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Does oral lichen planus aggravate the state of periodontal disease? A systematic review and meta-analysis

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Orientador: Prof. Associado Idelmo Rangel Garcia-Junior

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"O que vocês plantam é uma semente; ela pode ser uma simples semente, ou uma semente de amor para as gerações, onde o fogo não queima e a morte não devora; O que é plantado com honra e integridade, crescerá com honra, e assim jamais será destruído. Graças sejam dadas a Deus! Ele que nos dá vitória por meio de nosso Cristo Jesus. Portanto, permaneçam firmes e decididos. Entreguem-se completamente ao trabalho do Senhor, pois tudo o que está no Senhor, não é inútil. Floresce e vinga como uma boa semente, nem a morte destrói, tornando-se eterno".

1 Coríntios 15:37, 56-58 VFL

Resumo

Pirovani BO. Does oral lichen planus aggravate the state of periodontal disease? A systematic review and meta-analysis [dissertação]. Araçatuba: Faculdade de Odontologia, Universidade Estadual Paulista; 2022.

RESUMO

OBJETIVO: O objetivo desta revisão sistemática e metanálise (SRM) foi avaliar as evidências entre a associação de líquen plano oral (OLP) e doença periodontal, avaliando os parâmetros clínicos periodontais e os níveis de biomarcadores. **MATERIAIS E MÉTODOS**: Esta revisão sistemática e meta-análise seguiu PRISMA e foi registrada no PROSPERO (CRD42020181513). Foram realizadas buscas em bases de dados de artigos publicados até junho de 2021. A metanálise foi realizada com as variáveis: índice de placa (PI), índice gengival (GI), profundidade de sondagem (PD) e perda de inserção clínica (CAL). A diferença média foi aplicada com intervalo de confiança de 95%. **RESULTADOS**: 6 artigos foram incluídos. A análise qualitativa mostrou que os níveis de biomarcadores (metaloproteinases de matriz, interleucinas e perfil microbiológico periodontal) estão aumentados em indivíduos com doença periodontal e líquen plano oral. Na metanálise, esses indivíduos também apresentaram aumentos em todos os parâmetros clínicos periodontais avaliados: GI– gengivite 0,22 [0,14, 0,31] p<0,0001 e periodontite 0,12 [0,06, 0,19] p=0,0003; PI– gengivite 0,22 [0,12, 0,31] p<0,0001 e periodontite 0,15 [0,08, 0,23] p<0,0001; PD– gengivite 0,27 [0,06; 0,48] p=0,0107 e periodontite 0,11 [0,01; 0,21] p=0,0299; e CA – periodontite 0,06 [0,01, 0,12] p=0,0176. **CONCLUSÕES**: Evidências sugerem uma relação significativa entre a gravidade da doença periodontal e a presença de líquen plano oral. **RELEVÂNCIA CLÍNICA**: Este SRM fornece informações sobre a interação entre OLP e a doença periodontal e orienta os médicos a tomar decisões baseadas em evidências e sugere recomendações para estudos adicionais de alta qualidade.

Palavras-chave: Doença periodontal. Líquen plano oral. Odontologia baseada em evidências. Revisão sistemática. Meta-análise.

Abstract

Pirovani BO. Does oral lichen planus aggravate the state of periodontal disease? A systematic review and meta-analysis [dissertação]. Araçatuba: Faculdade de Odontologia da Universidade Estadual Paulista; 2022.

ABSTRACT

BACKGROUND: The objective of this systematic review and meta-analysis (SRM) was to assess the evidence between the association of oral lichen planus (OLP) and periodontal disease, evaluating the periodontal clinical parameters and biomarkers levels. **METHODS:** This systematic review and meta-analysis followed PRISMA and was registered in PROSPERO (CRD42020181513). Searches were accomplished in databases for articles published until June 2021. The meta-analysis was performed with the variables: plaque index (PI), gingival index (GI), probing depth (PD), and clinical attachment loss (CAL). The mean difference was applied with a 95% confidence interval. **RESULTS:** 6 articles were included. Qualitative analysis showed the levels of biomarkers (matrix metalloproteinases, interleukins, and periodontal microbiological profile) are increased in subjects with periodontal disease and oral lichen planus. In the meta-analysis, these subjects also presented increases in all periodontal clinical parameters evaluated: GI– gingivitis 0.22 [0.14, 0.31] p <0.0001 and periodontitis 0.12 [0.06, 0.19] p =0.0003; PI– gingivitis 0.22 [0.12, 0.31] p <0.0001 and periodontitis 0.15 [0.08, 0.23] p <0.0001; PD– gingivitis 0.27 [0.06; 0.48] p=0.0107 and periodontitis 0.11 [0.01; 0.21] p=0.0299; and CA – periodontitis 0.06 [0.01, 0.12] p=0.0176. **CONCLUSIONS:** Evidence suggests a significant relationship between the severity of periodontal disease and the presence of oral lichen planus. **CLINICAL RELEVANCE:** This SRM provides information on the interaction between OLP and periodontal disease and guides clinicians to make evidence-based decisions and suggests recommendations for further high-quality studies.

Keywords: Periodontal disease. Oral lichen planus. Evidence-based dentistry. Systematic review. Meta-analysis.

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LISTA DE ABREVIATURAS E SIGLAS

+ Minor Problem

++ Major Problem

0 No Problem

CAL Clinical Attachment Loss

CI Confidence Interval

G_1 No Oral Lichen Planus

G_2 Oral Lichen Planus Subjects

GI Gingival Index

IL Interleukins

MMP Matrix Metalloproteinases

n Number Of Subjects

OLP Oral Lichen Planus

PCR Polymerase Chain Reaction

PD Probing Depth

Peco Population, Exposure, Comparison, And Outcome Criteria

PI Plaque Index

Prisma Preferred Reporting Items For Systematic Reviews And Meta-Analysis

RA Rheumatoid Arthritis

SRM Systematic Review And Meta-Analysis

TIMP-1 Tissue Inhibitor of Metalloproteinase-1

Sumário

SUMÁRIO

Manuscrito para Publicação[*]

[*] Manuscrito elaborado segundo a normatização da revista Clinical Oral Investigations (Anexo A)

Does oral lichen planus aggravate the state of periodontal disease? A systematic review and meta-analysis

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ABSTRACT

BACKGROUND: The objective of this systematic review and meta-analysis (SRM) was to assess the evidence between the association of oral lichen planus (OLP) and periodontal disease, evaluating the periodontal clinical parameters and biomarkers levels. **METHODS:** This systematic review and meta-analysis followed PRISMA and was registered in PROSPERO (CRD42020181513). Searches were accomplished in databases for articles published until June 2021. The meta-analysis was performed with the variables: plaque index (PI), gingival index (GI), probing depth (PD), and clinical attachment loss (CAL). The mean difference was applied with a 95% confidence interval. **RESULTS:** 6 articles were included. Qualitative analysis showed the levels of biomarkers (matrix metalloproteinases, interleukins, and periodontal microbiological profile) are increased in subjects with periodontal disease and oral lichen planus. In the meta-analysis, these subjects also presented increases in all periodontal clinical parameters evaluated: GI– gingivitis 0.22 [0.14, 0.31] p <0.0001 and periodontitis 0.12 [0.06, 0.19] p =0.0003; PI– gingivitis 0.22 [0.12, 0.31] p <0.0001 and periodontitis 0.15 [0.08, 0.23] p <0.0001; PD– gingivitis 0.27 [0.06; 0.48] p=0.0107 and periodontitis 0.11 [0.01; 0.21] p=0.0299; and CA – periodontitis 0.06 [0.01, 0.12] p=0.0176. **CONCLUSIONS:** Evidence suggests a significant relationship between the severity of periodontal disease and the presence of oral lichen planus. Although the association is biologically plausible, further studies are needed using populations and well-defined biochemical and clinical outcomes with consideration of potential confounding factors. **CLINICAL RELEVANCE:** This SRM provides information on the interaction between OLP and periodontal disease and guides clinicians to make evidence-based decisions and suggests recommendations for further high-quality studies.

Keywords: Periodontal disease; Oral lichen planus; Evidence-based dentistry; Systematic review; Meta-analysis

1 INTRODUCTION

Periodontal disease is characterized by an immunoinflammatory disorder, in which structurally complex and organized oral biofilm in dysbiosis is the primary etiological factor. Periodontal diseases can be classified in different ways, wherein gingivitis and periodontitis are the most common forms of manifestation of the disease [1]. Periodontal disease, in the form of gingivitis, consists of inflammation associated with bacterial biofilm that affects the tooth's protective tissues (gums and oral mucosa). This condition is reversible through improved periodontal health; however, if it progresses to Periodontitis, it becomes irreversible [1,2]. Periodontitis, in turn, comprises a multifactorial chronic inflammatory disease associated with a dysbiotic biofilm that affects, beyond the gingiva, the supporting tissues of the dental element, and when untreated can lead to tooth loss [1-3]. It also exhibits a process of immunological dysregulation [3].

The scientific literature reports that, in general, the inflammation caused by periodontal disease, mainly periodontitis, is not limited only to periodontal tissues [4]. This is because the pathogenesis of the disease encompasses immunological and inflammatory processes capable of triggering the production of some inflammatory mediators such as cytokines, prostaglandins, C-reactive protein, and interleukins. These can spread systemically through the bloodstream and have a measurable impact on systemic inflammation [5], which in turn may injure tissues such as: articular [6], renal [5,7], cardiac [8], and hepatic [9,10] ones. In addition, a plausible association between periodontal disease and cancer risk has also been reported [11,12].

There is strong evidence that autoimmune inflammatory diseases, such as rheumatoid arthritis (RA), can worsen periodontal clinical parameters. Like Periodontitis, RA is also characterized by a hyper-inflammatory state and is the result of an unregulated immune response [13,14]. Although the mechanism of these interactions has not yet become clear, patients with periodontal disease and autoimmune diseases present altered levels of biological markers and more severe periodontal conditions [3,15,16].

