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Original Research

The adjuvant use of calcium fructoborate and borax with etanercept in patients with rheumatoid arthritis: Pilot study

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ABSTRACT

Objective: This study was designed to evaluate the effects calcium fructoborate (CFB) and sodium tetraborate (NTB) as supplements in Iraqi patients with active rheumatoid arthritis (RA) maintained on etanercept. **Materials and Methods:** A double-blind randomized placebo-controlled clinical trial with 60 days treatment period was carried out at Baghdad Teaching Hospital, Medical city, Baghdad, Iraq. Eighty RA patients were randomized into three groups to receive either 220 mg/day CFB, 55 mg/day NTB in capsule dosage form (equivalent to 6 mg elemental Boron), or placebo formula once daily. Only 72 patients completed the study. All patients were clinically evaluated utilizing DAS28-erythrocyte sedimentation rate (ESR), simple disease activity index-C-reactive protein (CRP), and clinical disease activity index scores at baseline, and at the end of the study. Venous blood was obtained at baseline and after 60 days, and utilized for the measurement of ESR, hemoglobin, in addition to evaluation of high-sensitivity CRP (hsCRP), tumor necrosis factor-α (TNF-α), interleukin-1α (IL-1α) and IL-6. **Results:** After 60 days, both types of boron significantly improve the clinical scores, in association with significant decrease in the serum levels of ESR, hsCRP, IL-1α, IL-6, and TNF-α with remarkable superiority for calcium fructoborate (CFB) over sodium tetraborate (NTB), compared to baseline and placebo-treated group. **Conclusion:** The use of boron, as adjuvant with etanercept, has potentiated therapeutic outcomes in RA patients, and may be a new strategy to improve treatment, and avoid the problems associated with biologics utilized in RA treatment.

KEY WORDS: Calcium fructoborate, etanercept, rheumatoid arthritis, sodium tetraborate

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disorder attributed to exaggerated and excessive implementation of inflammatory responses that finally predispose to synovial inflammation and destruction of joint tissues [1]. In medical practice, many therapeutic approaches are implemented and currently approved for clinical use in the treatment of RA, including disease-modifying drugs like methotrexate and biological agents like etanercept. However, the broad profile of adverse reactions and high cost burden limit the scope of effective and successful therapeutic use, especially in low-income communities [2,3]. Many consequences of inflammatory reactions, including oxidative stress and accelerated production of reactive oxygen species (ROS), can amplify the inflammatory response with consequent impact of increasing tissue damage and limited treatment outcomes [4,5]. Accordingly, the use of supplements from natural sources to attenuate the inflammation-induced oxidative damage, such as phytochemicals and trace elements, may provide further therapeutic benefits to the currently used antirheumatic agents [6,7]. Moreover, many of these natural supplements have the ability to potentially interfere with the inflammatory cascades, probably through attenuating the release of pro-inflammatory markers such as tumor necrosis factor-α (TNF-α) and other cytokines, which are clearly in many human and experimental animal studies [8,9]. The trace element boron is a necessary micronutrient for the proliferation of many biological systems [10]. Declaring various biological activities of boron as a regulator of many enzyme systems, membrane transporters, and biochemical processes represents the basis for developing new drugs and nutraceuticals that contain boron both as mineral and organic complex forms [11,12]. However, whether these supplements have clinical applications still represent a scientific dilemma in the practice of alternative therapy approach [13,14]. Current evidence indicated that boron concentration was significantly lower in the serum of RA patients and negatively associated with rheumatoid factor in those patients [15]. Accordingly, boron may have a relevant clinical role in the pathogenesis of RA, and suggest the importance of boron supplementation to

RA patients or to individuals who are at high-risk of developing RA [16]. This study was designed to evaluate the clinical benefits of CFB and borax, when used in pharmacological doses, as adjuvant with etanercept in the treatment of RA patients.

