The Effect of Zinc Gluconate Supplementation on Symptoms and Tongue Epithelium Regeneration in Non-psoriatic Patients with Migratory Glossitis

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ABSTRACT The aim of this study was to evaluate zinc gluconate as a treatment option in patients with symptomatic migratory glossitis (MG). Using simple random sampling, 28 non-psoriatic patients with symptomatic MG were divided into a test and control group. The test group took 20 mg/day of chelated zinc gluconate for one month, and was put on a diet rich in zinc. The control group was only put on a diet rich in zinc. Changes in the size of red atrophied areas (width and length) and the intensity of symptoms were evaluated as primary and secondary outcomes, respectively, at baseline, after therapy, and one month later. In the test group, the mean value of the red atrophy area width and length displayed some significant reduction as a primary outcome. There were no significant changes in the size of red patches in the control group. Secondary outcome showed that the intensity of subjective symptoms in the test group significantly decreased (P=0.042) compared with controls. The filiform papillae had partially or completely regenerated in 85.7% of cases in the test group and in 23.1% of the controls (P=0.001). Red patches with raised keratotic rims may have healed spontaneously and reappeared in constantly changing patterns that are typical for MG. This phenomenon was not observed in patients supplemented with zinc, and new atrophy areas occurred in only one case. Low-dose zinc gluconate supplementation may have a positive therapeutic effect on tongue epithelium regeneration and symptomatology in patients with MG.

KEY WORDS: zinc, zinc supplementation, migratory glossitis, geographic tongue, controlled clinical trials

INTRODUCTION

Benign migratory glossitis (MG) is an obscure condition, considered to be immune-mediated and associated with small to extensive areas of atrophy of the filiform papillae of the tongue with preservation of the fungiform papillae that individually regenerate in time, with a degree of hyperplasia of the filiform papillae and keratosis and fibrosis of their ends that give the borders of the recovering lesion a white halo, which may also appear yellow from the entrapment of food and bacteria in the now "shaggy" ends of the filiform papillae. It can be symptomatic, but likely due to the loss of the filiform papillae and atrophy of the dorsal tongue surface and resultant increased sensitivity to strongly favored foods and agents such as peppermint (in toothpaste), chili and alcohol (1-6). Prevalence in the general population fluctuates

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within the 1-2.5% range (2-6). The histopathology demonstrates Munro's microabscess (collections of neutrophils), also seen in classic psoriasis of the skin, hence the hypothesis that these two conditions may be associated (5,7-10). Except with fissured tongue (4,5) this condition may also coexist with a heightened level of IgE, atopic dermatitis, and asthma (11). Altaee (12) reports a decreased level of zinc concentration in saliva of individuals with MG, albeit without any significant difference in respect to the control group. A lower zinc concentration in serum was reported in a substantial number of individuals who suffer from tongue sensitivity and who are unresponsive to administered treatment (13). The positive therapeutic influence of zinc was also confirmed in treatment of burning mouth syndrome (BMS) (14) and dysgeusia (15).

Abe *et al*. (16) report a positive effect of cyclosporine on persistent MG. Zinc sulfate has been specified as one possible therapeutic approach in treating MG (17). MG presents as an enigmatic lesion due to its varied etiologies, thereby presenting a treatment dilemma (18,19). A review of the literature points to a scarcity of evidence about the therapeutic effects of zinc in patients with MG, especially when not associated with psoriasis. The aim of this paper was to test the effect of low-dose zinc gluconate replacement therapy on tongue epithelium regeneration and symptoms in non-psoriatic patients with MG.

