with the levels of MMP-8 (value = −0.900, $p < 0.05$) in the PC-H group
Varghese et al. (2019) [37]	*IL-6* in PCOS + PDD (Group A): 102.59 ± 18.2 with a significant increase ($p < 0.001$). *IL-6* in PCOS (Group B): 51.3 ± 25.3. *PD* in Group A: 4.23 ± 0.134 Group B: 1.30 ± 0.06. *BOP%* in Group A: 1.40 ± 0.40 Group B: 0.91 ± 0.18. *CAL* in Group A: 4.87 ± 0.124 Group B: 1.30 ± 0.06.

2.6. Quality Assessment of Systematic Reviews and Risk of Bias

This systematic review employed the tool outlined to evaluate both the quality of the review and the potential risk of bias: to assess the methodological quality of the case–control studies included in this review, the "Quality Assessment Tool for Case–Control Studies" developed by the National Heart, Lung, and Blood Institute (NHLBI), U.S. Department of Health and Human Services, was used [38]; this tool is specifically designed for observational studies with a case–control design. Each study was independently reviewed by two authors (F.G. and D.G.), with disagreements resolved by a third reviewer (S.B.).

3. Results

A schematic representation of the selection process is provided by the PRISMA diagram (Figure 1). Through the use of digital searches in four different databases (PubMed, Scopus, Google Scholar, and Web of Science), 3931 studies were identified. Among the identified items, 174 studies were spotted via the PubMed scientific research platform, 24 through a similar search in the Scopus database, 372 from Google Scholar, and finally 3361 from the Web of Science platform, all prior to the screening process. These studies were subjected to a preliminary analysis. Inclusion and exclusion criteria were applied, with no studies included from Pubmed, 1 from Scopus, 7 from Google Scholar, and 3 from Web of Science. The inter-rater agreement was evaluated using Cohen's Kappa coefficient, indicating almost whole agreement between reviewers both in the preliminary screening phase ($\kappa = 0.92$) and in the full-text eligibility assessment ($\kappa = 0.84$). Finally, 11 studies were chosen and considered eligible (Table 2, Refs. [16,20,23,30–37]), because they satisfied the selection criteria. The 11 included studies selected a population suffering from PCOS with or without periodontal disease, whose clinical picture was characterized by the analysis of different salivary values as biomarkers of inflammation associated with periodontal parameters to assess the possible risk of association with periodontal disease. The study population sample was recruited from specialized gynecological centers, selecting women diagnosed with PCOS according to the Rotterdam criteria. Subsequently, salivary sam-

ples from each participant were analyzed, and they underwent a dental examination for periodontal assessment.

3.1. Periodontal Clinical Parameters Studied

A complete clinical evaluation of the periodontium was conducted in all studies [13,16–21], including an examination to determine the periodontal probing depth (PPD), plaque index (PI), and bleeding on probing (BOP). Clinical attachment loss (CAL) was reported in 4 studies [32,35–37], and the gingival index (GI) was reported in 4 studies [20,30,32,35]. Two studies [31,33] reported the tooth loss rate between patients with and without PCOS.

3.2. Clinical and Immunoinflammatory Results

3.2.1. Salivary TT, IL-6, IL-1β, TNF-α as Clinical Parameters, and PI, GI, PD, and BOP% as Periodontal Indices

Wendland et al. observed that young women with PCOS who maintain good oral hygiene showed no significant differences in gingival indices (PI, BOP%, PD) compared to healthy controls ($p > 0.05$) [20]. However, PCOS participants exhibited significantly elevated salivary proinflammatory cytokines (TNF-α, IL-6, IL-1β; $p < 0.0001$) and testosterone ($p = 0.0007$), indicating systemic low-grade inflammation. Positive correlations were observed between gingival inflammation and plaque index in both groups, while gingival index negatively correlated with salivary testosterone in PCOS subjects. Additionally, testosterone correlated positively with TNF-α in controls, and TNF-α correlated with IL-6. The study highlights a possible bidirectional relationship between PCOS and periodontal disease but lacks critical evaluation of clinical relevance or causality, focusing primarily on data description without discussing diagnostic implications.

3.2.2. Salivary and Serum Levels of MMP-8 and TIMP-1 and PI, BOP, and PD as Clinical Parameters

Akali et al. found that women with PCOS exhibited increased serum and salivary MMP-8 levels, especially in gingival inflammation. In women with PCOS, salivary MMP-8 concentrations were notably higher in cases of gingivitis compared to those with healthy periodontal status [23]. Elevated MMP-8 and the MMP-8/TIMP-1 ratio in saliva and serum appeared to be more pronounced in women with PCOS and were exacerbated by gingival inflammation. MMP-8 levels and the MMP-8/TIMP-1 ratio positively correlated with PD, BOP%, and PI in PCOS patients. Conversely, salivary TIMP-1 levels negatively correlated with these periodontal measurements in healthy individuals, while the MMP-8/TIMP-1 ratio showed a positive correlation. The article does not critically explore the bidirectional relationship between PCOS and periodontal disease; rather, it suggests that alterations in the salivary microbiome in patients with PCOS might create a favorable environment for periodontal disease, but without providing causal evidence.

