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PERIODONTITIS AND SYSTEMIC LUPUS ERYTHEMATOSUS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Objective: This systematic review and meta-analysis evaluated the association between periodontitis (PD) and Systemic Lupus Erythematosus (SLE).

Methods: A systematic search was conducted through the following electronic databases: Cochrane Library, MEDLINE, EMBASE, Scopus, LILACS, CINAHL and SIGLE (System for Information on Grey Literature in Europe) for relevant publications up to September 2020 with no language restriction. The association between PD and SLE was assessed by the prevalence of PD in SLE patients (both sex and females only) as the primary outcome. Secondary outcomes included differences in common gingival parameters including probing pocket depth (PPD), clinical attachment level (CAL), Disease Activity Index (SLEDAI) scores of SLE patients with or without PD.

Results: 1183 citations and 22 full text articles were screened. Eighteen articles were included in the qualitative synthesis, and 13 in the quantitative analysis. SLE diagnosis was associated with greater odds of PD (OR=1.33, 95% Confidence Interval [CI]: 1.20-1.48), but these were non-significant when examined in females (OR=3.20, 95%CI: 0.85-12.02). Patients with SLE exhibited no differences in PPD (SMD: -0.09 mm, 95%CI: -0.45-0.27) and CAL (SMD: 0.05 mm, 95%CI: -0.30-0.40) when compared with systemically healthy controls. PD diagnosis was however associated with higher SLEDAI scores in patients suffering from SLE (SMD: 0.68, 95% CI: 0.03-1.32).

Conclusion: PD and SLE are both inflammatory diseases and their association could be bi-directional. This review suggested that the patients with SLE have greater odds of suffering with PD. However, the periodontal inflammation of the SLE patients was not observed worse than the patients without SLE. Further investigations are required to assess the significant association between PD and SLE.

Keywords: Periodontitis, Systemic Lupus Erythematosus, Inflammation, Systematic Review, Meta-Analysis

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic inflammatory disease mediated by immune complexes presenting with various systemic manifestations. Its prevalence has been estimated at 20 to 70 per 100,000 cases each year. Incidence rates for SLE demonstrates 1 to 10 per 100,000 each year and affecting mostly women in the second and third decade of their life (Pons-Estel et al. 2010).

SLE is characterized by a B-cell autoreactivity with increased release of pathogenic antibodies specifically immunoglobulin-G (IgG) leading to multiorgan inflammatory tissue destruction secondary to immune complexes deposition (Kobayashi et al. 2007; Zhang et al. 2017). T-cells are also instrumental in SLE pathogenesis by mediating differentiation, proliferation and maturation of B- cells also involved in autoantibody class-switching (Zhang et al. 2017). In addition, defective regulatory T-cell functions contribute to the perpetuation of inflammation in the pathogenesis of SLE (Suárez-Fueyo et al. 2016). Infections are thought to play a key role in the development of SLE, more specifically in genetically prone individuals (Navarra and Leynes 2010). Molecular mimicry and uncontrolled immune cell activation are among the mechanisms explaining this potential association (Fairweather and Rose 2004).

Almost one fifth of the patients with SLE exhibit poorer oral health which is characterised by a wide range of manifestations including erythematosus oral mucosa/gum/-palate ulcerations, angular cheilitis, glossitis, mucositis, delayed primary or permanent tooth eruption, Sjogren's syndrome and periodontal diseases (Rhodus and Johnson 1990; Srinivasan and Slomovic 2007).

Periodontitis (PD) is a common chronic inflammatory disease caused by a dysbiotic biofilm and characterized by the progressive loss of soft (gums) and hard (alveolar bone) tissues which if left untreated, would result in the loss of the dentition (Flemmig 1999; Cekici et al. 2014). PD affects up to 50% of the worldwide population, being associated with a significant impact on quality of life and high socioeconomic costs (Tonetti et al. 2017; Peres et al. 2019).

Observational evidence suggests a consistent association between PD and other systemic inflammatory diseases. Furthermore, one of the common PD pathogens *Porphyromonas gingivalis* (*Pg*) could plausibly trigger distant immune regulatory changes relevant to the rheumatic diseases (Hamamoto 2020). A limited number of clinical trials examined patients with periodontitis and SLE suggesting a relatively high prevalence of gingival diseases (ranging from 60 to 93.8%) (Rutter-Locher et al. 2017). Furthermore, some limited evidence suggests that PD treatment could improve markers of SLE disease activity (Fabbri et al. 2014) and the influence of periodontitis in the SLE clinical activity measures, such as the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) remains uncertain.

