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Effect of Zinc Gluconate Supplementation on C-Reactive Protein and Malondialdehyde in Patients with Behcet's Disease: A Double-Blind Randomized Controlled Clinical Trial

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ABSTRACT

Background: Behçet's disease (BD) with autoimmune and auto-inflammatory nature is more prevalent in Silk Road countries. The current study aimed to investigate the effect of zinc gluconate supplementation on C-reactive protein (CRP) and malondialdehyde (MDA) levels in BD patients. **Methods:** This randomized controlled clinical trial was conducted on 50 Iranian BD patients. Participants were randomly assigned into either placebo or zinc gluconate (30 mg/day) groups for 12 weeks. Before and after the intervention, serum MDA and CRP levels were measured. **Results:** Zinc supplementation led to a significant increase in serum zinc levels compared to the placebo group (P<0.05). There was no significant difference in MDA serum levels between the groups after adjusting for the baseline values and confounding factors (P>0.05). Zinc supplementation led to a significant improvement in CRP serum levels compared to the placebo group following adjustment for the effect of baseline values and confounding factors (P=0.012 and 0.04, respectively). **Conclusion:** Zinc supplementation in an elemental dose of 30 mg per day has an anti-inflammatory effect in BD patients by reducing CRP levels. The beneficial effect of zinc on lipid peroxidation in BD patients was not shown in the study.

Clinical trial registration: IRCT20100606004105N30

Introduction

Behçet's disease (BD) is a rare debilitating autoimmune vasculitis that can be associated with mucocutaneous lesions and can lead to serious complications and even death if not properly managed (Nair and Moots, 2017). Due to inflammation in the arteries and veins, BD causes

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inflammation in various body systems, including the respiratory system, digestive system, reproductive system, visual system, central nervous system, and eyes (Alibaz-Oner and Direskeneli, 2022). This disease is characterized by frequent recurrence of oral ulcers (appeared in 97.5% and 65.7% of patients, respectively), genital ulcers, skin lesions (appeared in 64.6% of patients), joint pain, and uveitis (Davatchi *et al.*, 2016, Khan *et al.*, 2020, Sakane *et al.*, 1999). The exact cause of BD is not known, but research has shown that genetic factors (HLA-B51) (Fei *et al.*, 2009, Kirino *et al.*, 2013, Lee *et al.*, 2013, Remmers *et al.*, 2010), viral and bacterial infections (Cho *et al.*, 2012), immune system imbalance (Ekinci *et al.*, 2010), environmental factors such as poor diet (Tanaka *et al.*, 1985), and using tobacco and cigarettes may play a role in the pathogenesis of this disease (Alpsoy, 2016, Aramaki *et al.*, 2007).

BD is considered a rare disease with an estimated prevalence of 13.5–500 per 100,000 people along the Silk Road (Shahram *et al.*, 2013). The prevalence of BD is not the same in different regions of the world and it is higher in certain regions such as the Silk Road, which includes the Middle East, the Mediterranean, and the Far East (Alpsoy *et al.*, 2007), where Turkey has the highest prevalence in the world with 1 in 250 people (Azizlerli *et al.*, 2003). In Western countries, this statistic is much lower, for example, in the United States and England, 0.3 and 1 out of every 100,000 people are affected by this disease, respectively (Woźniacka *et al.*, 2014). BD can occur at any age, but it mostly affects people in their 20s and 30s (Alpsoy, 2016). Epidemiological studies usually consider its prevalence to be the same in men and women. However, in some populations, such as the Far East, the disease is more common in women than in men, while in the Middle East, men predominate (Cho *et al.*, 2012).

Zinc is a mineral that is essential for the proper functioning of the epidermal, skeletal, digestive, reproductive, central nervous system, and immune system, and plays a role in the production of antibodies (Roohani *et al.*, 2013).It also plays a fundamental role in the activity of the innate and adaptive immune system (Wessels *et al.*, 2017). In BD, due to the presence of inflammation in the body, activated neutrophils can produce reactive oxygen species (ROS) in response to the inflammatory process, which causes damage to surrounding cells and tissues (Chambers *et al.*, 2001, Kökçam and Nazıroğlu, 2002, Köse *et al.*, 2001). Antioxidants can convert the generated ROS into safe derivatives. Zinc plays an important role in the body's antioxidant system, which is significantly reduced in serum in BD (Powell, 2000, Saglam *et al.*, 2002).