PATIENTS AND METHODS

Patients

This was a single-blind controlled clinical study with simple randomization. Eligible participants were all adults aged 18 year or above with MG. The diagnosis was established by an oral medicine specialist based on clearly defined criteria: presence of red atrophy areas of the filiform papillae with distinctly delineated whitish healthy papillae. Exclusion criteria were psoriasis (medical history and careful clinical morphologic evaluation of skin features due to lack of clear diagnostic criteria for psoriasis) (20), anemia, B12 or folic acid deficiency (confirmed through a complete blood analysis not older than three months), oral candidiasis (negative tongue swab), pregnancy, and indicators of localized irritations (dental caries-affected teeth, sharp teeth edges, dental calculus, faulty dental fillings, and faulty prosthetic procedures). A total of 47 non-psoriatic patients with MG visited the Oral Medicine Section at Dental Clinic of in the period between November 2013 and Jun 2015. The study was conducted in 28 patients with symptomatic MG (20 women and 8 men, age range 19-79 years, mean age 31.13 years). Changes in the size of red atrophied areas (width and length) and the intensity of symptoms were evaluated as primary and secondary outcomes, respectively. With the use of a calibrated periodontal probe, atrophy area length (AAL) and atrophy area width (AAW) were measured to determinate the size of the diagnosed red atrophic patch. In case of irregularly shaped lesions, their largest diameters were measured (Figure 1 and Figure 2). Seven days after the diagnosis was made and atrophy

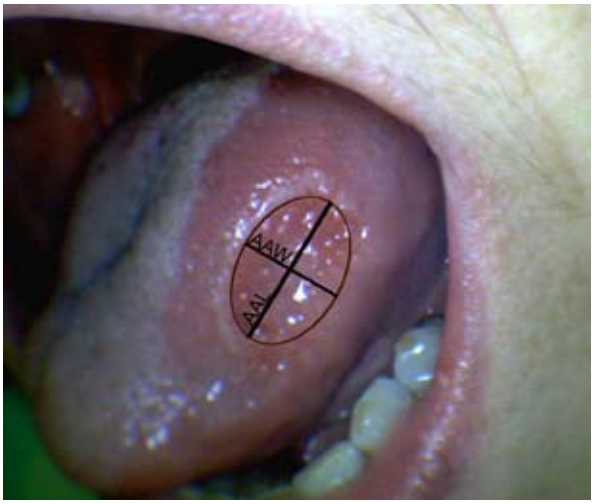

Figure 1. AAL: atrophy area length; AAW atrophy area width.

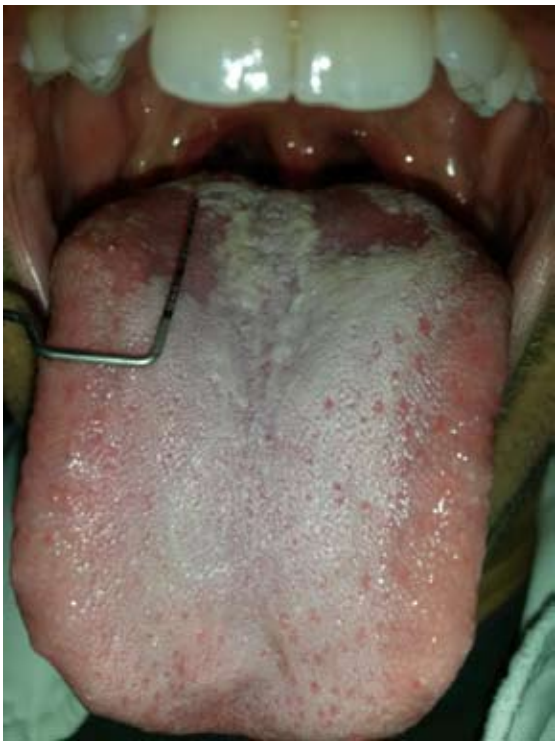

Figure 2. Measurement procedure.

