Concise Review

The Association Between Periodontal Disease and Chronic Migraine: A Systematic Review

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ABSTRACT

Migraine is a neurologic illness that produces intense throbbing pain on one side of the head and affects roughly 1 billion people worldwide. Recent research indicates a relationship between periodontitis and chronic migraines. This study aimed to review the association between chronic migraines and periodontitis through a systematic literature review.

Four research databases (Google Scholar, PubMed, ProQuest, and SpringerLink) were searched according to PRISMA guidelines to retrieve the studies included in this review. A search strategy was developed to answer the study question with appropriate inclusion and exclusion criteria. Out of 34 published studies, 8 studies were included in this review. Three of the studies were cross-sectional, 3 were case-control, and 2 were clinical report and medical hypothesis papers. Seven of the 8 included studies showed that there is an association between periodontal disease and chronic migraine. The elevated blood levels of some biomarkers such as leptins, ProCalcitonin (proCT), calcitonin gene-related peptides (CGRPs), Pentraxin 3 (PTX3), and Soluble Tumor Necrosis Factor-like Weak Inducer Of Apoptosis (sTWEAK) play a significant role in this association. The limitations include a small sample size, the influence of anti-inflammatory drugs, and a self-reported headache measure that is subject to misclassification bias.

This systematic review reveals a supposed correlation between periodontal disease and chronic migraine, as evidenced by various biomarkers and inflammatory mediators. This suggests that periodontal disease could potentially contribute to the development of chronic migraine. However, to further assess the potential benefits of periodontal treatment in patients with chronic migraine, additional longitudinal studies with larger sample sizes and interventional studies are needed.

Introduction

Migraine is the most common disabling headache disorder of the primary recurrent headaches.[1] It is characterised by persistent bouts of unilateral raised, pulsatile headaches that are exacerbated by routine physical activity and usually accompanied by visual and auditory intolerance.[1] Migraines can be aura-accompanied or aura-free.[2]

Aura is a reversible disorder of the neurologic system characterised by visual problems, dysarthria, and nausea.[3] The intensity of a person's migraines is defined by the frequency of their migraine episodes. According to the International Headache

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Society, chronic migraines are migraine headaches that occur more than 15 times per month and last longer than 3 months.[4]

In addition, many risk factors, including age, female gender, and obesity, have been related to migraine chronification.[5-7] Periodontal disease is a chronic inflammatory disease that affects the tooth support structure, resulting in an increase in attachment and bone loss.[8,9] An individual's susceptibility to infection is determined by the immune system's response to infection, which may be altered directly or indirectly by different variables such as systemic disorders.[10]

Several studies that highlight the involvement of periodontal disease in the chronification of migraines have also proposed a biological connection.[11-13] Periodontal disease is caused by bacterial pathogens interacting with the host, resulting in the production of local inflammatory mediators and neurogenic biomarkers,[14] which both play a significant role in the chronification of migraines.[15] Several molecular abnormalities, including inflammation, endothelial dysfunction, matrix protease dysfunction, and innate immunity, have been described in severe forms of periodontitis.[14,16,17] The gingival crevicular fluid and mucosa of periodontal disease patients had elevated levels of the neurogenic inflammatory mediators connected to the activation of the trigeminovascular system that is associated with migraines, according to a new study.[10]

Moreover, a case-control study was conducted to illustrate the pathophysiologic relationship that exists between chronic migraines and periodontal diseases. The investigatory results showed that patients who had periodontal diseases were more prone to chronic migraines compared to those without periodontal diseases.[11] This relationship could be explained by the significant increase in the levels of neuropeptides like Substance P and neurokinin A in both the gingival fluid and plasma of patients with periodontal disease. Another case-control study also supported this finding by investigating the possible link between periodontal disease and increased inflammatory mediators in the vascular system and accompanying activation in chronic migraine. The study reported higher levels of circulating calcitonin gene-related peptide, interleukin-6, and interleukin-10 in the blood samples of patients with chronic migraine who also had periodontitis.[18] Furthermore, it is also important to note that an identical pattern of inflammatory mediators was observed in chronic migraineurs.[19] There has been no systematic review done to gather the results of these studies and show the collective information available to address this association between periodontal diseases and chronic migraine. This study aimed to assess the association between chronic migraines and periodontitis through a systematic literature review.

Material and methods

Protocol development and research question

This systematic review was conducted with the standard regulations of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Figure 1).

