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Polycystic Ovarian Syndrome and Periodontal Disease - A Systematic Review

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Abstract

Background: Polycystic ovarian syndrome (PCOS) is a low-grade chronic inflammatory condition and a hormonal disorder common among women of reproductive age group. It is believed that sex hormones play a vital role in the maintenance of bone mass and directly or indirectly influence several cell types, including periodontal cells. A series of proinflammatory changes and hormonal imbalance associated with PCOS has been suggested to be associated with the Periodontal Disease (PD).

Objective: The aim of this study was to systematically review the published literature reporting the relationship between Polycystic Ovarian Syndrome and Periodontal disease.

Material and Method: A computer-based search of Medline, Google Scholar, Trip database, Ebsco, Cochrane database was performed from the year 2009-2019. Selection criteria: cross-sectional and case-control studies describing the link between PCOS and periodontal disease. Eligible articles were reviewed and analysed using the modified Newcastle Ottawa Scale for cross-sectional studies and the Newcastle Ottawa Scale for case-control studies. Results: 14 articles were found: 4 cross-sectional and 10 case-control studies. All the data extracted from the studies were assembled in tables and presented in a descriptive manner associating PCOS and PD. All the retrieved studies revealed a decisive and an association between PCOS and Periodontal disease.

Conclusion: Positive association has been implicated between PCOS and PD in all the studies in which the temporality has to be assessed

Keywords: Polycystic ovarian syndrome, Periodontal disease, Gingival disease, Oxidative stress

Introduction

Polycystic ovarian syndrome (PCOS), a hormonal condition considered to be one of the commonest reproductive disorders found in 6-10% of the female population[1] mostly affecting women of reproductive age group, with the prevalence ranging from 9.13% - 36% in

India.[2,3] The pathophysiology of PCOS involves primary defects in the hypothalamic-pituitary-gonadal axis; which results in disordered secretion of gonadotropin by the hypothalamus and elevated levels of luteinizing hormone (LH). The elevated LH levels, in turn, stimulate the ovarian theca interstitial cells to secrete excessive androgen. Theca cells can account for the steroidogenic abnormalities.[4] Women with PCOS were found to have excessive androgen secretion which may cause numerous small collections of soft fluid in the ovaries leading to cyst formation and also have abnormal and prolonged menstrual periods. There are various phenotypes characterized by this syndrome and the three common phenotypic features of PCOS are hyperandrogenism, polycystic ovaries, and ovulatory dysfunction.[5] Along with these leading phenotypic features, this condition can also be manifested with metabolic disorders including insulin resistance (found in 60-80% of women with PCOS)[6], obesity, type 2 diabetes mellitus (T2DM), hyperinsulinemia and increased risk factors for both cerebrovascular and cardiovascular disease.[7-10] As per the various literature analyses, PCOS is considered a multifactorial disorder and various other factors included are genetic, metabolic, endocrine and environmental abnormalities.[11] Additionally, women with PCOS have been found to have higher levels of depression and overall psychological morbidity and decreased quality of life[12,13] due to mood disturbances, decreased sexual satisfaction, weight gain, acne vulgaris, and alopecia.[14]

PCOS is associated with low-grade systemic inflammation and is indicated by elevation of multiple markers of inflammation such as C-reactive protein (CRP), proinflammatory cytokines and chemokines including interleukin 18 (IL-18), monocyte chemoattractant protein-1, macrophage inflammatory protein-1, and white blood count. Furthermore, increased oxidative stress and its biomarkers suggest PCOS as an inflammatory disease.[15]

It is a deep-rooted fact that periodontitis is a chronic inflammatory disease and it is the inflammation that links periodontitis with various systemic diseases.[16] C-Reactive Protein is one of the important markers of inflammation, produced under the stimulatory control of proinflammatory cytokines such as IL-6 and TNF-α. Literatures have suggested that chronic infections associated with increasing levels of reactive oxygen species, myeloperoxidase (MPO), oxidative stress, inflammatory cytokines (such as IL-6 and TNF-α), high-sensitivity C-reactive protein (hsCRP), adhesion molecules and blood lymphocytes and monocytes have a role in the etiology and pathogenesis of PCOS.[17-19] In PCOS there will be increased levels of androgens and estrogens which in turn affect the local microbiota sub gingivally and invariably acts on the gingival cells and change the effectiveness of the epithelium[20] leading to gingivitis and periodontitis in PCOS affected women. These sequential events of proinflammatory events and hormonal imbalance have been considered as a possible link between Periodontal Disease and Polycystic Ovarian Syndrome.

