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Comparative Study of Serum Zinc and Key Hematinic (Vitamin B12, Ferritin, Folate) in Patients with Minor Aphthous Stomatitis and Ulcerative Oral Lichen Planus

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ABSTRACT

Background and Objectives: Minor aphthous stomatitis (MAS) and ulcerative oral lichen planus (OLP) are chronic oral conditions with recurrent painful ulceration that significantly affects patients' quality of life. Despite extensive research, the precise etiopathogenesis of these conditions remains incompletely understood. Recent studies have found that a lack of micronutrients and key hematinics, such as zinc, vitamin B12, ferritin, and folate, may be associated with the start, severity, and recurrence of MAS and OLP. This study aimed to assess the association between these deficiencies and the occurrence of MAS and OLP compared with healthy controls.

Material and Methods: A cross-sectional, case-control study was conducted at Hawler Medical University/College of Dentistry in Erbil City, Iraq. From November 2024 to June 2025, a total of 160 participants were included: 40 patients with MAS, 40 with OLP, and 80 age- and gender-matched healthy controls. Serum levels of zinc, vitamin B12, ferritin, and folate were measured alongside hematologic indices (Hb, HCT, MCV). Data were analyzed using appropriate statistical tests.

Results: Both the MAS and OLP groups had much lower levels of zinc, vitamin B12, ferritin, and folate ($p<0.05$). Hematologic indices (Hb, HCT, MCV) were also lower in patients but still within the low-normal range. This finding suggests that subclinical hematinic deficiencies may exist, despite the absence of overt anemia. A female predominance and middle-age distribution were noted in both patient groups. When directly comparing MAS and OLP patients, the OLP group exhibited more pronounced deficiencies across all measured micronutrient and hematinic parameters, except folate, which showed higher levels of deficiency in MAS cases.

Conclusion: Subclinical micronutrient deficiencies may play a role in the pathogenesis of MAS and OLP. Routine nutritional assessment of zinc and key hematinics may improve diagnosis and management strategies for these chronic oral conditions.

Keywords: Hematinic indices, Minor aphthous ulcer, Nutritional deficiency, Oral lichen planus

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INTRODUCTION

Minor aphthous stomatitis (MAS) and ulcerative oral lichen planus (OLP) are chronic, inflammatory, painful oral mucosal conditions that significantly impair patients' quality of life. [1,2]

MAS typically presents as recurrent painful ulcerations of the non-keratinized oral mucosa that affect approximately 5% to 20% of the general population; they are marked by round or oval-shaped ulcers with a yellowish pseudomembranous base and erythematous halo.[3] RAS is classified into Three clinical types: minor (Mikulicz's, MiRAS), major (Sutton's, MaRAS), and herpetiform (HeRAS). based on lesion size, number, and healing pattern.[4] The eruptions are painful and significantly decrease the patients' quality of life.[5] Treatment of RAS remains challenging due to its uncertain etiology, and there is currently no approved treatment for the condition. Main objectives in RAS therapy are to lessen pain, speed up healing, and lessen the frequency of recurrences.[3,5]

OLP is a mucocutaneous disease of moderate prevalence (1 to 2 per cent of the population), the person affected being mostly the middle-aged adult in a female predisposition 2. It is a fact that OLP is an immune-related disease, where aberrant T- lymphocytes may be critical in its pathogenesis. Though a lot of researches have been conducted, it is not clear yet what causes the disease and what is the underlying pathogenesis of OLP, as further scientific research is needed.1 It was Presents with six distinct clinical forms, including reticular, papular, plaque, atrophic, bullous, and erosive forms. The erosive and atrophic types are more likely to be symptomatic, and in most instances, with pain and discomfort that can significantly impair the patient's quality of life.[2] However; both diseases are multifactorial in origin, despite their clinical differences, both conditions have unclear etiopathogenesis and are often associated with systemic or local contributing factors.[6,7] Recent research has shown that a lack of certain micronutrients and hematinics, especially zinc, vitamin B12, ferritin, and folate, may have played a role in the development and persistence of these lesions.[1]

The most common hematinic deficiencies are zinc, ferritin, folate and vitamin B12 deficiency that has been closely related to certain common oral mucosal diseases, including RAS and atrophic glossitis (AG). Besides influencing the integrity of the oral mucosa and predisposing the development of the secondary infection in the oral cavity, hematinic deficiencies may lead to the development of aberrant immune responses or form a part of the pathogenesis of the OLP.[1]