The study was preregistered with the appropriate guideline protocol in the Open Science Framework (OSF Registries https://osf.io/s32br).

The study research question is, "Is there an association between periodontal disease and the onset and chronicity of migraines?"

Data sources and search strategy

Between August 31, 2021, and February 27, 2022, systematic searches were conducted in a variety of scientific literature databases, including Google Scholar, PubMed, ProQuest, and SpringerLink, for this study. Only articles published between 2016 and 2022 in the English language were included.

The terms used for the search were (periodontal inflammation) OR periodontitis) OR chronic periodontitis) OR periodontal disease) OR periodontal health) OR Gingiva), Periodontal* AND migraine Periodontitis AND migraine OR throbbing headache, Periodontium, AND migraine, "Migraine risk factor", Chronic migraine AND periodontitis, Gingiva* AND chronic migraine, Periodontal disease, AND migraine certification.

Eligibility criteria

Studies that evaluated the association/relationship between periodontitis/periodontal disease and migraine.

Exclusion criteria

Studies with (a) patients with chronic diseases, (b) immunocompromised patients, or (c) disabled, alcoholic, or drug-abusing patients were all excluded. All these diseases and conditions will work as confounding factors, which is why they are excluded.

Data extraction

The authors independently identified literature by searching the databases specified above as well as other sources. The process is detailed in the PRISMA flowchart in Figure 1, and the search was conducted in four phases:

Identification phase: In all, 34 articles were collected from the databases. After comparing the article titles, 20 duplicates were identified and eliminated, leaving 14 articles for the remainder of this round.

Screening phase: By screening the abstracts of the 14 papers, 5 were eliminated, leaving a total of 9 articles.

Eligibility phase: One article was excluded in this phase as it included patients with chronic diseases.

Inclusion phase: Eight studies were included in the qualitative synthesis.

Risk of bias assessment

The Critical Appraisal Skills Programme (CASP) checklist was utilised to assess the quality of the case-control studies by evaluating their relevance and utility.[20] CASP checklist answers are either "YES" (1 point), "NO" (0 points), or "CAN'T

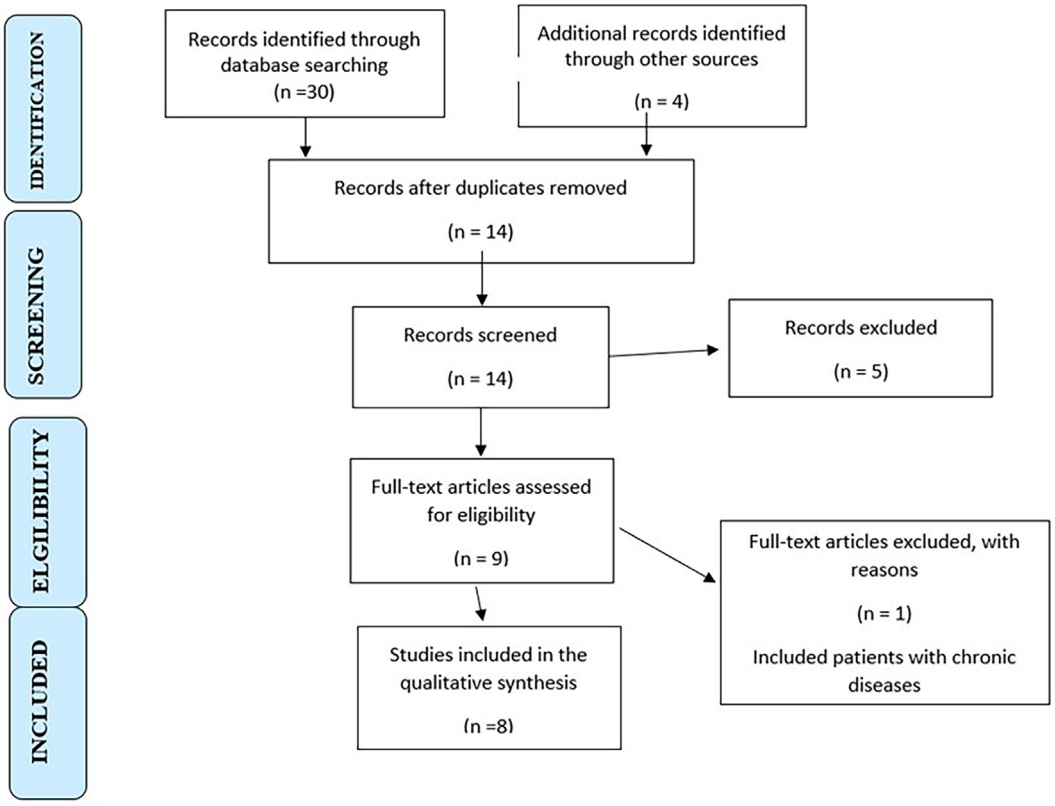

Fig. 1 – PRISMA flow chart of the selection process.