Limited studies have shown an inverse correlation between serum zinc levels and BD (Sharquie *et al.*, 2006). However, the number of studies conducted on the effect of oral zinc supplementation in BD was very limited (Faghfouri *et al.*, 2022a, Faghfouri *et al.*, 2022b, Sharquie *et al.*, 2006). Although, these studies demonstrated some aspects of the antioxidant and anti-inflammatory effects of zinc in BD, they recommended that more studies should be conducted to elucidate other aspects of zinc in BD to have a more comprehensive insight into the beneficial effects of zinc in BD. Since BD has an inflammatory nature and zinc has antioxidant and anti-inflammatory functions, and on the other hand, due to limited studies on the effect of oral zinc supplements on BD, this study aimed to investigate the relationship between zinc supplementation and BD with emphasis on the level of C-reactive protein (CRP) as a main biomarker of systemic inflammation and malondialdehyde (MDA) as one of the main biomarker of oxidative stress in the body.

Materials and Methods

Study design and participants

Fifty active BD patients (non-ocular IBDDAM > 0.45) enrolled from the BD clinic of Tabriz University of Medical Sciences between August 2020 to February 2021 were subjected to a double-blind, placebo-controlled, randomized, parallel clinical trial. A rheumatologist used the International Criteria for BD (ICBD) to diagnose

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BD (Davatchi, 2012). Adult active BD patients aged 20 to 50 (women in the pre-menopause age) (S. Lashkari and Anumba, 2017) were enrolled in the current study after providing written informed consent. Pregnant or lactating mothers, patients with a history of liver disease, diabetes, or kidney disease, smokers, and those who had taken nutritional supplements more than two months prior to the study were excluded. Demographics and BD history of each patient were also documented.

Sample size

The sample size was estimated using the effect of zinc gluconate supplementation on CRP (mean change and its related standard deviation (SD)) from Kim *et al.'s* study (Kim and Ahn, 2014). A total of 21 BD patients were chosen to be in each group using a power of 80% and a 95% confidence interval (CI) for two-sided tests. With a 20% dropout rate, 25 patients per cohort were considered.

Randomization and intervention

Using the blocking method, patients were randomly assigned to the zinc (ZG) or placebo group (PG) in a 1:1 ratio. Using STATA 16.0 software (StataCorp, College Station, TX), quadruple blocks (A, B, C, and D) were determined based on gender and age (20–35 and 35–50 years). Throughout the trial, both researchers and participants were blinded to the assignment group.

Zinc gluconate tablet containing 30 mg elemental zinc was the intervention and placebo tablet containing microcrystalline cellulose was the control (Dina Iran Company, Tehran, Iran). To prevent digestive problems, it is recommended that all tablets be taken with food. The ZG received one daily zinc gluconate tablet and the PG received the same amount of placebo for 12 weeks. Tablets were labeled and placed in containers by a third party based on random blocks. Each registered patient was assigned an order letter and pill container. In order to determine whether the 90% compliance threshold was met, we asked all patients to return the bottles at the end of the study.

Assessment of clinical manifestations

Before and after the intervention, a rheumatologist examined the clinical symptoms of BD. The Iranian Behcet's disease dynamic activity measure (IBDDAM) was scored based on a variety of BD-related clinical symptoms (Davatchi *et al.*, 1991).

Biochemical measures

Five milliliters of venous blood samples were collected in gel separator vacuumed tubes by venipuncture, both at the beginning of the study and at the end of the trial. Then, blood was freshly centrifuged at 4000 rpm for 15 minutes to extract serum, which was then stored at -80 $^{\circ}$C until measurement. Serum CRP concentration was measured by CRP-latex immunoturbidimetric assay (Biorex Fars; Iran), and MDA level was measured by a spectrophotometric assay utilizing thiobarbituric acid reactive substances (TBARS) (Janero, 1990) .

Ethical considerations

The Ethics Committee of Tabriz University of Medical Sciences approved the study protocol (IR. TBZMED. REC.1401.284). This study adheres to the standards of the Helsinki Declaration and current ethical guidelines. IRCT.ir (number IRCT20100606004105N30) was notified of and approved the study protocol. Consolidated Standards of Reporting Trials (CONSORT) was used to report the current study.

Data analysis

All statistical analyses were performed employing intention-to-treat (ITT) approach in STATA version 16.0 (Stata Corporation, College Station, TX, USA). Multiple imputation method was used to replace missing data (Sterne *et al.*, 2009). As described previously, descriptive statistics such as skewness, kurtosis, z value of skewness and kurtosis, and SD relative to the mean were evaluated to determine the normality of the data (Mishra *et al.*, 2019). The numerical and categorical data were reported as mean SD and frequency (%), respectively. The mean changes within each cohort were calculated using standard errors (SE). The differences within each group as

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well as those between groups were examined using independent and paired sample t-tests. Using analysis of covariance (ANCOVA), the effect of confounders and baseline values on the effect size of zinc on various dependent variables was adjusted. In all analyses, P-values of 0.05 or less were regarded as significant.