Zinc is important for the immune system, healing wounds, and keeping epithelial cells healthy. Its deficiency has been linked to delayed mucosal healing and chronic inflammation.[8,9]

Vitamin B12 and folate are also very important for DNA synthesis, controlling the immune system, and keeping the health of the oral epithelium.[10,11]

Ferritin is a crucial protein that stores and regulates iron, and it helps prevent oxidative damage by keeping iron in a non-reactive form that is easily accessible. Apart from aiding in iron homeostasis, ferritin acts as an inflammation and immune status marker. Ferritin not only shows how much iron is in the body, but it also shows how inflamed and how strong the immune system.[12,13]

These micronutrient imbalances are frequently associated with hematologic alterations such as low hemoglobin (Hb), hematocrit (HCT), and mean corpuscular volume (MCV), which can signal underlying deficiencies even in the absence of clinical anemia.[14,15] Although several previous studies have reported low levels of individual micronutrients in MAS or OLP separately, few have directly compared these conditions within a single population using matched healthy controls.[16,17] Both MAS and OLP present with recurrent painful oral ulcers, but they differ in aetiology; by comparing micronutrient and hematinic profiles, it may help to clarify both shared and disease-specific pathogenic factors. The aim of this study is to assess the association between micronutrient and hematinic deficiencies-specifically serum levels of zinc, vitamin B12, ferritin, and folate-and the occurrence of minor aphthous stomatitis and ulcerative oral lichen planus in comparison to healthy individuals.

METHODS

This study was designed as a cross-sectional, observational, case-control clinical study. The study was conducted at the department of Oral Medicine College of Dentistry Hawler medical University Erbil City, Iraq. The study took place be-

tween November 2024 and June 2025. All participants were of Kurdish ethnicity, and residents of Erbil Governorate, Iraq. A total of 160 participants were enrolled and divided into three groups: 40 patients with recurrent MAS, 40 patients with ulcerative OLP, and 80 healthy controls. The control group was subdivided into two subgroups (n=40 each), age- and gender-matched to the MAS and OLP groups. The ages of all participants ranged from 15 to 65 years. (2425136) approval date 02/02/2025.

Inclusion Criteria

Clinical diagnosis of MAS or ulcerative OLP confirmed by oral medicine specialists, with OLP cases further verified histopathologic ally, age ≥18 years, and no history of systemic disease known to affect hematologic or nutritional status. Healthy controls were selected from individuals attending routine dental checkups who met the same exclusion criteria.

Exclusion Criteria

Systemic autoimmune or gastrointestinal disease, pregnancy or lactation, recent micronutrient supplementation (within the last 3 months), active smoking, alcohol abuse, or use of medications affecting hematologic or immune function.

Ethical Consideration

The study protocol was submitted to and approved by the ethics committee at Hawler Medical University, College of Dentistry. and written consent was obtained from each of the participants.

A detailed questionnaire was used to collect demographic and clinical history data. All participants underwent complete oral examinations. The diagnosis of MAS was based on clinical history and recurrent minor ulcers (<10 mm), typically 1–5 in number, with a self-limiting healing pattern.[15] Ulcerative OLP was diagnosed according to the modified WHO criteria based on patient history, characteristic clinical features (e.g., bilateral white striations with erosive or ulcerative areas), and confirmed by histopathological examination.2 In addition, baseline laboratory investigations of biochemical tests were performed for all participants to assess serum levels of zinc, vitamin B12, ferritin, folate, and hematinic indices (Hb, MCV, and HCT). Fasting venous blood samples were collected and centrifuged to obtain serum. The following laboratory parameters were analyzed:

- Zinc: measured in µg/dL using spectrophotometric method
- Vitamin B12, Ferritin and Folate: measured using The Beckman Coulter Access 2 Automated Analyzer.
- Hematologic indices (Hb, HCT, MCV): analyzed using an automated hematology analyzer.

Statistical Analysis:

Data was tabulated using Microsoft Excel 2019 and analyzed using GraphPad Prism (version 7.0, GraphPad Software Inc., CA, USA). Statistical analysis included the Chi-square test for independence and the Wilcoxon Signed Rank Test to evaluate frequency data. A p-value of ≤ 0.05 was considered statistically significant

RESULTS

A total of 40 recurrent minor aphthous ulcer patients and 40 healthy controls were included in the final analysis. Table 1 summarizes the demographic information and characteristics of the study. The minor aphthous ulcer group comprised 40 subjects, 15 males (18.72%) and 25 females (31.25%), as compared with the control group, which was 14 males (17.5%) and 26 females (32.5%). There was no statistically significant difference between the minor aphthous ulcer and the control group regarding gender distribution, as shown in Table 1. On the other hand, the highest rates of minor aphthous stomatitis and control group were among the ages ≤ 40 years, which were 35 (43.75%) and 32 (40%), respectively. while the lowest rate was observed in the ≥ 61 years age group, with 0 participants in the MAS group and 1 (2.5%) in the control group. These differences in age distribution between the two groups were not statistically significant ($p > 0.05$).