TELL" (0.5 points); based on the total score, the quality of each study was ranked as strong (7–9), intermediate (4–6), or weak (1–3). To evaluate cross-sectional research, the critical appraisal tool to assess the quality of cross-sectional studies (AXIS) was utilised.[21] This evaluation method, which is comparable to CASP, consists of a set of 20 questions to which answers were either "YES" (1 point), "NO" (0 points), or "DON'T KNOW" (0.5 points), and the study was graded based on total score as strong (13–20), moderate (6–12), or weak (1–6). Based on the rating, all studies were divided into 3 categories: low risk of bias, moderate risk of bias, and high risk of bias.

Results

Literature search

Initially, a total of 30 articles were included from the designated databases, followed by the identification of 4 more articles from other sources. After a first screening of the article's titles and abstracts for relevance and elimination of duplicates, 9 publications were selected for additional examination and thorough evaluation by reading the complete text. After a closer inspection of the reference lists of the 9 chosen publications, one publication was omitted because it included individuals with chronic conditions. In the end, 8 papers were selected to be included in this systematic review. Data extraction and tabulation were done manually by investigators, and the Table provides the extracted information from included studies in detail.

General characteristics of the studies

This systematic review covered several study types, including 3 case-control studies, 3 cross-sectional studies, and 2 clinical report and medical hypothesis papers. The case-control studies comprised 296 chronic migraine patients and 226 migraine-free controls,[11,13,15] whereas the cross-sectional studies included 883 migraineurs.[12,18,22] The bulk of the included papers was conducted mostly in Spain.[10-13,15,22] The majority of research[11-13,15,18,22] identified chronic migraineurs using the International Classification of Headache Disorders, Third Edition criteria.[23]

Seven of the 8 included studies reported the potential confounding variables in the relationship between chronic migraine and periodontal disease[11-13,15,18,22,24]; 1 study showed no significant association between periodontal disease and migraine after multiple linear regression analysis with significant confounders adjusted; however, when comparing episodic migraineurs with chronic migraineurs, periodontal disease was more prevalent in chronic migraineurs. Whilst the other 5 studies[11-13,15,18] demonstrated an independent association between the 2 disorders in both adjusted and unadjusted models.

Five studies evaluated the association between periodontal disease and chronic migraine by collecting blood samples and evaluating the serum levels of potential biomarkers and