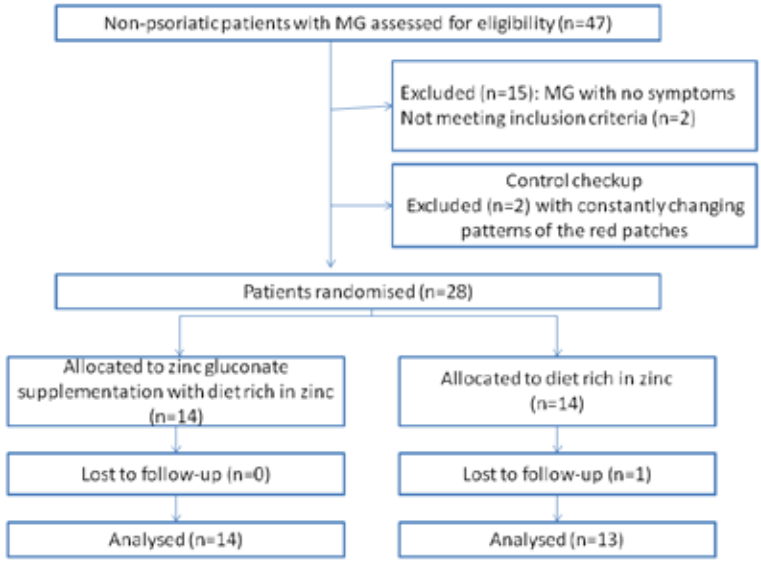

Figure 3. Flow diagram of zinc gluconate supplementation with diet rich in zinc compared with only diet rich in zinc. The diagram includes information on the excluded participants.

areas were determined, patients attended a control checkup in order to exclude those with constantly changing patterns of the red patches with raised keratotic rims. Only those patients who presented with atrophic patches bounded with circinate lines that remained constant at the control checkup were included during the study evaluation process. The size of the two largest atrophic patches per patient (most patients had one or two patches) was monitored at baseline and after the therapy. In the interest of more precise therapy effect monitoring, atrophy areas were displayed on the schematically presented tongue dorsal surface. Intensity of the discomfort, such as burning tongue sensation and sensitive tongue, were

Table 1. Baseline characteristics of randomized patients in the study

Variables	Test group n=14 (%)	Control group n=14 (%)	*P**
Age (mean and range)	35.7 (19-79)	26.5 (19-62)	
Men	3 (10.7)	5 (17.8)	
Women	11 (39.3)	9 (32.1)	
Blood glucose			
Normal value 4.6-6.2 mmoL/L	13 (46.4)	14 (100)	
Above normal value	1 (3.6)	0 (0)	
Antihypertensive drugs – yes	2 (7.1)	1 (3.6)	
Smoking – yes	3 (10.7)	2 (7.1)	
Alcohol yes <14 units per week†	7 (25.0)	5 (17.8)	
Serum zinc level (μg/dL)	85.6±0.2	86.4 ±0.2	*P*>0.05
Mesured oucomes (median)			
AAL I (mm)	15.0	12.0	0.497
AAL II (mm)	8.5	9.0	0.711
AAW I (mm)	13.0	5.0	0.83
AAW II (mm)	5.0	6.0	0.447
VAS	3.7	3.0	0.522

AAL: atrophy area length; AAW: atrophy area width; VAS: Visual Analogue Scale; *significance for chi-square, Student t-test and Mann-Whitney test; †One unit of alcohol is 10 mL (1 cL) by volume, or 8 g by weight, of pure alcohol. The percentage alcohol by volume (% abv) of a drink equals the number of units in one liter of that drink.

Table 2. Distribution of the single most provoking factor that caused soreness among subjects with migratory glossitis

Provoking factors	Subjects with symptomatic migratory glossitis (N=28)
Sour food	9 (32.1)
Toothpaste	8 (28.6)
Piquant food	4 (14.3)
Spicy food	1 (3.6)
Tomatoes	1 (3.6)
Nuts	1 (3.6)
Orange juice	1 (3.6)
Chocolate cream	1 (3.6)
Mouthwash product	1 (3.6)

estimated using the Visual Analogue Scale (VAS), 0-10 (with 1 cm increments, "0" indicated no discomfort, "10" unendurable, the worst imaginable discomfort). Patients were instructed to select a value on the VAS scale which best corresponded to the intensity of their symptoms. Using visual examination, the healing process of atrophy areas was also assessed based on the degree of filiform papillae regeneration. Complete regeneration was defined as complete resolution of red patches. Partial regeneration was defined as presenting with fine whitish newly-regenerated filiform papillae that protruded slightly above the lingual surface at the previously atrophied area. A specially designed protocol was included, consisting of: socio-demographic variables (sex, age); health risk habits (smoking, alcohol use); use of antihypertensive drugs, and the single most common provoking factor that caused subjective symptoms, such as burning tongue sensation and sensitive tongue. Patients gave their written informed consent after familiarizing themselves with the procedure. The study was approved by the Dental Clinic Ethics Committee (No. 01-5/4-2014) and was conducted in accordance with the code of ethics of the Helsinki Declaration of 1975, as revised in 2008.

