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Micronutrient Imbalance and Inflammatory Activity in Oral Mucosal Diseases

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Abstract

The objectives of this study were to assess the relationship between micronutrient status and inflammatory activity in patients with oral mucosal diseases and to investigate whether there was a relationship between clinical severity and the pathological pattern of oral mucosal lesions, and the micronutrient status. This clinical observational cross sectional study was carried out over patients diagnosed with oral mucosal diseases, and healthy control participants. All patients were clinically evaluated by oral medicine specialists and lesions were classified based on clinical diagnosis of recurrent aphthous stomatitis, oral lichen planus, glossitis/burning mouth syndrome, oral candidiasis and oral potentially malignant disorders. Blood samples were taken to examine the hemoglobin, serum ferritin, vitamin B12 and folate, zinc, vitamin D, and some inflammatory markers. Clinical severity was determined by pain intensity, lesion number, lesion size, frequency of recurrence and healing duration. Data were analyzed statistically to compare micronutrient and inflammatory profiles between patients and controls and to look for association between nutritional deficiency and disease severity. Micro-nutrient deficiencies were more common in patients with oral mucosal diseases than in healthy controls. Vitamin B12, ferritin, iron, zinc and Vitamin D deficiencies were more common in patients with recurrent aphthous stomatitis, glossitis, burning sensations and erosive oral lichen planus. Higher inflammatory activity is correlated with more severe clinical condition, delay in healing and reappearance of lesions. In patients with combined micronutrient deficiencies, the mucosal discomfort, recurrence frequency and the time for epithelial recovery were higher than in patients not deficient. There was a stronger correlation of the potentially malignant oral conditions with the oxidative and inflammatory markers than with single-nutrient deficiencies. Clinical presentation and inflammatory activity of oral mucosal diseases may be related to micronutrient imbalance. While these lesions may be attributed exclusively to nutritional deficiency, this could also serve as an important modifying factor and affect mucosal integrity, recurrence, healing and the severity of the disease. Oral medicine practice may benefit from incorporating nutritional and inflammatory assessment for better diagnosis, risk assessment, and personalized management of patients with oral mucosal diseases.

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Introduction

Oral mucosal diseases are an important group of diseases seen commonly in oral medicine and oral pathology. The conditions can manifest themselves by a recurrence of ulcerations, erythema, erosions, white plaques, burning sensations, glossitis, candidal infections, lichenoid lesions, or as possibly malignant lesions of the mucous membranes. Despite the

Vol 14, No 2 (2026) DOI 10.5195/d3000/2026.1542

variations in the clinical manifestation, biological behavior, histopathological findings and prognosis, the pathogenesis of oral mucosal diseases is commonly associated with disruption of epithelial barriers, immune disturbances, oxidative stress, impaired wound healing, dysbiosis of oral flora and chronic inflammation [1,2].

Oral mucosa is a very dynamic epithelial barrier which acts as a protection for the underlying tissues from mechanical, microbiological, chemical and thermal damage. It has a natural role that relies on continuous renewal of the epithelium, sufficient vascularization, protection by the saliva, immune surveillance, collagen synthesis and proper inflammatory response. Even a slight imbalance in these processes can make the mucosa friable and prone to ulceration, infection and burning sensations, and slow healing. The importance of nutritional status on these biological functions could not be underestimated since vitamins, minerals, proteins, and antioxidant nutrients have a crucial role in the integrity of epithelia, regulation of immune system, and tissue repair [1,3].

Several oral mucosal disorders are now known to be affected by possible modifying factors for micronutrient deficiencies. Vitamin B12, folate, iron, ferritin, zinc and vitamin D deficiencies can impact on epithelial turnover, synthesis of DNA, delivery of oxygen, collagen, immune response and antioxidant protection. The clinical findings might include repeated occurrence of aphthous-like lesions, glossitis, angular cheilitis, and/or pallor, burning sensation, taste alterations, delayed wound healing, or an increased incidence of oral infection. The clinical manifestations can be nonspecific and may overlap with the clinical manifestations of immune-mediated diseases, infectious, traumatic, allergic or systemic diseases; therefore, clinical evaluation is not enough in certain cases [1,4].

Recurrent aphthous stomatitis is a very common oral mucosal ulcerative condition. It's marked by recurring painful ulcers in non-keratinized mucosal surfaces. It is not known exactly what causes it, but several factors have been suggested such as genetic susceptibility, local trauma, psychological stress, immune dysfunction and abnormality, microbial factors, systemic disease, and nutritional deficiencies. Hematinic deficiency including B12, folate, iron, ferritin and hemoglobin deficits can have an adverse effect on epithelial regeneration and on mucosal healing. Thus, patients suffering from recurrent aphthous ulcers who experience frequent, severe, persistent lesions and/or systemic symptoms may benefit from laboratory analysis [5,6].

The role of vitamin B12, folate and iron in the processes of DNA synthesis, hematopoiesis, oxygen transport and epithelia renewal are particularly important for oral mucosal health. The oral symptoms of vitamin B12 deficiency can include glossitis, burning sensation, recurrent ulceration, dysgeusia and mucosal soreness. Similarly, folate deficiency may lead to changes for reasons of impaired cell replication and epithelial maturation. Mucosal pallor, angular cheilitis, epithelial atrophy, tongue pain and delayed healing may be associated with ID. Based on these results, it is not enough to consider these findings as "local" oral problems with each oral ulcer since in some cases, it may be a sign of hematinic or systemic imbalance [1,5].

