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ORIGINAL CONTRIBUTION

The effect of selenium supplementation on disease activity and immune-inflammatory biomarkers in patients with mild-to-moderate ulcerative colitis: a randomized, double-blind, placebo-controlled clinical trial

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Abstract

Purpose Selenium (Se) supplementation may help reduce inflammation and disease activity in ulcerative colitis (UC) patients. We investigated the therapeutic effects of Se administration in cases with mild-to-moderate active UC.

Methods A multicenter, double-blind, randomized clinical trial (RCT) was conducted on 100 cases with active mild-to-moderate UC. The patients were randomly allocated to be given an oral selenomethionine capsule (200 mcg/day, $n=50$) or a placebo capsule ($n=50$) for 10 weeks. The primary outcome was defined as disease activity via the Simple Clinical Colitis Activity Index (SCCAI), and secondary outcomes were measured at the end of the study.

Results After 10 weeks, the SCCAI score's mean was reduced in the Se group ($P<0.001$). At the end of the intervention, clinical improvement (decline of $3\geq$ score from baseline score) was observed in 19 patients (38%) of the Se group and 3 patients (6%) of the placebo group. The patients with clinical remission (defined as SCCAI ≤ 2) were assigned in the Se group ($P=0.014$). The Se group's quality of life and Se serum levels were enhanced at the end of the study ($P<0/001$). In the Se group, the mean concentration of interleukin-17 decreased ($P<0/001$). However, the levels of interleukin-10 showed no considerable change between the two groups in the 10th week ($P=0.23$).

Conclusion Se supplementation as add-on therapy with medical management induced remission and improved the quality of life in patients with active mild-to-moderate UC.

Trial registration number and date of registration IRCT20091114002709N51; 2020-04-13.

Keywords Selenium · Ulcerative colitis · Inflammatory bowel disease · Interleukin

Introduction

One of the main subtypes of inflammatory bowel disease (IBD) is ulcerative colitis (UC), which is considered an immune-mediated inflammatory disorder of the gastrointestinal tract, mainly affecting the colon and rectum mucosa [1]. The exact etiology of UC is still unknown. Different factors can play an essential role in inducing pro-inflammatory cytokines interleukin-17 (IL-17) and tumor necrosis factor-alpha (TNF-a), such as environmental,

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genetic, and immune factors. The inflammatory imbalance is damage to the colonic mucosa and cellular functions [2–5]. Treatment with immunosuppressive medicines can improve clinical symptoms in UC patients [6, 7]. On the other hand, the medications that are used to alleviate IBD symptoms [8] lead to significant harmful side effects and high costs, especially in the long term [9, 10]. Indeed, effective UC therapeutic strategies have not been discovered yet and novel management strategies with side effects are needed.

Selenium (Se), an essential mineral, has several physiological processes, including metabolism, immunomodulation, and antioxidant defense system [11]. It has been discussed that Se deficiency may be associated with chronic inflammatory processes and autoimmune disorders [12]. Since the 1980s, many investigators have shown a significant reduction in serum Se concentrations of UC patients [13]. Additionally, previous studies have indicated that the concentration of circulation Se was correlated with the activity and severity of UC [14]. An experimental study has proved that supplementation with a high dose of Se improved survival and lowered colitis-associated inflammation by upregulating the expression of pro-inflammatory and anti-inflammatory genes (Fig. 1). In contrast, colitis severity increased in Se-deficient or Se-adequate acute colitis mice [15]. In Sang et al. study, Se intake significantly mitigated the symptoms of colitis and histological damage by raising the proportion of regulatory T cells, reducing the expression of pro-inflammatory markers such as IL-17, and enhancing the expression of interleukin-10 (IL-10) [16]. Thus, Se supplementation may alleviate symptoms and severity of UC [17]. To the best of our knowledge, there is no well-designed study on the therapeutic effects of Se administration on UC severity and its outcomes in humans. Only a small-size pilot clinical trial in 1997 assessed the effects of Se intake on the clinical symptoms of UC patients [18].