Pre-specified outcome measure

Before randomization, blood samples for the analysis were successfully collected from all participants with symptomatic MG. Serum zinc concentration was measured using flame atomic absorption spectrophotometry, which is a common analytic method for measuring zinc in biological samples (Perkin Elmer HGA 460, Germany; reference range 65-110 µg/dL).

Randomization and treatment

All patients diagnosed with symptomatic MG were allocated to two groups in the order of their arrival through a simple random sampling method by using a free web service: "Research Randomizer" available from http://www.randomizer.org (Social Psychology Network, Lancaster, Pennsylvania, USA). Of the 28 subjects with the presence of symptomatic MG, 27 returned for a follow-up examination after one month and were included in the process of data analysis (Figure 3). The test group consisted of 14 patients who consumed 20 mg/day of chelated zinc gluconate (equivalent to about 2.8 mg/day of elemental zinc) over a period of 30 days, divided into two dosages, in the form of a commercial dietary supplement "Chelated Zinc" (Natural wealth®, New York, USA). Since 2012, only this zinc gluconate

Table 3. Differences between means of measured variables at baseline and after treatment in the test and control group

Measured values	Baseline/After (T1/T2)	Test group n=14 mean ± SD	Control group n=13 mean ± SD	*P* significance* Test group	Control group
AAL I (mm)	Baseline	20.14±14.07	17.29±17.58	*P*=0.31	*P*=0.17
	After	15.29±13.08	14.43±19.31		
AAL II (mm)	Baseline	11.00±6.16	9.60±6.95	*P*=0.049	*P*=0.28
	After	5.50±4.43	12.00±10.10		
AAW I (mm)	Baseline	16.86±12.66	12.57±16.92	*P*=0.02	*P*=0.89
	After	8.14±4.05	12.29±17.63		
AAW II (mm)	Baseline	5.00±1.63	5.80±1.30	*P*=0.28	*P*=0.59
	After	4.00±2.70	7.80±6.94		

SD: Standard Deviation; AAL I: first atrophy area length; AAL II: second atrophy area length; AAW I: first atrophy area width; AAW II: second atrophy area width; *Wilcoxon test; *P*<0.05 was considered statistically significant

Table 4. Mean changes (decrease) and difference within each subject in Visual Analogue Scale (VAS) at baseline, after treatment, and one month later for test and control groups

	Test group n=14 mean± SD			Control group n=13 mean± SD			Test group		Control group
	Baseline (T1)	After (T2)	1 month later (T3)	Baseline (T1)	After (T2)	1 month later (T3)	*P* value ANOVA		
VAS 1	4.59±3.29	1,90±2.06*	2.29±2.21*	3.04±1.31	2.49±1.05	2.81±1.10	0.042		0.167
	T1-T2	T1-T3	T2-T3	T1-T2	T1-T3	T2-T3	*P* value T test**		
VAS2	2.70±2.04	2.31±1.87	0.39± 0.63	0.56±1.05	0.23±0.56	0.33±0.50	T1-T2	T1-T3	T2-T3
							0.029	0.025	0.854