Results

Participants' characteristics

Five of the 50 patients who were recruited for the trial withdrew for reasons unrelated to the therapy. **Figure 1** shows the CONSORT flowchart for the investigation which was also presented in our previous studies (Faghfouri *et al.*, 2022a, Faghfouri *et al.*, 2022b). **Table 1** illustrates that there was no significant difference in demographic characteristics (age, gender, and BMI), BD history (disease duration, IBDDAM, and medication history), and blood zinc level between ZG and PG. Zinc supplementation led to a significant increase in serum zinc levels compared to the PG ($P<0.05$) as reported in our previous study (Faghfouri *et al.*, 2022b). This indicated the high patient compliance in the present study.

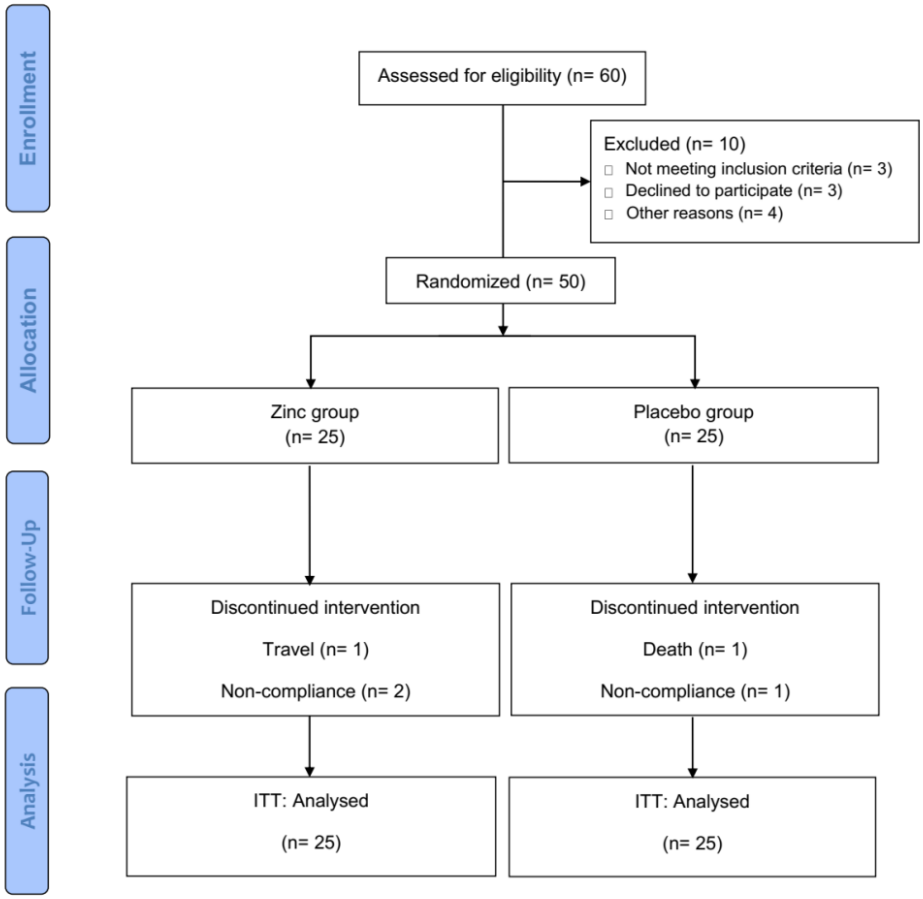

Figure 1. CONSORT flowchart of study (Faghfouri *et al.*, 2022a, Faghfouri *et al.*, 2022b).

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Table 1. Baseline characteristics of participants in zinc and placebo groups.

Variable	**Zinc group** (n=25)	**Placebo group** (n=25)	***P*-value**[a]
Age (y)	43.00 ± 11.18[b]	40.56 ± 9.33	0.406
Body mass index (kg/m^2)	27.02 ± 6.64	26.81 ± 5.95	0.907
Serum Zinc (µg/dl)	68.18 ± 5.71	65.35 ± 6.78	0.117
IBDDAM	1.62 ± 0.88	1.37 ± 0.74	0.297
Sex			
Male	18 (72.0)[c]	18 (72.0)	1.000
Female	7 (28.0)	7 (28.0)	
Duration of Behcet's disease (y)			
<1	3 (12.0)	0 (0.0)	0.235
>1	22 (88)	25 (100)	
Medications			
None	0 (0.0)	2 (8.0)	0.264
Prednisolone	14 (56.0)	16 (64.0)	
Colchicine	11 (44.0)	11 (44.0)	
Azathioprine	9 (36.0)	3 (12.0)	
Interferon α	0 (0.0)	2 (8.0)	
Methotrexate	4 (16.0)	2 (8.0)	
Cyclosporine	0 (0.0)	1 (4.0)	
Sulfasalazine	0 (0.0)	2 (8.0)	
NSAIDs	1 (4.0)	3 (12.0)	
Mycophenolate Mofetil	2 (8.0)	2 (8.0)	