MATERIALS AND METHODS

A double-blind, randomized placebo-controlled clinical study was conducted with 8-week treatment period over 8 months (from December 2015 to August 2016) at the Rheumatology Unit, Baghdad Teaching Hospital, Baghdad. Of the 111 patients screened for eligibility, 80 patients with active RA maintained on etanercept were randomly selected and evaluated to participate. Only 72 patients completed the study [Figure 1]. The patients were randomly allocated to receive either CFB (220 mg/day; Futureceuticals, Momence, IL, USA), NTB (55 mg/day; Merck, Germany) specially prepared as capsule dosage (contain 6 mg elemental boron) as single dose and administered once daily after a meal, or a capsule formula filled with starch as a placebo (once daily after a meal). The boron-containing formulations were administered as an adjuvant with the regularly used etanercept regimen (50 mg/week; Amgen Inc., Thousand Oaks, CA). The patients were instructed to continue their regular drug treatment schedule and were clinically observed every four weeks for any unusual adverse effects. All participants provide signed informed consent form according to the principles of the Declaration of Helsinki. The local scientific ethics committee of Baghdad University, College of Pharmacy and Baghdad Teaching Hospital, Rheumatology Department approved the study protocol. All patients included had active RA, as defined by the American College of Rheumatology (ACR) 1987 revised criteria [17]. Active RA was proven by calculating either 28-joint Disease Activity Score (DAS28) or the simple disease activity index (SDAI). All included patients were maintained on etanercept treatment for at least three consecutive months before the time of inclusion. At screening time, patients with the following health disorders were excluded: Patients using nonsteroidal anti-inflammatory drugs 2 days before inclusion, hypersensitivity or severe adverse effects to boron containing formulas, renal or hepatic damage, pregnant and breastfeeding women, juvenile RA, patients using disease-modifying antirheumatic drugs other than etanercept or high dose steroids, missing medication for two consecutive days, coexistence of other connective tissue disorders, and mild or inactive RA. The clinical outcome of the treatment was evaluated using the DAS28 [18], SDAI [19], and the clinical disease activity index (CDAI) [20] at the start (baseline) and end of the 8-week study period. Blood samples were obtained from each patient by vein puncture at baseline and the end of the study. Of the blood collected, 3 ml was kept in an ethylenediaminetetraacetic acid tube to be used for measurement of erythrocyte sedimentation rate (ESR) and hemoglobin utilizing standard procedures. The remaining blood was kept in plain tube and left to coagulate at room temperature for at least 30 min, and then, centrifuged for 10 min at 4000 rpm to obtain serum. Using ready-made enzyme-linked immunosorbent assay kits, the resultant serum was utilized for the measurement of high-sensitivity C-reactive protein (hsCRP), TNF-α, interleukin (IL)-1α and IL-6 (Demeditec, Germany). All data were statistically analyzed using Graph Pad Prism 5.1 software (Graph Pad Software Inc., California, US). Continuous variables were presented as mean ± standard deviation and discrete variables presented as numbers and frequencies. The Chi-square and Wilcoxon-rank tests were used for independence to test the significance of the association between discrete variables. The paired *t*-test was used to evaluate the difference between pre- and post-treatment values. Moreover, one-way analysis of variance was used to test the significance of the difference in means of independent samples, and supported by Bonferroni's *post-hoc* analysis. A $P < 0.050$ was considered significantly different.

RESULTS

Table 1 indicates that the demographic data and baseline characteristics were not significantly different among the three groups of patients included in the study. Table 2 shows a