SD: Standard Deviation; VAS1: visual analog scale mean for the group; VAS2 visual analog scale difference within each subjects and presented as mean for the group; *Statistically significantly different from Baseline (T1) (P<0.05), **differences between the groups

dietary supplement has been filed in the Registry of Dietary Supplements, issued by the Republic of Serbia Ministry of Health. Patients were advised to swallow the tablets on an empty stomach, before meals. During the same time period, patients were on a diet rich in zinc recommended by a nutritionist. The control group was composed of the same number of patients who only received a the zinc rich diet in the same period of time. A nutritionist advised patients to take one standard portion of food items with assumed zinc content of 2-5 mg every single day. Food items in the patients' diet with that zinc content were: beef (1 average slice), eggs with yolk (2 of average size), yogurt (1 cup), pork liver (1 average slice), beans (1 cup), dark turkey meat (1 average slice), shrimps (1 cup), peanuts (quarter of cup), pumpkin seeds (quarter of cup), barley kernel (1 cup), rye kernel (1 cup), and button mushrooms – *Agaricus bisporus* (2 cups) (20). Participants received no additional information about daily oral care. the date of therapy initiation and the date of evaluation one month later were set for each patient in both groups. The investigator had performed the interview, measurement, and clinical examination, at baseline (T1) and after (T2) the treatment, did not have any knowledge at the time as to whether the patients were being treated with zinc gluconate with a diet rich in zinc or only with a diet rich in zinc (single-blind). Patients were asked to re-evaluate subjective symptoms after therapy (T2) and on an additional follow-up one month after cessation of therapy (T3) using the VAS scale.

Statistical analysis

The sample size was calculated based on α=0.05 and β=0.20; treatment effect size for zinc sulfate therapy and placebo were 80% and 15% respectively (17). A minimum sample size of 8 subjects for each group was obtained. SPSS 17 for Windows for statistical analysis (WinWrap Basic, Nikiski, AK, USA). For categorical variables, data were displayed as absolute and relative values, and as mean values and measures of variability for numerical variables. When evaluating the variation of values at baseline and after the treatment, Student`s t-test, ANOVA, and Wilcoxon nonparametric signed-rank test was applied for numeric features and Chi-square test (Yates' Correction) for categorical data. A value of P<0.05 was considered statistically significant.

RESULTS

After simple random sampling, there was no difference in regards to socio-demographic and health risk habits between the groups. Baseline characteristics of the sample and the single most common provoking factor are presented in Table 1 and Table 2. In four subjects (14.3%), more than two tongue areas of atrophy were identified during the first or follow-up clinical examination, which were not included in the statistical analysis (the two largest lesions were selected). During and after the therapy in the test group a new (not previously observed) red patch occurred in only one case, while in such new patches were observed in three patients (23.1%) from the control group. A complete absence of subjective symptoms after the treatment was reported by four individuals from the test group (28.6%), and by none from the control group (P=0.122). In six cases (42.9%) on zinc therapy and in one control patient (7.7%) a complete regeneration of the observed red areas was found with no difference (P=0.100; Yates' Correction). The atrophy areas changed either through partial or complete regeneration in 12 (85.7%) patients from the test group and in three patients (23.1%) from the control grup (P=0.001; Yates' Correction). In the test group, there was a significant decrease in the mean of the first AAW and second AAL after the treatment

(*P*=0.02 *P*=0.049, respectively). The mean of the first AAL and second AAW also declined after the administered treatment, albeit without significant difference. In the control group, we found a decrease in mean values of first AAL and AAW and an increase of second the AAL and AAW, with no significance (Table 3). Table 4 summarizes VAS scores presented as mean (VAS1) or difference for each subjects and displayed as mean for the group (VAS2) at baseline (T1), after treatment (T2), and one month later (T3) for the test and control group. In the test patients, a statistically significant decrease ($P<0.05$) in mean VAS was observed at T2 (1.90±2.06; mean ± Standard Deviation) and T3 (2.29±2.21) respectively, in relation to T1 (4.59±3.29). In the control patients, no statistically significant decreases in mean VAS were observed. A different approach to statistical analysis also yielded a significant reduction of symptoms after therapy (*P*=0.029) and one month later (*P*=0.025) in the test group compared to controls.