3.2.3. Serum Levels of MMP-9 and GI, BOP, and PI as Periodontal Indices

Maboudi et al. reported that higher values of GI, BOP, and PI were present in patients affected by PCOS with gingivitis than in patients affected by PCOS without gingivitis and healthy women in the control group ($p < 0.05$) [30]. The mean salivary matrix metalloproteinase-9 (MMP-9) levels were significantly higher in PCOS patients ($388/37 \pm 75.05$) than in the control group ($166/25 \pm 35/43$). Patients affected by PCOS with good gingival health (233.00 ± 47.76) presented significantly higher levels of salivary MMP-9 than the control group ($p < 0.05$). The study suggests that alterations in the salivary microbiome in PCOS patients may create a favorable environment for periodontal disease, but it does not critically assess the bidirectional relationship between PCOS and periodontal disease or provide causal evidence.

3.2.4. IL-6, IL-17, TNF-α, MMP-8 Saliva and Serum Sample and FMPS, BOP, PD, CAL as Periodontal Indices

Hu et al. examined hormonal, metabolic, and inflammatory markers in individuals with and without PCOS and different periodontal statuses using Raman spectroscopy on serum and saliva samples [36]. They found higher probing depth (PD) and elevated salivary MMP-8 levels in periodontitis patients, especially those with PCOS. Significant correlations were observed between Raman intensities related to proteins and lipids and inflammatory markers such as IL-17A and MMP-8 across different groups. The cross-sectional design limits conclusions on causality. While associations between biomarkers and periodontal/PCOS conditions are evident, it remains unclear whether these biomarkers are causes or consequences of disease. Hu et al. (2024) investigated salivary inflammatory biomarkers (particularly MMP-8 and IL-6) in women with and without PCOS across different periodontal health statuses [31]. They found significantly elevated salivary MMP-8 levels in the periodontitis groups, especially in patients with both PCOS and periodontitis ($p < 0.05$). Clinical periodontal parameters (PD, BOP, CAL) were also worse in these groups and showed a progressive increase over a six-month follow-up period. Correlation analyses revealed a positive association between salivary MMP-8 levels and periodontal indices ($p < 0.01$), as well as between IL-6 and systemic inflammation. The study suggests a potential predictive role of salivary MMP-8 in periodontal progression in PCOS patients; it does not establish causality, focusing instead on statistically significant associations among inflammatory markers, sex hormones, and periodontal health.

3.2.5. Salivary PCR and PI, GI as Clinical Parameters

Women with PCOS have elevated salivary CRP levels and increased gingival inflammation, according to Abbas et al. [32]. They reported that women with PCOS exhibited significantly higher gingival and plaque indices compared to healthy controls (2.5 ± 0.4 vs. 1.4 ± 0.3 for GI; 2.4 ± 0.4 vs. 1.2 ± 0.2 for PI; $p < 0.05$). Salivary C-reactive protein (CRP) levels were also elevated in the PCOS group (226.8 ± 34 mg/L vs. 173.8 ± 22.5 mg/L), indicating increased local inflammation. Strong positive correlations were found between salivary CRP levels and both the gingival index ($R = 0.8$) and plaque index ($R = 0.7$), suggesting that salivary CRP may reflect periodontal inflammatory status in PCOS patients. However, the study does not explore causality or longitudinal outcomes, and its findings are based on cross-sectional associations.

3.2.6. Serum MDA,8-OHdG, Salivary TAS, and PPD, BOP, GI, PI, and CAL as Clinical Values

Saglam et al. examined oxidative stress markers in saliva among women with PCOS and/or chronic periodontitis (CP) [35]. Salivary 8-OHdG levels were significantly higher in both CP groups compared to periodontally healthy groups ($p < 0.05$), while levels were similar between healthy controls and PCOS patients without periodontitis. Salivary malondialdehyde (MDA) levels were elevated in individuals with periodontitis, showing a significant correlation with clinical periodontal parameters; however, no significant differences in MDA levels were found between PCOS + CP, CP, and PCOSPH groups ($p > 0.05$). Salivary total antioxidant status (TAS) was significantly higher in healthy controls ($p < 0.05$), whereas no significant differences in TAS were found between CP and PCOS groups. No correlation was observed between PI or BOP and serum MDA or salivary TAS, nor between CAL and oxidative stress biomarkers. These findings suggest that periodontal status more strongly influences salivary oxidative stress markers than PCOS itself, with no evidence of additive or synergistic effects in PCOS patients.