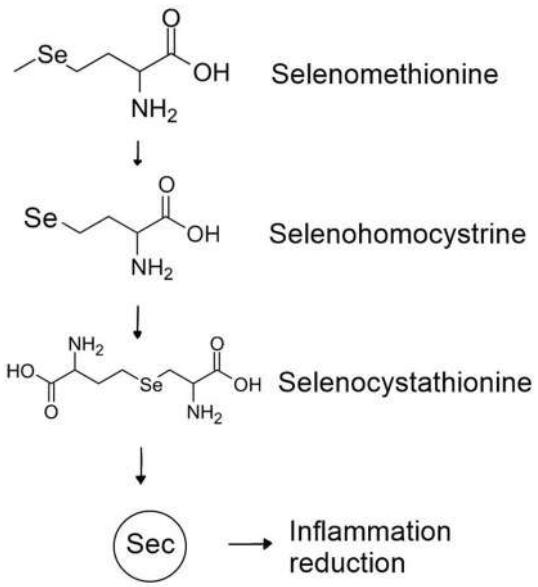

Fig. 1 Metabolism of selenomethionine

Given the important role of Se in the physiopathology of UC, and its critical properties in regulating inflammatory responses as well as immunomodulatory properties [19], we decided to design a multicenter placebo-controlled, double-blinded, randomized clinical study to assess the therapeutic effects of the Se supplementation on the disease activity, quality of life, and inflammatory markers of the mild-to-moderate active UC patients.

Methods

Study design and participants

Adult participants aged 18–70 years who suffered from mild-to-moderately active UC with body mass index (BMI) of 18.5–30 kg/m^2 were included in this placebo-controlled, double-blinded, randomized clinical trial study. Note that our cases were enrolled in three hospitals in Tehran, Iran. The participants' recruitment was based on pathological and endoscopic diagnoses. Simple Clinical Colitis Activity Index (SCCAI) was used for defining mild-to-moderately active UC where the score of ≥ 5 and < 12 represented this severity of disease (19). Participants were excluded if they received corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), anti-tumor necrosis factor agents (Anti-TNF), anti-histamine and calcium channel antagonists, oral contraceptive, anti-coagulants, lipid-lowering medications, any supplements of Se, multivitamins-mineral, omega-3, polyphenolic as well as antioxidants within the past 1 month. Patients who had a history of gastrointestinal disorders, renal, thyroid, pancreatic, liver diseases, cancers, other inflammatory diseases, diabetes mellitus, cardiovascular diseases, and pregnant or lactating women were also excluded. Patients required to change dosages or medicine types during the study were again excluded.

At the beginning of the study, cases were informed regarding the objectives and method of the study. All participants who met the study's eligibility criteria signed an informed consent, which allowed them to quit the study at any stage. Patients were instructed to maintain their normal diet during the study without any change. At the 1st and 10th weeks of the study, 3 day food records were filled out to control the confounder effects of dietary consumption. The ethics committee of Iran University of Medical Sciences (IUMS) approved the study protocol (IR.IUMS.REC.1397.688). The study is a section of a trial which was registered in the Iranian Registry of Clinical Trials (No.

IRCT20091114002709N51), and the genetic outcomes of the trial have already been published [20].

Intervention and randomization

In this study, eligible individuals who fulfilled the inclusion criteria were randomly arranged into two groups; one group received an oral capsule of Se and the other took a placebo daily. The capsules were similar in size, color, and flavor. The Se capsules (containing 200 mcg seleno methionine) were purchased from a twenty-first-century Company (Tempe, USA), and placebo capsules (containing rice flour) were produced by the faculty of pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran. According to permuted block randomization design, the random numbers (block size of four with six possible arrangements) were generated by the www.Randomization.com website. All intervention boxes were packed in envelopes separately and marked by numbers (1–100) to conceal randomization codes. A person not involved in the study prepared the intervention's randomization list and numbered packing. Participants, researchers, and staff were blind to the intervention schedule during the study.

Adherence was evaluated based on the unconsumed capsule count at each visit (5th, 10th). Patients who did not consume ˃85% of their capsules were excluded from the study. General demographic questionnaires were collected after enrollment. The participants were followed-up to check adherence to intervention by telephone each week, and clinic visits every 5 weeks of the study (5th and 10th).