In addition, many types of immune-mediated skin diseases are often seen in the oral mucosa region. These types of dermatoses mainly include oral lichen planus, bullous pemphigoid, erythema multiforme, and lupus erythematosus [17]. Oral lichen planus is a chronic

mucocutaneous inflammatory disease that affects from 1% to 2% of the population [18,19], demonstrating malignant changes at rates of 0.3% to 10% [20]. Although the etiological factors of oral lichen planus are not yet well defined, it is known that oral lichen planus is associated with mental stress, malnutrition, viral infection, mechanical trauma, and tobacco use [21,22]. A possible immunological cause of the disease has also been reported, in view of its frequent association with some autoimmune syndromes [23,24].

Studies have shown that biomarkers, previously described in several models of autoimmune diseases and inflammation-mediated destruction, are also present in periodontal diseases and in OLP, playing an important role in the pathogenesis of both diseases [25,26]. However, there is still no consensus in the literature regarding the interrelationship between the two diseases, and whether oral lichen planus is related to the worsening of periodontal disease [27,28]. Thus, due to the shortage of sufficient scientific evidence and systematic reviews addressing periodontal disease associated with oral lichen planus, and knowing that biological markers may be altered in patients with either of these diseases [28], there is a possibility that both conditions result from underlying common pathological features, demonstrating a strong association with each other. Therefore, a study with the objective of verifying whether oral lichen planus is a risk factor that may worsen periodontal disease is extremely relevant.

2 MATERIALS AND METHODS

2.1 Protocol and registry

This systematic review was structured according to the Checklist of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [29-31], in accordance with the guidelines in the Cochrane Handbook [32] and registered in the International Prospective Registry of Systematic Reviews (PROSPERO - CRD42020181513).

2.2 Eligibility criteria and question PECO

Inclusion criteria were; i) types of studies: observational studies performed with subjects with periodontal disease (gingivitis, periodontitis), comparing subjects with and without oral lichen planus, ii) types of participants: adult subjects over 20 years of age diagnosed with periodontal disease (gingivitis, periodontitis) [33]; studies in which the investigators diagnosed oral lichen planus according to its clinical manifestation and pathologic characteristics, on the basis of the definition of oral lichen planus by the World Health Organization [34] and criteria meet the current standards of oral lichen planus diagnosis [35]; and iii) studies with a sample size of at least 10 subjects who had not received any treatment for oral lichen planus and periodontal disease within 90 days before the periodontal evaluation and specimen collection. Studies not meeting the inclusion criteria were excluded. Additionally, studies with participants who had other infections, allergies, autoimmune diseases, or any systematic disease that may have influenced the evaluation of periodontal state and biological markers were excludes. As well retrospective studies, case series, case reports, non-human studies, literature reviews, and studies based on expert opinions were also excluded. No restrictions were applied related to language and publication period. A specific question was raised, based on the population, exposure, comparison, and outcome criteria (PECO): “Does oral lichen planus aggravate periodontal clinical parameters and biomarker levels in subjects with periodontal disease?” Regarding the criteria, P was composed of subjects with periodontal disease, E and C consisted of subjects with and without oral lichen planus, respectively, while O represented the clinical periodontal condition and biological marker levels.

2.3 Sources of information and search strategy

Two independent authors (GPN and BOP), guided by a specialized librarian, conducted an electronic search in the following electronic databases, until June 2021: PubMed/MEDLINE, Scopus, Web of Science, Embase, Cochrane Library. A specialized librarian guided the entire electronic search strategy. A manual search was also performed to identify manuscripts that might not have been retrieved by the electronic search. In order to find unpublished or ongoing studies, the registry of clinical trials was investigated on the website ClinicalTrials.gov

(www.clinicaltrials.gov), without restriction on the date or language of publication. A manual research was also performed for articles published in the following journals: Journal of Periodontology, Journal of Clinical Periodontology, Periodontology 2000, Journal of Periodontal Research, Journal of Dentistry, Journal of Dental Research, Archives of Oral Biology, Clinical Oral Investigations. In addition, the grey literature (produced at governmental, academic, entrepreneurial, and industrial levels, in printed or electronic format, yet not controlled by commercial publishers) was examined using the Open Grey database (http://www.opengrey.eu/http:// www.opengrey.eu/). The search strategy was accomplished using the search terms:((Periodontal Diseases)[All Fields] OR (Disease, Periodontal) [All Fields] OR (Diseases, Periodontal)[All Fields] OR (Periodontal Disease)[All Fields] OR Parodontosis [All Fields] OR Parodontoses [All Fields] OR (Pyorrhea Alveolaris) [All Fields] OR Periodontitis[All Fields] OR Periodontitides[All Fields] OR Pericementitis[All Fields] OR Pericementitides[All Fields] OR Gingivitis[All Fields] OR Gingivitides[All Fields]AND (Lichen Planus, Oral)[All Fields] OR (Oral Lichen Planus)[All Fields] OR (Lichen planus) [All Fields] OR (Lichen Ruber Planus)[All Fields] OR (Lichen Rubra Planus)[All Fields] OR (Lichen plan buccal)[All Fields].

2.4 Study selection and data extraction process

Initially, the articles were selected by the title and abstract according to the pre-established eligibility criteria, and all discrepancies were analysed by a third reviewer (TMF) through a consensus meeting. One of the authors (GPN) collected the relevant information from the articles and a second author (BOP) reviewed it. The following variables were collected from the articles: author/year (local), study design, number of subjects (*n*), and sex, for G_1 (no oral lichen planus) and G_2 (oral lichen planus subjects), mean age, characteristics of the samples included**,** use of medication and systemic disturbs, evaluation method, statistical analysis, and outcomes: clinical periodontal examination and biomarker. The kappa score was applied to calculate the interexaminer agreement during the inclusion process for publication-evaluated databases. Any disagreements were resolved by discussion and consensus of all authors.

2.5 Quality Assessment and Risk of Bias

The Fowkes and Fulton's checklist [36] was used in this systematic review to evaluate the quality and risk of bias of the included studies. In this checklist, the quality of the articles was assessed by seven central domains: “Study design appropriate to the objective”; “Study sample representative”; “Control group acceptable”; “Quality of measurements and outcomes”; “Completeness”; and “Distorting influences”.

Each domain was awarded 0 (no problem), + (minor problem), or ++ (major problem). The criteria for this evaluation were standardized by the evaluators and adapted from Fowkes and Fulton, 1991 [36] and Almeida et al. 2018 [37] (Supplementary File 2).

The risk of Bias was evaluated following three summary questions presented at the end of the checklist: “Bias: Are the results erroneously biased in a certain direction?” “Confounding: Are there any serious confusing or other distorting influences?,” and “Chance: Is it likely that the results occurred by chance?” Each question was answered as “Yes” or “No”. In case of a “No” answer to all questions, the study was considered as a low risk of Bias.

2.6 Meta-analysis

The data in the studies were analyzed using R software with Meta package, version 3.6.3 aided by the RStudio platform to evaluate the interaction between periodontal disease and oral lichen planus. Seven meta-analyses (3 for gingivitis and 4 for periodontitis) were performed with the main periodontal parameters analyzed by the studies: (1st) gingival index (GI), (2nd) plaque index (PI), (3rd) probing depth (PD), and (4th) clinical attachment loss (CAL). The mean and standard deviation of each parameter, and the total number of individuals of each group (case – with oral lichen planus- and control – without oral lichen planus) were used.

For parameters reported using similar methods, the mean difference was applied, and for parameters measurement in a variety of ways, the standard mean difference was applied [38], with 95% confidence interval (CI). Only studies free of bias were included in the meta-analysis.

If some of the information needed for the meta-analysis was absent from any of the selected studies, the authors were contacted to provide the missing data.

Heterogeneity was tested using the I^2 index, considering I^2 index $\geq$ 50% as substantial or considerable. A random effect model was employed as the studies were not functionally equivalent, with the objective of generalizing the results from the meta-analysis [39]. However, in the forest plot we also showed the fixed effect model. To access the publication bias was used the funnel plot (n=2) and the trim-and-fill method (n $\geq$ 3). In addition, the trim-and-fill method was also used to evaluate bias on meta-analysis [40].

3 RESULTS

3.1 Literature search

The database search retrieved 1573 studies: 436 from PubMed/MEDLINE, 495 from Scopus, 221 from Web of Science, 401 from Embase, and 18 from Cochrane Library (Figure 1). After removal of duplicates, a total of 852 studies remained for the evaluation of titles and abstracts. Subsequently, 9 articles were selected for full reading, with 3 articles excluded after the assessment of the eligibility criteria (Supplementary file) [41,42]. Thus, one cross-sectional study [43] and five case-control studies were included in the review [44-48]. The kappa score for articles included in all databases showed an acceptable level of interexaminer agreement (k = 0.89).

3.2 Description of the studies

The characteristics of the 6 studies are listed in Table 1. A total of 244 subjects with periodontal disease, with a mean age of 47.96 years, made up the samples of the studies, including 116 subjects with oral lichen planus and 128 subjects without oral lichen planus. The included studies were developed in China [44,45,48], Turkey [46,47], and Italy [43]. Of the studies included, regarding the type of periodontal disease, three studies evaluated only periodontitis [44,45,48], one study analyzed only gingivitis [43], and two studies analyzed both periodontal diseases [46,47]. None of the studies included subjects with systemic diseases.

The methods for the evaluation of periodontal parameters were plaque index [45-48], gingival index [44-48], probing depth [43-48] clinical attachment loss [43-48], bleeding on probing [44], full-mouth bleeding score [43], full-mouth plaque scores [43], and missing teeth [43]. For evaluation of biological markers, the methods used were polymerase chain reaction (PCR) for microbiological tests [43,46,47], ELISA [44,48] and immunohistochemistry and real-time PCR [45] to evaluate interleukins (IL); Enzyme-linked immunosorbent assay and immunohistochemical methods to analyze matrix metalloproteinases (MMP) and MMP inhibitors [47].