3.2.7. IL-6 Saliva Sample and BOP, PD, CAL as Periodontal Parameters

Varghese et al. investigated salivary IL-6 levels and periodontal parameters in women with PCOS and periodontitis (Group A) compared to systemically and periodontally healthy controls (Group B) [37]. PCOS patients with periodontitis exhibited significantly elevated periodontal inflammation: mean BOP was 1.40 ± 0.40 vs. 0.91 ± 0.18 ($p < 0.001$), PD was 4.23 ± 0.13 mm vs. 1.30 ± 0.06 mm ($p < 0.001$), and CAL was 4.87 ± 0.12 mm vs. 1.30 ± 0.06 mm ($p < 0.001$). Salivary IL-6 concentrations were nearly double in Group A (102.6 ± 18.2 pg/mL) compared to controls (51.3 ± 25.3 pg/mL), with a significant difference ($p < 0.001$). These findings support a strong association between PCOS, periodontal inflammation, and elevated proinflammatory cytokines. The study did not assess causality or control for confounding factors, limiting conclusions about the directionality of the relationship.

3.3. Microbiological Results; Alterations in the Salivary Microbiome and Their Impact on Inflammation and Implications in PCOS and Periodontal Disease

3.3.1. *S. Mutans*, Saliva ph, and DMFT Indices

Hilaloğlu et al. evaluated salivary S. *mutans* levels, pH, and DMFT index in women with PCOS. While salivary flow rates did not differ significantly between groups ($p > 0.05$), the PCOSID (+) group showed the highest levels of *S. mutans* and DMFT scores, along with the lowest salivary pH. In this group, *S. mutans* levels were strongly correlated with DMFT scores ($p < 0.05$), suggesting a link between PCOS-related salivary microbiota changes and caries risk, though no association was found with periodontal disease [34]. Salivary pH did not correlate with DMFT or *S. mutans* levels across groups. These findings suggest altered salivary ecology in PCOS, with implications primarily for caries susceptibility rather than periodontal status.

3.3.2. Microbial Diversity 16S rDNA and 16S rRNA Amplicon Sequences

Ghosh et al. and Lindheim et al. used salivary microbial diversity as an additional potential and economizing biomarker for PCOS [16,34].

After treatment with Alu I, the graphical representation of fragment lengths in PCOS and non-PCOS samples reveals distinct patterns. In PCOS samples, the restriction enzyme specifically cut fragments ranging from 200 to 225 bp, whereas in women without polycystic ovary syndrome, no distinct DNA fragment pattern was observed, with fragment lengths varying between 200 and 225 bp. Approximately 70% of the samples exhibited a consistent fragment length pattern (100 bp and 200 bp), suggesting a significant trend. This finding indicates the possible presence of a specific bacterial group in the oral cavity of women with PCOS. Lindheim et al. demonstrated how the salivary microbiome was predominantly composed of bacteria from the phylum *Bacteroidetes* (median relative abundance: 45%) and *Firmicutes* (26%), while bacteria from the phyla *Proteobacteria, Fusobacteria, Actinobacteria,* and *TM7* (*Candidatus Saccharibacteria*) each accounted for less than 10% of the total bacterial composition. At the genus level, Prevotella was the most dominant genus with a median relative abundance of 31%, followed by Streptococcus with 11%, while all other genera individually accounted for less than 10% of the total bacterial population. In saliva samples from PCOS patients, a significant decrease in the relative abundance of bacteria belonging to the phylum Actinobacteria was detected (FDR $p = 0.024$) [16]. However, no significant differences were found between patients and controls at the class, order, family, genus, or OTU levels.

The genus abundance curve followed a log distribution, with the ten most frequent genera together accounting for 86% of all identified bacteria. Therefore, the current data primarily support a preliminary association, without sufficient evidence for a causal relationship.

3.4. Evaluation of the Quality of Included Studies

Quality assessment revealed that all studies [16,23,30–32,35–37] received a quality rating of "fair," while studies [20,33] were rated as "good." Only the study by Ghosh received a "poor" rating. Overall, the quality of the included studies evaluating the connection between PCOS and PD was acceptable. A summary of the quality assessment for each study is presented in Table 4.

Table 4. NHLBI quality assessment of the reviewed papers.