Outcome measurements

Primary outcome

The primary outcome was defined as mean changes in the disease activity according to SCCAI scoring. SCCAI is based on six clinical parameters: defecation frequency (day and night), urgency of defecation, blood in stool, general well-being, and extra-colonic features. Higher scores represent severe activity of UC over the last 2 weeks. A single investigator completed each patient's score and scaled disease activity before and during the 10th week of intervention.

Secondary outcomes

Clinical improvement (the percentage of patients with a reduction of ≥ 3 scores of the SCCAI from baseline) and clinical remission (the percentage of patients with SCCAI score ≤ 2 at week 10) were assessed. UC patients' quality of life was assessed by the inflammatory bowel disease questionnaire-9 (IBDQ-9). This questionnaire comprises nine questions and evaluates four manifestations of IBD, including gastrointestinal, systemic, emotional, and social disturbances. The final sum of questions (9–63) represents patients' quality of life with UC. IBDQ-9 has been linguistically validated among Iranian patients [21]. Blood samples were taken after 10–12 h of starvation to measure the inflammatory biomarkers (IL-10 and IL-17) and serum Se levels. To obtain the serum, drawn blood was centrifuged at $3000 \times g$ for 10 min, and frozen at − 80 °C at the laboratory of the Nutrition of the Iran University of medical sciences until the end of the study. The enzyme-linked immunosorbent assay (ELISA) method (Crystal Day, Biotech Co., Ltd, China) was used to determine the serum concentrations of IL-10 and IL-17. The serum concentration of Se was analyzed using atomic absorption spectrophotometry (PerkinElmer; USA). Anthropometric measures, including weight and height of subjects, were assessed. BMI was measured through dividing weight (Kg) by height squared (m^2).

Statistical analysis

A sample size of 50 participants (in each group) was considered based on the clinical significance or minimal clinically important difference (MCID) of the study's main outcome. Thus, one score reduction in SSCAI was considered as MCID, ($\alpha = 0.05$, $b = 0.2$, and 10% dropout) [22]. STATA v.16 software was used for statistical analysis. The normality of study variables was examined by Shapiro–Wilks and histogram diagrams. The participant's characteristics, clinical improvement, and clinical remission were compared by independent *t* test/Mann–Whitney test for continuous variables or Chi-square/Fisher test for categorical variables. ANOVA test was performed on the initial and final values of study outcomes. The effects of possible confounders such as age, weight, BMI, dietary intake, duration of UC, disease extension, medication use, and baseline value of study variables were adjusted by analysis of covariance (ANCOVA). The analysis was reported by the treat-to-intention method. The magnitude of the therapeutic effect was stated through standardized mean difference (SMD) effect size (Cohen's d) and 95% confidence interval (CI). P value < 0.05 was considered significant.

Results

Patient characteristics

During the enrollment phase, 145 patients with UC were screened for the trial. Forty-five patients did not meet the inclusion criteria of this study. However, 100 patients with mild-to-moderately active UC were recruited and randomly assigned to receive either 200 mcg Se ($n = 50$)

or placebo ($n=50$). Of these, 44 patients in the Se group (88%) and 45 patients in the placebo group (90%) completed the study. Eleven participants (six in the Se and five in the placebo group) discontinued the study. The flowchart is shown in Fig. 2. There was no significant difference in dropout rates between the two groups ($P=0.739$). There was no considerable difference either in the baseline of weight, BMI, sex, smoking and alcohol use, duration of UC, disease extension, or oral medication use between the two groups. Although, at the beginning of the study, the mean values of age (Se group, 34.5 (11.2) years; and placebo group, 37.9 (10.8), years) and the number of patients with rectosigmoid colitis (10 in the Se group vs. 16 in the placebo group) were not significantly different between the 2 groups, we decided to adjust the study end-point results according to the confounders. The details of baseline demographic and clinical characteristics are shown in a previous study [20].