3.3 Characteristics of the included studies related to clinical periodontal evaluation and biological markers

All selected studies evaluated the periodontal clinical condition. All studies reported that the presence of oral lichen planus aggravated periodontal clinical parameters. For PI and GI, four studies showed an increase in these parameters for the oral lichen planus-group [45-48]. For PD and CAL, all studies included found less aggravation of these parameters for the non-oral lichen planus groups [43-48]. Likewise, two studies reported increased bleeding on probing in subjects with oral lichen planus [43,44]. Analyzing missing teeth, one study observed greater tooth loss for oral lichen planus subjects in comparison with non-oral lichen planus subjects [44].

The study that quantified periodontopathogenic microorganisms only in subjects with gingivitis concluded that there was a significant increase in the counts of these microorganisms in subjects with oral lichen planus compared with individuals without the disease [43]. Another study verified that detected percentages of periodontopathogen microorganisms in the oral lichen planus groups for the two periodontal diseases (gingivitis + oral lichen planus and periodontitis + oral lichen planus) were significantly higher than those in the non-oral lichen planus groups (controls: only gingivitis and periodontitis) [46]. The findings of these studies reveal that oral lichen planus subjects have a greater tendency to be infected with periodontal pathogens.

Moreover, when assessing the interleukin biomarkers, two studies showed a significant increase in the levels of IL-17 and IL-23 for subjects with periodontitis and oral lichen planus

[45,48], while another study also reported an increase for IL-35, in both the gingival crevicular fluid sample and in the serum sample, in the subjects of the exposure group compared to the control group [44]. These results showed higher interleukin levels in the periodontitis + oral lichen planus group compared with the periodontitis group, indicating the potential interaction between periodontitis and OLP.

In the investigation of MMP expression, Ertugrul et al [47] observed that MMP-1 and MMP-9 levels were higher and tissue inhibitor of metalloproteinase-1 (TIMP-1) level lower for the oral lichen planus group. Furthermore, it is worth mentioning that the MMP-1 and MMP-9 levels correlated positively with the clinical periodontal parameters (GI, PI, PD, and CAL). The TIMP-1 levels correlated negatively with the same clinical periodontal parameters.

3.4 Risk of bias within studies

During the analysis, some factors were considered in order to reduce the risk of bias and favor the applicability of this review and promote conclusions on the association between oral lichen planus and periodontal disease. Among them, the inclusion and exclusion criteria led to the inclusion of groups that presented similar characteristics differing only in the presence/absence of the oral lichen planus criterion. Thus, the variables oral lichen planus and periodontal disease were the primary variables related to the outcome.

All studies were classified with a low risk of bias [43-48]. However, minor pitfalls were identified among articles related to the sampling method, sample size, absence of description of randomization/matching process, and reproducibility (Table 2). Besides the standardized methods, the absence of systemic diseases and the use of statistical methods to reduce the confounding factors may reduce the risk of Bias of the included studies.

3.5 Meta-analysis and quantitative assessment of bias

All six studies were included in this analysis. For the data on biological markers, the studies did not contain sufficient data for quantitative analysis, even after contact attempts, and therefore were not included in the analysis.

3.5.1 Meta-analysis for the gingival index (GI)

Gingivitis: Two studies [46,47] evaluated the mean plaque index. Pooled results showed null heterogeneity ($I^2 = 0\%$). Individuals with and without oral lichen planus presented significant differences in the plaque index, 0.22 [0.14, 0.31] $p < 0.0001$ (Fig. 2A). Publication and meta-analysis bias were not observed with the funnel plot (Fig.2B).

Periodontitis: Five studies [44-48] evaluated the mean gingival index per site. Pooled results showed null heterogeneity ($I^2 = 0\%$). Individuals with and without oral lichen planus presented significant differences in the gingival index 0.12 [0.06, 0.19] $p = 0.0003$ (Fig. 2C). Publication and meta-analysis bias were not observed with the trim-and-fill method (Fig. 2D)

3.5.2 Meta-analysis for the plaque index (PI)

Gingivitis: Two studies [46,47] evaluated the mean plaque index. Pooled results showed null heterogeneity ($I^2 = 0\%$). Individuals with and without oral lichen planus presented significant differences in the plaque index, 0.22 [0.13, 0.31] $p < 0.0001$ (Fig. 3A). Publication and meta-analysis bias were not observed with the funnel plot (Fig.3B).

Periodontitis: Four studies [45-48] evaluated the mean plaque index. Pooled results showed null heterogeneity ($I^2 = 0\%$). Individuals with and without oral lichen planus presented significant differences in the plaque index, 0.15 [0.08, 0.23] $p < 0.0001$ (Fig. 3C). Publication and meta-analysis bias were not observed with the trim-and-fill method (Fig.3D).

3.5.3 Meta-analysis for the Probing depth (PD)

Gingivitis: Three studies [43,46,47] evaluated the mean probing depth. Pooled results showed high heterogeneity ($I^2 = 60\%$). Individuals with and without oral lichen planus presented significant differences in PD 0.27 [0.06; 0.48] $p=0.0107$] (Fig. 4A). Publication bias was observed in two articles with the trim-and-fill method [43,46]. Consequently, bias was also observed in the meta-analysis. Thus, individuals with and without oral lichen planus presented

significant differences in PD 0.18 [0.00; 0.36] *p*=0.0464, but with high heterogeneity (I^2=61%) (Fig. 4B).

Periodontitis: Five studies [45,48] evaluated the mean probing depth. Pooled results showed discrete heterogeneity ($I^2 = 36\%$). Individuals with and without oral lichen planus presented significant differences in PD 0.11 [0.01; 0.21] *p*=0.0299. (Fig. 4C). Publication bias was observed in three articles with the trim-and-fill method [44,45,48]. Consequently, bias was also observed in the meta-analysis. Thus, individuals with and without oral lichen planus did not present significant differences in PD 0.07 [-0.03; 0.17] p=0.1608. In addition, discrete heterogeneity remained ($I^2 = 34\%$) (Fig. 4D).

3.5.4 Meta-analysis for clinical attachment loss (CAL)

Periodontitis: Five studies [44-48] evaluated the mean CAL. Pooled results also showed null heterogeneity ($I^2 = 0\%$). Individuals with and without oral lichen planus presented significant differences in CAL 0.06 [0.01, 0.12] *p*=0.0176 (Fig. 5A). Publication bias was observed in three studies with the trim-and-fill method [44,45,47]. Consequently, bias was also observed in the meta-analysis. Thus, individuals with and without oral lichen planus did not present significant differences CAL 0.04 [-0.01; 0.09] *p*=0.0886. In addition, null heterogeneity remained ($I^2 = 0\%$) (Fig. 5B).

4 DISCUSSION

To the authors' knowledge, this is the first systematic review and meta-analysis to assess the potential evidence associating the worsening of the periodontal state to oral lichen planus and periodontal diseases (gingivitis and periodontitis), as well as to analyze the biological markers present. Based on the results, oral lichen planus is a risk factor for periodontal diseases, since the periodontal parameters evaluated in the studies were intensified when compared to patients without oral lichen planus [43-48], and there was an increase in cytokine levels, such as IL-17, IL-23, and IL-35 [44,45,48].

Periodontal diseases are caused by the development of oral biofilm in dysbiosis and are modulated by the host's immune-inflammatory response [49,50]. Regarding the periodontal parameters adopted by the studies and evaluated by the present review, of the six articles included, four investigated and showed significant results for the increase in plaque and gingival indices in the presence of oral lichen planus [45-48]. Our results corroborate those found in the study by Rai et al [51], in which higher PI and GI were reported for patients with OLP, when compared to the healthy control group, with respective means and standard deviations of (GI 4.66 ± 0.76, PI 2.56 ± 0.60), control group (GI 1.78 ± 0.57, PI 1.15 ± 0.41) p-value = 0.0001. The authors infer that the accentuated periodontal state in this group of patients with oral lichen planus is due to poor oral hygiene, related to the difficulties encountered in its performance, thus leading to an increase in gingival inflammation and periodontal problems.

The spread of bacterial endotoxins from the periodontal pocket induces activation of the chronic inflammatory response against periodontopathogens, resulting in intense production of pro-inflammatory cytokines, such as IL-1β, IL-6, IL-8, IL-10, IL-12, IL-17, TNF-α, chemokines, and prostaglandins [52,53]. The results presented reiterate the study by Lin et al [6], who observed that the activity of cytokines and inflammatory mediators is closely related to the worsening of periodontal clinical parameters [54], such as the presence of monocytes, that can promote the differentiation of bone resorption cells under bacterial stimulus, which in turn are responsible for the bone loss seen in periodontitis [55]. In addition, the data indicated statistically significant changes in the subgingival plaque in the OLP group compared to that in the non-OLP group, implying a correlation between the changes in subgingival microbial composition and OLP incidence. The relationship between subgingival plaque microorganisms and OLP could be explained because the number and compositions of plaque microorganisms change as OLP lesions are formed. Subgingival plaque, as an initial factor of periodontal disease, might prevent OLP gingival lesions from healing, as well as subgingival plaque microbiome, which plays a direct or indirect role in the development of OLP lesions and may lead to the aggravation of periodontal disease and opportunistic infection. Future research in this area should be oriented toward the quantitative assessment of periodontitis microflora cohabitants in well-designed prospective studies. With evidence that the periodontal disease microbiologic profile is complex

and determined by complex interrelationships, we cannot afford to ignore that more specific methods are needed for risk estimation in future research.