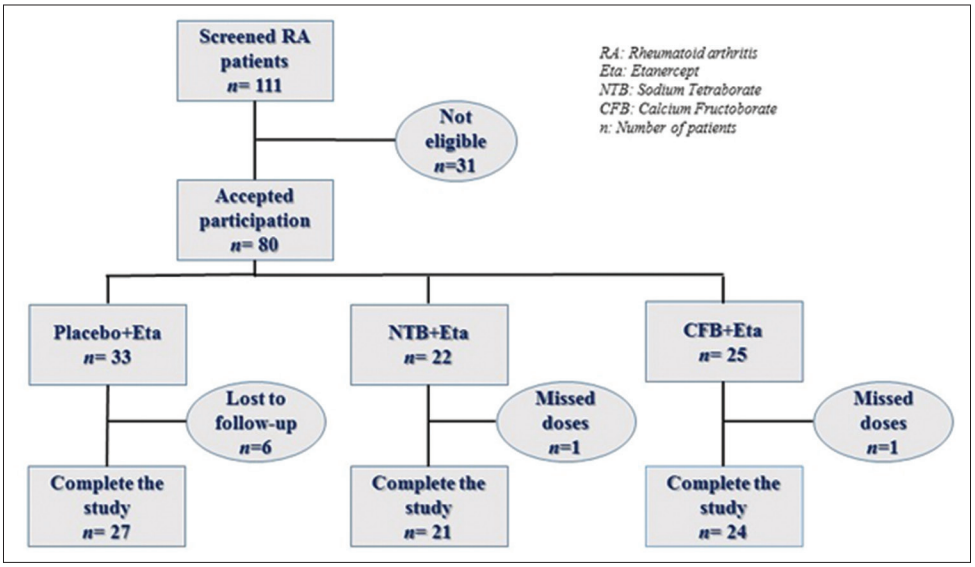

Figure 1: Flowchart of patient allocation and study follow-up

nonsignificant difference in tender joint counts (TJC) at the pretreatment level between NTB, CFB and placebo groups. At the end of the study, there was a significant decrease in TJC of NTB and CFB groups (37.14% and 33.96%) compared to placebo (12.3%). Meanwhile, there was a significant decrease in swollen joint counts (SJC) of CFB (40.54%) and NTB (30.23%) groups compared to baseline and placebo group (10.64%). Both CFB and NTB groups showed significant decrease in visual analog scale (VAS) (33.33% and 23.18%) compared to baseline and placebo group (10.45%). Moreover, both CFB and NTB groups showed significant decrease (35.38% and 23.8%, respectively; $P < 0.05$) in EGA compared to baseline and the placebo group; however, they are not significantly differ when compared with each other. Table 3 shows that all types of treatment significantly decreased the DAS28 score compared with baseline values. However, in CFB group 21.2% decrease in DAS28 score was achieved and represent a significant improvement compared to placebo group. Meanwhile, NTB group showed only 15.14% decrease in DAS28-ESR, which was also significantly different compared to placebo group. Table 3 also shows that CDAI score was not significantly changed in control group after 60 days of treatment. Meanwhile, both CFB and NTB groups showed a significant decrease in CDAI (32.75% and 25.35%) compared to both pretreatment value and placebo group, and CFB seems to be more effective in this regard although not significantly differ. Regarding the effect on SDAI score, the results of this study demonstrate no significant difference among three groups at baseline level, while at the end of treatment all types of treatment significantly decreased, the SDAI score compared with baseline values. The use of NTB produced 29.4% decrease in SDAI score, while using CFB resulted in 28.8% decrease in SDAI, and both represent a significant improvement in SDAI compared to pretreatment level and posttreatment value of the placebo group (10.8%) [Table 3]. Table also demonstrates that all types of treatments produced significant improvement in the duration of morning stiffness after 60 days compared with baseline values. The two forms of boron supplements (NTB and CFB) produced 39% and 61.3% decrease in the duration of morning stiffness, while the placebo formula resulted in 28.5% in this regard only. However, these effects are found nonsignificantly different when compared with each other. Regarding, the effect on the ESR, the results indicated that the placebo formula did not significantly change ESR compared with baseline value (11.8%). Meanwhile, both types of boron supplements (NTB and CFB) significantly decreased ESR value (72.8% and 32.5%, respectively) compared with baseline. However, when the three treatment approaches were compared among each other, the data reflects no significant differences in this regard [Table 4]. Table 4 revealed that the placebo formula produced nonsignificant decrease in hsCRP levels after 60 days (10.1%) compared with baseline values. Meanwhile, both NTB and CFB significantly decreased hsCRP levels compared with baseline values (47.1% and 47.8%, respectively). However, when posttreatment values of hsCRP were compared among each other, nonsignificant differences were reported in this respect. The data presented in Table 4 showed that treatment with placebo formula did not change TNF-α level significantly (0.6%) compared with the baseline values. Meanwhile, both boron supplements (NTB and CFB) significantly decreased serum TNF-α levels (20.3% and 35.0%, respectively) compared to baseline values. In addition, the effect of CFB was significantly greater than that produced by NTB in this regard. In this study, serum IL-1α levels were decreased significantly in all treated groups compared with baseline values, where placebo formula resulted in 15.7% decrease in these levels, while NTB and CFB produced comparable and nonsignificant decrease in this regard (25.0% and 37.1%, respectively); however, both of them are