Primary outcome

According to Table 1, there was no significant difference between the two groups in terms of disease activity according to SCCAI, at the baseline ($P=0.081$). Supplementation with Se for 10 weeks reduced (mean change (SD):− 1.79(1.83)) the mean SCCAI score compared to the placebo group ($P<0.001$; SMD, − 1.52; 95%CI, − 1.96 to − 1.07). No significant changes were seen after adjustment for study confounders (Table 1).

Secondary outcomes

Clinical improvement was statistically increased in the Se group (19/50 [38%]) compared to the placebo group (3/50 [6%]) after the 10th week ($P\leq 0/001$) (Fig. 3). Also, clinical remission (defined as SCCAI ≤ 2) at the end of the study occurred in 10 of 50 (20%) of participants receiving Se and 2 of 50 (4%) in the placebo group ($P=0.014$) (Fig. 3).

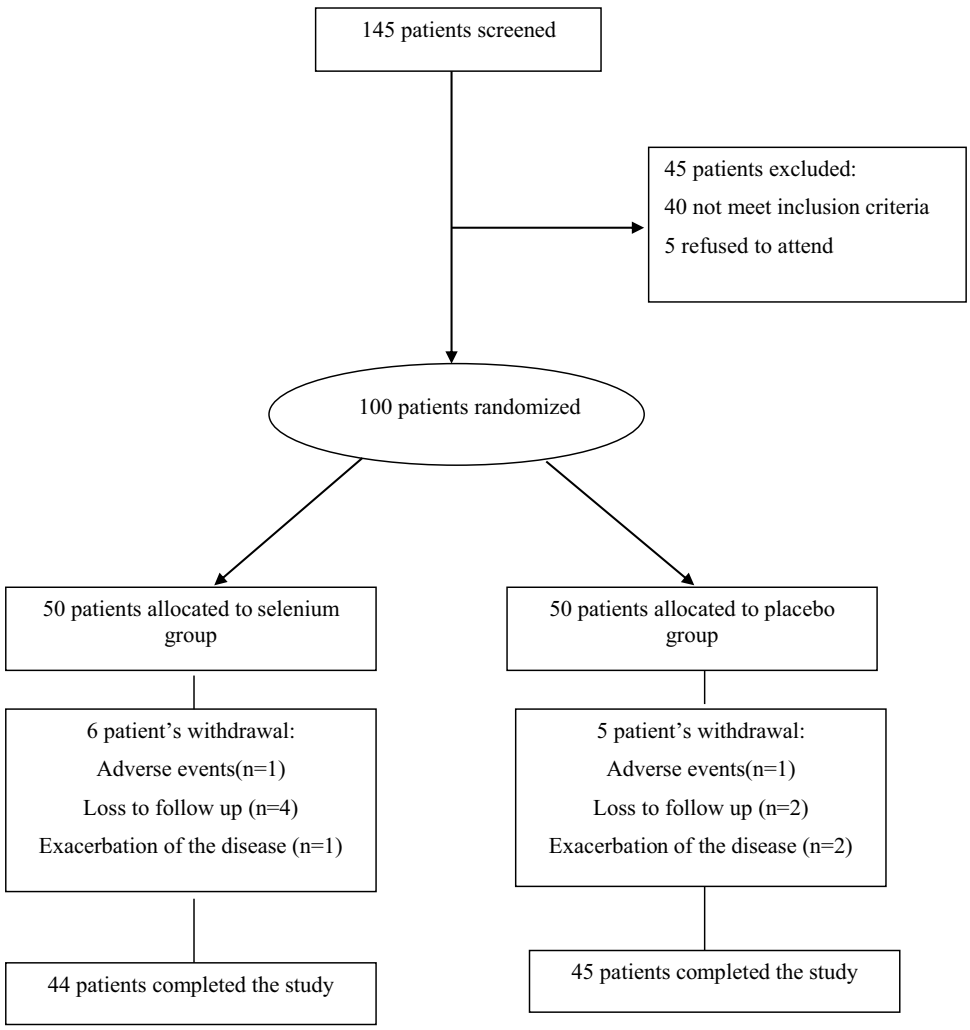

Fig. 2 PRISMA flow diagram for study selection

Table 1 Comparison study outcomes in pre- and post-intervention between groups

Variable	Timepoint	Selenium ($n=50$)	Placebo ($n=50$)	Cohen's d (95% CI)	P value	Adjusted R^2	P value adjusted[A]	P value adjusted[B]
SCCAI score	Pre	6.98 (1.63)	6.34 (1.98)	–	0.081*	–	–	–
	Post	4.88 (1.35) $<0.001^{\dagger}$	6.67 (1.25) $0.636^{\dagger}$	− 1.52 (− 1.96, − 1.07)	< 0.001**	0.62	< 0.001	< 0.001
IBDQ-9 score	Pre	34.34 (5.40)	36.42 (7.34)	–	0.158*		–	–
	Post	38.90 (3.42) $<0.001^{\dagger}$	34.49 (3.42) $0.328^{\dagger}$	1.28 (0.85,1.72)	< 0.001**	0.81	< 0.001	< 0.001
IL-17 (ng/l)	Pre	99.89 (17.88)	95.17 (21.62)	–	0.313*	–	–	–
	Post	77.90 (16.86) $<0.001^{\dagger}$	100.60 (16.86) $0.408^{\dagger}$	− 1.28 (− 0.85, − 1.72)	< 0.001**	0.35	< 0.001	< 0.001
IL-10 (ng/l)	Pre	122.35 (50.44)	128.40 (56.24)	–	0.576*			
	Post	136.14 (48.46) $0.521^{\dagger}$	124.50 (46.24) $0.504^{\dagger}$	0.24 (− 1.54, 0.63)	0.230**	0.09	0.241	0.276
Selenium (µg/l)	Pre	73.19 (21.49)	75.14 (21.49)	–	0.642*	–	–	–