*[a]: P-values are for comparison of variable between zinc and placebo groups (qualitative variables were analyzed by Chi-squared test and quantitative variables were analyzed by t-independent test); [b]: Mean±SD; [c]: n (%); **NSAIDs**, Non-steroidal anti-inflammatory drugs; **IBDDAM**: Iranian Behcet's disease dynamic activity measure.*

Clinical assessments of BD

Zinc supplementation had a significant improvement in nonocular IBDDAM score compared to the placebo treatment after baseline adjustment (mean change: -0.43±0.15 in the ZG; mean change: -0.04±0.07 in the PG, *P*=0.046) and adjusting based on the confounding factors, i.e., age, BMI, and BD duration (*P*=0.026) (Faghfouri *et al.*, 2022b). Zinc led to a significant improvement in genital ulcers (*P*=0.19). Other clinical manifestations did not change significantly in ZG compared to PG (*P*>0.05) (Faghfouri *et al.*, 2022a).

The serum levels of MDA

The baseline MDA levels did not differ significantly between groups (*P*>0.05). A paired t-test revealed that MDA level in ZG decreased significantly after 12 weeks (*P*=0.044), which is shown in **Table 2**. There was no significant difference in MDA serum levels between the groups after adjusting for baseline values (*P*>0.05).

The serum levels of CRP

The baseline CRP levels did not differ across the groups (*P*>0.05, **Table 2**). CRP decreased significantly in ZG (*P*=0.006), according to a paired t-test. After adjusting for baseline values, ANCOVA test showed that zinc supplementation led to a significant improvement in CRP serum levels compared to the placebo group (*P*= 0.012).

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Table 2. Comparison serum levels of Malondialdehyde and C-reactive protein in zinc and placebo groups.

Variable	Group Zinc (n=25)	Placebo group (n=25)	P-value[a]
Malondialdehyde (µmol/l)			
Baseline	9.19 ± 2.15[c]	9.08 ± 2.20	0.85
After 12 weeks	8.77 ± 2.30	9.1 ± 2.34	
P-value[b]	0.044	0.830	
Change	-0.42 ± 1.97	0.02 ± 0.11	
C-reactive protein (mg/l)			0.591
Baseline	23.71 ± 4.63	22.96 ± 5.09	
After 12 weeks	22.25 ± 4.83	23.23 ± 5.53	
P-value	0.006	0.529	
Change	-1.46 ± 0.48	0.27 ± 0.42	

[a]: Independent samples t-test; [b]: Paired samples t-test; [c]: Mean±SE.

Discussion

The current double-blind clinical trial study showed that zinc gluconate supplementation at an elemental dose of 30 mg per day led to a significant decrease in the CRP level of BD patients compared to the placebo group. However, it had no significant effect on MDA. The result of CRP was consistent with a previous recent meta-analysis that pooled all clinical trial studies in this regard (Ghaedi *et al.*).

Three studies were conducted on the effect of zinc supplementation on BD patients. In two studies conducted in Iran, a dose of 30 mg of elemental zinc in gluconate form for 12 weeks led to significant improvement in immune system markers (TLR-2 gene and surface expression), genital ulcer, NLRP-3 inflammasome complex, and BD activity. Regarding inflammatory markers, these studies showed that zinc led to a significant reduction in IL-1β, although it had no significant effect on TNF-α levels. However, as many symptoms of BD, including digestive symptoms, neurological symptoms and joint disorders, require longer treatment to recover, these two studies suggested that zinc supplementation may have more improving effect on BD for periods longer than 12 weeks (Faghfouri *et al.*, 2022a, Faghfouri *et al.*, 2022b). However, it must be noted that zinc in a long-term administration and higher doses can have pro-oxidant effect through disrupting of mitochondria homeostasis and excessive ROS production (Lee, 2018). Moreover, zinc overload can be related to increase in pro-inflammatory cytokine production (Plum *et al.*, 2010) . Therefore, high doses and long-term administration of zinc should be used with precaution. In another study, a dose of 300 mg of zinc sulfate per day for 3 months without side effects led to an improvement in clinical manifestations index (Sharquie *et al.*, 2006). CRP and TNF-α respond differently to inflammation. CRP increases slightly with mild inflammation and higher levels are observed in severe inflammation. In contrast to CRP, TNF-α is an early indicator of inflammation and increases in the first times of exposure to the inflammatory stimulus and then has a decreasing trend (Kumolosasi *et al.*, 2014, Yousef *et al.*, 2010). Most of the participants were not new cases. As a result, this difference in kinetics of CRP and TNF-α production can be the cause of difference in the effect of zinc on these two markers in BD patients. Future studies should investigate the effect of zinc on TNF-α in new case BD patients to get a complete picture of anti-inflammatory effects of zinc in BD.