NHLBI Quality Assessment Tool for Controlled Trials	Wendland et al. (2021) [20]	Akcali et al. (2014) [23]	Maboudi et al. (2023) [30]	HU et al. (2024) [31]	Abbas et al. (2014) [32]	Hilaloğlu et al. (2022) [33]	Ghosh et al. (2023) [34]	Lindheim et al. (2016) [16]	Saglam et al. (2017) [35]	Hu et al. (2023) [36]	Varghese et al. (2019) [37]
1. Was the research question or objective in this paper clearly stated and appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Did the authors include a sample size justification?	Yes	NO	NO	NO	NO	Yes	NO	NO	Yes	NO	Yes
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	Yes	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	CD	Yes
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	Yes	No	Yes	NR	NR	Yes	NR	Yes	Yes	Yes	Yes
6. Were the cases clearly defined and differentiated from controls?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?	NR	NO	NO	NR	CD	NR	NR	CD	CD	NR	CD
8. Was there use of concurrent controls?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	CD	NO	NO	NO	NO	CD	CD	NO	NO	NO	CD
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were the assessors of exposure/risk blinded to the case or control status of participants?	NR	NO	NO	NR	NO	NR	NR	CD	NR	NO	CD
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	Yes	Yes	NO	Yes	NO	Yes	NO	NO	NO	Yes	NO
Total score (Yes out of 11)	9	8	7	6	6	8	5	7	8	8	8
Overall Quality Rating	Good	Fair	Fair	Fair	Fair	Good	Poor	Fair	Fair	Fair	Fair

Yes, criterion satisfied. NO, criterion not satisfied. NR, not reported. CD, cannot determine. 0–4, Poor. 5–8, Fair. 9–11, Good.

4. Discussion

PCOS is a complex endocrinopathy with a wide range of variants and clinical manifestations, with no single etiological factor fully explaining the entire spectrum of abnormalities associated with the condition [39]. Inflammation is a common condition in PCOS and

PD, as well as the systemic involvement that results in cardiovascular disease, diabetes, neurogenic inflammation [40], periodontal disease, and other related conditions [41]. Considering the link between chronic systemic inflammation and the underlying mechanisms of both PCOS and PD, this systematic review aims to investigate their bidirectional relationship, achieved by analyzing immune-inflammatory and microbiological markers in saliva. The observed associations should be interpreted with caution, as clinical factors such as BMI, insulin resistance, dietary habits, and oral hygiene could also have influenced periodontal outcomes, acting as potential confounding variables [40]. In any case, the contribution of confounding factors, such as diet, stress, and oral hygiene practices, requires further investigation to shed light on the effects of PCOS on periodontal health [42]. Due to variability in biomarker measurement techniques and periodontal indices, a meta-analysis was not feasible. Future studies should standardize salivary sampling protocols and periodontal assessments to enable quantitative synthesis. In this systematic review, Ozcaka et al. reported that PCOS and gingival inflammation act synergistically on proinflammatory cytokines IL-6 and TNF-α [21] and IL-1 [22], suggesting that PCOS may influence gingival inflammation or vice versa. IL-6 is a crucial cytokine associated with insulin resistance (IR), as it induces IR by decreasing the tyrosine phosphorylation of the insulin receptor substrate-1 and reducing the association of the p85 subunit of phosphatidylinositol 3-kinase [21]. The study by Varghese et al. reflects the importance of periodontal health and the prevention of periodontal disease to avoid increased IR in patients with PCOS, using salivary IL-6 as a marker [37]. This study reveals that IL-6 levels were two times higher in PCOS patients with periodontitis compared with PCOS patients without periodontitis. So, these researchers report that periodontal indices are worse in women with PCOS and state that in patients with PCOS, increased production of proinflammatory cytokines such as TNF-α, IL-6, and IL-17 results in a constant low-grade inflammatory response, with adverse effects on periodontal tissue [43,44]. In support of these findings, Vidal et al., 2009 described that nonsurgical periodontal therapy effectively improved clinical periodontal data and reduced plasma levels of IL-6 in patients with severe periodontitis [45]. Mammen et al. reported that effective periodontal therapy decreased insulin resistance (IR), enhanced periodontal health, and improved insulin sensitivity in patients with type II diabetes mellitus and chronic periodontitis [46], showing that periodontal therapy is an important means of reducing IL-6 levels and improving insulin sensitivity in such patients. Wendeland et al., like Varghese et al., examined salivary proinflammatory cytokines as a marker of inflammation. However, the results of the study indicate that young women with PCOS who maintained good oral health showed no significant differences in gingival indices compared to healthy controls [18,37]. The gingival health of the population examined was mainly associated with oral hygiene and, to a lesser extent, with hormonal and metabolic profiles. Thus, in the examined group of patients with PCOS, the low-grade chronic systemic inflammation associated with PCOS prevailed over local cytokine secretion, which led to higher salivary levels of IL-1b, IL-6, and TNF-α. An additional proinflammatory parameter to consider, implicated in various inflammatory physiological phenomena and pathological processes, is a specific family of proteolytic enzymes known as matrix metalloproteinases (MMPs). The MMPs and their tissue inhibitors (TIMPs) regulate the localization and remodeling of ovarian tissue, influencing processes such as follicular development, ovulation, corpus luteum formation and regression, and follicular atresia. In PCOS, there are disturbances in ovarian tissue degradation and alterations in MMP expression, leading to an imbalance between serum MMP and TIMP levels [47,48]. Elevated levels of the MMP-8/TIMP-1 ratio in serum and saliva may indicate a critical balance between MMPs and TIMPs, which results in extracellular matrix degradation. Alterations in this ratio may lead to disease. From the study by Akali et al., it can be concluded that increased MMP-8 and the MMP-8/TIMP-1