	Post	117.49 (20.18) $<0.001^{\dagger}$	76.42 (19.95) $0.621^{\dagger}$	2.04 (1.55, 2.52)	< 0.001**	0.59	< 0.001	< 0.001

Data presented as mean (SD)

SCCAI simple clinical colitis activity index, *IBDQ-9* inflammatory bowel disease questionnaire-9, *IL-17* interleukin-17, *IL-10* interleukin-10

†Calculated based on pair t test

*Calculated based on independent t test

**Calculated based on ANOVA model

[A]Adjusted for potential covariate (the baseline value, age) (calculated based on ANOVA/ANCOVA model)

[B]Adjusted for potential covariate (the baseline value, colitis groups) (calculated based on ANOVA/ANCOVA model)

The quality of life assessed by IBDQ-9 was not significantly different between the groups. Meanwhile, the mean of the IBDQ-9 score increased (mean change (SD): 4.41(4.4)), after 10 week supplementation in the Se group compared to the placebo (P ˂ 0/001; SMD, 1.28; 95%CI 0.85–1.72) (Table 1).

The baseline serum concentrations of the inflammatory markers (IL-10 and IL-17) were similar between the groups ($P>0.05$). Considering IL-17 serum concentration, the mean concentration of IL-17 decreased (mean change (SD): − 22.70(23.8)), in the Se group compared to the placebo group at the end of the 10 week intervention ($P\leq 0/001$; SMD, − 1.28; 95%CI − 0.85 to − 1.72) (Table 1). However, the levels of IL-10 showed no significant change (mean change (SD): 11.64(9.4)), between the two groups at the end of the study ($P=0$ 0.23; SMD, 0.24; 95%CI − 1.54 to 0.63) (Table 1).

As reported in Table 1, the initial plasma concentration of Se was not different between the groups, while comparison of the values after the 10th-week intervention demonstrated a considerable increase (mean change (SD):41.07(28.4)), in the Se group ($P\leq 0/001$; SMD, 2.04; 95%CI 1.55–2.52) (Fig. 4). Plasma Se concentration of study participants (post-intervention vs. baseline) in both groups is shown in supplementary file.

