

Effectiveness of Zinc Supplementation in management of patients with symptomatic Benign Migratory Glossitis: A randomized control clinical and biochemical Study

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Aim: To assess the effect of zinc supplements in management of symptomatic benign migratory glossitis patients as a primary outcome and to evaluate levels of salivary zinc before and after treatment as a secondary outcome.

Materials and Methods: A randomized controlled clinical and biochemical study was carried out on 48 patients diagnosed with geographic tongue. Patients were divided equally into two groups; the study group received zinc supplements along with a zinc-rich diet for one month, while the control group was given only a zinc-rich diet for the same duration. Clinical parameters including the size of red atrophic areas (atrophic area length, atrophic area width), and visual analogue scale pain score. Both parameters were recorded at baseline, after one month of treatment and after one month later without treatment. Salivary samples were collected from both groups for biochemical analysis (measuring zinc levels) at baseline and one month after treatment.

Results: Reduction in values of atrophic area length (9.88 ± 5.51), atrophic area width (6.5 ± 4.26) in study group compared to (10.88 ± 2.31), (7.38 ± 2.14) respectively in control group, significantly higher median values of visual analogue scale pain score in control group (5.5), in comparison to study group (3.5), ($p=0.004$), as well after one month of treatment, the study group exhibited a significantly higher salivary zinc mean value compared to the control group ($p=0.045$).

Conclusion: Low dose of zinc sulphate has a significant therapeutic effect on the relief of subjective symptoms in patients with BMG.

Keywords: symptomatic, geographic tongue, benign migratory glossitis, zinc sulphate.

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Introduction

Geographic tongue (GT) can be identified as benign inflammatory disease which occurs on the dorsum surface of the tongue and can probably expand to the lateral borders. The site and the pattern however can change over time, thus justifying the name benign migratory glossitis (BMG).^{1,2}

BMG is considered the third most significant tongue condition, following scrotal tongue and tongue varices in importance. The lesions of BMG have been stated as wandering rash, marginal exfoliative glossitis, lingua geographica, lingual dystrophy, pityriasis linguae, exfoliatio areata linguae, transitory benign plaques of the tongue, superficial migratory glossitis, and glossitis areata migrans. However, the condition is frequently known today as benign migratory glossitis or geographic tongue.³

GT is a chronic immune-mediated oral condition of unknown cause. It impacts around 4.8% of the global population, showing a slight inclination towards females.⁴ The incidence of geographic tongue varies among different populations. In children, it is approximately 1.33%, while in adults, it ranges from less than 1% to 16%.⁵ A recent meta-analysis indicated that geographic tongue has 3% of period prevalence and 3% of point prevalence in world population.⁶

Clinically GT appear as multifocal, annular, erythematous, and circular patches measuring between 0.5 to 1.5 cm in diameter, exhibit atrophy of the filiform papillae and redness of the fungiform papillae. These patches are characterized by absence of taste buds.⁷⁻⁹

GT presents with symptoms such as burning sensation, pain, discomfort, altered taste (dysgeusia), heightened sensitivity to hot, spicy, and sour food, increased salivation, pain during eating and drinking, and patient anxiety about probable malignancy or precancerous

conditions (cancerphobia), in addition to cosmetic matters or bad appearance.^{10,11} Furthermore, some patients make a complaint of diminished taste sensation and difficulty in recognizing some flavors. This sensation alters the functioning of the tongue, in some cases.²

The diagnosis of geographic tongue is usually clinical and established on history and physical examination, characterized by multiple migratory lesions that differ in size, affected areas, and clinical appearance.¹²

A definitive cure is not available for now, and current therapeutic approaches focus on symptoms relief using analgesics, antihistamines, anti-inflammatory agents, mouth rinses containing topical anesthetics, topical corticosteroids, and topical analgesics.^{4,13-15} Many of these treatments have side effects or other drawbacks that raise questions about their clinical use. A key challenge in patient management is to effectively promote healing and reduce discomfort without causing side effects.^{16,17}