It is important to note that the majority of these cytokines present in periodontal disease are also seen in oral lichen planus, playing an important role in mediating inflammation and regulating the immune response [56]. This was verified in three of the studies included in this review, in which there was a significant increase in the levels of cytokines IL-17 and IL-23 in patients with periodontal involvement in the presence of oral lichen planus, when compared to the group of subjects with only periodontitis, subjects with only oral lichen planus, or healthy controls [44,45]. In the study by Wang et al [44], the increased expression of IL-35 was evaluated, with significantly higher levels in the group of individuals with periodontitis and oral lichen planus, which the authors correlated with more exacerbated periodontal parameters.

In addition, adaptive immunity cells and their cytokines have been cited as important factors in the pathogenesis of periodontal disease, especially CD4 T cells (T helper cells) [57]. These cells are subdivided according to their production of cytokines [58], into T-helper 1 cytokines, which are related to infectious inflammatory bone destruction, or T-helper 2 cytokines that minimize bone loss [59]. There are also T-helper subsets with prominent roles in modulating host responses, Th17 cells. These promote osteoclastic activity through the production of IL-17, causing destructive periodontal inflammation [60], in addition to presenting inflammatory properties involved in a series of infectious and autoimmune processes, including periodontal diseases and oral lichen planus [28]. As indicated above, oral lichen planus is a chronic inflammatory oral mucosal disease accompanied by high prevalence of $CD4^+$ T helper cell-mediated immune response, while chronic periodontitis is also a chronic inflammation triggered by hazardous microorganisms and the consequent immune-inflammatory responses.

IL-17, as shown in the results of this study, presents increased levels in the association of periodontitis with OLP, linked to a more intensified periodontal condition, correlated to the interaction of both diseases [44,45], and reaffirming the findings of previous studies [26,28]. In the meantime, our results also present important findings for IL-23 and IL-35, which were found at significantly increased levels in the presence of oral lichen planus and periodontitis. From this finding, these cytokines can be seen to have an important role in the association between these

two diseases, and the analysis of their expression in genetic studies with larger sample sizes is necessary, to identify them as future genetic markers in the pathogenesis of both diseases.

Another relevant piece of information that should be highlighted concerns MMPs, which are related to the preservation of periodontal connective tissue in healthy individuals [61] and to the performance of pathophysiological functions [62]. It is important to mention that MMP-1 has a relevant role in connective tissue, being present in great concentrations in inflamed sites, as in the case of periodontal disease [63]. MMP-9, on the other hand, is actively related to denatured collagen (gelatine), type IV collagen, and has a proteolytic action on elastin and proteoglycans [64]. TIMP-1 is an enzyme inhibitor, and together with MMP provides maintenance of physiological processes in an organism [61]. In our findings [47], levels of MMP-1 and MMP-9 were reported to be higher, and the level of TIMP-1 lower for the OPL group, being positively correlated with periodontal parameters (GI, PI, PD, and CAL), while TIMP-1 levels were negatively correlated with these parameters. These findings are reported and corroborated by studies in the literature [65,66]. Thus, the increase in MMP-1 and MMP-9 and decrease in TIMP-1 in subjects with oral lichen planus leads to periodontal damage and progression, in a way that causes exacerbation of periodontal clinical parameters, with strong interaction of both diseases. Thus, this seems to highlight the influence of immuno-biopathogenic mechanisms of OLP on periodontal disease. Hence, since the population analyzed in this systematic review was patients with periodontal disease, it is suggested that OLP may favor the aggravation of these oral diseases (gingivitis and periodontitis). In addition, it is also pertinent to eventually assess in healthy patients (control) whether exposure to oral lichen planus (case) can increase the possibility (risk) of acquiring periodontal diseases in the long term. Although studies have indicated this relation, it cannot be stated so confidently.

The absence of analyses that verify publication-related biases can lead to statistical controversies, especially in clinical studies. This fact has already been evidenced for systematic reviews and meta-analyses in clinical studies in oncology, and these studies used graphic funnel analysis in most cases [67]. In the present work, we chose to perform a quantitative analysis called the trim-and-fill test. The trim-and-fill test identifies studies with the possibility of presenting publication biases and, in addition, corrects the values found for mean and standard deviation by estimating these parameters. In addition, by correcting the values, we were able to

perform another meta-analysis, also identifying bias related to the meta-analysis [40,68]. This fact is clear when comparing the different forest plots. The results of the present study showed publication and meta-analysis biases for gingivitis and periodontitis in the following clinical parameters: “probing depth” and “clinical attachment loss”. Therefore, the significant results in periodontitis found for the clinical parameters “plaque index” and “gingival index” are more reliable to be inferred for other populations. Thus, long-term prospective studies are required for such an important issue; but, based on these data, maybe a higher level of attention in patients with periodontal disease and OLP lesions seems prudent.

5 CONCLUSION

Within the limitations of the present systematic review, it can be concluded that oral lichen planus aggravates the periodontal clinical parameters and increases the levels of biomarkers for periodontal disease.

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Figures

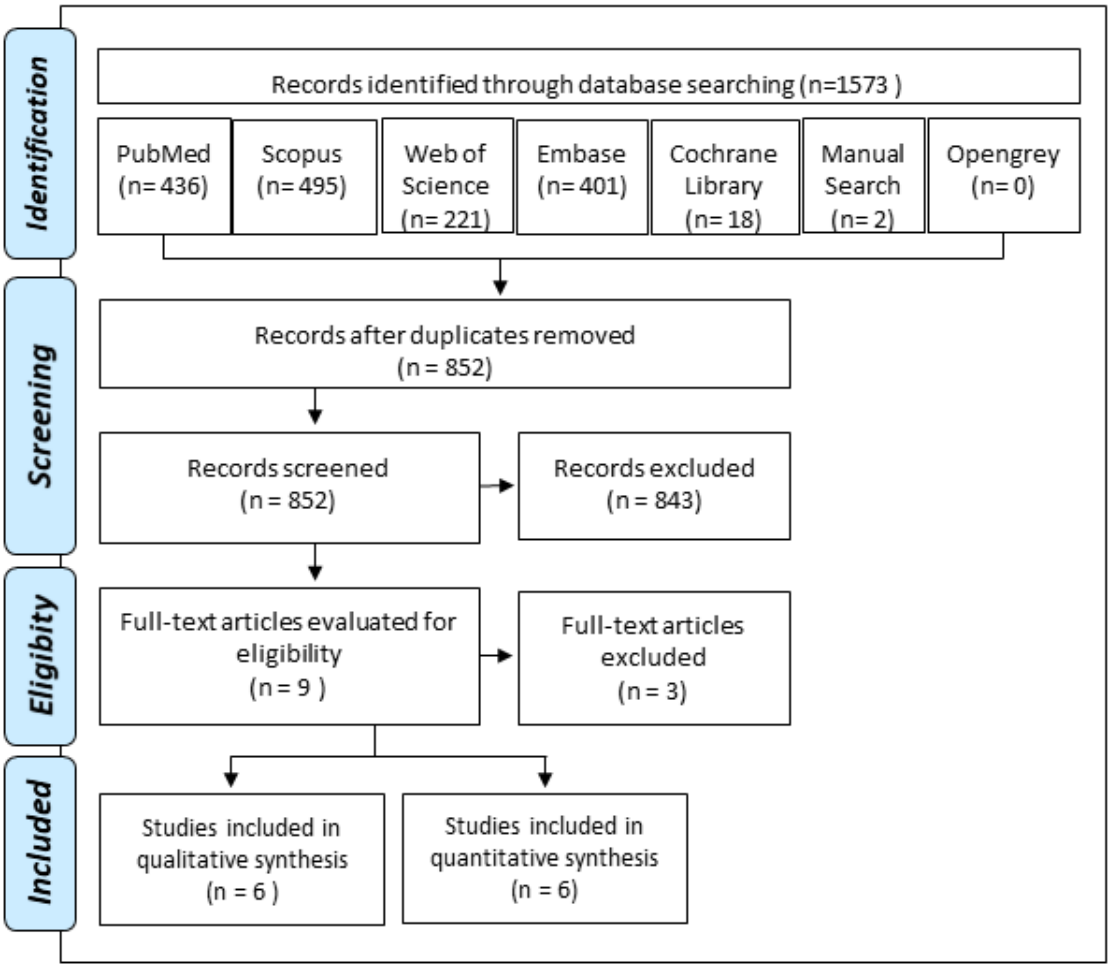

Fig. 1 Flow diagram of search in databases according to PRISMA Statement.

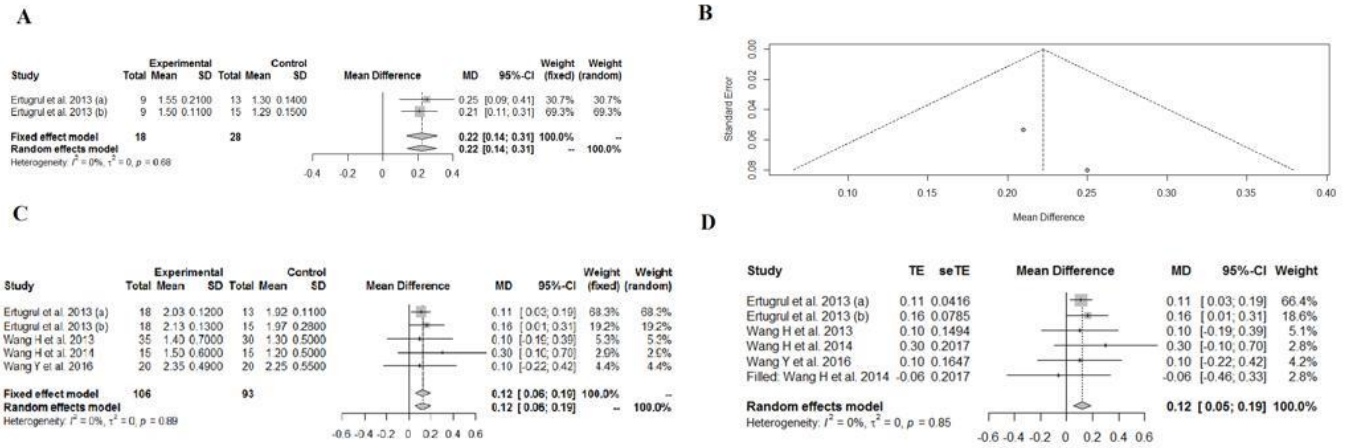

Fig. 2 Forest plot of mean Gingival Index (GI) in individuals with gingivitis or periodontitis (control), gingivitis or periodontitis + oral lichen planus (experimental). A: Meta-analysis GI in gingivitis; B: Publication/ meta-analyses biases – funnel plot in GI/gingivitis; C: Meta-analysis GI in periodontitis; D: Publication/ meta-analyses biases - trim-and-fill method in GI/periodontitis. SD = standard deviation; MD = mean difference; CI = confidence interval; TE = estimated mean; SeTE = estimated standard deviation.