The aim of this systematic review was to comprehensively appraise the evidence on the relationship between PD and SLE.

METHODS

Protocol and Registration

The protocol was finalized and subsequently registered on PROSPERO (registration number CRD42018084748). A Prisma checklist (Supplementary 1, Appendix 1) was adopted when reporting rationale and content of this review (Beller et al. 2013).

Focused question and Eligibility criteria

A broad research question was chosen to minimize bias when analyzing the association between PD and SLE: “Is there a bidirectional association between PD and SLE?”, with the following specific questions:

1. “Are patients with SLE more likely to have PD compared with those without SLE?”
2. “Is the severity of PD influenced by the presence of SLE?”
3. “Does SLEDAI score worsen with the presence of PD?”

The following PECO strategy has been employed:

Population: Adults; **Exposure:** Presence of SLE; **Comparison:** Individuals with no SLE; **Outcome(s):** odds ratio of association between SLE with PD, probing pocket depth (PPD), clinical attachment loss (CAL), effect of PD on SLEDAI score in SLE patients and effect of periodontal treatment on SLE clinical parameters.

Primary and Secondary Outcomes

The primary outcome was the prevalence (odds ratio) of PD in patients with SLE compared with patients without SLE. Secondary outcomes included differences in dental parameters (PPD and CAL) with SLE compared with controls.

According to the disease exposure and diagnosis, the data from the included studies were divided into three groups for PPD and CAL. The mean and standard deviation of PPD and CAL was estimated by using the formula introduced by (Hozo et al.).The Hozo's method is a mathematical equation to estimating the mean and variance from the median, range, and size of a sample (Hozo et al. 2005). Further secondary outcomes included the effect of PD diagnosis on SLEDAI scores in patients with SLE and lastly the impact of PD treatment on SLE clinical parameters.

Inclusion and Exclusion criteria

Observational studies (cohort studies, case-control studies, and cross-sectional studies) and experimental studies (randomized controlled trials, controlled clinical trials) including participants older than 18 years of age with SLE diagnosis according to the American college of Rheumatology (ACR) criteria have been included. Review articles, case reports, animal studies, and studies with participants less than 18 years of age were excluded.

Search methodology

Detailed search strategies followed by manual searching were conducted through the following electronic databases: Cochrane Library, MEDLINE, EMBASE, Scopus, LILACS, CINAHL and SIGLE (System for Information on Grey Literature in Europe) until September 2020 with no language restrictions.

Search was done using the following MeSH terms: “(Systemic Lupus Erythematosus OR Lupus Erythematosus OR SLE OR Systemic OR Lupus) AND (periodontal diseases OR gum disease)” (Supplementary 1, Appendix 2).

Manual searches through published bibliographies of original manuscripts and reviews within the field of periodontal research, rheumatology over the past 10 years were completed.

Study Selection

Titles and abstracts were screened and independently assessed for eligibility by two reviewers (BH and YL). Full-text papers meeting the inclusion criteria were evaluated in duplicate by the same two reviewers. Any disagreement regarding their eligibility was resolved by discussion with a third person (MO). The agreement between the reviewers was assessed by Kappa statistic.

Data Extraction and Synthesis

Independent data extraction was completed by two reviewers (BH and YL) and discrepancies were resolved through discussion with a third reviewer (MO) if necessary. Discrepancies were reduced as per the AMSTAR2 guideline (Shea et al. 2017). The following information was retrieved from all the eligible studies: 1) Year of publication and Country of publication; 2) Study design; 3) Sample size; 4) Periodontal criteria; 5) Periodontal parameters: CAL, PPD, bleeding on probing (BOP), visible plaque index (VPI) and gingival index (GI); 6) SLE diagnosis based on the ACR criteria; 7) Main findings; 8) Published conclusion (Supplementary 1, Appendix 3, Table 1). When data was not located in the manuscripts, every effort was made to contact the authors and requesting the missing information.

Risk of Bias (RoB) and Quality Assessment

The methodological quality of studies included in this review was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies (Wells et al. 2012). Studies were scored as low RoB (7-9 stars), moderate RoB (4-6 stars) and high RoB (1-3 stars). Criteria for

qualitative assessment comprised the following items: sample selection, comparability, and exposure. Each of the items was assessed and graded (1 or 2 points) according to the suggested criteria. In this analysis, studies with NOS scores of 1–3, 4–6, and 7–9, were defined as of low, intermediate and high quality, respectively (Supplementary 1. Appendix 4, Table 2). Randomized controlled trial was appraised (Supplementary 1, Appendix 5, Table 3) using the relevant Cochrane tool (ROB 2.0) (Sterne et al. 2019).