The study results did not change after adjusting for age and extension of colitis as confounders. According to the study results, there was no significant difference in dietary intake between the study groups ($P>0.05$) (20). The association between the Se concentration and the study outcomes was assessed via regression analysis. However, despite the positive effects of Se in the decrease of disease activity and inflammation, and increase of quality of life, the results of regression analysis have shown no significant relationship between the variables, in the end of the study. It seems the mechanism of the effect of Se on human being is more complicated than linear relation. Data are shown in supplementary file.

Discussion

To the best of the authors' knowledge, this is the first double-blinded RCT designed to assess efficacy of Se supplementation in the management of patients with UC. Our study revealed that 10 weeks of add-on oral 200mcg/d Se supplementation could improve disease activity, and induce clinical remission, in active mild-to-moderate UC patients.

Few clinical trials have investigated the therapeutic effects of Se supplementation in IBD. Results of Stedman

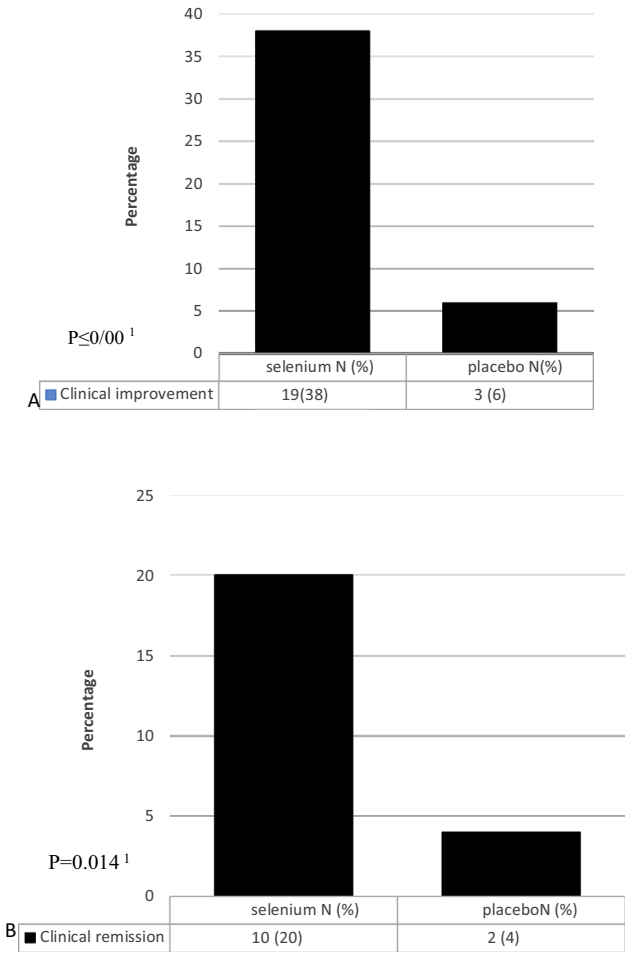

Fig. 3 **A** Clinical improvement at the end of the study; **B** Clinical remission at the end of the study. **A** The percentage of patients with a decrease of ≥ 3 scores of the SCCAI from baseline. **B** The percentage of patients with SCCAI score ≤ 2 at week 10. 1 *P* value according to *T* test