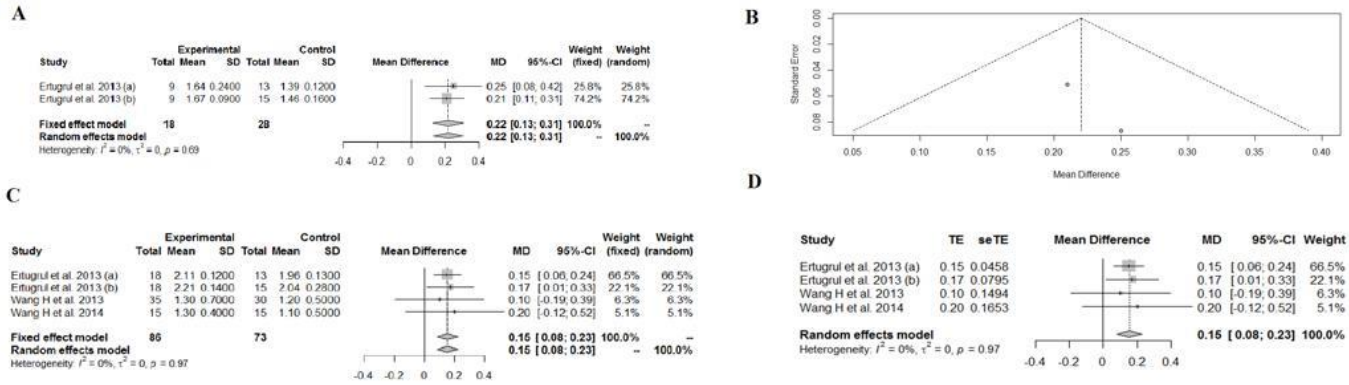

Fig. 3 Forest plot of mean Plaque index (PI) in individuals with gingivitis or periodontitis (control), gingivitis or periodontitis + oral lichen planus (experimental). A: Meta-analysis PI in gingivitis; B: Publication/ meta-analyses biases – funnel plot in PI/gingivitis; C: Meta-analysis PI in periodontitis; D: Publication/ meta-analyses biases - trim-and-fill method in PI/periodontitis. SD = standard deviation; MD = mean difference; CI = confidence interval; TE = estimated mean; SeTE = estimated standard deviation.

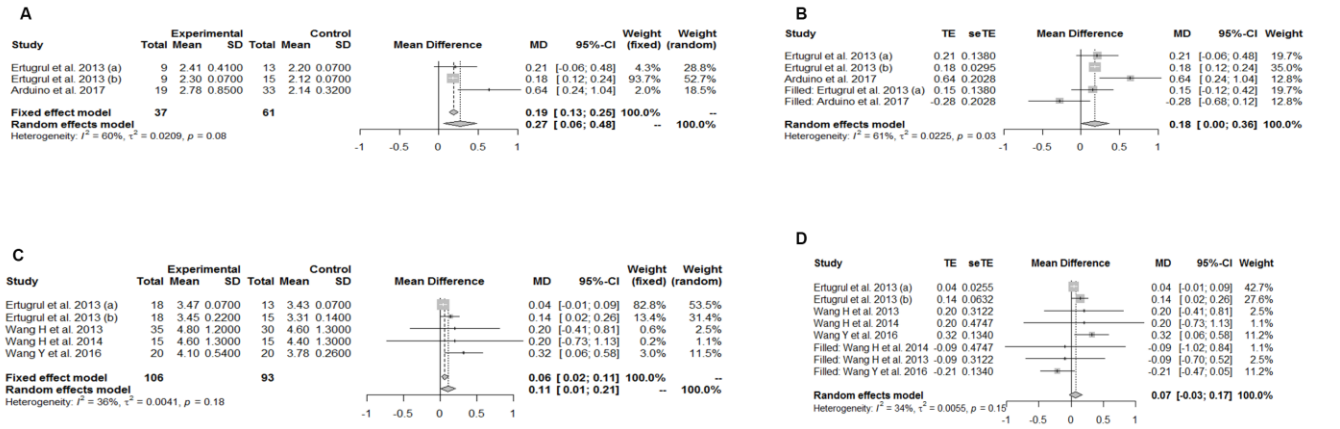

Fig. 4 Forest plot of mean Probing depth (PD) in individuals with gingivitis or periodontitis (control), gingivitis or periodontitis + oral lichen planus (experimental): A: Meta-analysis PD in gingivitis; B: Publication/ meta-analyses biases - trim-and-fill method in PD/gingivitis; C: Meta-analysis PD in periodontitis; D: Publication/ meta-analyses biases - trim-and-fill method in PD/periodontitis. SD = standard deviation; MD = mean difference; CI = confidence interval; TE = estimated mean; SeTE = estimated standard deviation.

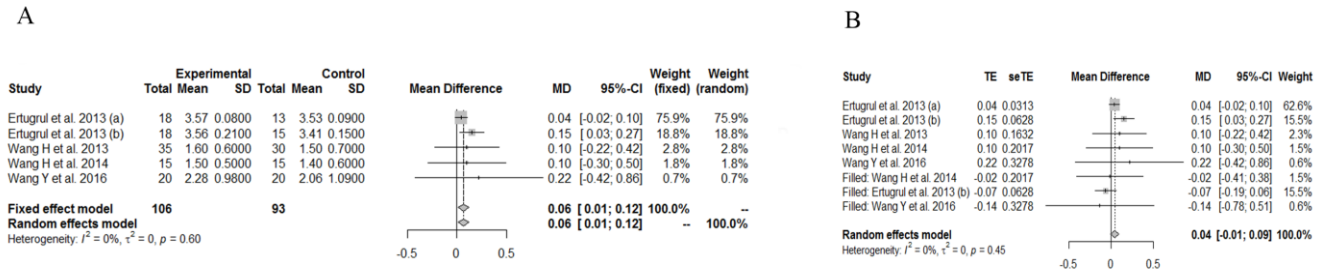

Fig. 5 Forest plot of mean Clinical Attachment Loss (CAL) in individuals with gingivitis or periodontitis (control), gingivitis or periodontitis + oral lichen planus (experimental). A: Meta-analysis CAL in periodontitis; B: Publication/ meta-analyses biases - trim-and-fill method in CAL/periodontitis. SD = standard deviation; MD = mean difference; CI = confidence interval; TE = estimated mean; SeTE = estimated standard deviation.

Tables

Table 1 General characteristics of included studies

Authors, year (local)	Study Design	Number of patients (n) and sex (M/F): G1: Control group; G2: Case group	Mean Age	Characteristics of the samples included	Use of medication and systemic disturbs	Evaluation Method	Statistical analysis	Outcomes	
								Clinical Periodontal examination (Mean ± SD)	Biological Marker
Arduino et al., 2017 (Turin, Italy) [28]	Observational: Cross-Sectional	G1: 33 (M: 8; F:25) G2: 19 (M:1; F:18)	G1: 57.5 G2: 73	G1: Patients with plaque-induced gingivitis G2: Patients with gingivitis and oral lichen planus	None	Clinical periodontal evaluation and microbiologic evaluation by PCR	Wilcoxon or χ^2 test. Fisher exact test	**PD** G1: 2.14 ± 0.32 G2: 2.78 ±0.85 **FMPS %** G1: 53.58 ± 20.92 G2: 79.05 ± 18.42 **FMBS %** G1: 58.51 ± 11.55 G2: 71.48 ± 24.69 **Missing Teeth** G1: 2.18 ± 3.47 G2: 9.36 ± 5.04	**Microbiologic Analysis (Mean ±SD)** ***A. Actinomycetemcomitans*** G1: 0.12 ± 0.70 / G2: 0.63 ± 1.34 ***P. gingivalis*** G1:0.88 ± 1.36 / G2: 1.37 ± 1.34 ***P. intermedia*** G1: 0.39 ± 1.06 / G2: 0.74 ± 1.33 ***T. forsythia*** G1:0.91 ± 1.23 / G2: 1.74 ± 1.33 ***T. denticola*** G1: 0.61 ± 1.00 / G2: 0.89 ± 1.24 ***P. micra*** G1: 0.79 ±1.05 / G2: 0.58 ± 0.96 ***F. nucleatum/periodonticum*** G1: 2.00 ±1.25 / G2: 2.53 ± 1.39 ***C. rectus*** G1: 0.58 ± 1.12 / G2: 0.42 ± 0.84 ***E. nodatum*** G1: 0.15 ± 0.62 / G2: 0.26 ± 0.93 ***E. corrodens*** G1: 0.91 ± 1.16 / G2: 1.63 ± 1.57 **Capnocytophaga spp.** G1: 1.30 ±1.33 / G2: 1.16 ± 1.26