Zinc deficiency is recognized as a predisposing factor for geographic tongue. It has been reported that a lack of zinc can lead to changes in the epithelium of oral cavity and the composition of saliva, as well as atrophy and flattening in the lingual papillae of the tongue.^{10,18}

Zinc is a crucial trace element with a key role in several basic cellular functions in human. The value of zinc in human nutrition, human health and disease have been recognized.¹⁹⁻²¹ Research has demonstrated zinc's role in maintaining a healthy epithelium, wound healing and regenerating filiform papillae, which is relevant as geographic tongue affects the lingual papillae.^{10,18}

Zinc is present in several biological tissues and fluids such as plasma, serum, erythrocyte, leukocyte, and saliva. It was recommended that zinc levels in saliva may

be outstanding way to evaluate zinc nutritional status of human subjects.²²

So, the current study aims to evaluate the impact of zinc supplements in management of patients with geographic tongue by evaluation of changes in the size of atrophic areas clinically, and intensity of symptoms subjectively, as well as to assess the salivary levels of zinc in these patients before and after receiving the supplements.

Materials and Methods

This study is a randomized control clinical trial with biochemical analysis. The study was conducted at the Oral Medicine, Periodontology and Oral Diagnosis Department, Faculty of Dentistry, Ain Shams University, Egypt, the study spanned from September 2021 to May 2023. The current clinical trial has been approved by ClinicalTrials.gov and registered (NCT05190562). Ethical approval of the study was acquired from the Faculty of Dentistry Ain Shams University Research Ethics Committee (FDASU-REC-022124). Participants were given a written informed consent after receiving a clear explanation of the study details. Salivary samples were used only for the study's purposes, and individual patient results were kept confidential.

To calculate the sample size, a power analysis was conducted to ensure sufficient power to test the research hypothesis statistically. A total sample size of 48 participants (24 in each group) was determined to be adequate to detect an effect size ranging from 0.77 to 0.83, was calculated based on the findings of a previous study conducted by Čanković et al²³ with a power (1- β error) of 0.8 (80%) using a two-sided hypothesis test and a significance level (α error) of 0.05. The calculations were performed using G*Power (version 3.1.2.9), (G*3 power3: flexible statistical power analysis program for the social, behavioral, and biomedical sciences).

A total of 48 patients with symptomatic benign migratory glossitis were chosen for the study. They exhibited symptoms such as pain, a burning sensation, discomfort, and to be sensitive to hot, spicy, and sour food. The diagnosis was confirmed through an oral examination, following specific criteria: the presence of red atrophic areas on the filiform papillae, clearly bordered by white healthy papillae. The inclusion criteria stayed as follows: both genders were eligible aged above 18 years old diagnosed with symptomatic benign migratory glossitis. Patients with oral candidiasis, indicators of localized irritation (such as the dental caries, the sharp tooth edges, the defective dental fillings, and the improper prosthetic procedures), as well as those with psoriasis and vulnerable groups including those with mental disabilities, physical impairments, and pregnant females, were excluded.

Forty-eight eligible patients were randomly and equally divided into two groups using computer-generated allocation concealment. The study group (Group A) consisted of 24 patients with symptomatic benign migratory glossitis who received zinc supplements 110mg zinc sulphate equivalent to approximately 25 mg of elemental zinc once daily for one month (OCTOZINC capsules produced by October Pharma S.A.E), they were advised to swallow the capsules on an empty stomach before meals. Additionally, during the treatment period, patients were encouraged to follow a zinc-rich diet. Control group (group B) included 24 patients with symptomatic benign migratory glossitis following only a zinc-rich diet for one month. Patients were informed to consume one standard portion of food containing 2-5 mg of zinc daily. The recommended food items included one slice of beef, two eggs with yolk, one cup of yogurt, one cup of beans, one slice of dark

turkey meat, one cup of shrimp, a quarter cup of peanuts, and button mushrooms.^{23,24}