ratio in saliva and serum appear to be more pronounced in women with PCOS and potentiated by gingival inflammation [23]. The results of Akali et al. also show significant positive correlations between PD, BOP, PI, and MMP-8/TIMP-saliva, probably due to the degree of gingival inflammation, as postulated by a previous study [49]. Also, in the study by HU et al., MMP-8 levels in serum samples were significantly higher in patients with PCOS than in participants without PCOS [36]. In addition, salivary levels of MMP-8 were markedly higher in patients with periodontitis than in subjects without periodontitis. These results suggest that MMP-8 in serum might be positively related to PCOS, while its presence in saliva indicates periodontitis. Therefore, as this review shows, MMP-8 is currently considered one of the most important biomarkers for PD. MMP-8 is a key indicator of periodontal inflammation. Among the investigated biomarkers, salivary MMP-8 appears to be the most promising early screening tool for periodontal risk in PCOS patients, as it reflects local periodontal inflammation more accurately than serum measures [36]. It is closely involved in the progression of periodontitis and promotes periodontal disease development at active sites of inflammation. An analysis of the Raman spectra of saliva samples was also performed to further investigate the results obtained from this systematic review, as it is known that IL-6, IL-17A, and MMP-8 are assigned to characteristic protein peaks in Raman spectra [50,51]. As mentioned, PCOS is linked to periodontitis in the lipid and protein profiles of Raman spectra. The average Raman peak intensities at 747 cm^{-1} (hemoglobin) and 1574 cm^{-1} (protein) are higher in the PC-Perio group than in the H-Perio group, suggesting that PCOS may affect hemoglobin in patients with periodontitis. In this context, hemoglobin might mainly result from gingival bleeding, indicating that PCOS might amplify inflammation in patients with periodontitis [52,53]. In addition, hemoglobin is a type of iron-containing protein [54]. Therefore, PCOS could also affect protein and iron metabolism in patients with periodontitis. In fact, Spearman's correlation analysis further demonstrates that protein levels in Raman spectra are positively linked with IL-6 levels. Hu et al. reported Spearman's correlation analysis revealing that salivary MMP-8 levels were positively correlated with periodontal parameters, including PD, BOP, full mouth plaque score (FMPS), the percentage of sites with PD $\geq$ 4 mm and the percentage of sites with CAL between 1 and 2 mm [31]. These results suggest that the level of MMP-8 in saliva better reflects the degree of local periodontal inflammation than its concentration in serum. These results are consistent with evidence from current research. A statistical difference in the mean serum IL-6 level was found between groups B and C, and a positive correlation with BOP suggests that periodontitis might promote IL-6 production more than PCOS. IL-6 is mainly synthesized in local lesions in the early stages of inflammation and is more common in chronic inflammatory processes and autoimmune reactions [55]. In fact, a significant difference was noted in the average Raman spectra of saliva samples among the four groups with different PCOS and periodontitis disease ($p < 0.05$), while no significant differences emerged among serum samples. Since various systemic conditions and confounding factors often influence serum compounds, it is complicated to distinguish between periodontitis and non-periodontitis using only serum samples. In addition, PCOS is an endocrine and metabolic disorder that substantially affects serum components. Overall, the actual study suggests that salivary component analysis by Raman spectroscopy could be a new approach to evaluating periodontal conditions, enabling earlier diagnosis and more effective health care. An analysis of an additional type of metalloproteinase, MMP-9, also emerged in this review. MMP-9 is the only member of the metalloproteinase family that can bind and digest collagen, which is the most important component of the basement membrane due to its 3-bronectin structure [56]. Maboudi et al. reported that the salivary MMP-9 level in patients with PCOS was significantly higher than in the control group and in patients with PCOS who had a healthy periodontium [30]. Their results