Table – General characteristics and outcomes of the included studies

Study	Study design	Sample characteristics	Periodontal measure	Confounding factors	Results	Limitations	Conclusions	Risk of bias
Ameijeira 2019 Spain[11]	Case-control	Cases = 102, controls = 91, females = 98%, mean age, 44.3 ± 12.3 y	PPD CAL FMPS FMBS	Obesity, depression, low SES	The prevalence of CP was found to be greater in the CM group compared to the non-CM group (58.8 vs 30.8%, $P < .0001$) and logistic regression showed independent association after adjusting confounding factors.	Influence of anti-inflammatory drugs	Significant association	Low
Ameijeira 2017 Spain[10]	Medical hypothesis				PD was found to be a risk factor for chronic migraine due to released inflammatory mediators and neurogenic biomarkers (CGRP)			
Leira 2017 Spain[13]	Case-control	Cases = 92, controls = 58, females = 94.7%, mean age 45.7 ± 11.0 y	CAL PPD FMPS FMBS	BMI, female gender, low SES	CP independently contributed to increased leptin levels In patients with CM. Cases with CM showed higher mean serum leptin levels than non-CM (16.4 vs 7.2 ng/mL, $P < .0001$)	Influence of anti-inflammatory drugs	Significant association	Low
Leira 2019 Spain[22]	Cross-sectional	N = 651, females = 84.9%, mean age 44.3 ± 12.3 y	Self-reported questionnaire present/absent	Anxiety, depression, low SES	Self-reported PD was associated with CM with an OR of 1.456. After adjusting confounding factors, there was a drop in OR (OR, 1.100; 95% CI, 0.784 to 1.543, $P > .05$). PD was more common in the CM group compared with the EM group (53.9% vs 44.6%, $P = .019$).	Use of a self-reported measure of periodontal disease	No significant association	Moderate
Leira 2020 London[18]	Cross-sectional	N=94, mean age 47.2 ± 10.6 y, females = 97.9%	PPD, CAL Rec, BoP by PISA	Depression, opioid use	In patients with CM, PD was independently associated with increased levels of PTX3 and sTWEAK (2475.3 ± 1646.8 pg/mL vs 516.6 ± 1193.8 pg/mL, $P < .0001$ and 672.4 ± 118.2 pg/mL vs 485.7 ± 112.2 pg/mL, $P < .0001$).	Low sample number	Significant association	Moderate
Leira 2018 Spain[12]	Cross-Sectional	N = 138, mean age 46.3 ± 10.1 y, females = 96.4%	PPD, CAL FMBS FMPS	BMI, age, low SES, depression	CP was highly associated with increased levels of serum proCT in patients with CM (0.056 ng/mL, $R^2 = 0.293$, $P < .001$).	Larger samples are needed	Significant association	Low
Leira 2019 Spain[15]	Case-control	Cases = 102, controls = 77, mean age 47.0 ± 10.2, females = 98%	PD CAL FMBS FMPS Rec (by PISA)	Age, depression, obesity, low SES	CP was associated with increased levels of CGRP in CM cases independent on confounding variables. (β=4.354; 95% CI, 1.685 to 7.024, $P < 0001$)	Influence of anti-inflammatory drugs	Significant association	Low
Watanabe 2018 Japan[25]	Clinical report	Case 1: 29-year-old female, case 2: 36-year-old female			Concurrent dental disease (eg, periapical lesions) in patients with migraine may aggravate the migraine condition, and it can be alleviated by dental treatment.			

BMI, body mass index; BoP, bleeding on probing; CAL, clinical attachment loss; CGRP, calcitonin gene-related peptide; CM, chronic migraine; CP, chronic periodontitis; FMBS, full-mouth bleeding score; FMPS, full-mouth plaque score; PD, periodontal disease; PISA, periodontal inflamed surface area; PPD, probing pocket depth; ProCT, procalcitonin; PTX3, pentraxin 3; Rec, gingival recession; SES, socioeconomic status; sTWEAK, soluble tumour necrosis factor-like weak inducer of apoptosis.

pro-inflammatory mediators that are believed to be involved in the process of migraine chronification and are elevated in periodontal disease; all 5 studies concluded a significant association between periodontitis and pro-inflammatory mediators in chronic migraineurs.[10,12,13,15,18] One study investigated the link between dental illness and midface migraine based on the review of 2 case reports and indicated that dental care may alleviate migraine discomfort.[25]

Risk of bias within studies

The quality assessment of the included studies using the CASP checklist showed that 3 of the included studies have a moderate risk of bias and the other 5 a low risk of bias, as shown in the Table.

Due to the differences between the population comparisons or outcomes, multiple confounding factors, and different limitations in the included studies, low certainty in the evidence should be expected.

Discussion

A limited number of studies have been conducted to determine the association between chronic migraines and periodontal disease. The principal complication of migraines is their proclivity to become chronic. In this work, we systematically reviewed and discuss the results of each of 8 research papers that provide detailed data on this process. Seven of the 8 articles reported positive connections between chronic migraines and periodontal disorders, whereas one study found no such association. In this positive relationship, periodontal disease was identified as a potential risk factor for the chronification of migraines due to elevated blood levels of leptins, ProCalcitonin (proCT), calcitonin gene-related peptides (CGRPs), Pentraxin 3 (PTX3), and Soluble Tumor Necrosis Factor-like Weak Inducer Of Apoptosis (sTWEAK).[12,13,15,18] It is believed that certain inflammatory mediators generated during periodontal inflammation are involved in the initiation of migraine attacks (Figure 2).