Prior to the initiation of the treatment protocols at first visit, patients were subjected to the following: detailed information about each patient including the age, the gender, the disease progression, the family history, the medical history, the drug history, and the clinical signs and symptoms, was recorded using a structured questionnaire.

seven days after the diagnosis of patients with symptomatic benign migratory glossitis and the selection of red atrophic areas by taking photos of the patients' tongue and the selected atrophic areas, patients exhibiting changes of the red atrophic areas with the raised white keratotic margins were excluded. Just those with consistent red atrophic areas with white keratotic margins were included during the study evaluation. Size of the selected red atrophic areas (Atrophic Area Length AAL, Atrophic Area Width AAW) for both groups were assessed using a calibrated periodontal probe at baseline, after one month of treatment and after one month later without treatment as objective assessment as shown in figures (1,2). The largest atrophic area for each patient was monitored. If irregularly shaped atrophic areas were present, their largest diameters were measured.²³



Figure 1: Measurement procedure.

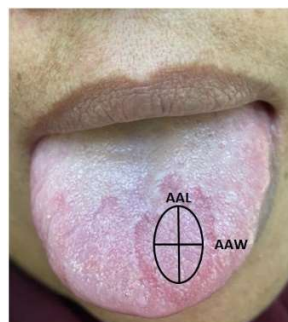


Figure 2: AAL atrophic area length, AAW atrophic area width.

All Patients monitored the intensity of discomfort, including burning sensation and sensitivity of the tongue, using the Visual Analogue Scale (VAS) at baseline, after one month of treatment, and after one month later without treatment as a subjective assessment. VAS consisted of 10-cm horizontal line segmented into 1-centimeter increments, ranging from 0 to 10. A score of "0" denoted no discomfort, while "10" signified the most severe, intolerable discomfort imaginable. Patients were asked to mark the point on the VAS that best reflected the intensity of their symptoms. The VAS was presented on a single sheet of paper, encouraging patients to consider changes in their symptoms rather than absolute values.²³

Salivary samples were collected from all patients in both groups for biochemical analysis to measure salivary zinc levels at baseline and after one month of treatment. As well as salivary samples were collected from ten healthy participants to recognize the mean value of salivary zinc level in the healthy individual. To minimize the effects of diurnal variations in salivary composition, samples were collected between 8:00 am and 11:00 am. The samples were taken either before meals or at least two hours after eating. Saliva was collected through unstimulated spitting method (saliva was collected in their mouths for about 5 minutes and then spitted into the cups), during the

collection process, subjects refrained from eating, drinking, or talking.²⁵ Patients were asked to sit in an upright position with their heads slightly tilted forward, they were given plastic cups and they were asked to collect saliva and spit into the cups. Samples were then transferred into sterile graded Eppendorf tubes using disposable syringes which were immediately capped and stored at (2 - 8°C) or below as the analysis was not done immediately. Each salivary sample was centrifuged at 4000xg for 10 minutes. The supernatant was used for determination of zinc using colorimetric method (5-Brom-PAPS, Cat.No. MG330 00).²⁶

Statistical analysis:

To evaluate the effectiveness of zinc supplementation on symptomatic benign migratory glossitis, independent t-test was used to compare the two patient groups: the study group (receiving zinc supplements along with a zinc-rich diet) and the control group (following only a zinc-rich diet).

Statistical analysis and data management were performed utilizing the SPSS version 20 (Statistical Package for Social Sciences, an IBM company). Numerical data were summarized using mean, standard deviation, median and range. The normality of the data was assessed by examining the data distribution and applying the Kolmogorov-Smirnov and Shapiro-Wilk tests.

Comparisons between groups for numeric variables with normal distribution were performed using the independent t-test. Comparisons between different observations were conducted using ANOVA test or the paired t-test.

The Mann-Whitney U test was used to compare groups for non-parametric numerical variables. For comparing different observations, the Wilcoxon signed-rank test and the Friedman test were employed. Categorical data (ender) were compared using chi square test.