The mean serum zinc concentration for the minor aphthous ulcer patients was found to be 85.97±1.51 µg/dL, while the control group was slightly higher at 89.73±2.88 µg/dL in zinc concentration, with a significant difference determined by the Wilcoxon Signed Rank Test ($p < 0.0001$). Patients with MAS exhibited lower ferritin concentrations (73.18±10.85 µg/dL) than the healthy control group (93.81±9.97 µg/dL).

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Table 1. Demographic information of the RAS patients and controls groups

Characteristics		MAS	%	H.C	%	P.Value
Sex	Male	15	18.75	14	17.5	0.8161
	Female	25	31.25	26	32.5	
Age	≤ 40	35	43.75	32	40	0.6744
	41-50	4	5	6	7.5	
	51-60	1	1.25	1	1.5	
	≥61	0	0	1	1.5	

Statistical Test Used: Chi-square test of independence.
Level of Significance: $p \leq 0.05$

The mean serum zinc concentration for the minor aphthous ulcer patients was found to be 85.97±1.51 µg/dL, while the control group was slightly higher at 89.73±2.88 µg/dL in zinc concentration, with a significant difference determined by the Wilcoxon Signed Rank Test ($p < 0.0001$). Patients with MAS exhibited lower ferritin concentrations (73.18±10.85 µg/dL) than the healthy control group (93.81±9.97 µg/dL). Additionally, folate and vitamin B12 levels in the minor aphthous ulcer group were significantly reduced when compared with the control group. Furthermore, the levels of hemoglobin (Hb), mean corpuscular volume (MCV), and hematocrit (HCT) were significantly higher in the control group compared to the aphthous ulcer group, as illustrated in Table 2.

Table 2. Comparison between patients and control groups in hematological parameters in recurrent minor aphthous stomatitis group

Characteristics	MAS Mean± Std. Error	H.C Mean± Std. Error	P Value
Zinc(µg/dL)	85.97±1.51	89.73±2.88	<0.0001****
Ferritin (µg/mL)	73.18±10.85	93.81±9.97	<0.0001****
Folate (ng/mL)	11.47±2.167	11.66±0.504	<0.0001****
B12 (pg/mL)	267.2±14.43	278.4±17.54	<0.0001****
Hb(g/dL)	12.72±0.235	13.73±0.1816	<0.0001****
MCV (fL)	80.99±1.115	88.73±0.588	<0.0001****
HCT %	38.09±0.684	42.49±0.6607	<0.0001****

Statistical analysis was performed using the Wilcoxon signed-rank test.
Level of significance: A p-value of <0.0001 indicates a highly statistically significant

In the oral lichen planus group, there were 16 males (20%) and 24 females (30%). There were twenty males (22.5%) and twenty-two females (27.5%) in the healthy control group. The participants' ages ranged from 33 to 72 years, with a mean age of 51.88 ± 9.98 years. The largest proportion of patients in the oral lichen group was found in the 51–60 age group (13 patients, 16.25%) and the 41–50 age group (12 patients, 15%). Conversely, the lowest proportion was observed in those aged ≤40 years, with 6 patients (7.5%) in the OLP group and 7 patients (8.75%) in the healthy control group. Statistical analysis revealed that there are no significant differences in age or gender distribution between the oral lichen and control groups, as shown in Table 3.

Table 3. Demographic information of the oral lichen planus patients and controls groups

Characteristics		OLP	%	H.C.	%	P. value
Sex	Male	16	20	18	22.5	0.651
	Female	24	30	22	27.5	
Age	≤ 40	6	7.5	7	8.75	0.9872
	41-50	12	15	12	15	
	51-60	13	16.25	13	16.25	
	≥61	9	11.25	8	10	

Statistical Test Used: Chi-square test of independence.
Level of Significance: $p \leq 0.05$

In this study, we noticed that patients with oral lichen planus demonstrated significantly lower levels of serum zinc, ferritin, folate, and vitamin B12 compared to the healthy control group. These differences were statistically significant. Additionally, as shown in Table 3.4, the levels of hemoglobin, MCV, and HCT were also much lower in the oral lichen planus group compared to the healthy control group ($p < 0.0001$).