Another significant mucosal disease is oral lichen planus, in which there may be interaction between nutrition, inflammation and oral pathology. It is a chronic autoimmune disease, which typically occurs as white reticular lines, erythematous lesions, erosions or ulcers. The histopathology of oral lichen planus shows basal cell degeneration and band-like lymphocytic infiltration at the interface of the epithelium and the connective tissue. Nutrition factors potentially modulating immune regulation (vitamin D and zinc) have been strongly associated with disease activity, severity of symptoms, epithelial repair and inflammatory response in the disease [7,8].

The effects of vitamin D on immune regulation, epithelial barrier function, antimicrobial peptide expression, and cytokine balance could all play a role in the connection between vitamin D and oral mucosal disease. Recent studies have shown that patients with oral lichen planus (OLP) may have lower vitamin D levels when compared to normal individuals reflecting a possible role for vitamin D deficiency as a contributing or modifying factor in OLP. Zinc could also have a clinical relevance as a contributor of epithelial healing, antioxidant defense, immune regulation and wound repair. Vitamin D and zinc however are considered as supportive measures, not stands for conventional oral medicine diagnosis and treatment [7,9,10].

Symptoms associated with burning mouth and glossitis also apply. Diffuse mucosal discomfort, taste alterations, tongue soreness or burning may be their complaints, and in some cases, there are no obvious clinical changes. Secondary burning symptoms such as epithelial atrophy, changes in sensory function, anemia-induced tissue hypoxia, and impaired mucosal renewal could be caused by B12, folate, iron, zinc and vitamin D deficiencies. The identification of primary burning mouth syndrome from secondary burning syndrome is of importance since correction of underlying deficiencies could resolve symptoms in certain patients [1,4].

Some predisposing factors like denture use, poor oral hygiene, antibiotic therapy, corticosteroid therapy, diabetes mellitus and immunosuppression are commonly associated with oral candidiasis. In addition, susceptibility could be due to mineral deficiencies which compromise epithelial resistance and/or host immune defense. Impairments in mucosal immunity and recovery may be due to iron deficiency, vitamin deficiency, protein deficiency or vitamin D inadequacy. Recurrent or treatment-resistant candidiasis might require more systemic and nutritional assessment [1].

Oral potentially malignant disorders (OPMDs) such as leukoplakia and erythroplakia pose a danger of malignant transformation and clinical and histopathological assess are important. Although nutrition is not a substitute for biopsy, histopathological grading, control of risk factors or long-term surveillance, but levels and activity of antioxidant nutrients and nutrients levels may affect oxidative stress, epithelial stability, chronic inflammation and tissue response. Oxidative stress can cause DNA damage, lipid peroxidation, inflammatory amplification and cell injury of the oral mucosal tissues. Hence, the correlation between the nutrition imbalance and inflammatory activity could give further insights into the behavior of the mucosal disease [2,11,12].

The rationale for nutritional status being related to the severity of oral mucosal disease may be explained by the aspects of inflammation. C-reactive protein, interleukin-6, tumor necrosis factor-alpha and other pathways involving cytokines may indicate of systemic or local inflammatory activity. If patient has micronutrient deficiencies they might have changes in immune responses, changes in epithelial repair and increased inflammatory burden. Together with nutritional parameters, the study of these markers potentially can help to explain why some patients experience more severe, recurrent, or persistent oral mucosal reactions, compared to others [1,5].

Although oral mucosal diseases are increasingly being considered a nutritional disease, they are not routinely assessed for nutritional status (micronutrient) or inflammatory profiles, except in clinical settings where the primary emphasis is placed on the symptoms of the disease. This might result in suboptimal care for patients with oral changes that are affected by systemic or dietary causes. Further, a clinical study investigating micronutrients and inflammatory markers in oral mucosal diseases may shed more light on the role of nutrition disorders, inflammatory activity, and clinical severity of the condition and type of lesion [4,5].

Vol 14, No 2 (2026) DOI 10.5195/d3000/2026.1542

So, the present study aimed to evaluate micronutrient status and inflammatory profiles in patients with OMD than that of healthy controls. Selected nutritional parameters (vitamin B12, folate, iron, ferritin, zinc and vitamin D) and markers related to mucosal disease activity (C-reactive peptide, tumor necrosis factor α and interferon γ) are studied. It also compares the relationship of these biological variables with clinical severity measures like pain intensity, number of lesions, size of lesions, recurrence rate and healing time.

Material and Methods

Study Design

This study aimed to be an observational cross sectional clinical study to assess the relationship of micronutrient status, inflammation and severity of oral mucosal diseases. This study compared patients with various oral mucosal lesions and patients without apparent oral lesions (controls). The primary aim was to identify whether the micronutrient deficiencies and inflammatory markers were more prevalent in patients with OM and whether these micronutrient deficiencies were correlated with disease (recurrence and delayed healing) severity.

Survey Sampling and Designs, Study Setting and Duration.

Oral Medicine and Oral Diagnosis Clinic, College of Dentistry was the study site for 6 months. Collection of samples, lesions and clinical examination were carried out under the standardized conditions. All laboratory analyses were performed in the accredited clinical laboratory to use the biochemical and immunological standard methods.

Study Population

In all, 120 subjects participated in the study. They were split into 2 main categories: OMD and control groups. OMD patients consisted of 90 oral mucosal disease patients who were clinically diagnosed. Controls were normal with no disease (healthy). We included 30 apparently healthy individuals in this group without any active oral mucosal lesions or inflammatory systemic diseases.