The percentage change was determined using the formula:

(value after-value before)/ value before X100

All p-values were two-sided, with p-values \leq 0.05 considered statistically significant.

Results

Both groups consisted of twenty-one females (87.5%) and three males (12.5%) with mean age 27.17 ± 10.49 in study group and mean age 29.42 ± 11.31 in control group. History of chief complaint was 9 ± 6.94 (years) in study group, and it was 9.71 ± 6.35 (years) in control group. Covid-19 history was 2 (8.33%) in study group and 7 (29.2%) in control group. Family history was present in 4 patients (16.7%) in study group, in comparison to 8 patients (33.3%) in control group.

For atrophic area length (AAL) a higher mean value was recorded after one month of treatment in control group (10.88 ± 2.31) millimeter (mm), in comparison to study group (9.88 ± 5.51) mm without any significant difference between the groups ($p=0.419$). Intragroup comparison in study group, the mean value at baseline (13.04 ± 4.38) was significantly higher compared to value after one month of treatment (9.88 ± 5.51) ($p=0.000$). The value one month later without treatment (13.71 ± 4.14) was significantly higher than value recorded after one month of treatment (9.88 ± 5.51) ($p=0.00$). The mean value in control group at baseline (11.83 ± 2.06) was significantly higher compared to value after one month of treatment (10.88 ± 2.31). The value one month later without treatment (12.79 ± 2.26) was significantly higher than value recorded after one month of treatment (10.88 ± 2.31) ($p=0.00$), results are shown in table (1).

For atrophic area width (AAW) a higher mean value was recorded after one month of treatment in control group

(7.38±2.14) mm, in comparison to study group (6.5±4.26) mm without any significant difference between the groups ($p=0.375$). In study group, the mean values at baseline (10.17±3.66) and one month later without treatment (10.17±3.66) were significantly higher than the value recorded after one month of treatment (6.50±4.26) ($p=0.000$). The mean value in control group at baseline (8.04±1.52) was significantly higher compared to value after one month of treatment (7.38±2.14). The value one month later without treatment (9.25±1.98) was significantly higher than value after one month of treatment (7.38±2.14) ($p=0.00$), results are shown in table (2).

Table 1: Descriptive statistics and comparison of Atrophic Area Length (AAL) between groups (independent t test)

AAL	Groups	Mean	Std. Dev	Difference		P value
				Mean	Std error	
Baseline	Group A	13.04	4.38	1.21	.99	0.230 ns
	Group B	11.83	2.06			
After 1month.ttt	Group A	9.88	5.51	1.00	1.22	0.419 ns
	Group B	10.88	2.31			
1month. later. without ttt	Group A	13.71	4.14	.92	.96	.348 ns
	Group B	12.79	2.26			

Significance level $p \leq 0.05$, ns=non-significant

For Visual Analogue Scale (VAS) the control group exhibited a higher significant median value (5.5) compared to the study group (3.5), ($p=0.004$) after one month of treatment. In study group the median value at baseline (7) was higher significantly than the value after one month of treatment (3.5). The value one month later without treatment (6) was higher significantly than value after one month of treatment (3.5) ($p=0.00$). In control group the median value at baseline (7) and the median value one month later without

treatment (6) were significantly higher compared to the value recorded after one month of treatment (5.5) ($p=0.009$), results are shown in table (3).

Table 2: Descriptive statistics and comparison of Atrophic Area Width (AAW) between groups (independent t test)

AAW	Groups	Mean	Std. Dev	Difference		P value
				Mean	Std error	
Baseline	Group A	10.17	3.66	2.125	.808	.013*
	Group B	8.04	1.52			
After 1month.ttt	Group A	6.50	4.26	.875	.974	.375 ns
	Group B	7.38	2.14			
1month. later. without ttt	Group A	10.17	3.66	.917	.849	.286 ns
	Group B	9.25	1.98			

Significance level $p \leq 0.05$, ns=non-significant

For biochemical analysis, mean salivary zinc value in normal individuals was (15.85±3.33) milligrams per deciliter (mg/dl). A significant higher value was observed in study group (13.20±1.75) compared to control group (12.78±1.30) ($p=0.045$) after one month of treatment. The mean value of salivary zinc in study group at baseline was (10.39±0.83), and after one month of treatment was (13.20±1.75). In control group the mean value of salivary zinc at baseline was (11.59±0.91) and after one month of treatment was (12.78±1.30), results are shown in table (4).

