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Burning mouth syndrome and micronutrient deficiency: a systematic review protocol

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ABSTRACT

Introduction Burning mouth syndrome (BMS) is a complex orofacial pain disorder characterised by chronic intraoral burning or dysesthesia, typically occurring daily for more than 2 hours per day and persisting for over 3 months. The absence of identifiable causative lesions defines BMS, and symptoms may appear with or without accompanying somatosensory changes, such as altered taste or tactile sensations. This article outlines the development of a systematic review protocol to investigate the prevalence of micronutrient deficiency in patients with BMS and enhance our understanding of possible diagnoses and management of patients with this disorder.

Methods and analysis This systematic review will include observational studies that assessed micronutrient levels (such as iron, folate, cobalamin, zinc and homocysteine) to identify which micronutrients are lower than the normal range in patients with BMS. A literature search will be conducted on 25 August 2025, using the following databases: MEDLINE, Embase, LILACS, Scopus, Web of Science and the grey literature. Key terms such as "Burning Mouth Syndrome", "stomatodynia", "glossopyrosis", "micronutrients" and "vitamins" will be used in our search strategies. Experts in the topic and reference lists of included studies will also be consulted. Two independent reviewers will select the study using a two-phase process. Data collection will be performed by one author and cross-checked by another. The risk of bias assessment will be conducted following the JBI tool. Meta-analyses may be performed to analyse the proportion of patients with micronutrient deficiency for each micronutrient investigated.

Ethics and dissemination This systematic review does not require ethical approval. On completion, it will be published in a peer-reviewed academic journal and presented at a conference.

PROSPERO registration number CRD42024626960.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is based on a protocol developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for protocol statement and registered on PROSPERO.
⇒ No restrictions were placed on language or publication period for the search and eligibility criteria.
⇒ Two independent reviewers conducted all review stages.
⇒ The limitations include possible heterogeneity in the methodological characteristics and small sample sizes in some primary studies.

INTRODUCTION

Burning mouth syndrome (BMS) is a chronic, often debilitating condition characterised by the sensation of burning or dysesthesia in the oral cavity, typically without any visible lesions or identifiable physical causes.[1] The pathophysiology of BMS remains poorly understood, but it is generally considered idiopathic, with emerging evidence suggesting a predominant neuropathic origin.[2] Central nervous system dysfunction, involving sensory processing abnormalities and dysregulation of pain perception, is thought to play a key role in developing the condition.[3] Additionally, peripheral nerve damage or dysfunction may contribute to the abnormal sensations experienced by patients.[2]

Epidemiologically, BMS is more prevalent in postmenopausal women, with studies suggesting that it affects between 0.7% and 5% of the population, particularly those aged 50 years and older.[4–6] Despite its significant impact on quality of life, BMS often goes undiagnosed or misdiagnosed due to its ambiguous presentation and lack of objective clinical findings. The condition significantly impacts patients' quality of life, and is frequently related to chronic pain, anxiety and depression.[7] The persistent discomfort can interfere with daily activities, such as eating, speaking and sleeping, and may result in social isolation and reduced emotional well-being.[4 5]

Several systematic reviews have appraised the diverse pharmacological and non-pharmacological treatment options for the management of patients with BMS.[8–10] From clonazepam and capsaicin gel to

photodynamic therapy to cognitive behavioural therapy, the management strategies may include addressing any underlying medical conditions and using medications to alleviate oral dysesthesia.[8–10] Additionally, recent research has highlighted the potential benefits of supplementing micronutrients, such as zinc, iron, folate and vitamins, to alleviate the symptoms of the disease,[11 12] suggesting a possible link between micronutrient deficiencies and the development or exacerbation of BMS.[13–15] Deficiencies in cobalamin, folate, iron and other essential nutrients have been reported in patients with BMS, suggesting that nutritional imbalances may contribute to the pathogenesis or persistence of the condition.[15 16] This emerging understanding emphasises the importance of assessing the nutritional status of patients with BMS to understand whether these patients may be undergoing nutritional deficiencies and to collaborate on understanding the disease aetiology, potentially offering new avenues for therapeutic intervention. Thus, this systematic review aims to determine the prevalence of micronutrient deficiency in patients with BMS.

METHODS

Protocol and registration

A systematic review protocol based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols[17] was developed and registered at the International Prospective Register of Systematic Reviews (online supplemental appendix 1). This article will be reported according to this protocol. The study protocol planning started in October 2024, with plans to complete the study by August 2025.