The patients were sub-grouped based on clinical diagnosis as follows:

Sub-group	Clinical diagnosis	Number of patients
A	Recurrent aphthous stomatitis	25
B	Oral lichen planus	22
C	Glossitis or burning mouth-related symptoms	18
D	Oral candidiasis	13
E	Oral potentially malignant disorders	12
Total	Oral mucosal disease patients	90

Sample Size Justification

The number of patients was chosen with the intention of making a reasonably sized comparison group of patients who had oral mucosal diseases with healthy controls. A sample size of 120 participants was deemed adequate to detect differences in micronutrient/ inflammatory markers between groups as well as subgroups analyses by lesion type. Sample size was also determined by the feasibility, availability of patients and the anticipated prevalence of oral mucosal diseases in clinical oral medicine practice.

Patients included in the oral mucosal disease group in the study if they were between 18 and 70 years with recurrent aphthous stomatitis, oral lichen planus, glossitis/burning mouth related symptoms, oral candidiasis, or oral potentially malignant disorder. They were required to have the capacity to give informed consent and not have received nutritional support over the last 3 months. Also, no systemic antibiotic, corticosteroid or immunosuppressive therapy done in the 4 weeks prior to surgery not done.

Healthy controls had no lesions on the oral mucosa, no history of recurrent oral ulceration, absence of any known systemic inflammatory, autoimmune, malignant or hematological disorder and no recent supplementation of micronutrients.

The participants were not included if they had a presence of a current pregnancy, lactation, past cancer or chemotherapy treatment, autoimmune disease on diagnosis and/or a history of autoimmune disease requiring immunosuppressive therapy, uncontrolled diabetes mellitus, chronic liver disease or chronic kidney disease, oral surgery, or trauma-induced ulceration, within the past three months, past use of vitamins and/or minerals, smoking more than 10 cigarettes a day, alcohol abuse, systemic infection at the time of the examination which is acute, or denied giving blood samples.

Clinical Examination

All participants were asked to have a thorough oral exam performed by qualified dental clinicians. Examination was carried out with the use of dental mirror, probe, sterilized gauze and good lighting. The oral mucosa was systematically examined consisting of buccal mucosa, labial mucosa, tongue, floor of the mouth, palate, gingiva and oropharyngeal region.

We recorded type of lesion, site of lesion, number of lesions, size of lesions (in mm), erythema, ulceration, white striae, plaque, atrophy or erosion present, pain intensity, burning sensation, duration of symptoms, recurrence frequency, healing duration, previous history of similar lesions, diet history, history of restricted diet, medication history, systemic disease history.

The standard oral medicine criteria were used for clinical diagnosis. Recurrent aphthous stomatitis was diagnosed when patients presented with recurrent, painful, round or oval ulcer(s) with erythematous margins, typically located in the non-keratinized oral mucosa.

Oral lichen planus

The clinical diagnosis was made based on the presence of bilateral reticular white striae, erythema, erosions or ulcerative areas. Biopsy was carried out in lesions with atypical appearance, erosive type lesions, unilateral lesions and lesions showing persistence, for histopathological diagnosis.

The diagnosis of glossitis/burning mouth related symptoms was established when patients came in complaining of tongue soreness, tongue burning, smooth tongue, taste change or generalized oral soreness, and/or with or without a visible tongue surface change.

The diagnosis of oral candidiasis was made when there was a removable plaque of white appearance, an erythematous appearance, angular cheilitis, or an erythema associated with denture. If necessary, diagnosis was made using a cytological smear or by the response to the antifungal treatment.

Pathologically, the OPDs included clinically suspicious leukoplakia, erythroplakia or a combination of both. Where clinically indicated these cases were referred for biopsy and histopathological assessment.

Clinical Severity Assessment

A composite oral mucosal severity score was used to determine clinical severity. The five clinical parameters were included in the score.

Parameter	Score			
	0	1	2	3
Pain intensity using VAS	No pain	Mild pain	Moderate pain	Severe pain
Lesion number	No lesion	1 lesion	2–3 lesions	More than 3 lesions
Lesion size	No lesion	<5 mm	5–10 mm	>10 mm
Recurrence frequency	No recurrence	Rare	Monthly	Frequent or continuous

Healing duration	Normal	<7 days	7–14 days	>14 days

The clinical severity score was a total score that ranged from 0 to 15. The severity of diseases was ranked as: Mild: 1–5, Moderate: 6–10, or Severe: 11–15.

To assess the links between micronutrient deficiency, inflammatory activity and clinical severity, this scoring system was used.

Blood Sample Collection

Under aseptic condition 5ml venous blood was obtained from each of the participant. The blood samples were separated in to EDTA and plain tubes depending upon the laboratory tests required. The samples were centrifuged at 3000 rpm for 10 minutes, and the serum was separated and kept at −20°C until the biochemical and inflammatory markers were measured.

Laboratory Assessment

Hematological, nutritional and inflammatory parameters studied were hemoglobin concentration, serum ferritin, serum iron, vitamin B12, serum folate, serum zinc, serum 25-hydroxyvitamin D, C-reactive protein, interleukin-6, and tumor necrosis factor-alpha.

The hemoglobin values were determined by an automated hematology analyzer. The serum levels of ferritin, Vitamin B12, folate and Vitamin D were determined by chemiluminescent immunoassay technique. Serum iron and zinc were estimated by colorimetric/ spectrophotometric method following laboratory procedures. The amount of interleukins were examined by enzyme-linked immunosorbent assay (ELISA) kits as per the manufacturer's instructions: Interleukin-6 and tumor necrosis factor alpha.