However, there is still limited information about periodontal health, oral microbiota, and its association with PCOS. The aim of the present study was to explore the link between PCOS and periodontal health by focussing on the oral aspects of PCOS through a systematic review of indexed literature.

Materials and Methods

Design: A systematic review was undertaken using objective and transparent methods as per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, to identify, evaluate and summarize all relevant research findings. The protocol for

systematic review was registered first with PROSPERO (International Prospective Register of Systematic Review) Register ID CRD42020171430

Eligibility criteria

On applying the PECO analysis to the articles searched, the criteria were set as shown below: PECO analysis

Population: Polycystic ovarian syndrome women with the reproductive age group of 15-49 years

Exposure: Proinflammatory cytokines, Oxidative stress biomarkers, and Oral microbiological parameters

Comparison: Healthy women with the reproductive age group of 15-49 years

Outcome: Clinical Periodontal parameters like probing depth (PD), plaque index (PI) and bleeding on probing (BOP)

Inclusion and Exclusion Criteria

Inclusion criteria

1. Women with the reproductive age group of 15-49 years.
2. Women with the history of Polycystic ovarian syndrome, as defined by Rotterdam's criteria.[5]
3. Cross-Sectional and case-control studies are included.
4. Studies published in the past 10 years were included (From 2009-2019).
5. Studies which was written in English languages were only included

Exclusion criteria

1. Qualitative studies, reviews, expert opinion, systematic reviews, meta-analysis, and case studies/series.
2. Publications with no abstract and those which were widely out of the scope of the study were eliminated.
3. Studies that required translation to the English Language.

The remaining studies were sorted out on the basis of their title and abstract. Finally, those studies in which the abstract fulfilled all the inclusion criteria were selected for full-text reading. In those cases, in which a study met the eligibility criteria but the information in the abstract was insufficient, full texts of the articles were also obtained. A further literature search was performed based on the references of the selected articles.

Search Strategy

To identify the pertinent studies, a broad search of the literature was done using PubMed, Google-Scholar, Tripdatabase, Cochrane from the year 2009-2019 (Table 1). A detailed search strategy was developed for MEDLINE through the use of MeSH terms and was revised for Google Scholar. The first set of terms include ‘Polycystic ovarian syndrome’, ‘Periodontitis' separated by Boolean operator OR. The second set included the term ‘women with Polycystic Ovarian Syndrome', ‘periodontal disease’ separated by Boolean operator “AND” and the third set included the term ‘Association of PCOS and periodontitis,’ separated by Boolean operator “AND. Hand searches of reference lists of included studies were conducted to ensure additional relevant references. Although systematic reviews, qualitative studies were excluded, reference lists were checked to ensure all primary research was located for inclusion. Only full papers written in English were included. Where multiple publications reporting on the same study existed in different databases, data from the study were extracted and reviewed only once. Duplication of the article was identified using the Zotero.

Study Selection

Study selection was conducted by two authors who independently screened titles and abstracts against the inclusion/exclusion criteria and identified relevant papers. Then the same two authors independently reviewed the full-text studies unable to be excluded by title and abstract

alone. A Comparison of papers was completed between the two authors with no disagreements.

Data Extraction

The data extraction from the final 14 articles was done using a data extraction form. It includes the first author name, year of publication of the article, the aim of the study, objectives of the study, study design, study summary, results, and outcome.

Quality Assessment Of The Included Studies

The final analysis included 4 cross-sectional studies and 10 case-control studies the methodological quality of the selected articles were assessed using the modified Newcastle Ottawa Scale for cross-sectional studies (Table 2) and the Newcastle Ottawa Scale for case-control studies. (Table 3)

Results

While typing the meSH terms, 1380 relevant articles were identified (Pub med=9, Google scholar=1360, TRIPDATABASE=7, Cochrane Database =1, EBSCO =3). Thousand two thirty-eight articles were eliminated after reading the title. Four articles were eliminated due to duplication. one forty-two articles were selected for the abstract reading. After the abstract reading, one twenty-one article was excluded and twenty-one articles were included. After reading the full text, seven articles were excluded and fourteen studies that met the inclusion and exclusion criteria were included. Figure 1 shows the search strategy according to PRISMA guidelines

Types of participants

The participants included were Polycystic ovarian syndrome women with the reproductive age group of 15-49 years. In all studies PCOS was diagnosed according to the criteria of Rotterdam[5] with the presence of at least two of the following: (1) polycystic ovaries (presence of >12 follicles in each ovary measuring 2–9mm in diameter and/or increased ovarian volume >10ml), (2) oligomenorrhea and/or anovulation and (3) hyperandrogenism (Clinical: Acne, Hirsutism, acanthosis nigricans, Biochemical: Total T >70ng/dL, Androstenedione >245ng/dL, DHEA-S >248µg/dL).