Wang Y. et al., 2016 (Liaoning, China) [29]	Observational: Case-control Study	G1: 20 (M: 8; F:12) G2: 20 (M:12; F:8)	G1: 41.6 G2: 45.9	G1: Patients with chronic periodontitis G2: Patients with chronic periodontitis and oral lichen planus	None	Clinical periodontal examination. The expression of IL-35 in GCF and serum by ELISA	One-way ANOVA; Pearson correlation coefficient analysis method.	**PD** G1: 3.78 ± 0.26 G2:4.10 ± 0.54 **CAL** G1: 2.06± 1.09 G2: 2.28 ±0.98 **GI** G1: 2.25± 0.55 G2: 2.35± 0.49 **BOP** G1:3.05± 0.76 G2: 3.20± 0.70	**Expression level IL-35 (Mean-pg/ml)** **GCF** G1: 12 G2: 15 **Serum** G1: 33 G2: 45
Wang H. et al., 2014 (Beijing, China) [30]	Observational: Case-control Study	G1: 15 (M:5; F:10) G2: 15 (M:6; F:9)	G1: 41.2 G2: 42.4	G1: Patients with periodontitis G2: Patients with periodontitis and oral lichen planus (erosive and reticular)	None	Clinical periodontal examination. Immunohistochemistry (IHC) IL-17, IL-23. Real-time quantitative PCR (qPCR)	One-way ANOVA test with Tukey's HSD post hoc test	**PD** G1: 4.4 ± 1.3 G2:4.6 ± 1.3 **CAL** G1: 1.4±0.6 G2: 1.5 ± 0.5 **GI** G1: 1.2 ±0.5 G2: 1.5± 0.6 **PI** G1:1.1 ± 0.5 G2: 1.3 ± 0.4	**Analysis of IL-17 and IL-23p19 positive reaction level (Mean ± SD)** **IL-17 (%)** G1: 15 ± 8.4 G2: 33 ± 15.7 **IL-23p19 (%)** G1: 18 ± 7.5 G2: 37 ± 14.9 **Gene expression (x 10^{-3})** G1: 0.03 G2: 0.05
Ertugrul et al., 2013a (Selçuk, Turkey) [31]	Observational: Case-control Study	G1: 26 (M:12; F:14): Gingivitis = 13 (M:5; F: 8); Periodontitis =13 (M:6; F:7) G2: 27 (M:14; F:13) Gingivitis + OLP = 9 (M:3; F: 6); Periodontitis + OLP =18 (M:8; F:10)	Gingivitis G1: 41.6 G2: 42.12 Periodontitis G1: 51.46 G2: 50.15	G1: Patients with gingivitis (n:13); patients with periodontitis (n:13) G2: Patients with gingivitis and oral lichen planus (n:9);	None	Clinical periodontal examination. PCR with subsequent reverse hybridization method (micro-IDent)	Kolmogorov–Smirnov test; A Mann–Whitney *U* test	**Gingivitis** **PD ± SD** G1: 2.20 ± 0.07 G2:2.41 ± 0.41 **GI ± SD** G1: 1.30± 0.14 G2: 1.55± 0.21 **PI± SD** G1:1.39± 0.12 G2: 1.64± 0.24 **Periodontitis** **PD ± SD** G1: 3.43 ± 0.07 G2:3.47 ± 0.07	**Microbiological Analysis (Relative densitometry %)** ***A. actinomycetemcomitans*** In general G1: 7.6% / G2: 18.5% Gingivitis G1: 0% / G2: 0% Periodontitis G1: 15.3% / G2: 27.7% ***P. gingivalis*** In general G1: 50% / G2: 85.1% Gingivitis G1: 23% / G2: 66.6% Periodontitis G1: 77% / G2: 94.4% ***P. intermedia*** In general G1: 46.1% / G2: 81.4% Gingivitis

				patients with periodontitis and oral lichen planus (n:18)				**CAL± SD** G1: 3.53± 0.09 G2: 3.57 ± 0.08 **GI ± SD** G1: 1.92± 0.11 G2: 2.03± 0.12 **PI± SD** G1:1.96± 0.13 G2: 2.11± 0.12	G1: 15.3% / G2: 55.5% Periodontitis G1: 77% / G2: 94.4% ***T. forsythia*** In general G1: 73% / G2: 88.8% Gingivitis G1: 69.2% / G2: 66.6% Periodontitis G1: 92.3% / G2: 100% ***T. denticola*** In general G1: 57.7% / G2: 74% Gingivitis G1: 23% / G2: 22.2% Periodontitis G1: 77% / G2: 100%
Ertugrul et al., 2013b (Selçuk, Turkey) [32]	Observational: Case-control Study	G1: 30 (M:11; F:19): Gingivitis = 15 (M:5; F: 10); Periodontitis =15 (M:6; F:9) G2: 27 (M:14; F:13): Gingivitis + OLP = 9 (M:3; F: 6); Periodontitis + OLP =18 (M:8; F:10)	Gingivitis G1: 41.6 G2: 42.1 Periodontitis G1: 51.4 G2: 50.1	G1: Patients with gingivitis; patients with periodontitis; G2: Patients with gingivitis and oral lichen planus plaque and reticular; patients with periodontitis and oral lichen planus erosive, plaque and reticular	None	Clinical periodontal examination. Enzyme-linked immunosorbent assay and immunohistochemical staining	Kolmogorov–Smirnov; Kruskal Wallis test and Mann–Whitney U with Bonferroni correction	**Gingivitis** **PD ± SD** G1: 2.12 ± 0.07 G2:2.30 ± 0.07 **GI ± SD** G1: 1.29± 0.15 G2: 1.50± 0.11 **PI± SD** G1:1.46± 0.16 G2: 1.67± 0.09 **Periodontitis** **PD ± SD** G1: 3.31 ± 0.14 G2:3.45 ± 0.22 **CAL± SD** G1: 3.41± 0.15 G2: 3.56 ± 0.21 **GI ± SD** G1: 1.97± 0.28 G2: 2.13± 0.13 **PI± SD** G1:2.04± 0.28 G2: 2.21± 0.14	**Mean ± SD** **MMP-9** Gingivitis G1: 0.80 ± 0.29 G2: 2.47± 0.33 Periodontitis G1: 1.60 ± 0.36 G2: 3.37± 0.50 **TIMP-1** Gingivitis G1: 36.71 ± 7.83 G2: 24.69± 6.98 Periodontitis G1: 22.21± 4.04 G2: 13.02± 4.49 **MMP-1** Gingivitis G1:19.66 ± 4.79 G2:37.50 ± 19.20 Periodontitis G1: 35.85 ± 8.68 G2: 66.18 ± 16.31

Wang H. et al., 2013 (Chengdu, China) [33]	Observational: Case-control Study	G1: 30 (M:12; F:18) G2: 35 (M:13; F:22)	G1: 42.8 G2: 45.9	G1: Patients with chronic periodontitis G2: Patients with chronic periodontitis and oral lichen planus form reticular and erosive.	None	Clinical periodontal examination. Expression levels of IL-17 and IL-23 in serum by ELISA.	One-way ANOVA testwith Tukey's HSD post hoc test	**PD** G1: 4.6± 1.3 G2:4.8± 1.2 **CAL** G1: 1.5±0.7 G2: 1.6± 0.6 **GI** G1: 1.3±0.5 G2: 1.4± 0.7 **PI** G1:1.2± 0.4 G2: 1.3 ± 0.5	**In serum: IL-17 (Mean -pg/ml)** G1: 40 G2: 50 **In serum: IL-23 (Mean - pg/ml)** G1: 20 G2: 25

Table 2 Quality assessment of studies included, according to Fowkes and Fulton, 1991

Guidelines	Checklist	Arduino et al. 2017 [28]	Wang Y. et al. 2016 [29]	Wang H. et al. 2014 [30]	Ertugrul et al. 2013a [31]	Ertugrul et al. 2013b [32]	Wang H. et al. 2013 [33]
Study design appropriate to objectives?	Objective common design	–	−	−	−	−	−
	Prevalence cross-sectional	−	−	−	−	−	−
	Prognosis cohort	−	−	−	−	−	−
	Treatment controlled trial	−	−	−	−	−	−
	Cause cohort, case–control, cross-sectional	0	0	0	0	0	0
Study sample representative?	Source of sample	0	0	0	0	0	0
	Sampling method	0	0	0	0	+	0
	Sample size	0	++	++	0	0	0
	Entrycriteria/exclusion	0	0	0	0	0	0
	Non respondents	0	0	0	0	0	0
Control group acceptable?	Definition o fcontrols	0	0	0	0	0	0
	Source of controls	0	0	0	0	0	0
	Matching/randomization	0	+	0	+	+	0
	Comparable characteristics	0	0	0	0	0	0
Quality of measurements and outcomes?	Validity	0	0	0	+	0	0
	Reproducibility	0	+	0	0	0	+
	Blindness	0	0	0	0	0	0
	Qualitycontrol	0	0	0	0	+	0
Completeness	Compliance	0	0	0	0	0	0
	Dropouts	+	0	0	0	0	0
	Deaths	NA	NA	NA	NA	NA	NA
	Missing data	0	0	0	0	+	0
Distorting influences?	Extraneous treatments	0	0	0	0	0	0
	Contamination	NA	NA	NA	NA	NA	NA
	Changes over time	0	0	0	0	+	0
	Confounding factors	+	0	0	0	0	0

	Distortion reduced by analysis	0	0	0	0	0	0
Summary questions	Bias: Are the results erroneously biased in a certain direction?	No	No	No	No	No	No
	Confounding: Are there any serious confusing or other distorting influences?	No	No	No	No	No	No
	Chance: Is it likely that the results occurred by chance?	No	No	No	No	No	No

0 = no problem; + = minor problem; ++ = major problem; NA = not applicable

Supplementary file

Supplementary file 1. Reasons for the exclusion of articles

Reasons	References
Interventional study, absence of control group	Romano et *al*. 2019
Absence of periodontal disease - control group	Azizi et *al*. 2012 [41] ; Russo et *al*. 2010 [42]

Supplementary file 2. Domains considered in risk of bias evaluation according to Fowkes and Fulton