Statistical analysis

Quantitative analyses were performed and estimates were calculated using a DerSimonian-Laird random-effects model (Schwarzer et al. 2015) using R statistical software (version 3.4.1, R Studio Team, 2018) as previously described (Schwarzer et al. 2016). Mean and standard deviations were estimated by using the formulas introduced by Hozo et al. 2005 (Hozo et al. 2005). Forest plots provided visualization of estimates and their 95% confidence intervals (CIs). Random-effects meta-analysis and forest plots were produced using ‘meta’ package (Higgins et al. 2019).

Subgroup meta-analyses according to the periodontal status was conducted for PPD and CAL. Overall, this subgroup approach considered studies of three types: studies with data concerning PD patients (both SLE and control groups); studies with data concerning non-PD studies (both SLE and control groups); and studies that have not report the prevalence of PD (in both SLE and control groups). This last subgroup was named as “PD and non-PD patients” for PPD and CAL analyses (Figure 3 and 4).

Quantity I2 measured the degree of dispersion of effect sizes (ES) estimates and χ^2 test assessed the overall homogeneity statistical significance (Galbraith 1988). According to the Cochrane Handbook, thresholds for the interpretation of I2 can be misleading as the importance of inconsistency depends on several factors. A rough guide to interpretation is as follows: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity*; 50% to 90%: may represent substantial heterogeneity*; 75% to 100%: considerable heterogeneity* (Higgins et al. 2019).

All tests were two-tailed, with alpha set at 0.05 except for the homogeneity test whose significance level cut-off was set at 0.10, due to the low power of the χ^2 test in the context of a limited number of eligible studies. Overall ES estimates were reported with 95% confidence intervals (CI).

RESULTS

Study selection

A total of 1183 studies were identified using the search strategy. After removal of duplicates (n=892) further 870 articles were excluded as did not fulfil the inclusion criteria. Out of the remaining 22 full-length articles that were screened, 4 were further excluded leaving a final sample of 18 manuscripts deemed appropriate to be included in the qualitative analysis whilst 13 were selected for quantitative analysis (Figure 1). Good agreement between the reviewers was achieved (k-value = 0.947, 95% Confidence Interval [CI]: 0.932-0.962).

Assessment Risk of Bias within studies

The majority of the observational studies included in this review presented with a moderate risk of bias (Novo et al. 1999; Meyer et al. 2000; Kobayashi et al. 2003; Kobayashi et al. 2007; Al-Mutairi et al. 2015; Wang et al. 2015; Marques et al. 2016; Calderaro et al. 2017; Corrêa et al. 2017; Wu et al. 2017; Zhang et al. 2017; Corrêa et al. 2018; Gofur et al. 2019), one with high (Mutlu et al. 1993) and three with low risk of bias (Mendonça et al. 2019; Pessoa et al. 2019; Rezaei et al. 2019) (Supplementary 1, Appendix 4, Table 2). Amongst the main factors behind study bias we have identified: definition adequacy, representativeness of the cases, selection and definition of the controls, representativeness of exposed cohort and demonstration that outcome of interest was not present at start of study. One randomized controlled trial was identified and presented with high risk of bias (Supplementary 1, Appendix 5, Table 3) (Fabbri et al. 2014).

Primary Outcome

From a cumulative sample of almost 80,000 individuals, patients with SLE had greater odds of PD diagnosis when compared with controls without SLE (OR=1.33-95%CI: 1.20-1.48) for both sex (Figure 2). When studies including only female patients were evaluated, the odds of PD were not significantly different between groups (OR= 3.20-95%CI: 0.85-12.02) (figure 3).

Secondary Outcomes

Effect of SLE on Dental Parameters

When gingival parameters were compared between patients with and without SLE, no statistically significant differences were noted. No difference in PPD was observed between patients with SLE and controls (SMD of -0.09 mm-95%CI: -0.45-0.27) but with a high level of heterogeneity (I²=90.0%, p<0.01) (Figure 4).

Similarly, no difference in CAL was observed when SLE patients with PD were compared with controls with PD (WMD of 0.05 mm-95%CI: -0.30-0.40), with high level of heterogeneity (I²=89.0%, p<0.01) (Figure 5). Limited data for the remaining periodontal parameters (BOP, GI and VPI) did not allow to perform further meta-analyses.