Types of outcome measures

Primary Outcome: Clinical Periodontal Parameters

In all 14 studies, a comprehensive clinical periodontal examination was performed using different periodontal parameters like probing depth (PD), plaque index (PI) and bleeding on probing (BOP), Clinical attachment loss (CAL) and gingival index (GI) were reported respectively. One study reported the rate of tooth loss among patients with and without PCOS. Intraoral radiographs were used in four studies and panoramic radiographs were used in one study to assess bone loss. Diagnostic methods and altered clinical parameters of the analysed studies are shown in (Table 4) .

Discussion

All the analyzed studies revealed a definite relationship between PCOS and PD (gingivitis and/or periodontitis), and hence, it is possible to associate both PCOS and PD.

Literature review has demonstrated an increased production of sex steroidal hormones like estrogen might lead to increased gingival enlargement, followed by gingival bleeding and microbial changes. Increased estrogen levels could also be noted in the PCOS condition, which could explain its impact on the periodontium as demonstrated in a case report done by Asnani et al.[21], In this study, the author compared the gingival biopsy specimen of PCOS patients with and without gingivitis for estrogen and progesterone receptor levels. This study concluded that estrogen receptors were present in the gingival biopsy specimen of PCOS patient with gingivitis with the absence of other receptors in both case and control. Also, precisely, estrogen receptors beta (ERbeta) produced estrogenic effects in PDL cells, but there were

no immunoreactivity expressions for progesterone receptors in these cells, which implies that progesterone does not have a direct effect on PDL cell function.[22]

Studies have also demonstrated an altered immuno-inflammatory response of the periodontium in the presence of various systemic disorders. This altered host response could be attributed to the increased pro-inflammatory cytokines along with hormonal changes leading to an alteration in the oral microflora, eventually, even a sub minimal plaque deposits in a susceptible host could lead to greater periodontal destruction within a shorter period of time. Altered host response in the gingiva may lead to greater periodontal destruction adversely affecting the alveolar bone and adhesive joints, eventually leading to tooth loss. Of late the role of oxidative stress in complementing this disease progress has also been kindled.

Studies have associated the increased prevalence of periodontal disease among patients with certain non-communicable diseases like diabetes and cardiovascular disease. Bleeding on probing could be attributed to the role of oxidative stress on the periodontium. Similar phenomena could also play a vital role in the association between PCOS and PD.

Saglam et al.[23] and Varadhan et al.[24] reported significant positive correlations with all clinical periodontal parameters and oxidative stress markers of MDA levels. Dursun et al. [25] detected that MPO activity was significantly higher in PCOS women which were inconsistent in the study done by Varadan et al. [24] who suggested that MPO levels were not found to be significantly different. The higher BOP rates in PCOS group can be attributed to the influence of hyperandrogenism which causes excessive proliferation of vascular endothelial cells and epithelial keratinization in the gingiva.[22]

Innumerable studies like (Ghiraldini B et al. [26] and oates TW et al.[27] have demonstrated the advantage of non-surgical periodontal therapy in not only improving periodontal health but also in improving the glycemic control levels in patients with type II diabetes mellitus. Javed et al. [28] his study had demonstrated the additive benefits of non-surgical periodontal therapy combined with adjuvant laser therapy on reducing the levels of serum pro-inflammatory cytokines in patients with coronary heart disease. Taking a leaf from these studies it could be hypothesized that non-surgical periodontal therapy could play a vital role in improving periodontal health in patients with PCOS by its positive effect on pro-inflammatory events. However, this phenomenon has to be further explored by longitudinal studies by not only assessing subjective oral markers but also an objective clinical assessment of periodontal health.

Limitations

The outcomes of this systematic study have to be interpreted with the following limitations. Since all studies included in this review were cross-sectional in nature the temporality of this association cannot be well estimated. Being a hormonal disease, PCOS could also initiate a variety of inflammatory biomarkers independent of periodontal disease. Hence, the role of pro-inflammatory markers could always be confounded by the combined effect of disease as both the studies of interest have an inflammatory origin. As a result, a single biomarker assessing the association between PCOS and Periodontal disease could not be demonstrated. The studies included in this review assessed a variety of biomarker making meaningful interpretation difficult. This was a reason why the authors restricted the present study to a systematic review rather than a meta-analysis.