Guidelines	Checklist	Description
Study design appropriate to objectives?	Objective common design	The type of study was marked in the appropriate type of study. If the type of study was appropriate according to the study design, it was labeled as "0," and as "++" if it was not appropriate
	Prevalencecross-sectional	
	Prognosiscohort	
	Treatmentcontrolledtrial	
	Cause cohort, case–control, cross-sectional	
Studysample representative?	Sourceof sample	The domain was considered "0" in cases of detailed origin, "+" to a specified origin of only one group and "++" in cases of absence of specification of the source of the groups
	Samplingmethod	The item was assigned "0" for a full description of sampling method, "+" for poor or no explanation of sample method, with no problem in matching between groups, and "++" for poor or no description of sample method, interfering in the matching of the groups
	Sample size	A minor problem "+" was considered when the sample was not representative or did not report a sample calculation. To a major problem, "++" was considered when no sample calculation was provided, and the number of participants was less than 50 participants, "0" was considered in the absence of the above factors
	Entrycriteria/exclusion	A minor problem "+" was attributed when the control and case group reported current use of antibiotics or anti-inflammatories, diabetes, smoking or pregnancy. In the case of presence of more than two previously mentioned items, it was considered as a major problem "++"
	Nonrespondents	The "0" was attributed when there was no refusal to participate in the study, "+" was assigned when there was the refusal, but did not compromise the sample, and "++" when there were refusal and impairment of the sample size
Controlgroupacceptable?	Definitionofcontrols	It was attributed "0" when all characteristics of the control group were described, "+" when any information was pendent as the origin of the control group, the selection criterions and a different origin between case and control groups and "++" when two or more items described in previously items
	Sourceofcontrols	It was considered "0" when the control group was referred, "+" when the origin of groups was different, but with reasons and "++" when the groups presented different origins without reasons
	Matching/randomization	In this item, "0" was assigned to cases of randomized/matched groups, "+" to cases of no description of randomization, but with a matching of groups and "++" to no explanation of randomization or matching
	Comparablecharacteristics	It was attributed "0" to matched groups or not matched by the impossibility of being subsequently adjusted and "++" the presence of unpaired variables that were not paired or adjusted
Quality of measurements and outcomes?	Validity	It was considered "0" when the evaluation method applied is appropriate; "+" when using a single method, but with appropriate sensitivity with good specificity; "++" when using a single method, without an adequate specificity or good sensitivity
	Reproducibility	It was considered "0" whether the evaluation methods were well described; "+" when a lack description of any step of the method was presented, for example, the identification of the patients of the groups studied in laboratory samples, evaluations at different times or application of various methods between groups of individual pathology; "++" when two or more of the previous items are present
	Blindness	The condition of the study participants was considered to be "Blind," in this case being assigned the signal "0," in cases of "not blind" the signal "++" was attributed

	Qualitycontrol	It was considered a problem when the examiner was not qualified; a partial periodontal exam was performed [not in all teeth or not in all the six periodontal sites/teeth], the measurement of periodontitis was only radiographic or the absence of the number of evaluated teeth sites. A minor problem "+" was considered when two of these characteristics were present, and a major problem "++" if more than two of these characteristics were present
Completeness	Compliance	It was assigned "0" for a sample size that remains the same from the beginning to the end or decreases without compromising the power of the test; "+" for differences in sample size at the end of the study, compromising the power of the test, but with reasons and adjusts; "++" for difference in sample size at the end of the study, compromising the power of the test, without reasons
	Dropouts	The "0" was scored when there is no loss during the study, "+" when there is a withdrawal that involves the inclusion criteria, such as age, sex, "++" when there is withdrawal and it compromises more than one criterion
	Deaths	This item was scored as Not Applicable "NA," due to the type of PECO strategy
	Missing data	In this item, "0" was assigned to cases of randomized/matched groups, "+" to cases of no description of randomization, but with a matching of groups and "++" to no description of randomization or matching
Distortinginfluences?	Extraneoustreatments	In this item, "0" was considered when there were no external influences; "+" when there are external influences, but that does not interfere in the results; "++" when there are external influences and interferes with the results
	Contamination	This item was scored as Not Applicable "NA," due to the type of PECO strategy
	Changes over time	In this item, "0" was attributed to data collected in the same period; "+" to data obtained from the control group and the study group at different times that may cause distortions; "++" when the previous item was associated with data from studies already published
	Confoundingfactors	A problem was assigned when the data analysis involved enrollment of persons < 5 years. Menopausal woman, smokers, diabetics and obese. A minor problem "+" was assigned when 1 or 2 of these characteristics were present and a major problem "++" if there were 3 or more
	Distortionreducedbyanalysis	It was considered "0" when it cites the adjustments of the covariates that present distortions; "+" when the article report adjustment, but does not say the criteria; "++" when distortion was identified, without adjustment
Summaryquestions	Bias: Are the results erroneously biased in a certain direction?	YES or "NO" answers were assigned to each question. If the answer is NO to the three questions, the article is considered reliable, with low risk of bias
	Confounding: Are there any serious confusing or other distorting influences?	
	Chance: Is it likely that the results occurred by chance?	

Anexos

Anexo A – Normas para publicação no periódico "*Clinical Oral Investigation*"

Contents

Instructions for Authors

Types of papers

Papers may be submitted for the following sections:

- Original articles
- Invited reviews
- Short communications – with up to 2000 words and up to two figures and/or tables
- Discussion paper
- Letters to the editor

It is the general policy of this journal not to accept case reports and pilot studies.

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If you have any questions please contact:

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University Hospital of Saarland

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66421 Homburg/Saar

Germany

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Manuscript Submission

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- The name(s) of the author(s)
- A concise and informative title
- The affiliation(s) and address(es) of the author(s)
- The e-mail address, telephone and fax numbers of the corresponding author

Abstract

Please provide a structured abstract of 150 to 250 words which should be divided into the following sections:

- Objectives (stating the main purposes and research question)
- Materials and Methods
- Results
- Conclusions
- Clinical Relevance

These headings must appear in the abstract.

Keywords

Please provide 4 to 6 keywords which can be used for indexing purposes.

Text

Text Formatting

Manuscripts should be submitted in Word.

- Use a normal, plain font (e.g., 10-point Times Roman) for text.
- Use italics for emphasis.
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- Do not use field functions.
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- Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

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Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols.

Always use footnotes instead of endnotes.

Acknowledgments

Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

References

Citation

Reference citations in the text should be identified by numbers in square brackets. Some examples:

1. Negotiation research spans many disciplines [3].

2. This result was later contradicted by Becker and Seligman [5].

3. This effect has been widely studied [1-3, 7].

Reference list

The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text.

The entries in the list should be numbered consecutively.

If available, please always include DOIs as full DOI links in your reference list (e.g. “https://doi.org/abc”).

- Journal article

  Gamelin FX, Baquet G, Berthoin S, Thevenet D, Nourry C, Nottin S, Bosquet L (2009) Effect of high intensity intermittent training on heart rate variability in

prepubescent children. Eur J Appl Physiol 105:731-738. https://doi.org/10.1007/s00421-008-0955-8

Ideally, the names of all authors should be provided, but the usage of "et al" in long author lists will also be accepted:

Smith J, Jones M Jr, Houghton L et al (1999) Future of health insurance. N Engl J Med 965:325–329

- Article by DOI

  Slifka MK, Whitton JL (2000) Clinical implications of dysregulated cytokine production. J Mol Med. https://doi.org/10.1007/s001090000086

- Book

  South J, Blass B (2001) The future of modern genomics. Blackwell, London

- Book chapter

  Brown B, Aaron M (2001) The politics of nature. In: Smith J (ed) The rise of modern genomics, 3rd edn. Wiley, New York, pp 230-257

- Online document

  Cartwright J (2007) Big stars have weather too. IOP Publishing PhysicsWeb. http://physicsweb.org/articles/news/11/6/16/1. Accessed 26 June 2007

- Dissertation

  Trent JW (1975) Experimental acute renal failure. Dissertation, University of California

Always use the standard abbreviation of a journal's name according to the ISSN List of Title Word Abbreviations, see

ISSN.org LTWA

If you are unsure, please use the full journal title.

Authors preparing their manuscript in LaTeX can use the bibliography style file sn-basic.bst which is included in the Springer Nature Article Template.

Tables

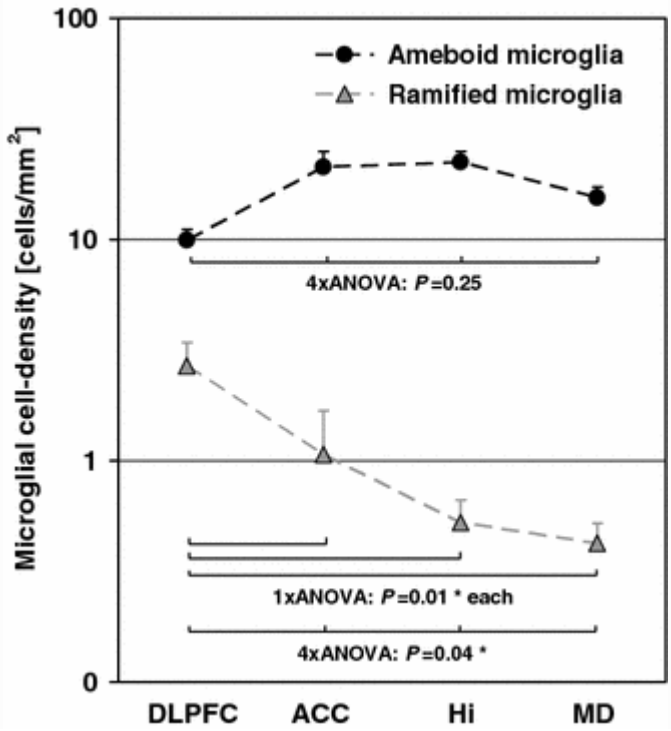
- All tables are to be numbered using Arabic numerals.
- Tables should always be cited in text in consecutive numerical order.
- For each table, please supply a table caption (title) explaining the components of the table.
- Identify any previously published material by giving the original source in the form of a reference at the end of the table caption.
- Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.