Effect of PD on SLEDAI scores

Diagnosis of PD was associated with greater SLEDAI scores in patients with SLE (SMD of 0.68-95% CI-I²=72.0%-p=0.03) (Figure 6).

DISCUSSION

This systematic review suggests that patients with SLE have moderately greater odds of suffering from PD but not necessarily presenting with worse periodontal parameters when compared with controls. Further, patients suffering SLE when diagnosed with PD exhibit worsen SLEDAI scores which may be a novel meta-analytical result however, limited evidence exists on the beneficial effect of PD on SLE outcomes.

A previous systematic review published in 2017 concluded that SLE is associated with a higher risk of PD compared with controls (RR = 1.76-95% CI-1.29-2.41) (Rutter-Locher et al. 2017) which support the results of this systematic review. Another systematic review by Zhong et al in 2020 has confirmed the association between PD and SLE however, the data does not represent the observations of the current studies which has been updated through this review (Zhong et al. 2020).

In contrast, this review gathered additional data from more recent publications which resulted in a reduced estimate of association between the two diseases. Further we investigated the impact of sex differences in the association between PD and SLE. This disease is far more common in women and this might be related to Estrogen/Progesterone imbalance and its impact on the host inflammatory response (Lahita 1999; Doria et al. 2002). This could also play a role in the increased susceptibility to periodontitis. Notwithstanding, our meta-analytical results were not able to confirm the link between diagnosis of SLE and periodontitis in females' participants. Further research in understanding the potential mechanisms of sex influence on the association between SLE and periodontitis are needed. The focal point for the interaction of the body with the external environment is the oral cavity, which is consist of different surface types and each is colonized by several species. These species include *bacteria, fungi, protozoa and viruses* (Aas et al. 2005; Jin et al. 2016). The makeup of the oral microbiome is majorly impacted by the level of the oral hygiene of an individual. A healthy individual with better oral hygiene will have an unpretentious flora which is dominated by the *gram-positive rods and cocci* with few *gram-negative cocci*. Whereas individuals with poor oral hygiene will have a more complicated flora dominated by the *an-aerobic gram-negative bacteria* (Scannapieco 2013). Regular dental care can prevent periodontal disease and benefit the patients who are at a higher risk of developing more serious systemic conditions (Haumschild et al. 2009).

Several mechanisms have been proposed to explain the association between auto-immune diseases and periodontitis. SLE is characterized by a loss of self-tolerance, uncontrolled

activation of autoreactive T and B cells leading to production of pathogenic autoantibodies, as well as deficits in apoptosis leading to chronic inflammation and damage (Kobayashi et al. 2007). SLE is assumed to occur when there is an environmental stimulus that initiates inflammation in a 'genetically primed individual'. In a similar fashion, periodontitis is characterized by a deregulated inflammatory response triggered by a dysbiotic dental biofilm (Cekici et al. 2014).

Further evidence of a link between periodontitis and SLE comes from reports confirming expansion of B-cells and plasma cells in oral lesions and peripheral blood or affected organs (Mackler et al. 1977). Common genetic predisposition has been suggested as a plausible mechanism of association between periodontitis and SLE, indeed Fc γ receptor polymorphisms have been identified in both diseases (Kobayashi et al. 2003). Further TLR-4 stimulation by bacteria promoted development of SLE in an experimental mouse model (Marques et al. 2016).

Infectious agents including those from the oral/periodontal environment can interfere with the immune system in various ways such as exposure of camouflaged antigens to the immune cells, an altered apoptosis of host cells or molecular mimicry (Fairweather and Rose 2004).. The most studied is the bacterial contribution of *Pg* through mechanisms of substrate-specific and site-specific citrullination (Bingham and Moni 2013). In SLE patients, neutrophils had an increased capacity to form NETosis (neutrophil extracellular traps) that can anchor auto-antigens that may include dsDNA, granular proteins and chromatin (Tsokos 2020).

Wang et al. found that patients with SLE who also harbored *Treponema denticola* (*Td*) and *Pg* or combination of both had increased titers of anti- β 2-glycoprotein I and anti-cardiolipin antibodies (Wang et al. 2015). Similarly *Aggregatibacter actinomycetemcomitans* (*Aa*) is known to be a potential trigger of autoimmune response in diseases such as RA and SLE (Rutter-Locher et al. 2017). Bagavant et al. identified that the presence of submucosal bacterial infection had impact on SLE disease activity. Anti-dsDNA antibody titer (used as a biomarker in SLE) strongly associated with the presence of *Aa* in patients with periodontitis, suggesting that these bacteria might contribute towards accelerating the anti-dsDNA activity in patients with SLE (Bagavant et al. 2019). A recent study by Sete et al. also identified that patients with juvenile SLE have worse periodontitis and this was associated with altered levels of pro-inflammatory cytokines in gingival crevicular fluid and increased number of *Aa* in the intrasulcular biofilm (Sete et al. 2019).