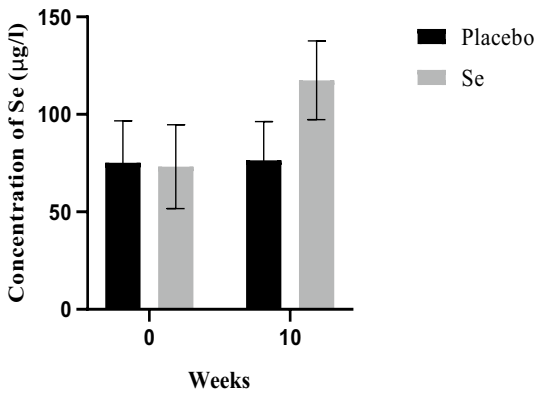

Fig. 4 Compare of Selenium concentration between study groups

et al. in 1997 illustrated that 600mcg/dose supplementation for 4 weeks significantly improved clinical symptoms, including stool frequency, bleeding, and diarrhea in patients with active mild-to-moderate UC [18]. In addition, the finding of Shapira et al. in line with our result, demonstrated that the combination therapy of two tablets of Coltect (500 mg curcumin, 250 mg green tea, and 100mcg selenomethionine) in patients with mild-to-moderate UC reduced colitis symptoms and disease activity after 8 weeks. In the study, the authors stated Se was the more active component of Coltect [23]. We used selenomethionine in the study as it is the most effective form in elevating the serum concentration without any toxic effects in short-term studies. Se in the form of selenomethionine is efficiently and effectively absorbed from the intestine [24–26]. The formation of selenoproteins was brought about by the transformation of selenomethionine into selenocysteine via the transsulfuration route [27]. Glutathione peroxidases (GPXs) is one of the main selenoproteins with a significant role in regulating inflammatory responses and antioxidant defense in the pathophysiological processes. [27–29]. Previous documents have declared that Se plays a potential role in the prevention and/or improvement of some autoimmune disorders, such as IBD [30, 31]. Further, different experimental studies have shown that the beneficial roles of Se include ameliorating disease activity as well as clinical symptoms, and helping with histological injury, along with regulating the inflammatory response and increasing survival rates in colitis [15, 16, 31]. Various studies have focused on several mechanisms of Se effects on colitis treatment, and some of the underlying mechanisms have been elucidated.

Since 70 years ago, researchers announced that Se and selenoproteins as antioxidants could protect against inflammation and malignancy in the bowel [13]. Recent investigations have illustrated that Se potently modified functional immune cells and some transcription pathways such as nuclear factor-kB (NF-kB) [15, 32]. NF-kB is considered a key regulator of the physiological and pathophysiological mechanisms related to inflammation, oxidative stress, and tumorigenesis [33]. Activation of the intestinal NF-kB may be related to disease severity and more significant histological lesions in IBD patients [34]. Some studies have exhibited that Se supplementation may downregulate NF-kB and reduce the expression of pro-inflammatory genes as well as the synthesis of inflammatory cytokines [35, 36]. Furthermore, the Se anti-inflammatory activities were mediated by modulation of arachidonic acid (AA) metabolism and prostaglandins (PGs) at transcription levels [37–39]. In other words, the formation of PGs is affected by the expression of different isoforms of cyclooxygenase (COX) that are closely controlled by selenoproteins [15, 37]. Also, various studies have shown that during the inflammation in Se-deficient situations, the AA cascade predominantly

shifts to the production of pro-inflammatory metabolites via COX-$_2$ induction and upregulation of prostaglandin E_2 (PGE_2). Elevation of levels of COX-2 and PGE_2 is a hallmark of inactive colitis [40–42]. In contrast, the levels of prostaglandin D_2 (PGD_2) intensify in the remission phase of UC patients [43]. Some documents have reported that in Se-supplemented cells, COX-1 was expressed before COX-2, and thus AA is utilized by COX-1 and promotes synthesis of PGD_2 plus its anti-inflammatory metabolites 15-deoxy-$\Delta^{12,14}$-prostaglandin J2(15d-PGJ2) [15, 38, 44]. 15d-PGJ2 is involved in immune response via several mechanisms, including the activation of nuclear hormone receptor (peroxisome proliferator-activated receptor-γ) PPARγ, and inhibition of the NF-kB signaling pathway [38, 45].