Definition of Micronutrient Deficiency

The reference ranges established by the clinical lab were used for micronutrient deficiency. For consistency, the following common cutoff points were used:

Parameter	Deficiency cutoff
Hemoglobin	<13 g/dL in males; <12 g/dL in females
Ferritin	<30 ng/mL
Vitamin B12	<200 pg/mL
Folate	<4 ng/mL
Zinc	<70 µg/dL
Vitamin D	<20 ng/mL
C-reactive protein	>5 mg/L considered elevated

The participants were also classified based on number of deficiencies. Normal micronutrient profile meant no deficiency. The Single Deficiency indicated one parameter that was missing. Single Deficiency means that a single parameter was deficient. Multiple deficiencies equaled to two (or more) parameters found to be deficient

Histopathological Assessment

Biopsy was indicated for clinically suspicious, persistent, atypical, erosive, unilateral or potentially malignant lesions. Tissue samples were fixed in 10% neutral buffered formalin, processed, embedded in paraffin, sectioned at 4-5 microns and stained with hematoxylin and eosin.

A histopathological examination was conducted on epithelial thickness, presence of ulceration, basal cell degeneration, lymphocytic infiltration, hyperkeratosis, epithelial dysplasia, Fungi hyphae with the diagnosis of candidiasis, and inflammatory intensity.

Histopathological result was correlated with clinical diagnosis and biochemical parameters if a biopsy was available.

Data Collection

A standardized data collection sheet was used to record the data. The following variables were recorded: demographics, clinical diagnosis, lesion description, severity score, recurrence pattern, healing time, micronutrient levels, inflammatory marker levels and histopathology.

Statistical Analysis

The data were analyzed with Statistical Package for Social Studies software. Data for the continuous variables were presented as mean ± SD. Frequencies and percentages were used to describe categorical variables.

Independent samples t-test was used to compare the mean laboratory values of oral mucosal disease group and healthy control group. The levels of micronutrients and inflammatory markers were compared between the disease subgroups using one-way analysis of variance. The frequency of micronutrient deficiencies was compared to the patient and the control groups using a chi-square test. The correlation of clinical severity score with laboratory parameters was assessed in both Pearson correlation or Spearman tests.

Multiple logistic regression was used to explore the independent risk factors for oral mucosal disease moderate to severe. The variables included in the model were: vitamin B12 deficiency, ferritin deficiency, zinc deficiency, vitamin D deficiency, elevated C-reactive protein, elevated interleukin-6 and multiple micronutrient deficiencies. P-value < 0.05 was taken as a statistical significance.

Ethical Considerations

The study was carried out in accordance with the principles of the declaration of Helsinki. Prior to data collection, an institutional scientific and ethical committee had granted ethical approval. All the participants were briefed on the study, clinical examination procedure, collection of blood samples and their confidentiality. All participants were signed up after written informed consent was obtained.

Outcome Measures

The main results of the study were differences in the micronutrient status between patients with oral mucosal diseases and healthy controls.

Secondary outcomes included difference in inflammatory markers between patients and controls, strong negative correlation was noticed between micronutrient deficiency and clinical severity score, relationships between inflammatory markers and recurrence rate, the relationship between multiple micronutrient deficiencies (MMD) and delayed healing, and the different nutritional and inflammatory characteristics in sub-groups of the oral mucosal diseases.

Results

The general characteristics of the study population are summarized in Table 1 below.

The total sample size in the study was 120. A group of 90 patients with oral mucosal disease and 30 apparently healthy persons were included in the control group. The mean age of oral mucosal patients was 39.8 years ± 12.6 years and that was 37.4 years ± 10.9 years for the control group. The age and sex distribution of the two groups was not statistically different from each other.

Within the oral mucosal disease group, recurrent aphthous stomatitis (RAS) was most common, followed by oral lichen planus, oral burning mouth symptoms, oral candidiasis and oral potentially malignant disorders. Most of the patients were clinically moderate whereas severe clinical manifestation was more seen in patients of erosive oral lichen planus, recurrent aphthous stomatitis and oral potentially malignant disorders.

Distribution of Oral Mucosal Diseases

The most common oral mucosal disease was recurrent aphthous stomatitis with 27.8% of the patients. Oral lichen planus constituted 24.4% and glossitis and/or burning mouth syndrome 20.0%. In 14.4% of the patients, the oral diagnosis was candidiasis and in 13.3% oral potentially malignant disorders were found (Table 2).

Micronutrient Status in Patients and Controls

Oral mucosal disease patients had significant lower mean levels of vitamin B12, ferritin, iron, zinc, and vitamin D levels than healthy controls. Compared with the control group, the folate levels were also lower, but not as significantly as the differences noted with the vitamin B12, ferritin, zinc and vitamin D.

Vitamin B12 deficiency was found in 31.1 % of patients and 10 % of controls. 37.8% of patients had a deficiency of ferritin, whilst 13.3% of controls had a deficiency. The prevalence of

zinc deficiency in patients was 34.4% and vitamin D deficiency was observed in 46.7% of patients. Patients with recurrent aphthous stomatitis (RAS), glossitis or oral lichen planus (burning mouth symptoms) and erosive oral lichens had a higher prevalence of multiple micronutrient deficiencies (Table 3).

Frequency of Micronutrient Deficiencies

Oral mucosal disease group showed a significantly higher prevalence of micronutrient deficiencies when compared to the control group. Vitamin D deficiency was the most common abnormality followed by deficiency of ferritin, zinc, vitamin B12 and folate. 42.2% of patients had multiple deficiencies, but only 10.0% of controls had multiple deficiencies (Table 4).

Inflammatory Marker Profile

The inflammatory markers were significantly raised in patients with OMD as compared to healthy controls. CRP, IL-6 and TNF-α were found to be elevated in the patient group. Patients with erosive oral lichen planus, recurrent aphthous stomatitis (severe) and oral potentially malignant disorders showed the highest inflammatory marker values (Table 5).