Artwork and Illustrations Guidelines

Electronic Figure Submission

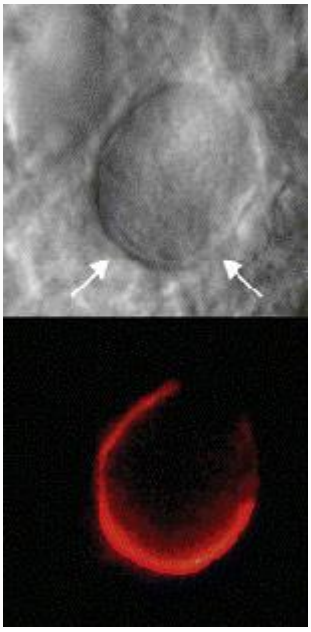
- Supply all figures electronically.
- Indicate what graphics program was used to create the artwork.
- For vector graphics, the preferred format is EPS; for halftones, please use TIFF format. MSOffice files are also acceptable.
- Vector graphics containing fonts must have the fonts embedded in the files.
- Name your figure files with "Fig" and the figure number, e.g., Fig1.eps.

Line Art



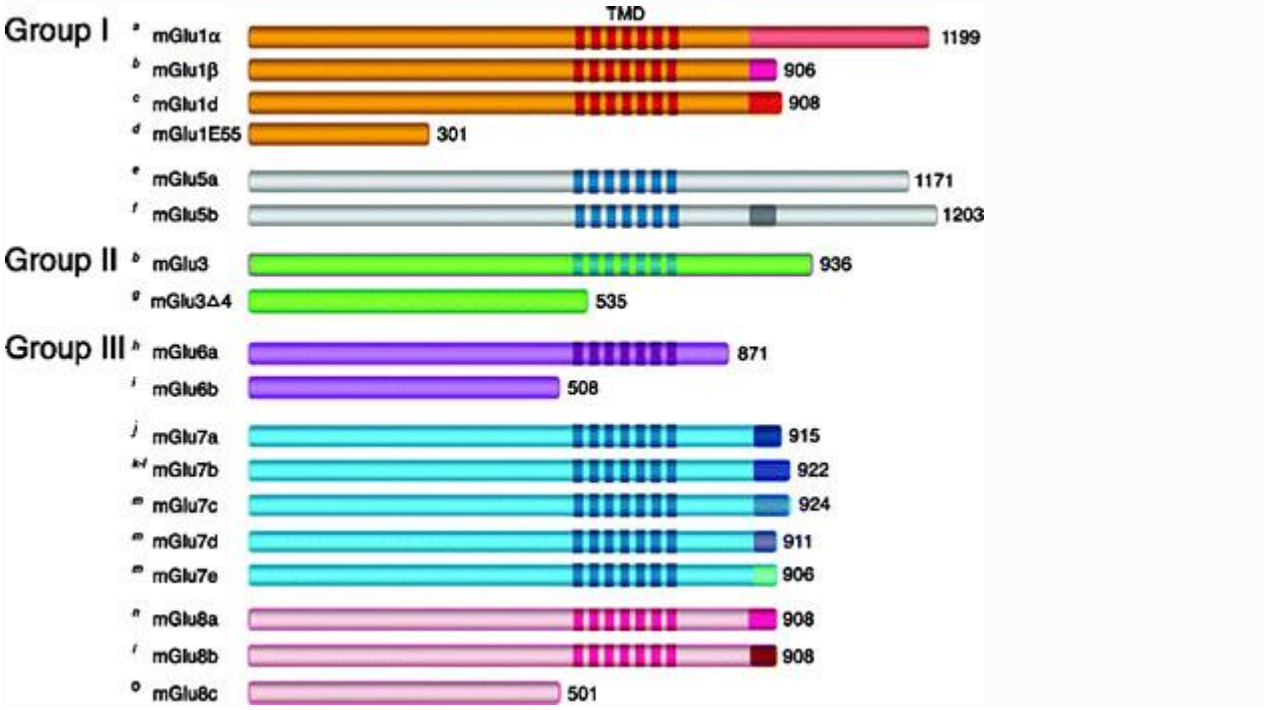
- Definition: Black and white graphic with no shading.
- Do not use faint lines and/or lettering and check that all lines and lettering within the figures are legible at final size.
- All lines should be at least 0.1 mm (0.3 pt) wide.
- Scanned line drawings and line drawings in bitmap format should have a minimum resolution of 1200 dpi.
- Vector graphics containing fonts must have the fonts embedded in the files.

Halftone Art



- Definition: Photographs, drawings, or paintings with fine shading, etc.
- If any magnification is used in the photographs, indicate this by using scale bars within the figures themselves.
- Halftones should have a minimum resolution of 300 dpi.

Combination Art



- Definition: a combination of halftone and line art, e.g., halftones containing line drawing, extensive lettering, color diagrams, etc.
- Combination artwork should have a minimum resolution of 600 dpi.

Color Art

- Color art is free of charge for online publication.
- If black and white will be shown in the print version, make sure that the main information will still be visible. Many colors are not distinguishable from one another when converted to black and white. A simple way to check this is to make a xerographic copy to see if the necessary distinctions between the different colors are still apparent.
- If the figures will be printed in black and white, do not refer to color in the captions.
- Color illustrations should be submitted as RGB (8 bits per channel).

Figure Lettering

- To add lettering, it is best to use Helvetica or Arial (sans serif fonts).
- Keep lettering consistently sized throughout your final-sized artwork, usually about 2–3 mm (8–12 pt).

- Variance of type size within an illustration should be minimal, e.g., do not use 8-pt type on an axis and 20-pt type for the axis label.
- Avoid effects such as shading, outline letters, etc.
- Do not include titles or captions within your illustrations.

Figure Numbering

- All figures are to be numbered using Arabic numerals.
- Figures should always be cited in text in consecutive numerical order.
- Figure parts should be denoted by lowercase letters (a, b, c, etc.).
- If an appendix appears in your article and it contains one or more figures, continue the consecutive numbering of the main text. Do not number the appendix figures,"A1, A2, A3, etc." Figures in online appendices [Supplementary Information (SI)] should, however, be numbered separately.

Figure Captions

- Each figure should have a concise caption describing accurately what the figure depicts. Include the captions in the text file of the manuscript, not in the figure file.
- Figure captions begin with the term Fig. in bold type, followed by the figure number, also in bold type.
- No punctuation is to be included after the number, nor is any punctuation to be placed at the end of the caption.
- Identify all elements found in the figure in the figure caption; and use boxes, circles, etc., as coordinate points in graphs.
- Identify previously published material by giving the original source in the form of a reference citation at the end of the figure caption.

Figure Placement and Size

- Figures should be submitted separately from the text, if possible.
- When preparing your figures, size figures to fit in the column width.
- For large-sized journals the figures should be 84 mm (for double-column text areas), or 174 mm (for single-column text areas) wide and not higher than 234 mm.
- For small-sized journals, the figures should be 119 mm wide and not higher than 195 mm.

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If you include figures that have already been published elsewhere, you must obtain permission from the copyright owner(s) for both the print and online format. Please be aware that some publishers do not grant electronic rights for free and that Springer will not be able to refund any costs that may have occurred to receive these permissions. In such cases, material from other sources should be used.

Accessibility

In order to give people of all abilities and disabilities access to the content of your figures, please make sure that

- All figures have descriptive captions (blind users could then use a text-to-speech software or a text-to-Braille hardware)
- Patterns are used instead of or in addition to colors for conveying information (colorblind users would then be able to distinguish the visual elements)
- Any figure lettering has a contrast ratio of at least 4.5:1

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Supplementary Information (SI)

Springer accepts electronic multimedia files (animations, movies, audio, etc.) and other supplementary files to be published online along with an article or a book chapter. This feature can add dimension to the author's article, as certain information cannot be printed or is more convenient in electronic form.

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Submission

- Supply all supplementary material in standard file formats.
- Please include in each file the following information: article title, journal name, author names; affiliation and e-mail address of the corresponding author.
- To accommodate user downloads, please keep in mind that larger-sized files may require very long download times and that some users may experience other problems during downloading.

- High resolution (streamable quality) videos can be submitted up to a maximum of 25GB; low resolution videos should not be larger than 5GB.

Audio, Video, and Animations

- Aspect ratio: 16:9 or 4:3
- Maximum file size: 25 GB for high resolution files; 5 GB for low resolution files
- Minimum video duration: 1 sec
- Supported file formats: avi, wmv, mp4, mov, m2p, mp2, mpg, mpeg, flv, mxf, mts, m4v, 3gp

Text and Presentations

- Submit your material in PDF format; .doc or .ppt files are not suitable for long-term viability.
- A collection of figures may also be combined in a PDF file.

Spreadsheets

- Spreadsheets should be submitted as .csv or .xlsx files (MS Excel).

Specialized Formats

- Specialized format such as .pdb (chemical), .wrl (VRML), .nb (Mathematica notebook), and .tex can also be supplied.

Collecting Multiple Files

- It is possible to collect multiple files in a .zip or .gz file.

Numbering

- If supplying any supplementary material, the text must make specific mention of the material as a citation, similar to that of figures and tables.
- Refer to the supplementary files as “Online Resource”, e.g., "... as shown in the animation (Online Resource 3)", “... additional data are given in Online Resource 4”.
- Name the files consecutively, e.g. “ESM_3.mpg”, “ESM_4.pdf”.

Captions

- For each supplementary material, please supply a concise caption describing the content of the file.

Processing of supplementary files

- Supplementary Information (SI) will be published as received from the author without any conversion, editing, or reformatting.

Accessibility

In order to give people of all abilities and disabilities access to the content of your supplementary files, please make sure that

- The manuscript contains a descriptive caption for each supplementary material
- Video files do not contain anything that flashes more than three times per second (so that users prone to seizures caused by such effects are not put at risk)