DISCUSSION

As an asymptomatic inflammatory disorder in most cases, benign migratory glossitis may present similar genetic, histopathological, and clinical features as oral psoriasis (21). Although the existence of oral psoriasis is disputed, association between psoriasis and migratory glossitis or stomatitis has been confirmed in previous studies (9,10). Due to similar clinical features in benign migratory glossitis and skin disease, histological assessment may be needed for definitive diagnosis. Due to asymptomatic oral lesions, clinicians find it difficult to carry out biopsies for histological examination in order to establish definitive diagnosis of oral psoriasis. Detailed patient and family history, data for disease recurrence, and careful clinical inspection may be useful in making oral diagnosis. Having such a complexion of the tongue can induce feelings of anxiety in patients due to suspected malignancy, and that is one of the reasons for the increased importance of finding a treatment for this condition (22).

Positive effect of MG treatment with local anesthetics, corticosteroid therapy, antihistamines, and tacrolimus have not yet been thoroughly elucidated (18,19). To the best of our knowledge, only one clinical study in the literature reported data on the therapeutic effect of zinc sulfate in patients with MG (17), which were in agreement with our findings.

Zinc deficiency can be easily overlooked because its clinical features are non-specific. The required daily intake of elemental zinc through food varies from 6 to 15 mg/day for healthy adults and absorption amounts to about 20%. The RDA (Recommended Dietary Allowance) is 0.2 mg/kg/day for adults (14). A chelated form of zinc insures its better utilization due to greater absorptive capacity. The conclusions of many pharmacokinetic studies of zinc are that zinc absorption can be improved by its complexation with organic compounds. Furthermore, by comparing organic forms of zinc (citrate, gluconate) with inorganic forms (sulfate, oxide) in terms of absorption and plasma concentrations, it has been found that organic forms have better properties (23). On the other hand, there was no difference when comparing utilization of individual organic forms of zinc (24). Therefore, the clinical outcomes of our study are comparable with those of the previously mentioned zinc sulfate study despite the difference in zinc dose. Vahedi *et al.* (17) used 220 mg of zinc sulfate, which is 50 mg of elemental zinc, and we used 20 mg of zinc gluconate, which is 2.8 mg of elemental zinc, to achieve similar results. We tried to achieve the same clinical outcomes using a lower zinc dose because we were aware that the increase in elemental zinc concentration can change the status of trace elements absorbed competitively with zinc (Cu, Fe). This was demonstrated in the Zenith Project, where supplementation with zinc gluconate at 15 or 30 mg per day increased serum Zn levels in volunteers aged 55-85 years regardless of the applied dose. A Zn dose of 30 mg/day in the same subjects led to alterations in serum Fe and Cu status, which was not observed in the group with a lower zinc dose (25).

One limitation of this study was that it is focused on a relatively small number of subjects and was not a double-blind clinical trial. As we stated before, each patient signed informed consent that she/he will follow study procedures, including the nutritionists' recommendations. However, we are aware that patient compliance could also be a limitation of the present study. Therefore, it can be considered a pilot study in examining the efficacy of low doses zinc gluconate in patients with MG. In contrast to our study, Vahedi *et al*. (17) evaluated the therapeutic effect of zinc sulfate by recording only complete resolution of lesions. Furthermore, unlike in his study, we excluded subjects without subjective symptoms. In the literature, a 3-month period of zinc treatment was usually recommended as the therapy for dysgeusia (15), or 6 months in case of BMS (14). We believe that 10 days without follow-up in a previous study (17) was not long enough to completely evaluate the treatment effects.

It would be desirable to determinate serum or saliva zinc levels before the supplementation treatment, regardless of the fact that no association

between MG and salivary or serum zinc levels has been established (12). Therefore, we suggest further double-blind randomized studies on a larger sample over a longer period of treatment with follow-ups.

CONCLUSION

The results of the present study showed that a low dose of chelated zinc gluconate may have a positive therapeutic effect on the regeneration of tongue epithelium and significantly help alleviate subjective symptoms in patients with MG. In contrast, successful therapy only by a diet rich in zinc seems to be insufficient in patients with this condition. Regardless of the diet rich in zinc we recommend supplementation of about 3-5 mg/day of elemental zinc in subjects with MG.

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