Table 1: Demographic data and baseline characteristics of the RA patients

Parameters	Placebo group *n*=27	NTB group *n*=21	CFB group *n*=24	*P* value
Gender				
Male *n* (%)	2 (7)	3 (14.3)	1 (4.2)	0.36
Female *n* (%)	25 (93)	18 (85.7)	23 (95.8)	0.37
Age (years)	51.9±9.3	49.4±11.2	47.4±9.4	0.62
Body weight (kg)	84.6±18.6	89.2±14.2	77.6±12.1	0.10
BMI (kg/m^2)	33.6±6.7	35.5±6.3	31.2±4.4	0.12
Disease duration (month)	10.8±7.7	10.9±8.6	9.5±5.5	0.13
Etanercept treatment (months)	12.6±11.8	16.9±14.7	11.3±12.3	0.56
ESR (mm/h)	36.8±19.8	35.6±20.8	48.5±28.7	0.12
hsCRP (μg/ml)	6.9±5.2	8.7±5.9	9.2±7.2	0.38
DAS28 score (4 values)	5.7±0.60	5.6±0.84	5.9±0.61	0.48
SDAI score	29.01±5.8	28.9±8.4	28.7±5.7	0.98
Joint deformities *n* (%)	4 (14.8)	7 (33.3)	8 (33.3)	0.40
Associated diseases				
Hypertension *n* (%)	11 (40.7)	7 (33.3)	11 (45.8)	0.39
Diabetes mellitus *n* (%)	7 (26)	5 (23.8)	6 (25)	0.40
Smoking habits *n* (%)	1 (3.7)	1 (4.7)	1 (4.2)	0.34

Values are presented as mean±SD, *n*: Number of patients, NTB: Sodium tetraborate, CFB: Calcium fructoborate, SD: Standard deviation, SDAI: Simplified disease activity index, NTB: Sodium tetraborate, CFB: Calcium fructoborate, ESR: Erythrocyte sedimentation rate, hsCRP: High-sensitivity C-reactive protein

Table 2: Effect of treatment with NTB and CFB on different functional areas of DAS28 score of patients with active RA maintained on etanercept compared with placebo

Clinical score	Placebo (*n*=27)		NTB (*n*=21)		CFB (*n*=24)	
	Baseline	After 60 days	Baseline	After 60 days	Baseline	After 60 days
TJC	10.6±4.1	9.3±5.3[a]	10.5±4.7	6.6±5.4[a]*	10.6±3.8	7.0±3.3[a]*
SJC	4.7±2.5	4.2±1.6[a]	4.3±2.6	3.0±1.8[b]*	3.7±1.8	2.2±1.9[b]*
VAS (cm)	6.7±1.3	6.0±1.5[a]	6.9±1.7	5.3±1.7[a]*	7.2±1.3	4.8±1.0[b]*
EGA (cm)	6.3±0.8	5.6±1.1[a]*	6.3±1.3	4.8±1.5[b]*	6.5±1.0	4.2±1.0[b]*

Values are presented as mean±SD, *n*: Number of patients, *significantly different compared to pretreatment ($P<0.05$), posttreatment values with different superscripts [(a,b)]within each parameter are significantly different ($P<0.05$). SD: Standard deviation, NTB: Sodium tetraborate, CFB: Calcium fructoborate, TJC: Tender joint counts, SJC: Swollen joint counts, VAS: Visual analog scale

significantly greater than that produced by the placebo formula in this regard [Table 4]. Regarding, the effect on serum IL-6 levels, Table 4 revealed that the placebo formula produced nonsignificant decrease in IL-6 levels (3.7%) compared with baseline values. Meanwhile, both NTB and CFB significantly decreased IL-6 levels compared with baseline values (24.9% and 42.8%, respectively). However, when posttreatment values of IL-6 were compared among all groups, nonsignificant differences were reported in this respect [Table 4].