The percentage of vitamin B12, ferritin and iron deficiency was seen to be the highest in patients with recurrent aphthous stomatitis. There was also a high prevalence of vitamin B12, iron and zinc deficiencies in patients who had glossitis or burning mouth related symptoms. Patients with oral lichen planus had lower levels of vitamin D and zinc, particularly for erosive and symptomatic OLP. Iron and vitamin D levels were often found to be deficient among oral candidiasis patients. There were a higher level of inflammatory markers and a relatively lower antioxidant-related micronutrient status on patients with potentially malignant disorders of the oral cavity (Table 6).

Relationship Between Micronutrient Deficiency and Clinical Severity

Median scores of clinical severities were significantly greater in the patients with multiple micronutrient deficiencies than in the patients with single deficiency and no deficiency groups. The patients showing multiple deficiencies had a higher recurrence rate, pain score, lesion size and longer healing duration.

Clinical severity scores were similar for patients without deficiency (5.4 ± 2.1), a single deficiency (7.6 ± 2.8) and multiple deficiencies (10.2 ± 3.1). This difference was statistically significant (Table 7).

Correlation Analysis

Correlation between clinical severity score and vitamin B12, ferritin, zinc and vitamin D levels were negative. This implies the lower levels of micronutrients correlated with higher severity of disease. CRP, IL-6 and TNF-α level were positively associated with clinical severity. (Table 8).

Logistic Regression Analysis

Using the multiple logistic regression analysis, independent predictors of moderate-CD to severe-CD OMD were sought. Multiple micronutrient deficiency, vitamin D deficiency, ferritin deficiency, IL-6 and C reactive protein (CRP) were all statistically significantly correlated with the moderate to severe clinical presentation (Table 9).

Histopathological Findings

If the lesion has persisted or is atypical or erosive, or if it could be malignant, a biopsy will be performed in 26 patients. Of these 10 patients had associated oral leukoplakia with varying degrees of epithelial hyperkeratosis or dysplasia and 4 patients had chronic inflammatory mucositis that was not diagnosed as OLP nor lichenoid mucositis.

Those with erosive oral lichen planus exhibited basal cell degeneration, band-like lymphocytic infiltrate and varying epithelial atrophy. Selected cases of potentially malignant oral conditions demonstrated hyperkeratosis, epithelial hyperplasia and mild to moderate epithelial dysplasia. Higher levels of inflammatory markers occurred more often in the patients of dense inflammatory infiltration or epithelial dysplasia.

Discussion

A direct correlation between the nutritional status of micronutrients, inflammatory activity and clinical severity in oral mucosal diseases was evaluated through the present clinical study. Results revealed that patients with oral mucosal lesions had significant reductions in Vitamin B12, ferritin, serum iron, zinc and vitamin D levels when compared to healthy controls. In addition, inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-a (TNF-alpha) were significantly elevated in the patient group. This study supports the idea that oral mucosal diseases are not purely local clinical and pathological entities but could be indicative of systemic nutritional and inflammatory imbalance. The results must, however, be considered in the context of association rather than a cause-and-effect relationship between the investigated effects, as oral mucosal diseases are multifactorial and may be caused by immune, microbial, traumatic, systemic, psychological and nutritional factors [1,13].

The result of this study that was particularly important was that oral mucosal diseases have significantly more cases of hematinic deficiencies than the controls. Vitamin B12 deficiency, low ferritin, low serum iron, and low hemoglobin levels were more prevalent in the patients compared to controls, especially in those with recurrent aphthous stomatitis, glossitis, and burning mouth symptoms. These findings are biologically plausible, as the vitamin B12, folate and iron, along with hemoglobin, are vital for DNA synthesis, epithelial renewal, oxygen transport and mucosal tissue metabolism. The deficiency of these factors could be associated with decreased epithelial turnover, increased fragility of mucosal barrier, delay in healing wound, and recurrent ulceration [5,6].

Recurrent aphthous stomatitis had a particular association with the hematinic deficiency in the current study. Vitamin B12, ferritin and iron deficiency were common in patients with recurrent aphthous stomatitis, with many of those with recurrent lesions, pain and delayed healing. This discovery is consistent with other reports that recurrent aphthous stomatitis patients tend to have lower levels of vitamin B12, ferritin, hemoglobin, or folate than healthy people. Recurrent aphthous stomatitis is not the only disorder caused by hematinic deficiency; it can, however, be an important modifying factor that enhances disease frequency and aggravates its severity, with regards to mucosal sensitivity and delayed healing of epithelia [5,14].

The present findings also demonstrated that vitamin B12, iron and zinc levels were low in a significant proportion of patients with glossitis and BMS symptoms. This finding is consistent with the clinical significance of distinguishing primary burning mouth syndrome from secondary burning symptoms due to nutritional and/or hematological abnormalities. Vitamin B12 deficiency might play a role in burning sensation, tongue soreness, dysgeusia and mucosal discomfort via the impairment of epithelial renewal and potential neurological involvement. Iron deficient anemia can cause mucosal pallor, sore tongue and epithelial atrophy and zinc deficiency can cause altered taste function and mucosal repair. Hence, laboratory measurement of micronutrients might be helpful in the patients who have persistent oral burning especially in combination with glossitis and mucosal atrophy, or any unexplained oral discomfort [1,4].