Table 3: Descriptive statistics and comparison of Visual Analogue Scale (VAS) between groups (Mann Whitney U test)

VAS	Groups	Median	Min	Max	Mean	Std. Dev	Difference		P value
							Mean	Std error	
Baseline	Group A	7	3	10	7.00	2.54	.83	.63	.224 ns
	Group B	7	3	9	6.17	1.74			
After 1month.ttt	Group A	3.50	0	7	3.38	2.16	1.96	.58	.004*
	Group B	5.50	2	8	5.33	1.83			
1month. later. without ttt	Group A	6	0	10	5.63	3.69	.21	.88	.934
	Group B	6	1	9	5.83	2.18			

Significance level $p \leq 0.05$, ns=non-significant

Table 4: Descriptive statistics and comparison of salivary Zinc levels between groups (independent t test)

Salivary samples	Groups	Mean	Std. Dev	Difference		P value
				Mean	Std error	
Baseline	Group A	10.39	.83	-1.20	.25	.06 ns
	Group B	11.59	.91			
After 1month.ttt	Group A	13.20	1.75	.42	.44	.045 *
	Group B	12.78	1.30			

Significance level $p \leq 0.05$, ns=non-significant

Discussion

In the current study, Clinical evaluation of both groups, study group (received zinc sulphate combined with zinc-rich diet for one month) and control group (received only zinc-rich diet for one month) was determined objectively by assessment changes in the size of red atrophic areas of geographic tongue in all patients of the two

groups. Atrophic area length AAL, and atrophic area width AAW were measured with the use of a calibrated periodontal probe. As well as evaluation in this study was determined subjectively in all patients by assessment intensity of the discomfort which was monitored by the patients using the Visual Analogue Scale (VAS).²³ Both objective and subjective assessment were evaluated at base line, after one month of treatment then the patient was reassessed after one month later without treatment as a primary outcome. Additionally, salivary samples were evaluated biochemically to determine salivary zinc levels at baseline and after one month of treatment in all patients of the two groups as a secondary outcome.

The recommended daily intake of elemental zinc through diet for healthy adults is up to 15 mg/day, with an absorption rate of approximately 20%. Chelated zinc forms are more effectively utilized due to their superior absorption capabilities. Various pharmacokinetic studies have indicated that zinc absorption can be enhanced when it is complexed with organic and inorganic compounds.^{27,28} Octozinc (110mg zinc sulphate) was used in this study once daily over 30 days, which is commercially available and affordable to the patients. This the lowest dose of zinc sulphate in the market for elemental zinc (25mg).

Patients with symptomatic geographic tongue included in this study were above 18 years old as, it was reported that the highest incidence of GT among adults, from 21 to 30 years of age.^{29,30} Psoriatic patients with symptomatic geographic tongue were not included in this study as, the histopathology of geographic tongue exhibits clusters of neutrophils (Munro's microabscess), like those seen in typical skin psoriasis. This suggests a potential correlation between these two conditions.^{31,32} And this study concentrated on patients with

symptomatic geographic tongue without association with any dermatologic disorder like psoriasis. Additionally, pregnant women were also excluded from this study as zinc sulfate is classified in group C drug.¹⁸