Table 4. Comparison between oral lichen patients and control groups in hematological parameters

Characteristics	OLP Mean ± Std. Error	H.C. Mean ± Std. Error	P value
Zinc(µg/dL)	83.03±1.781	85.97±1.512	<0.0001
Ferritin (ng/mL)	66.81±8.933	93.81±9.977	<0.0001
Folate (ng/mL)	11.54±1.020	11.66±0.5048	<0.0001
B_{12} (pg/mL)	267.2±14.43	308.1±47.34	<0.0001
Hb (g/dl)	12.41±0.3461	13.73±0.1816	<0.0001
MCV (fl)	76.9±2.047	88.73±0.5887	<0.0001
HCT (%)	38.67±0.9757	42.49±0.6607	<0.0001

Statistical analysis was performed using the Wilcoxon signed-rank test. Level of **significance:** A p-value of <0.0001 indicates a highly statistically significant.

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The sex and age distribution of patients with recurrent minor aphthous ulcer and ulcerative OLP are presented in Table 3. The prevalence of both minor aphthous ulcer and oral lichen planus was slightly higher among female cases compared to male cases; however, this difference was not statistically significant ($p = 0.8185$). For age, the most cases of minor aphthous ulcers were found in people aged 40 and younger (43.75%), while the most cases of oral lichen planus were in the 51 –60 years age group (16.25%), and these differences between age groups were statistically significant ($p < 0.0001$).

Table 5. Demographic information of MAS and ulcerative OLP patients

Characteristics		MAS	%	Ulcerative OLP	%	P value
Sex	Male	15	18.75	16	20	0.8185
	Female	25	31.25	24	30	
Age	≤ 40	35	43.75	6	7.5	<0.0001
	41-50	4	5	12	15	
	51-60	1	1.25	13	16.25	
	≥61	0	0	9	11.25	

Statistical Test Used: Chi-square test of independence.
Level of Significance: $p \leq 0.05$

Table 6 shows the mean blood concentrations of zinc, ferritin, folate, and vitamin B12 in the study groups. The average levels of zinc, ferritin, and vitamin B12 were much higher in patients with recurrent minor aphthous ulcers than in those with oral lichen planus ($P < 0.0001$). The level of folate was much lower in patients with minor aphthous ulcers compared to those with oral lichen planus. Also, the average amounts of hemoglobin, MCV, and HCT (12.72±0.235, 80.99±1.115, and 38.09±0.684) in patients with minor aphthous ulcers were greater than in the oral lichen planus group (12.41±0.3461, 76.9±38.67, and 24.07±0.9757), respectively, and these differences were statistically significant.

Table 6. Comparison between aphthous ulcer and oral lichen patients' groups in hematological parameters

Characteristics	MAS Mean± Std. Error	OLP Mean± Std. Error	P value
Zinc	89.73±2.88	83.03±1.781	<0.0001
Ferritin	73.18±10.85	66.81±8.933	<0.0001
Folate	11.47±2.167	11.54±1.020	<0.0001
B_{12}	278.4±17.54	267.2±14.43	<0.0001
Hb	12.72±0.235	12.41±0.3461	<0.0001
MCV	80.99±1.115	76.9±2.047	<0.0001
HCT	38.09±0.684	38.67±0.9757	<0.0001

Statistical analysis: the Wilcoxon signed-rank test was used
Level of significance: A p-value of <0.0001 indicates a highly statistically significant.

DISCUSSION

This study found that patients with recurrent minor aphthous stomatitis and ulcerative oral lichen planus exhibited significantly lower serum levels of zinc, vitamin B12, ferritin, and folate in their blood than healthy control subjects. Most of the measured values in patients were still in the low-normal physiological range, but the fact that both disease groups had consistently lower levels of micronutrients suggests that there may be a link between subclinical deficiencies and these chronic oral mucosal disorders. These results suggest that even small amounts of imbalance in essential micronutrients may play a contributory role in the pathogenesis or chronicity of MAS and OLP 1,4 Regarding the serum zinc level in both RAS patients and H.C., in the current study, it has been found that the average serum zinc concentration was significantly less in MAS patients than in H.C. group. Zinc is the second trace metal that is present in the body in the highest quantity that follows iron. However, contrary to iron, there is no special zinc shop. Zinc has three groups of roles that include catalytic, structural and regulatory. The insufficient level of zinc in the body may lead to the imbalance in the immune system, which is manifested in the fact that the immune system is more vulnerable to infections in case of severe deficiency.[18]