suggested that local/periodontal oxidation status is compromised in women with PCOS, making them significantly more vulnerable to periodontal disease [8]. In support of the analyzed Maboudi study, Lewandowski et al. reported similar results with significantly higher serum concentrations of MMP-2, MMP-9, and TIMP-1 levels in women with PCOS compared with healthy controls [57]. Although these findings demonstrate an important interaction between PCOS and gingival inflammation, due to the case–control nature of the studies, it is not easy to draw conclusions about the exact mechanism underlying the involvement of the MMP-8 TIMP-1 system and its relationship. Prospective longitudinal studies would be better suited to probe this link and reveal whether a causal or causal relationship exists. In the literature, increased systemic levels of C-reactive protein (CRP) have been observed in PCOS patients with periodontal disease, indicating an additional marker of inflammation and, thus, a possible synergistic factor that could be mediated at the periodontal level. Abbas et al. showed that CRP is produced in the liver in response to inflammation and that this marker may measure the extent of chronic inflammation in the body, particularly at the cardiac level [33]. New studies suggest that CRP levels exceeding the normal range may serve as a more accurate predictor of heart attack and stroke than high cholesterol levels. CRP can be used to detect inflammation at an early stage, before it progresses to chronic disease, as obesity and insulin resistance influence cells in ways that heighten inflammation [58]. Furthermore, in the study by Abbas et al., an increase in CRP levels was found to have a direct and significant relationship with increased values of the gingival indices (GI) and plaque index (PLI) [33]. This positive correlation suggests that salivary CRP may be a marker of oral disease in patients with PCOS. This result also confirms the findings of the study by Kamil et al. [58]. These responses are associated with the induction of other inflammatory markers, such as ROS [59]. Under normal conditions, ROS production and antioxidant defense systems are generally maintained in equilibrium. However, when this balance is interrupted, leading to an increase in ROS production, oxidative stress can result in damage to the organism. Both free radicals and ROS can oxidize nucleic acids, causing DNA to become damaged. The most common stable product of oxidative DNA damage in the nucleus is 8-hydroxy-2′-deoxyguanosine (8-OHdG), formed by enzymatic cleavage following the 8-hydroxylation of guanine [60]. Elevated ROS levels also promote lipid peroxidation, leading to malondialdehyde (MDA) production and damage to cell membrane lipids [61]. Total antioxidant status, which is sensitive to fluctuations in oxidative stress levels, is a reflection of the concentrations of various antioxidants and the potential synergistic and antagonistic interactions between oxidants and antioxidants. Most published data on oxidative DNA damage report higher levels of 8-OHdG in the saliva of periodontitis patients [62]. Similarly, in the study by Saglam et al., salivary levels of 8-OHdG in both CP groups were statistically higher than in both groups of periodontally healthy patients, and in the latter, salivary levels of 8-OHdG were similar whether the patients had PCOS or not [35]. These results suggest that PCOS does not affect salivary levels of 8-OHdG or that this effect is undetectable. On the other hand, few studies have analyzed serum levels of 8-OHdG in subjects with PCOS [63]. Moreover, the results are contradictory to each other [63–65]. According to Saglam's results, PCOS itself appears to be more powerful in increasing serum rather than salivary levels of 8-OHdG than CP alone. This may be because PCOS's systemic and metabolic effects are more pronounced than those of chronic periodontitis. Another biomarker of oxidative stress, namely MDA, was also evaluated in this study. Salivary MDA levels in both CP groups were found to be significantly different when compared with those in the control group. CP and PCOS alone enhanced salivary MDA levels, but these increases did not translate into a beneficial action in patients with PCOSCP. This condition may be due to other factors, such as dietary habits or challenges in establishing uniform criteria for PCOS, which may have a more