It has already been proposed that patients with periodontitis might be at increased risk of RA and SLE due to a hyper-inflammatory trait (Bae and Lee 2020). There is however no current consensus regarding periodontal screening of SLE patients. Further research should promote discussion amongst health professional and recognition of the close link between these diseases.

This review observed the potential impact of SLE on clinical periodontal measures and although there was no statistical difference in common measure of periodontal health, it was

obvious an opposite trend of gingival inflammation/loss in patients with or without SLE. Therefore, patients with SLE and periodontitis had a tendency of presenting with minimal periodontal inflammation but greater gingival attachment loss. This preliminary finding could be linked to the effect of SLE treatments on periodontal tissues. Non-steroidal anti-inflammatory (NSAIDs) and immunosuppressive drugs, commonly prescribed to patients with SLE, could have an impact on CAL and PPD. Further investigations are needed to understand the relative role of immunomodulators in SLE and their impact on periodontal tissues.

The association of Periodontitis with SLE disease activity is confirmed by a worsened SLEDAI score (0.68, $p=0.039$). Two studies used the classic SLEDAI score (Zhang et al. 2017; Gofur et al. 2019) whilst Correa et al. adopted its updated version (SLEDAI-2K) (Corrêa et al. 2018). The two indices are comparable but not similar. SLEDAI assesses only new features of SLE while the SLEDAI- 2K version also rates the deteriorating symptoms and existing symptoms in some domains. The impact of periodontitis on SLEDAI reported in this review (SMD=0.68) could have limited clinical significance, nevertheless it is plausible to consider that the periodontitis host response could represent an overlooked factor of SLE symptoms exacerbation. Pessoa et al. already hypothesized that the inflammatory response initiated by the oral microbiota *Pg* could influence the severity of SLE.

. Periodontal treatment may lower systemic inflammation and decrease of systemic inflammation in these patients (Sete et al. 2019). The interventional evidence of a potential benefit of managing periodontitis in SLE is however limited. There is only one randomized controlled trial reporting the effects of periodontal treatment on SLEDAI scores in SLE patients (Fabbri et al. 2014) reporting an improvement in SLEDAI scores following periodontal therapy.

These findings are in line with previous evidence supporting a role in treating periodontitis and a significant decrease in DAS28 in RA patients (Al-Katma et al. 2007; Ortiz et al. 2009). PD has been consistently linked to an endothelial dysfunction, it might also be possible that periodontitis in SLE patients could contribute to their raised vascular risk (Sete et al. 2019). Future research should focus on the potential impact of periodontitis and its associated cardio-metabolic derangements in patients with SLE and the potential of intervention trials to explore causality.

There are some limitations in this review that should be highlighted. Firstly, we identified a high level of heterogeneity between the included studies which prevents drawing any definitive conclusions on the impact of PD on SLE. The presence of the substantial heterogeneity might be due to the existence of the clinical diversity in the studies included which could be inappropriate to derive an estimate of an overall effect from that particular set of studies or it could be related to the clinical diversity of SLE, design of study, method of diagnosis. Limited number of studies and patient's evaluation is still far from ideal to formulate valid conclusions on this association. A compelling limitation in our systematic

review is the realization of an inconsistent use of periodontitis case definitions within the included studies. This review has however comprehensively appraised all the evidence linking SLE and periodontitis using a robust methodology. Further our aim was to assess the association between the two diseases without focusing only on a unidirectional link (SLE causing periodontitis) but reviewing the potential impact of periodontitis on SLE and its complications/outcomes. There is no doubt that more high-quality evidence should be produced on this topic: better observational studies should be conducted as well as experiments on understanding the exact mechanisms linking periodontitis and SLE and inevitably efforts should be devoted to ascertaining the potential benefit of promoting periodontal health in patients with SLE to demonstrate systemic health benefits.

CONCLUSION

This review suggests that patients with SLE have greater odds of suffering from PD but not necessarily presenting with worse periodontal inflammation as compared to the PD patients without SLE. Further research is warranted to investigate the association between PD and SLE and if the resolution of periodontal inflammation could be a novel non-pharmacologic intervention to improve SLE outcomes.

Conflict of Interest

The author declares that no conflict of interest is related to this study.

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