Clinical findings of the present study revealed female gender predilection in prevalence as (87.5%) for each group, this was compatible with studies demonstrated that geographic tongue was more common in females than males.^{10,29,33} As well it was reported in another study that geographic tongue is more prevalent in women than in men, with a ratio of 1.5:1.³⁰ Family history in patients of this study was found in (16.7%) in study group, and (33.3%) in control group. Concerning the role of genetic factors in the occurrence of geographic tongue, it was previously informed a high incidence of geographic tongue in first-degree relatives of the patients. It was also reported that siblings with one parent affected by geographic tongue had a higher significant prevalence of the condition in comparison to siblings of unaffected parents, indicating a role for familial and hereditary factors. Geographic tongue was defined as a hereditary disease with a polygenetic nature.^{14,34} According to medical history of the patients in this study, it was reported that (29.2%) of control group patients were with history of COVID-19 infection. It was reported in the literature a possible correlation between geographic tongue (GT) and SARS-CoV-2 infection, newly coined as 'COVID tongue', informing it as a part of COVID-19 illness.³⁵⁻³⁷ Some studies have found that geographic tongue might be linked to increased levels of the inflammatory cytokine interleukin-6 (IL-6), which is also elevated in severe COVID-19 cases.³⁸ Additionally, it is noteworthy that the expression of angiotensin-converting enzyme 2 (ACE2) receptors is more pronounced in the tongue compared to other oral soft tissues. These receptors act as the entry point for the SARS-CoV-2 virus.³⁹

Clinical evaluation objectively showed improvement in geographic tongue lesions severity as measured by significant reduction in AAL (Atrophic area length), AAW (Atrophic area width) in both groups after treatment period.

Results justified improvement after treatment as in study group treated by zinc sulphate combined with Zinc-rich diet for one month it was found that the mean value of AAL at baseline was significantly higher in comparison to the mean value after one month of treatment ($p=0.000$) as well as the value one month later without treatment (free treatment period) was higher significantly than that recorded after one month of treatment ($p=0.00$). In control group treated with only zinc-rich diet for one month, the mean value of AAL at baseline was significantly higher compared to mean value after one month of treatment. Additionally, the value one month later without treatment (free treatment period) was higher significantly than the value recorded after one month of treatment ($p=0.00$). As for intergroup comparison, a higher mean value of AAL after one month of treatment was recorded in control group (10.88 ± 2.31), in comparison to study group (9.88 ± 5.51), that proved more improvement in study group than control group after treatment.

As well as, Atrophic Area Width (AAW), in study group the mean value at baseline and the mean value one month later without treatment were significantly higher compared to the mean value recorded after one month of treatment ($p=0.000$), proved improvement in AAW of geographic tongue lesions after treatment. In control group the mean value at baseline was significantly higher compared to mean value after one month of treatment, in addition the mean value of one month later without treatment was significantly higher than the mean value after one month of treatment ($p=0.00$). Intergroup comparison in Atrophic Area

Width (AAW) showed a higher mean value after one month of treatment in control group (7.38 ± 2.14), in comparison to study group (6.5 ± 4.26). As more improvement was seen in study group than control group in AAW after treatment.

These results were compatible with previous studies. One study demonstrated in Iran as, the role of zinc sulfate on geographic tongue healing was established based on the results showing healing in 80% of patients of experimental group (treated by 220 mg of zinc sulphate capsules once daily for 10 days only).¹⁸ Another study demonstrated in Serbia as, in the test group treated by zinc supplements, it was found significant decrease in the mean value of the AAW and non-significant decrease in AAL after treatment. In the test group, 85.7% of patients experienced either partial or complete regeneration of the atrophic areas.²³ In the present study, sufficient lower dose of zinc sulphate (110 mg once daily for 30 days) was used to avoid any toxic effect for longer period, given that a 10-day period of treatment without follow-up in the earlier Iranian study¹⁸ was insufficient to fully evaluate the treatment outcomes.