important effect on salivary biochemical indicators. According to the TAS criterion analysis, PCOS and CP cause a decrease in salivary TAS levels, but CP has no or minimal effect on salivary TAS levels of subjects with PCOS or vice versa. The discrepancy between results may be explained by methodological differences or variable systemic and periodontal status of the PCOSCP, CP, and ePCOSPH groups. To minimize the effects of interactions in such complex diseases, large sample sizes, less diversity of Rotterdam criteria, fewer differences in participants' diets within groups, and the relatively small size of the present study were important limitations. Another important salivary biomarker for diagnosing PCOS is salivary microbiome diversity. In women with polycystic ovary syndrome (PCOS), significant alterations in the composition of the salivary microbiome have been observed; Ghosh et al. reported that there is growing evidence linking oral and salivary microbiome composition to PCOS [16,23,34,66]. Female sex hormone levels have been associated with oral microbiome composition linked to oral diseases such as periodontal disease, thus indicating a possible effect on oral microbial organization [67]. However, it is interesting to note that less oral microbial alpha diversity was observed in women with PCOS than in controls. The Alu I restriction enzyme cut fragments between 200 and 225 bp in length in women with PCOS, whereas in non-PCOS, the range of fragments was much more diverse, varying from 100 bp to 550 bp. Because all study participants belonged to a single ethnic population, India, it was possible to minimize the confounding effects of endogenous and exogenous factors, such as oral hygiene, diet, smoking (absent), and alcohol consumption (absent), which were found to be similar between the groups with and without PCOS. Most studies in humans have shown differences in microbial communities between women with and without PCOS [68]. Lindheim et al. also reported a profile of the salivary microbiome in patients with PCOS based on next-generation sequencing [16]. These researchers demonstrated that PCOS is associated with a reduced relative abundance of salivary Actinobacteria and a significant tendency to cluster bacterial profiles in unweighted UniFrac analysis. A decreased abundance of Actinobacteria, a phylum typically linked to a healthy oral microbiota, may favor the proliferation of periodontopathogenic species commonly associated with periodontitis. This microbial imbalance (dysbiosis) promotes a proinflammatory environment that stimulates the production of cytokines such as IL-1β, IL-6, IL-17, and TNF-α, amplifying the immune response and worsening tissue inflammation [34]. In women with PCOS, salivary dysbiosis may not only reflect systemic inflammation but also actively contribute to its persistence and worsening, with potential implications for periodontal health [66]. Beyond overall diversity, specific taxa may have functional implications for inflammation in PCOS. The observed reduction in health-associated Actinobacteria (e.g., *Rothia/Actinomyces*) may weaken commensal functions and host defense, favoring a proinflammatory milieu. Conversely, increases in *Prevotella* and cariogenic *Streptococcus* can enhance acidogenic and proinflammatory activity, while periodontal pathogens such as *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Aggregatibacter actinomycetemcomitans* may promote biofilm maturation and matrix degradation, thereby contributing to periodontal tissue breakdown and potentially sustaining systemic low-grade inflammation in PCOS [16,66]. Therefore, salivary microbiome alterations in PCOS may not only reflect systemic low-grade inflammation but also contribute to its persistence, worsening periodontal tissue breakdown. Recently, the prevention and treatment of pathogenic oral biofilms have become a significant global challenge, probably due to the increasing microbial virulence and antibiotic resistance in oral biofilms or dental plaque: this issue was deeply explored by several and recent studies, which investigated the synergistic effect of different compounds, in the reduction in populations of viable bacteria in established biofilms [69,70]. According to these studies, the selected hydrogels were promising biomaterials, with interesting therapeutic effects on the treatment of oral

infections, and a fundamental tool to develop advanced therapeutic strategies against persistent biofilms [69,70]. Other studies, instead, suggested the potential of nanodroplets for dental caries prevention, demonstrating the feasibility of the synergistic antimicrobial system in treating oral biofilm-related infections [71,72].

Akcali et al. employed quantitative real-time polymerase chain reaction to demonstrate differences in the presence of different bacterial species in women with PCOS and gingivitis compared to healthy women with gingivitis [23]. However, the authors did not observe differences between periodontally healthy women with and without PCOS. Because the PCOS patients included in the study were periodontally healthy and did not have or detect an association between the salivary microbiome and markers of inflammation, we hypothesize that the reduction in the relative abundance of Actinobacteria in the context of PCOS is not a cause of the disease, but instead creates a more favorable environment for disease-associated bacteria, which may lead to periodontal disease in the presence of other predisposing factors. This hypothesis is supported by the fact that the prevalence of periodontal disease is higher in patients with PCOS than in healthy people [14]. Other parameters associated with salivary microbiome diversity, besides *S. mutans* concentration, are salivary pH measurement and DMFT indices. Hilaloğlu et al. analyzed these oral health parameters. *S. mutans* salivary counts and DMFT index values of the groups with PCOS were higher than those of the control groups [33]. Hyperglycemia caused by insulin resistance and increased estrogen levels associated with PCOS are believed to be the main factors influencing the results of this study. Reduced salivary flow leads to alterations in the oral microbiota, resulting in an increased presence of *S. mutans* in the oral cavity [73]. In this research, the effect of insulin resistance on the oral microbiota can be explained as follows: elevated estrogen levels in PCOS patients lead to increased vascularization and inflammatory responses in the estrogen receptors of the gingiva [74]. Due to increased estrogen levels, the oral microflora becomes more acidic, increasing the number of microorganisms in saliva and the level of *S. Mutans* [75]. However, it is important to note that although a significant increase in Streptococcus mutans was observed in women with PCOS, likely reflecting salivary microbiome alterations, this finding was not associated with periodontal disease in this study, as *S. mutans* is primarily linked to dental caries rather than periodontitis. Studies suggest that the inflammation and depression experienced by women during the premenstrual phase, due to fluctuations in estrogen and progesterone levels, may be reflected in salivary components [76]. An increase in *S. mutans* is observed in the oral microbiota when salivary flow decreases. In this study, the influence of PCOS on the oral microbiota can be explained by these factors. Increased DMFT index values in PCOS patients are closely related to salivary pH, salivary flow, and *S. mutans* levels [77]. However, PCOS significantly increased DMFT index values, independent of intra-oral factors. This cascade of proinflammatory events and modification of the salivary microbiome has been suggested as a possible cause to explain the link between periodontal disease and PCOS. This process may play a role in the etiology and pathogenesis of PCOS [78,79]. Integrating microbiological analysis with salivary inflammatory biomarkers provides new insights into the bidirectional link between PCOS and periodontal disease. Combined diagnostic markers could enhance early risk detection and personalized prevention. Future research should explore the relationships between bacterial taxa, cytokine profiles, and disease severity to clarify shared pathogenic mechanisms. Indeed, from this review, patients with PCOS tend to have a higher prevalence of periodontal disease. Nevertheless, given the bidirectional link between PCOS and PD, inflammatory biomarkers related to PD could serve as diagnostic tools for PCOS prevention.