Patient and public involvement

This study does not involve patients. The data to be obtained are from published primary studies.

Rationale

Micronutrient deficiencies—particularly in iron, zinc, vitamin B12, folic acid and vitamin D—have been frequently associated with BMS. Yet, no systematic review has rigorously synthesised the prevalence of these deficiencies in patients with BMS. A systematic review is therefore warranted to critically assess existing evidence and clarify the potential role of nutritional imbalances in BMS pathogenesis.

Research question

The participants, exposure, outcomes and study design (PEOS) mnemonic was used as a guide to identify the research question. Box 1 represents the structuring of PEOS used in the review question:

What is the prevalence of micronutrient deficiency in patients with BMS?

Box 1 'PEOS' mnemonic as a guide to identifying the research question

- ⇒ Participants: Patients ≥18 years old presenting with burning mouth syndrome (BMS) according to established diagnostic criteria in the International Classification of Orofacial Pain, 1st edition (ICOP-1).
- ⇒ Exposure: Lower than normal serum levels of iron, zinc, folate, cobalamin and other micronutrients.
- ⇒ Outcomes: Primary: global prevalence of patients with micronutrient deficiency. Secondary: proportion of patients with deficiency for each micronutrient.
- ⇒ Study design: Descriptive studies (case series) and cross-sectional studies.

PEOS, participants, exposure, outcomes and study design.

Eligibility criteria

Inclusion criteria

Studies involving female and male patients (≥18 years old) with primary or secondary BMS (primary BMS: intraoral burning or dysesthetic sensation, recurring daily for more than 2 hours per day over more than 3 months, without evident clinical lesions or laboratory abnormalities that could explain the symptoms. Secondary BMS: refers to cases in which the burning sensation is attributable to an identifiable local or systemic cause (eg, nutritional deficiencies, hormonal changes or medication side effects). Oral mucosa is of normal appearance, and clinical examination, including sensory testing, is regular.), regardless of ethnicity. The search will be carried out without time restrictions, including studies published since the inception of each database up to the date of the search, in June 2025.

Exclusion criteria

1. Studies in patients diagnosed with systemic autoimmune conditions such as lupus erythematosus, rheumatoid arthritis, pemphigus vulgaris and cicatricial pemphigoid, studies involving children and adolescents. These autoimmune conditions can lead to oral discomfort and signs, which may prevent the patient from being clinically diagnosed with BMS or could be a confounding factor in the diagnosis. Additionally, the age-related hormonal, neurological, psychological and systemic factors which appear to contribute to BMS are largely absent in children. Thus, children were not our target population.
2. Articles for which we could not obtain the entire document, even after contacting the authors, studies lacking quantitative data, case reports, letters to the editor and conference panels.

Outcomes

The primary outcome of this study will be the proportion of patients with BMS with vitamin deficiency. The secondary outcome is the identification of the most common micronutrients reported as deficient in patients with BMS, such as folate, iron, zinc, magnesium, cobalamin and other B complex vitamins.

Information sources and search strategy

A health sciences librarian helped develop search strategies for the selected databases (see online supplemental

appendix 2). These strategies will be applied across the following databases: MEDLINE (via PubMed), Embase, LILACS (in Spanish: *Literatura Latinoamericana y del Caribe en Ciencias de la Salud*), Scopus and Web of Science. In addition, a search for grey literature will be conducted through Google Scholar, ProQuest Dissertations and Theses Global. Manual searches of the bibliographies of included studies and consultations with subject matter experts will be undertaken to identify further pertinent studies.

Data management

The files with the references of each database will be imported into Zotero (V.7.0.11, George Mason University, Fairfax, Virginia, USA), where duplicate articles will be organised and excluded through two stages. Then, a file containing all the records after duplicate removal will be exported to Rayann Online Software (Qatar Computing Research Institute, Data Analytics, Doha, Qatar) for screening.

Selection process

A two-phase process will select the studies based on the eligibility criteria. Before the screening, two authors will be calibrated to the process by reading five abstracts. After that, the two independent reviewers (EAB, RD) will read all the titles and abstracts. The second stage will be a complete reading of the articles selected in Phase 1. A consensus meeting will be held if these two reviewers do not agree on the inclusion or exclusion of an article. If there are still disagreements, a third reviewer (EG) will assess the inclusion or exclusion of such studies.