Vitamin D deficiency was the most common deficiency in this study. It was more prevalent in the individuals with oral lichen planus, oral candidiasis and oral potentially malignant disorders. Vitamin D has significant immunomodulatory effects and could have a role in epithelial barrier function, antimicrobial peptide expression, cytokine regulation and T-cell activity. Oral lichen planus is an immune-mediated mucosal disorder, associated with chronic T-cell related epithelial injury, the vitamin D insufficiency may lead to enhancement of the inflammatory activity or to impairment in immune balance. The recently conducted studies support the findings of the present study,

indicating that there is a relationship between low levels of Vitamin D and OLP, but that supplementation should be used as an adjunct and should not replace the conventional treatment of oral medicine management (Egido-Moreno et al., 2024; García-Pola & Rodríguez-Fonseca, 2024).

Patients were also significantly more likely to have a deficiency in zinc than controls, particularly patients with oral lichen planus, burning symptoms and delayed healing. Zinc is involved in the repair of epithelial cells, regulation of immunity, antioxidant defense, enzyme functions, taste and wound healing. In the current study, lower zinc concentrations were associated with clinical severity, suggesting that decreased zinc status may be linked with clinically more severe and/or persistent mucosal disease. This discovery aligns with earlier studies that have indicated the potential of zinc as a supportive agent in oral mucosal healing and its potential benefits as an adjunct to conventional treatments in specific cases of OLP (Aboushousha et al., 2025; Bechara et al., 2022).

Another important finding is the increase in inflammatory markers in the oral mucosal disease group. The concentrations of C-reactive protein, interleukin-6 and tumor necrosis factor-alpha were significantly elevated in patients compared with controls. The systemic inflammatory markers were also positively correlated with clinical severity scores, indicating that systemic inflammation may be a sign of clinical severity, recurrence, or persistence of OMLs. Interleukin-6 and tumor necrosis factor-alpha are associated with signaling inflammatory processes, activation of the immune system, damage to epithelial structures and processes of tissue repair. They are elevated in patients with more severe lesions further supporting the concept that the inflammatory burden plays a role in the clinical expression of OM. (Bačun et al., 2024; Iones.

There is potential for a bidirectional relationship between micronutrient deficiency and inflammation. Immunoregulatory and epithelial repair mechanisms may be impaired due to nutritional deficiencies, leading to elevated inflammatory activity. The inflammation of the mouth may also cause aversion to eat and a decrease in food consumption because of pain, burning sensation, trouble chewing and shying away from certain food items over a prolonged time. This can exacerbate nutritional issues and lead to a vicious cycle of deficiency, inflammation, and impaired healing. This is corroborated by the present finding that patients with multiple micronutrient deficiencies had higher severity scores. Bačun et al. (2024) and Mousavi et al. (2024) found that patients with multiple deficiencies experienced greater pain, higher recurrence rates, larger lesions, and slower healing rates compared to those with no deficiency or a single deficiency.

In the present study, the prevalence of vitamin D deficiency, zinc deficiency and high inflammatory markers were associated with oral lichen planus patients. Clinically relevant, because oral lichen planus is an immune-mediated disease with different clinical features, from asymptomatic reticular lesions to erosive or ulcerative lesions that cause pain. Micronutrient deficiency can be present but not be a trigger for the disease, but can affect symptoms, epithelial repair, oxidative balance, and inflammation. Thus, nutritional assessment might be beneficial within a comprehensive approach, especially in cases with symptoms or erosion [8,9].

Iron deficiency, Vitamin D deficiency and multiple micronutrient deficiencies were found commonly in patients with oral candidiasis in the present study. Local and systemic predisposing factors, including denture use, xerostomia, antibiotics, corticosteroids, diabetes mellitus and immunosuppression, are typically associated with oral candidiasis. Deficiency of the nutrients, however, may play a role by compromising epithelial resistance and host immune defense. Iron deficiency can impact epithelial integrity and vitamin D deficiency can impact antimicrobial response. Thus, clinicians should consider more than just predisposing factors at the local level when dealing with a patient with recurrent or resistant Candida infection, but rather systemic and nutritional background [1,15].

The present study revealed that patients with oral potentially malignant disorders had elevated levels of inflammatory markers and moderately decreased levels of antioxidant-related micronutrient status. Oral potentially malignant disorders are complex lesions which demand biopsy, histopathological diagnosis and grading, control of risk factors and long-term follow-up. These lesions should not be given as an alternative explanation for nutritional imbalance. The micronutrient deficiency and oxidative stress, however, can affect the stability of the epithelium, chronic inflammation and susceptibility of cells. Antioxidant nutrients, including vitamins A, C, and E, selenium, zinc, and vitamin D, may aid in epithelial defense, but may not supplant standard diagnostic and surveillance practices [2,11].

In this study, clinical severity score was negatively correlated with vitamin B12, ferritin, zinc and vitamin D. This implies that the clinical presentation was more severe with lower micronutrient levels. Clinical severity, however, was positively correlated with C-reactive protein, interleukin-6 and tumor necrosis factor-alpha. The findings indicate that micronutrient deficiency and inflammatory activation could be more clinically relevant than micronutrient deficiency alone. The logistic regression analysis confirmed that multiple micronutrient deficiencies, vitamin D deficiency, ferritin deficiency, elevated C-reactive protein and interleukin-6 were significant predictors of moderate-to-severe oral mucosal disease, which was the target of the study [1,5].

The results of this study are applicable in the field of oral medicine. Selective laboratory tests, such as complete blood count, ferritin, serum iron, vitamin B12, folate, zinc, vitamin D, and inflammatory markers, at clinically appropriate intervals, may be warranted for those who have recurrent, persistent, unexplained, severe or treatment-resistant oral mucosal lesions. Not all minor oral ulcers need extensive testing, but this does not imply that such testing is not necessary. Instead, clinical findings like recurrence, failure to heal, glossitis, burning sensation, and pallor of the mouth, as well as systemic symptoms or unresponsiveness to traditional treatment, should guide the nutritional and inflammatory assessment [4,6].