Limitations

The reviewed studies are characterized by a positive approach to the assessment of outcomes and provide a thorough evaluation, but they used different methods for the qualitative analysis of salivary sampling, both in terms of sample type and the different inflammatory biomarkers analyzed. As a result, it is not possible to compare the data with a higher degree of precision to highlight the advantages or disadvantages of using one salivary inflammatory biomarker over another to assess the risk of periodontal disease in women with PCOS. At the same time, the periodontal parameters used are not fully comparable across all studies included in the review. As a consequence of the analysis strategy, this systematic review is limited to a qualitative interpretation of the results; it should be noted that many of the studies retrieved using the keyword-based search had limited methodological quality. This is an important limitation of this systematic review.

In addition, unmeasured factors such as BMI, insulin resistance, dietary habits, and oral hygiene could act as confounding variables, partially contributing to the observed PCOS–PD association and biomarker differences. Furthermore, the small sample sizes and lack of longitudinal follow-up in most studies limit the ability to establish causality in the PCOS–PD relationship. It should be noted that there is a lack of standardization of methods used by the studies and an inadequate sample size.

Inconsistencies in saliva collection protocols and biomarker detection methods reduce the comparability of findings across studies. Due to this variability, a meta-analysis was not feasible. Standardized methodologies, such as the use of ELISA for cytokine assessment and fixed time points for saliva sampling, are needed in future investigations. Variability in PCOS diagnostic criteria and periodontal disease staging further complicates cross-study comparisons.

5. Conclusions

This systematic review indicates a consistent association between polycystic ovary syndrome (PCOS) and periodontal disease, supported by converging evidence across inflammatory, hormonal, and microbiological parameters. Women with PCOS showed significantly higher salivary and serum levels of proinflammatory cytokines (e.g., IL-6, IL-1β, TNF-α), matrix metalloproteinases (MMP-8, MMP-9), and C-reactive protein compared with healthy controls. These biomarkers correlated positively with periodontal indices such as probing depth, bleeding on probing, and clinical attachment loss, suggesting that systemic low-grade inflammation in PCOS may contribute to periodontal susceptibility. Alterations in the salivary microbiome, including increased *S. mutans* load and reduced diversity of Actinobacteria, were also reported, although evidence remains preliminary. Furthermore, oxidative stress markers (8-OHdG, MDA) appeared to be driven more by periodontal status than by PCOS itself, highlighting the complexity of this relationship. Taken together, these findings suggested a bidirectional interaction; women with PCOS have a higher risk of suffering from periodontal disease, and patients with PCOS indeed show a higher incidence of periodontal disease. However, considering the bidirectional relationship between PCOS and PD, inflammation markers associated with PD could be used as diagnostic indicators for the prevention of PCOS. A collaborative approach between dentists and gynecologists has the potential to significantly improve women's oral health, overall well-being, and quality of life in the future. However, further studies on inflammatory salivary biomarkers are recommended for women with PCOS, as the number of current studies is still limited, and the results are highly heterogeneous regarding which biomarker to use for early and meaningful screening of periodontal disease. The results presented and investigated in this review will probably encourage the scientific community to conduct higher-quality studies, enabling more robust and reliable evidence-based conclusions to

be drawn than are currently available in the literature, thus, reducing the summary of the evidence. Future investigations should focus on longitudinal cohort studies employing standardized assessments of salivary biomarkers and periodontal health to better explore potential causal relationships. Specifically, longitudinal studies evaluating PCOS patients before and after periodontal treatment would help clarify causal pathways and strengthen current evidence. Clinicians are encouraged to incorporate routine periodontal screening in the management of PCOS patients to detect early signs of inflammation, supporting Goal 3 (Good Health and Well-being) of the UN 2030 Agenda.

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