Zinc exerts its anti-inflammatory action through down-regulating Nuclear Factor-Kappa-B (NF-κB). Some zinc finger proteins like A20 and growth factor independence-1 (Gfi-1) are involved in the inhibition of NF-κB dimerization (Faghfouri *et al.*, 2020). It has been reported that zinc supplementation can lead to induction of A20 binding to mRNA and DNA through the upregulation of mRNA and DNA-specific sites (Prasad *et al.*, 2004). Moreover, zinc status can contribute to the expression of a cytokines via

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binding to metal response elements (MREs) on the promoter of target genes (Bao *et al.*, 2003, Cousins, 1998). Moreover, immunomodulatory effects of zinc can balance inflammatory responses (Faghfouri *et al.*, 2022b). It should also be mentioned that inflammation and oxidative stress have a two-way relationship and an increase in one leads to the stimulation of the other. The antioxidant effects of zinc can also lead to anti-inflammatory consequences. Zinc is effective as a cofactor in the action of superoxide dismutase (SOD) as an anti-oxidant enzyme (Mariani *et al.*, 2008). Zinc also leads to membrane strength through competition with toxic metals and prevents the oxidation of sulfhydryl groups of proteins (O'Dell, 2000). Zinc leads to the maintenance of mitochondrial homeostasis, thereby reducing ROS production (Lee, 2018) .

It was reported that superoxide radical anion generation can lead to lipid peroxidation in BD patients. Lipid peroxidation is the main cause of atherosclerosis pathogenesis in BD (Orem *et al.*, 1997). MDA level is considered as the main marker of lipid peroxidation. MDA level has been reported to be higher in BD patients compared to healthy subjects (Mungan *et al.*, 2006, Sandikci *et al.*, 2003). The results of previous studies on the effect of zinc on MDA levels are contradictory. Some studies showed a positive effect of zinc (Momen-Heravi *et al.*, 2017, Velázquez-Pérez *et al.*, 2011), while some other studies failed to show an improvement effect (Aboomardani *et al.*, 2012, Ribeiro *et al.*, 2016). A meta-analysis study combining studies in this field showed that doses less than 40 mg per day do not have a significant effect on MDA. However, doses higher than 40 mg per day lead to a significant decrease in MDA. Dose-response analysis also showed that the relationship between zinc and MDA level was dose-dependent (Mousavi *et al.*, 2020). As a result, the lack of significant effect of zinc on MDA in the present study may be related to the prescribed dose. However, as mentioned above, zinc overload has pro-oxidant effects. Therefore, future studies should compare effects of different doses of zinc on MDA levels in order to obtain the optimal dose using dose-response analysis.

The present study had some limitations. First, CRP was measured as the only inflammatory factor. Although in our previous studies we examined TNF-α and IL-1β in these patients in response to zinc gluconate supplementation (Faghfouri *et al.*, 2022a, Faghfouri *et al.*, 2022b), other inflammatory indicators should also be performed in future studies to fully determine the anti-inflammatory effects of zinc supplementation in BD patients. Second, we could not administer doses higher than the upper safety level (40 mg/day), due to ethical constraints. The observed lack of significant effect on MDA may be due to the administered dose. However, the study has some strengths. First, it is registered in IRCT and is reported based on the CONSORT checklist. Second, this is the first study that examines the effect of zinc on CRP and MDA in BD patients.

Conclusion

Zinc supplementation in an elemental dose of 30 mg per day has an anti-inflammatory effect in BD patients by reducing CRP levels. The beneficial effect of zinc on lipid peroxidation in BD patients was not shown in the present study.

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Authors' contributions

AH Faghfouri and B Alipour designed the study, collected the data, analyzed the data, drafted, and prepared the manuscript. AA Khodabandehloo, G shahhosseini and SM Seyyed Shoura. collected the data, drafted, and prepared the manuscript. V Musazadeh and A Khabbazi designed the study, collected the data, and critically revised the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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