An intriguing aspect of this study is the multimodal assessment of oral mucosal diseases that combined oral medicine, oral pathology, nutritional, and inflammatory assessment. This clinical model is more comprehensive than clinical examination only and gives a better understanding of disease behavior. Another advantage was the inclusion of various subgroups of oral mucosal diseases, facilitating the cross comparison of micronutrient and inflammatory patterns in various clinically relevant disease states. Furthermore, the use of a clinical severity score facilitated the linkage of laboratory data with expression of disease at the level of the patient.

There are a few limitations, however, to this study. Firstly, the cross-sectional design can only establish associations and not causal relationships. Second, some subgroups of diseases were small, such as oral candidiasis and oral potentially malignant disorders. Third, detailed validated diets questionnaires were not used to measure dietary intake but instead was done clinically. Fourth, local inflammatory biomarkers in saliva/tissue were not measured and systemic serum markers may not completely reflect local mucosal inflammation. Fifth, there was no follow-up after correcting nutritional deficiencies, and the clinical improvement after supplementation could not be evaluated.

Larger patient numbers, a longer follow-up period, dietary evaluation, assessment of salivary inflammatory markers, markers of oxidative stress, and intervention arms evaluating the impact of correction of certain deficiencies are indicated to be evaluated in future studies.

Randomized controlled trials are required to confirm if vitamin B12, vitamin D, iron and zinc supplementation benefits clinical parameters like ulcer recurrence, severity of pain, healing time, inflammatory marker levels and quality of life. The extent of histopathological correlation should also be increased in some lesions including OLP and OPMDs to understand the association between micronutrient status, epithelial changes and inflammatory infiltration [10,11].

In general, the present study confirms the hypothesis that there is a link between micronutrient imbalance, inflammatory activity and oral mucosal diseases and that these relationships may play a role in the clinical presentation of the diseases. Although nutritional deficiencies should not be viewed as the only cause of oral mucosal lesions, they can be important modifying factors that influence oral mucosal integrity, recurrence, immune response and healing potential. Selective nutritional and inflammatory assessment can enhance the diagnosis, risk assessment and individualized management of oral medicine practice.

Conclusion

Main findings of the study were:

1. Patients with oral mucosal diseases had significantly lower levels of vitamin B12, ferritin, iron, zinc, and vitamin D compared with healthy controls.
2. Vitamin D deficiency was the most frequent deficiency among patients, followed by ferritin, zinc, vitamin B12, and iron deficiencies.
3. Multiple micronutrient deficiencies were significantly more frequent in patients with oral mucosal diseases than in controls.
4. Patients had significantly elevated levels of inflammatory markers such as C-reactive protein, interleukin-6 and tumor necrosis factor-alpha compared to healthy controls.
5. Clinical severity was negatively correlated with vitamin B12, ferritin, zinc, and vitamin D levels.
6. Clinical severity was positively correlated with inflammatory marker levels.
7. Multiple micronutrient deficiencies and elevated inflammatory markers were associated with moderate-to-severe oral mucosal disease.
8. The strongest association was found in recurrent aphthous stomatitis, glossitis, symptoms related to burning mouth and erosive oral lichen planus.
9. The association of potentially malignant disorders of the oral cavity was stronger with inflammatory and oxidative changes than with a single nutrient deficiency.

Study Limitations

There are several limitations to this research. Firstly, the cross-sectional design enabled associations to be assessed between micronutrient status, inflammatory activity and severity of oral mucosal disease, but causal relationships could not be established. Hence, it is not possible to deduce that the oral mucosal lesions were due to micronutrient deficiency.

Secondly, the sample size was rather small, particularly when analyzed by individual disease subgroups like oral candidiasis and oral potentially malignant disorders. The results should be replicated in larger, multicenter studies to validate the findings and enhance the generalizability of the results.

Third, this study investigated selected micronutrients (vitamin B12, folate, iron, ferritin, zinc, vitamin D) but other potentially relevant nutritional factors, including protein status, vitamin A, vitamin E, selenium, and omega-3 fatty acids, were not properly evaluated.

Fourth, detailed nutritional questionnaires were not used for assessing dietary intake. Therefore, it is not possible to draw a conclusion if it is due to poor nutrition, malabsorption, or systemic illness or disease, or simply by the decreased appetite due to painful oral lesions.

Fifth, inflammatory activity was determined based on serum inflammatory markers. C-reactive protein, interleukin 6 and tumor necrosis factor alpha are helpful to determine systemic inflammatory processes but may not be accurate indicators of local inflammatory activity at the site of the oral mucosa. Salivary biomarkers and inflammatory assessment at the tissue level should be included in future studies.

Sixth, histopathological evaluation was done in clinically indicated cases (persistent, erosive, atypical, potentially malignant); in other cases, no evaluation was performed. Thus, there was no histopathology correlation for all subjects.

Seventh, the study failed to have a follow-up (after nutritional correction and/or supplementation). Therefore, it could not be determined if treatment for micronutrient deficiencies would lead to better symptom response or decrease in levels of inflammatory markers, or if it would reduce the incidence of recurrence or speed healing.

Finally, oral mucosal disease is a multifactorial condition where local trauma, microbial factors, immune status, psychological stress, systemic disease, medication use, oral hygiene and nutrition status play a role. The study aimed to control as many major confounding conditions as possible, but several possible confounders were not completely controlled.

Further studies should focus on larger populations, longitudinal studies, dietary intake, salivary and tissue markers, markers of oxidative stress, and controlled supplementation studies to further elucidate the clinical significance of nutritional correction in oral mucosal disease management.