In contrast to this study the role of zinc sulfate in geographic tongue healing was not recognized in a previous study demonstrated in Tehran as healing was identified as complete resolving of tongue lesions. The results indicated that the patients who were on zinc sulfate treatment did not show any cure rate.⁴⁰

Positive effect of zinc sulfate in treatment of geographic tongue, elimination of its symptoms, effectiveness in maintaining healthy epithelial tissues and renewing of filiform papillae in patients were clearly detected in a previous study. Accordingly, zinc was hypothesized could be the element responsible for GT inhibition.¹⁸

Concerning Visual analogue scale (VAS), in the present study improvement was

recorded in symptoms of geographic tongue in study group after one month of treatment as the median value of VAS at baseline was higher significantly than the value recorded one month after treatment. As well, the value one month later without treatment was higher significantly than value after one month of treatment ($p=0.00$), which indicated that symptoms of geographic tongue came back gradually after cessation of treatment with zinc supplements. Additionally, improvement was recorded in symptoms of geographic tongue in control group after one month of treatment with only zinc-rich diet as the median value at baseline and the median value one month later without treatment were significantly higher in comparison to the value recorded after one month of treatment ($p=0.009$). Intergroup comparison revealed a significantly higher median value in control group (5.5), in comparison to study group (3.5), ($p=0.004$) after one month of treatment, indicated that enhancement in symptoms of geographic tongue after treatment with zinc supplements combined with zinc-rich diet (study group) was higher significantly than that after treatment only with zinc-rich diet (control group).

There were extremely limited studies in literature which determined salivary zinc levels in geographic tongue patients so, in the present study salivary zinc levels were measured in all patients of the two groups at baseline and after one month of treatment. In study group the mean value at baseline was lower significantly than that recorded after one month of treatment ($p=0.000$), indicating increased salivary zinc levels after treatment with zinc supplements for one month. In control group salivary zinc levels increased after treatment with only zinc-rich diet for one month as the mean value at baseline was lower significantly than that recorded after one month of treatment ($p=0.000$). The study group exhibited a significant higher mean salivary zinc value compared to the control

group ($p=0.045$) after one month of treatment.

The findings of this study indicated that a deficiency in salivary zinc plays a role in the development of geographic tongue. This conclusion was supported by the observed positive effects of zinc sulfate treatment, which led to improvements in the atrophic regions, filiform papillae, and symptoms experienced by patients with geographic tongue.

Conclusion

Zinc sulphate has a significant therapeutic effect on the relief of subjective symptoms in patients with BMG as well as a zinc-rich diet looks to be helpful to improve symptoms in BMG patients. Salivary zinc deficiency may be one of the predisposing factors associated with the development of symptomatic BMG.

Funding: The study is self-funded.

Data availability: The datasets used during the study are available from the corresponding author on reasonable request.

Declarations:

Ethics approval and consent to participate: Ethical approval of the study was acquired from the Faculty of Dentistry Ain Shams University Research Ethics Committee (FDASU-REC-022124) on 17/2/2021. All patients gave written informed consent after receiving a clear explanation of the study details.

Competing interests: The authors declare no competing interests.

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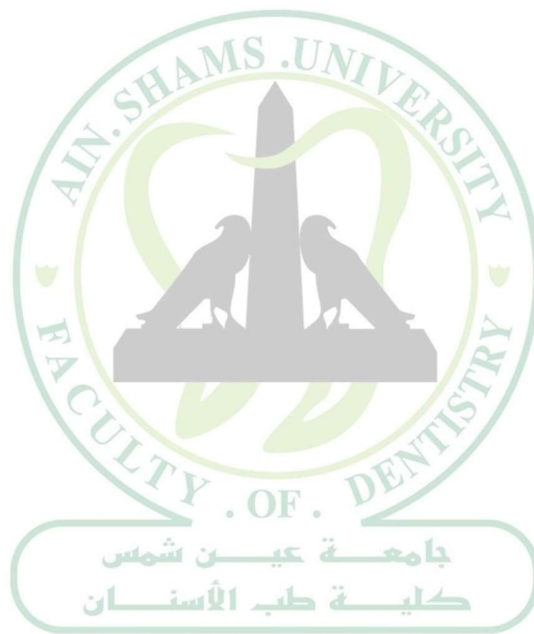
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