If relevant data are missing or incomprehensible, an attempt will be made to contact the author of the respective study to clarify these inconsistencies.

Data collection process

After the selection and reading stages, one independent reviewer (EAB) will collect data from the selected articles and export it into an Excel file. A second reviewer (RD) will cross-check the data gathered for completeness and accuracy. If disagreements occur, the reviewers will discuss and resolve them. If essential data are missing or unclear, efforts will be made to contact the study's corresponding author for clarification. If no response is received after three attempts within 3 weeks, the missing or unclear data will be recorded as such.

Data items

The information to be collected will include:

- Author.
- Year of publication.
- Country.
- Type of study.
- Sample size.
- Sex at birth.
- BMS diagnosis method.
- Type of micronutrients and assessment method.
- Individual micronutrient quantification (levels).
- Main conclusions.

Risk of bias assessment

The risk of bias in individual studies will be assessed using the Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data.[18] This tool evaluates various aspects of the included studies, including the sample structure (ie, how it was selected and calculated), the level of detail in the study description, the assessment of outcomes, the standardisation of the evaluation process and the response rate among study participants included in the prevalence systematic review. For each study, the first (EAB) and second (RD) reviewers attributed responses to each checklist item to assess its methodological quality and determine whether the study met the required criteria. For this review, an overall subjective assessment of the assigned responses was made for each study based on the judgement of the checklist items. Before this, the reviewers held a discussion to identify the most critical methodological components and determine which elements carried more weight when evaluating the study's overall quality. Studies that presented key components with more positive responses were classified as having a low risk of bias. In contrast, those with negative or uncertain responses were rated as having a high risk of bias. Figures will be created on the *robvis* website (https://www.riskofbias.info/welcome/robvis-visualization-tool).

Synthesis methods

A narrative synthesis will describe the overall study characteristics. Data regarding micronutrient type and concentration will be collated for the quantitative assessment. The data will be entered on an Excel spreadsheet by the first reviewer (EAB) and checked for accuracy by the second reviewer (RD). We plan to conduct a proportion meta-analysis and subgroup analysis using the Comprehensive Meta-Analysis software, V.3.0 (CMA 3.0) (Biostat, Englewood, New Jersey, USA). Effect sizes with a 95% CI will be calculated using random-effects models for the overall meta-analysis and subgroup analyses. Heterogeneity will be assessed using the I^2 statistics and Cochran's Q test (Higgins *et al* 2003).[19] I^2 estimates the percentage of variability in results across studies due to fundamental differences and not chance. An I^2 of less than 25% is usually considered as low heterogeneity, between 25% and 50% as moderate and over 50% as high heterogeneity. Based on a χ^2 distribution, Cochran's Q test generates a probability that, when significant, indicates larger variation across studies rather than within subjects in a study. A low p value (or a large χ^2 statistic relative to its degree of freedom) provides evidence of heterogeneity of intervention effects. Forest plots will be used to visually present the results of the meta-analyses, including confidence intervals for each study and overall pooled estimates.

Ethics and dissemination

This systematic review does not require ethical approval. On completion, it will be published in a peer-reviewed academic journal and presented at a conference. This review protocol was registered on the PROSPERO platform.

Strengths and limitations of this study

This study will identify a series of elements reported as deficient in patients with BMS. This will open a new window for investigating the aetiological factors for BMS, which remain unknown. It also provides insights into possible therapeutic targets for future interventional studies.

Limitations

While this study will follow high standards required for a systematic review, its results will be as solid as the quality of the published primary studies identified in our database search, and limited by the certainty level of the available evidence.

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Contributors This protocol was carefully designed, concluded, reviewed and approved with the communion of all authors. RD worked on study conceptualisation, design, data collection, data analysis, and manuscript review and approval. PP participated in the study design, data collection and approved the final manuscript as submitted. EG worked on the conceptualisation and design of the study and approved the final manuscript as submitted. FFS participated in the conceptualisation and design of the study and approved the final manuscript as submitted. VFMT worked on study conceptualisation, study design, data analysis and critical revision of the manuscript and approved the final manuscript as submitted. EMQA worked on study conceptualisation, study design and data collection and approved the final manuscript as submitted. GDLC worked on the study design, data analysis and critical manuscript revision and approved the final manuscript as it was submitted. EAB worked on the conceptualisation and design of the study, drafting the article, critical manuscript revision, and approval and submission of the final version. The guarantor is EAB.

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