Additionally, zinc is essential for epithelial healing, immune modulation, and anti-inflammatory activity. However, its deficiency is strongly implicated in the pathogenesis of aphthous ulcers. This observation aligns with previous studies that found a significant prevalence of zinc deficiency in MAS patients and its protective role in oral mucosal health.[19,20] Vitamin B12 and folate levels were also significantly lower in the MAS group, consistent with results that were reported previously.[21] These hematinic factors are vital for mucosal regeneration and immune response, and their deficiency may impair healing process or predispose to recurrence. B12 is necessary for DNA synthesis, cellular turnover, and immune function; thus, a B12 deficiency may contribute to a greater frequency and severity of recurrent oral ulcers. This finding supports earlier reports by Katebi et al. and Mousavi et al.[22,23] who observed significantly reduced B_{12} levels in patients with recurrent aphthous ulcers. Similarly, supplementation with vitamin B_{12} may reduce the duration of ulcers and enhance the healing process. These findings further underscore the critical role of this micronutrient in the modulation of disease.[24,25] Similarly, Compared to both the MAS group and healthy controls, the OLP group exhibited more significant deficiencies in zinc, vitamin B12, and ferritin. This finding is consistent with previous studies.[1,26] That have reported reduced hematinic and trace element levels in ulcerative forms of OLP. With OLP being a chronic illness that has episodes of a high level of exacerbation and remission, it can lead to the feeling of discomfort or even pain and inability to eat or drink.[1] The comparative data show more hematinic and hematological disruptions in ulcerative OLP than MAS. That is consistent with the hypothesis that both conditions may share a common nutritional factor in their etiopathogenesis; however, ulcerative OLP appears to be associated with more substantial immune, inflammatory, and micronutrient dysregulation. This finding suggests that considerations for hematinic screening should be part of the clinical evaluation, and there are implications for nutritional management as part of the overall therapeutic plan for both oral disease conditions. OLP is a chronic immune-mediated disorder that is often associated with persistent inflammation. This condition increases metabolic demands while oral symptoms (e.g., pain, burning) drive dietary changes. Patients often adopt soft, nutrient-poor diets to avoid discomfort, leading to significantly lower intake of essential micronutrients like compared to healthy individuals directly impacting micronutrient intake.[27] Such deficiencies impair immune and neuropsychologic functions, potentially worsening OLP progression.[28] On the other hand, MAS is more episodic, which means that patients can go back to their normal eating habits more quickly and have a lower risk of long-term deficiencies. Both conditions are more common in middle-aged women, but things like menstrual blood loss and differences in age and gender may also affect the levels of micronutrients in OLP patients. Also, autoimmune or malabsorptive conditions that haven't been diagnosed yet, which are more common in OLP, may make it harder for the body to absorb micronutrients. All of these things together help explain why OLP has more serious nutritional problems than MAS.[29,30]

Hematologic indices, including hemoglobin (Hb), hematocrit (HCT), and mean corpuscular volume (MCV), were significantly lower in both MAS and OLP patients compared to controls, though most

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values did not meet the clinical threshold for anemia. These borderline changes, suggest subclinical hematinic in sufficiency. Such deficiencies may weaken mucosal defenses and contribute to lesion persistence or delayed healing.[1,14]

Female predominance and a higher prevalence among middle-aged adults were evident in both MAS and OLP groups Menstrual blood loss and pregnancy-related iron depletion contribute to lower hemoglobin and serum iron levels in female patients compared to males.[31] These demographic patterns are consistent with previous studies and may reflect both hormonal and behavioral influences on immune and nutritional status.[2,12]

This study revealed significant correlations between micronutrient levels and chronic oral mucosal disease, the direction of causality remains unclear. It is possible that nutritional deficiencies contribute to disease susceptibility, but also that chronic pain or mucosal damage limits dietary intake or nutrient absorption. Further investigation is needed to explore whether supplementation improves clinical outcomes.

CONCLUSIONS

Patients with minor aphthous stomatitis and oral lichen planus demonstrate significant deficiencies in zinc, vitamin B12, ferritin, and folate-particularly zinc-which may contribute to inflammation and delayed healing. These findings highlight the importance of incorporating routine micronutrient screening into the clinical evaluation of patients with chronic oral lesions. Targeted nutritional supplementation should be considered as part of management, and further large-scale, longitudinal studies are recommended to clarify causal relationships and evaluate the therapeutic benefits of correcting these deficiencies.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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