In one of the studies, it was shown that the circulating levels of the biomarkers PTX3 and sTWEAK were considerably greater in patients with severe periodontal disease than in those without,[18] although there were no significant differences for the remaining biomarkers. Another study also showed that existing oral problems, such as periapical lesions, may exacerbate migraine symptoms and that dental therapy may reduce them.[25] In another investigation, there were no significant differences between groups; nevertheless, an association between the periodontal pathogen *Porphyromonas gingivalis* and migraines was reported.[24]

Multiple pathophysiologic mechanisms explain the plausible link between periodontal disease and migraines (ie, systemic and neurogenic inflammation, endothelial dysfunction, matrix protease dysfunction). In addition, both diseases share several systemic conditions including hypercholesterolemia, hypertension, insulin resistance, and vascular atherosclerotic diseases.[10] In addition, chronic low-grade inflammation releases a large number of inflammatory mediators and biomarkers, which could account for the overexpression of these biomarkers (CGRP, substance P (SP) and neurokinin A (NKA)).[15] Further, the periodontal infection may stimulate the trigeminovascular system, which comprises tiny pseudounipolar sensory neurons originating from the trigeminal ganglion and upper cervical dorsal nerve root, both of which are involved in the chronification of migraine.[13]

There are some studies that focused on the inflammatory markers and whether they are associated with migraines, including C-reactive protein (CRP), tumour necrosis factor alpha (TNF-α), interleukin (IL)-6, and CGRP. High serum levels of CGRP and IL-6 have shown great significance to the occurrence of migraines compared with the control groups.[26,27] On

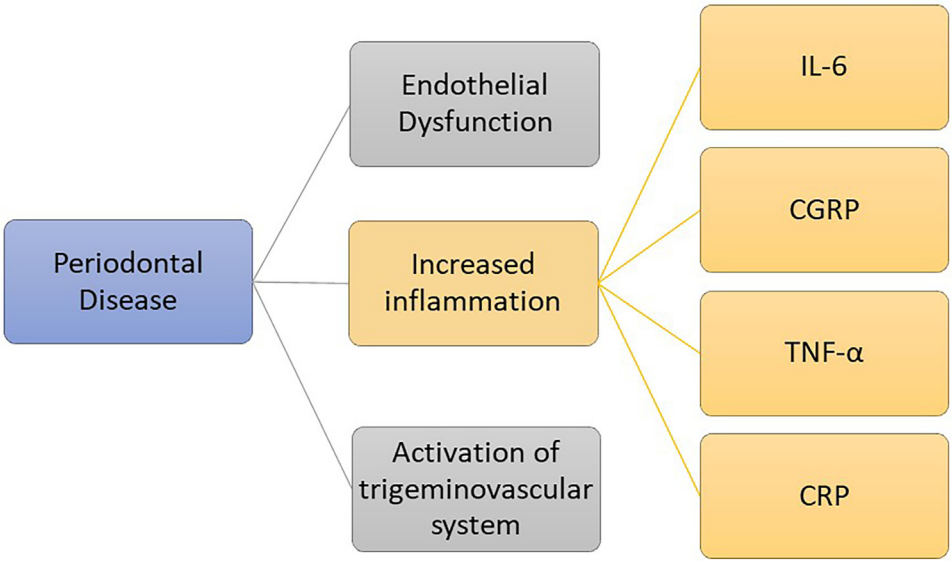

Fig. 2 – Mechanisms that are postulated to be involved in the association of periodontal disease with chronic migraine.

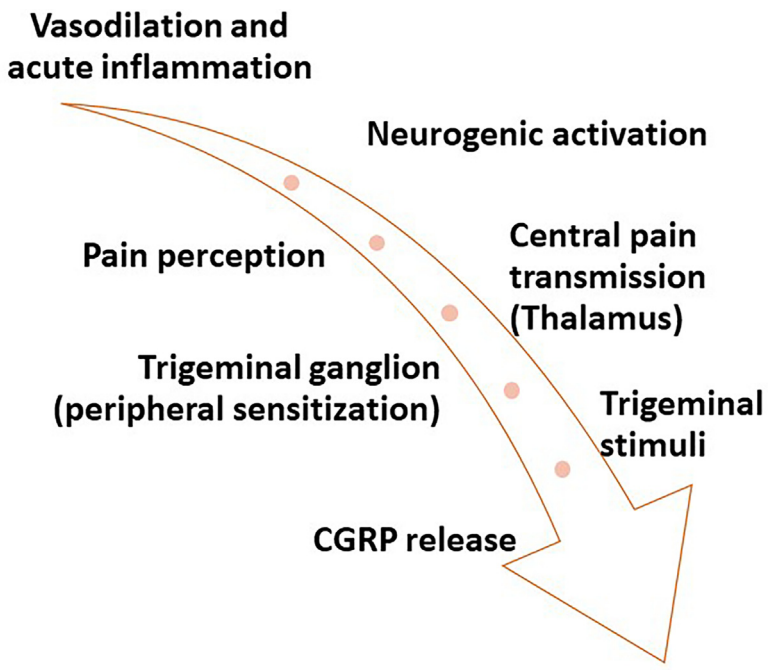

Fig. 3 – Schematic showing sequential events and putative connecting links between inflammatory periodontal disease and chronic migraine.