Conclusion

Within the constraints of the present design, our systematic review clearly demonstrates an association between PCOS and periodontal disease. All 14 studies included in this review demonstrated this association unanimously. In the absence of a possible explanation for this phenomenon, the authors suggest well designed longitudinal studies which might throw light on the missing link between PCOS and PD.

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Legends Tables and Figure

Table 1: Broad search of the literature

Database	Search Pattern
Pubmed	("polycystic ovary syndrome"[MeSH Terms] OR ("polycystic"[All Fields] AND "ovary"[All Fields] AND "syndrome"[All Fields]) OR "polycystic ovary syndrome"[All Fields] OR ("polycystic"[All Fields] AND "ovarian"[All Fields] AND "syndrome"[All Fields]) OR "polycystic ovarian syndrome"[All Fields]) AND ("periodontal diseases"[MeSH Terms] OR ("periodontal"[All Fields] AND "diseases"[All Fields]) OR "periodontal diseases"[All Fields] OR ("periodontal"[All Fields] AND "disease"[All Fields]) OR "periodontal disease"[All Fields])) AND ("gingival diseases"[MeSH Terms] OR ("gingival"[All Fields] AND "diseases"[All Fields]) OR "gingival diseases"[All Fields] OR ("gingival"[All Fields] AND "disease"[All Fields]) OR "gingival disease"[All Fields])
Google Scholar	Polycystic ovarian syndrome, periodontal disease, gingival disease, oxidative stress, cytokines
EBSCO	Polycystic Ovarian Syndrome, periodontal disease, gingival disease
Tripdatabase	Polycystic Ovarian Syndrome, periodontal disease, gingival disease, oxidative stress.
Cochrane	Polycystic Ovarian Syndrome, periodontal disease, gingival disease.

Quality Assessment Scale

A study can be awarded a maximum of one star (*) for each numbered item within the Selection and Outcome categories.

A maximum of two stars can be given for Comparability.

Table 2: Modified Newcastle Ottawa Scale – Cross Sectional Studies.

	STUDY	Ebru Saglam,2017	Aliye Akcali, 2017	Sai Dharshana nair,2017	Najafi,2017
Selection	Representativeness of the sample	*	*	*	*
	Sample size	-	-	-	-
	Non-respondents	*	-	-	-
	Ascertainment of the exposure	**	**	**	*
Comparability	The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled	*	*	*	*
Outcome	Assessment of the outcome	**	**	**	*
	Statistical test	*	*	*	*

Table 3: New Castle Ottawa Scale – Case Control Studies

	STUDY	Dursun, 2011	Ozcaka, 2012	Ozgun, 2013	Porwal 2014	Akcali, 2014	Akcali, 2015	Rahiminejal, 2015	Ayser, 2017	Dhamya, 2017	Manjusha, 2018
Selection	Is the case definition adequate?	*	*	*	*	*	*	*	*	*	*
	Representativeness of the cases	-	*	-	*	-	-	*	-	*	*
	Selection of controls	*	-	-	-	-	*	*	*	-	*
	Definition of controls	**	*	**	**	**	*	**	*	*	**
Comparability	Comparability of cases and controls	*	*	*	*	*	*	*	*	*	*

	on the basis of the design or analysis										
Outcome	Ascertainment of exposure	**	*	**	**	*	*	**	*	**	*
	Same method of ascertainment for cases and controls	-	-	-	-	-	-	-	*	*	*
	Non-respondent	*	*	*	-	-	*	*	*	*	*

Table 4: Diagnostic methods and altered clinical parameters of the analysed studies