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Table 1. Demographic and clinical distribution of the study participants is described.

Variable	Oral mucosal disease group (n = 90)	Control group (n = 30)	p-value
Age, years, mean ± SD	39.8 ± 12.6	37.4 ± 10.9	0.341
Male, n (%)	39 (43.3%)	14 (46.7%)	0.748
Female, n (%)	51 (56.7%)	16 (53.3%)	0.748
Pain/burning symptoms, n (%)	68 (75.6%)	2 (6.7%)	<0.001
Recurrent lesions, n (%)	52 (57.8%)	0 (0%)	<0.001
Delayed healing, n (%)	37 (41.1%)	1 (3.3%)	<0.001
Mean clinical severity score	8.1 ± 3.2	0.8 ± 0.6	<0.001

Table 2. The distribution of oral mucosal disease subgroups.

Oral mucosal disease subgroup	Number of patients	Percentage
Recurrent aphthous stomatitis	25	27.8%
Oral lichen planus	22	24.4%
Glossitis or burning mouth-related symptoms	18	20%
Oral candidiasis	13	14.4%
Oral potentially malignant disorders	12	13.3%
Total	90	100%

Table 3. Micronutrient levels in patients and controls.

Parameter	Oral mucosal disease group (n = 90)	Control group (n = 30)	p-value
Hemoglobin (g/dL)	12.4 ± 1.5	13.5 ± 1.2	0.002
Serum ferritin (ng/mL)	28.6 ± 14.9	46.8 ± 18.7	<0.001
Serum iron (µg/dL)	61.7 ± 21.4	82.5 ± 24.6	<0.001
Vitamin B12 (pg/mL)	246.3 ± 91.8	334.6 ± 105.7	<0.001
Folate (ng/mL)	5.2 ± 2.1	6.7 ± 2.4	0.006
Zinc (µg/dL)	68.9 ± 15.3	82.7 ± 14.8	<0.001
Vitamin D (ng/mL)	18.6 ± 7.9	27.4 ± 9.5	<0.001

Table 4. The proportion of micronutrient deficiencies in the study groups.

Deficiency	Oral mucosal disease group (n = 90)	Control group (n = 30)	p-value
Low hemoglobin	29 (32.2%)	4 (13.3%)	0.047
Ferritin deficiency	34 (37.8%)	4 (13.3%)	0.012
Iron deficiency	31 (34.4%)	5 (16.7%)	0.071
Vitamin B12 deficiency	28 (31.1%)	3 (10%)	0.021
Folate deficiency	18 (20.0%)	2 (6.7%)	0.091
Zinc deficiency	31 (34.4%)	4 (13.3%)	0.027
Vitamin D deficiency	42 (46.7%)	7 (23.3%)	0.026
Multiple deficiencies	38 (42.2%)	3 (10%)	0.001

Table 5. The level of inflammatory markers was compared between patients and controls.

Inflammatory marker	Oral mucosal disease group (n = 90)	Control group (n = 30)	p-value
C-reactive protein (mg/L)	6.8 ± 3.7	2.4 ± 1.3	<0.001
Interleukin-6 (pg/mL)	9.6 ± 4.8	3.9 ± 1.7	<0.001
Tumor necrosis factor-alpha (pg/mL)	18.4 ± 7.2	10.1 ± 3.6	<0.001

Vol 14, No 2 (2026) DOI 10.5195/d3000/2026.1542

Table 6. Oral mucosal disease subgroup (OMDS) and severity of micronutrient deficiency pattern (MDP).

Disease subgroup	Most frequent deficiencies	Main clinical association
Recurrent aphthous stomatitis	Vitamin B12, ferritin, iron	Recurrent ulcers, pain, delayed healing
Oral lichen planus	Vitamin D, zinc	Erosive lesions, burning symptoms, inflammatory activity
Glossitis/burning mouth symptoms	Vitamin B12, iron, zinc	Tongue soreness, burning sensation, dysgeusia
Oral candidiasis	Iron, vitamin D, multiple deficiency	Recurrent infection, erythema, mucosal soreness
Oral potentially malignant disorders	Vitamin D, zinc, low antioxidant profile	Chronic inflammation, epithelial alteration

Table 7. Clinical severity according to micronutrient deficiency status.

Deficiency status	Number of patients	Mean severity score	p-value
No deficiency	21	5.4 ± 2.1	—
Single deficiency	31	7.6 ± 2.8	0.018
Multiple deficiencies	38	10.2 ± 3.1	<0.001

Table 8. Clinical severity scores and laboratory parameters correlations.

Parameter	Correlation coefficient (r)	p-value
Vitamin B12	−0.41	<0.001
Ferritin	−0.38	0.001
Serum iron	−0.29	0.009
Zinc	−0.35	0.002
Vitamin D	−0.44	<0.001
C-reactive protein	+0.46	<0.001
Interleukin-6	+0.49	<0.001
Tumor necrosis factor-alpha	+0.42	<0.001

Table 9. The predictive factors for moderate to severe oral mucous disease.

Variable	Odds ratio	95% confidence interval	p-value
Multiple micronutrient deficiencies	3.82	1.58–9.21	0.003
Vitamin D deficiency	2.74	1.16–6.48	0.021
Ferritin deficiency	2.61	1.08–6.29	0.033
Vitamin B12 deficiency	2.18	0.91–5.24	0.079
Zinc deficiency	2.36	0.98–5.71	0.056
Elevated C-reactive protein	3.11	1.29–7.49	0.011
Elevated interleukin-6	3.69	1.47–9.24	0.005
Elevated TNF-alpha	2.42	1.01–5.82	0.048