the other hand, the opposite was shown when IL-10 was measured: Individuals with migraines showed lower serum levels of IL-10 compared with individuals that do not experience migraines. This study has also shown that chronic migraines and periodontitis can be associated mainly with the inflammatory mediators' effect and their entry into the bloodstream, reaching the cerebral vessels and aggravating the condition. This also led to the conclusion that patients who have both periodontitis and chronic migraines have both increased levels of IL-6 and decreased levels of IL-10.[28,29]

As for CGRP, when this inflammatory mediator is released from the periphery, it causes vasodilation and results in greater CGRP release by altering the trigeminovascular system (Figure 3). This was confirmed by giving intravenous CGRP infusion, which triggers delayed migraine-like attacks in patients with migraine, although it did not affect healthy individuals.[30] Patients with both migraines and periodontitis have a very high level of serum CGRP.[15]

In one study, CRP and TNF-α were assessed in terms of whether they are associated with migraines and whether they affect migraine episodes or chronification.[31] They developed a hypothesis that inflammation only affects susceptible individuals and did not affect the migraine's chronification or its frequency. TNF-α is a pain mediator that increases the sensitisation of nociceptors that are responsible for pain transmission. Even though there is no direct evidence of whether the migraines or the pain levels have affected the TNF-α levels, it was found that the latter was elevated among migraine patients. CRP levels are also high in migraineurs, although they showed no significant difference between chronic and episodic migraine.

The Women's Health Initiative OsteoPerio ancillary study includes an investigation of all relevant and possibly confounding aspects in the link between periodontal disease and its subsequent inflammatory response in headache disorders. The factors from the OsteoPerio research were carefully selected, gathered, and quantified, and a hypothesis relating migraines to mouth bacteria that produce nitrous oxide (NO) was also examined.[32]

NO works as a key mediator in migraines[33]; it intervenes in vasodilation and activates the trigeminovascular system, which causes migraines and other vascular headaches. Also, periodontal inflammation starts due to plaque accumulation and bacterial toxin release, which means that NO levels increase and trigger a positive feedback cycle, which can lead to cell toxicity by different mechanisms that eventually lead to periodontal breakdown and destruction.[14] Thus, increased levels of NO during inflammation can worsen disease status.

The main limitation of this systematic review is that the bulk of the included studies were done by the same research group. As such, it is highly probable that the findings of this systematic review originate from a shared population or that the articles included in the review share several patients in common.

Several other limitations in the studies were also noted, including the possibility of misclassification bias with self-reported headaches, the lack of bacterial quantification to limit statistical analysis (the bacterial species were either present or absent), and the fact that headache disorders are more prevalent in younger age groups,[34] whereas periodontal disease, also known as periodontal destruction, is more prevalent in older people and involves both past and present periodontal destruction.[35-38] Other limitations of the included studies are listed in the Table.

Multiple pathophysiologic pathways may trigger the possible association between periodontal disorders and migraines. This is because gingival periodontitis releases pro-

inflammatory mediators that are believed to play a role in the course of migraine episodes, hence chronifying the migraine in patients. To further support the pathophysiologic association between these 2 illnesses, more epidemiologic research, population monitoring, and inclusion of surveys that target periodontal diseases and migraine patients are required.

Conclusions

This systematic review has shown the positive association and correlation between periodontal diseases and chronic migraine through different biomarkers and inflammatory mediators, thus suggesting that periodontal disease can be associated with the development of chronic migraine. Yet more longitudinal studies with larger samples and interventional studies are required to evaluate the benefit of periodontal treatment in chronic migraineurs.

Author contributions

Data extraction, data analysis, results interpretation, and writing–original draft by Danah Almayeef, Dania Abbas, Maha Ali, Maha Haissam, Rawya Mabrook, Riham Nizar, and Tuleen Eldoahji. Conceptualisation, writing–review, editing, and supervision by Marwan Mansoor Ali Mohammed and Natheer Hashim Al-Rawi. All authors have approved the final article.

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Conflict of interest

None disclosed.

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