S.NO	AUTHORS (region of study, year)	Diagnostic methods		Altered Parameters in PCOS patients		
		Periodontal Status	PCOS	Clinical (primary outcome)	Immunoinflammatory	Microbiological
1.	Saglam et al Turkey,2017	PD, CAL, BOP, GI, PI Serum and salivary levels of 8-OHdG, MDA, and TAS	Medical history, Rotterdam criteria, Ultrasound, Serum and salivary levels of 8-OHdG, MDA and TAS	PD, BOP, GI, PI	8-OHdG in serum and saliva, MDA in serum	-
2.	Aliya Ackali et al Turkey,2017	PD, BOP, PI, Intraoral radiographs, serum and salivary levels of MMP-8, TIMP-1, MPO and NE	Medical history, Rotterdam criteria, Ultrasound, serum and salivary levels of MMP-8, TIMP-1, MPO, and NE	PD, BOP, PI	Serum and salivary levels of MMP-8, TIMP-1, MPO, and NE	-
3.	Nair et al, India,2017	CAL, GI	Medical history, Rotterdam criteria, Ultrasound	CAL, GI	-	
4.	Najafi et al, Iran 2017	CPI, PDI, Panoramic radiographs, serum TAS	Medical history, Rotterdam criteria, Serum TAS	CPI	-	-
5.	Dursun et al, Turkey, 2011	PD, CAL, GI, BOP, PI, Radiographs, MPO and NO in GCF	Medical history, Rotterdam criteria, Ultrasound, Serum NO level	PD, GI, BOP, PI	MPO and NO levels in GCF	-
6.	Ozgun Ozcaka et al, Turkey,2012	BOP, PD, CAL, PI, Radiographs, TNF-α, TNF-αR1, TNF-αR2, IL-6 in GCF and saliva	Medical history, Rotterdam criteria, Ultrasound, TNF-α, TNF-αR1, TNF-αR2, IL-6 levels in serum, FGS	PD, BOP, PI	IL-6 in GCF, saliva and serum TNF-α in saliva	-
7.	Ozgun Ozcaka et al, Turkey,2013	BOP, PD, PI, CAL, IL-17 in GCF and saliva	Medical history, Rotterdam criteria, Ultrasound, IL-17 levels in serum, FGS	PD, BOP, PI	IL-17A, IL-17F and IL-17A/F in serum IL-17A and IL-17F in GCF and saliva	-
8.	Surya Porwal et al, India, 2014	GI, BOP, PD, CAL, PI	Medical history, Rotterdam criteria, Ultrasound, WC and WHR, hsCRP Serum level	BOP, PD, CAL		
9.	Aliya Akcali et al, Turkey,2014	PD, PI, BOP, qPCR for salivary bacteria quantification	Medical history, Rotterdam criteria, Ultrasound, Serum antibody levels	PD, PI, BOP		Saliva:P. gingivalis,F. nucleatum Serum antibodies: P. intermedia P. gingivalis, S. oralis

10.	Aliya Akcali et al, Turkey,2015	BOP, PI, PD, MMP-8 and TIMP-I levels in GCF	Medical history, Rotterdam criteria, Ultrasound, MMP-8 and TIMP-I in serum	PD, PI, BOP	MMP-8 levels in GCF	
11.	Rahiminejad et al, Iran,2015	BOP, PD, CAL, PI, tooth loss	Medical history, Rotterdam criteria, Ultrasound.	BOP, CAL, PI		
12.	Ayser et al, 2017	PI, GI, BOP, PD, CAL	Medical history, Rotterdam criteria, Ultrasound, SOD levels in serum	PD,CAL	SOD levels in serum	
13.	Hamed et al,2017	PI, GI, BOP, PD, CAL	Medical history, Rotterdam criteria, Ultrasound, Hcy and NO levels in serum	PI, GI, BOP, PD, CAL	Hcy and NO levels in serum	
14.	Manjusha Varadan et al, India,2018	PI, BOP, mGI, MDA and MPO levels in GCF	Medical history, Rotterdam criteria, Ultrasound, MDA and MPO levels in serum	PI, BOP, mGI	MDA and MPO levels in serum and GCF	

Abbreviations: Probing Depth (PD), Clinical Attachment Loss (CAL), Plaque Index (PI), Bleeding On Probing (BOP), Gingival index (GI), modified Gingival Index (mGI), Community Periodontal Index (CPI), Periodontal Disease Index (PDI), Salivary 8-Hydroxy-2'-deoxyguanosine (8-OHdG), Malondialdehyde (MDA), Total Antioxidant Status (TAS), Matrix Metalloproteinase (MMP), Tissue Inhibitor Matrix Metalloproteinase (TIMP), Myeloperoxidase (MPO), Neutrophil Elastase (NE), Nitric Oxide (NO), Tumour Necrosis Factor (TNF), Interleukins (IL), High sensitive C-Reactive Protein (CRP), Superoxide Dismutase (SOD), Homocysteine (Hcy)

Figure 1: The search strategy according to PRISMA guidelines