According to some evidence, Se regulates T-cell response, promotes T-regulatory cells, as well as reduces T helper 1 and 17 in experimental models [16, 46]. In experimental studies, Se supplementation would reduce formation of pro-inflammatory cytokines such as IL-17, IL-6 or IL-21 and TNF-α, while elevating forkhead box protein P3 (FOXP3+) cells and IL-10 [47]. Previous studies have indicated that IL-17 is implicated in the activation of NF-kB signaling and produces inflammatory cytokines, which can exacerbate symptoms and severity of the disease in patients with IBD [48, 49]. In human studies, IL-17 concentration is intensely associated with the severity of clinical disease in UC patients. Hence, levels of IL-17 in UC patients are higher than in healthy controls [49, 50]. Our results revealed that Se supplementation significantly lowered IL-17 levels compared to the placebo. This finding agrees with the experimental studies that show the level of IL-17, IL-2, or IL-23 dropped following Se treatment in dextran sodium sulfate (DSS)-induced colitis [16, 51]. However, in contrast with the animal study [16], no remarkable difference was detected between groups in IL-10 concentrations at the end of the study. In line with our findings, in Karanikas et al. study, Se administration (200 mcg /d) for 3 months did not alter IL-10 concentrations in autoimmune thyroiditis patients [52]. The observational study results showed that serum IL-10 levels are high in active UC patients and return to normal levels in the remission phase [53]. The results of clinical studies of Se administration effects on IL-10 concentrations are controversial. Se supplementation is thought to suppress or reduce some pro-inflammatory pathways, and related mechanisms have a potential role in alleviating disease activity in UC patients. However, contrary to the main mechanism explained in the experimental studies, we did not evaluate the exact mechanisms in the study.

Se supplementation can restore the serum levels of Se, which can lead to increased selenoprotein synthesis and reduced chronic inflammation [47]. Epidemiological studies have demonstrated that the Se concentration diminishes in patients with IBD even in patients with mild-to-moderate activity [54, 55]. Various mechanisms such as reduced food intake, impaired absorption, nutrient deficiencies, altered intestinal flora, medicine side effects, and increase of energy expenditure due to inflammation have been considered to be the main reasons for nutrient deficiencies in IBD [56–58]. The results of a cross-sectional study on UC patients in Iran demonstrated that serum levels of Se were significantly lower in the patients [14]. Also, an inverse association was observed between the level of Se and the duration as well as activity of IBD [59]. Our study showed that the level of Se was at low levels in both groups at the baseline. At the same time, after 10 weeks of intervention, a significant rise in the serum concentration of Se occurred in the intervention group. This result concurs with previous reports, which showed that the level of Se was remarkably lower in patients with IBD [54, 60]. The pathophysiology of Se deficiency is not exactly understood. However, it may be recommended to take major sources of selenomethionine such as meat, fish, nuts, or cereals as a possible helpful strategy [27].

Regarding the IBDQ-9 score, quality of life was significantly enhanced in patients receiving Se supplementation than in the placebo group after 10 weeks. Quality of life indicates the effect of disease on function and daily performance. Thus, Se enhances the quality of life through controlling and mitigating the symptoms of the disease. As a result, the present study suggests that Se exerts a positive effect on patients with mild-to-moderate UC by improving the symptoms and quality of life.

We first investigated the effect of the potent form of Se as selenomethionine on the appropriate sample size of actively mild-to-moderate UC patients in multicenter RCT. Additionally, the study assessed clinical outcomes and the inflammatory cytokines serum concentrations to detect underlying mechanisms of Se effects. However, our study had some limitations. First, 10-week supplementation with Se cannot represent long-term effects on UC patients. Second, a colonoscopy was not possible for the macroscopic mucosal and histological evaluation because of ethical concerns. However, SCCAI was used in this study which correlated relatively well with colonoscopy and gastrointestinal symptoms [61]. Finally, due to the invasive methods of providing tissue samples, the potential mechanisms of Se in reducing colitis symptoms and disease activity were not assessed in the present study. Thus, it is suggested that further RCT studies with invasive evaluations such as endoscopy would be required to determine the exact mechanisms of Se supplementation effects on UC patients.

Conclusion

In conclusion, this randomized, double-blind, placebo-controlled study found that 200 mcg Se supplementation as add-on therapy with medical management could induce

remission and improve quality of life in patients with active mild-to-moderate UC. We observed that these effects were achieved at least partially by improvement in the serum concentration of Se and inflammatory biomarkers. Further multicenter clinical trials with a more extensive intervention period and different dosages of Se are needed to confirm our results for finding a precise mechanism of action for Se.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00394-023-03214-9.

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Availability of data and materials The datasets generated and/or analyzed during the current study are not publicly available due to security issues but are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

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