DISCUSSION

According to the currently available evidence related to the beneficial effects of supplementary boron in RA, the presented study was designed to evaluate the possibility of utilizing this concept in the clinical practice. Because, it is ethically unaccepted to use boron alone as a separate arm in such type of clinical trials, the principle of its adjuvant use with the biological agent etanercept was followed. Although baseline laboratory evaluations that include many biochemical markers are important for diagnosis and management of RA, clinical assessment with scored, standardized and reproducible tools are necessary both for scoring disease activity and treatment follow-up [21]. Accordingly, we utilized more than one type of internationally accepted disease activity indices to overcome the limitations that may be associated with any one of them. Assessment of tender and swelling joints is considered as one of the important parameters during evaluation and treatment decision making in RA [22]. In this study, both forms of boron produced significant decrease in TJC and SJC compared to baseline values; although the changes were remarkably greater than that reported in placebo group, they were not significantly different. This may be attributed to sample size limitation. These results were in tune with those reported previously regarding the use of boron as adjuvant in patients with knee OA, where inclusion of boron in the currently used treatment modulates the symptoms of arthritis and joint degeneration and improves the clinical scores [23,24]. The anti-inflammatory activity of boron was reported in animal models of inflammation [8,9]; however, no previous data declared its role as adjuvant with etanercept to improve the clinical outcome of RA treatment. The reported improvement may be due to long-term inhibition of the pro-inflammatory mediators, which may indirectly lead to reduction in the followed clinical scores. According to many epidemiological data, it is well-known that in countries with low quantities of boron in the soil there is much more arthritis, while the incidence decreases with the increase in soil boron content [25,26]. In addition, Al-Rawi *et al.* reported the correlation between disease activity and serum boron levels in Iraqi patients with active RA [15]. This may explain the achieved improvement in response to RA treatment by the addition of supplemental boron. Unfortunately, we failed to measure serum boron levels to add more support to the current idea, probably due to technical and financial limitations. In this study, although the reported improvement in pain severity of RA is well recognized with both forms of boron, it may be comparable with that reported in an open-label pilot clinical trial, where CFB improves mild and moderate pain in patients with osteoarthritis [27]. Many studies have addressed the benefits of boron as a therapeutic option in arthritic pain, which may be attributed to various effects including inhibition of the oxidative burst associated with the inflammatory reactions, improvement of the antioxidant defense systems and inhibition of the collagenase activity [8,16,28,27]. In this study, we rely on the outcome of two important clinical scoring systems for assessment of disease activity in RA, SDAI, and DAS28.

Table 3: Effect of treatment with NTB and CFB on different clinical scores of patients with active RA maintained on etanercept compared with placebo

Clinical Score	Placebo (n=27)		NTB (n=21)		CFB (n=24)	
	Baseline	After 60 days	Baseline	After 60 days	Baseline	after 60 days
DAS28-ESR	5.68±0.6	5.36±0.7[a]*	5.68±0.8	4.82±0.9[b]*	5.84±0.6	4.60±0.5[b]*
CDAI	28.3±5.7	26.9±6.0[a]	28.5±7.7	21.3±7.6[b]*	27.9±5.7	18.8±4.9[b]*
SDAI	29.0±5.7	25.9±7.5[a]*	28.9±8.4	20.5±9.1[b]*	28.7±5.7	20.4±5.6[b]*
MS time (min)	43.3±37.3	31.0±36.1[a]*	31.4±29	19.1±22[a]*	35.8±37.2	13.9±13.1[a]*

Values are presented as mean±SD, n: Number of patients, *significantly different compared to pretreatment ($P<0.05$), posttreatment values with different superscripts [(a,b)]within each parameter are significantly different ($P<0.05$). DAS: Disease activity score, CDAI: Clinical disease activity index, SDAI: Simplified disease activity index, MS: Morning stiffness, SD: Standard deviation, NTB: Sodium tetraborate, CFB: Calcium fructoborate, ESR: Erythrocyte sedimentation rate

Table 4: Effect of treatment with NTB and CFB on inflammatory markers of patients with active RA maintained on etanercept compared with placebo

Markers	Placebo (n=27)		NTB (n=21)		CFB (n=24)	
	Baseline	After 60 days	Baseline	After 60 days	Baseline	After 60 days
ESR (mm/h)	27.2±6.1	24.0±7.8[a]	28.3±8.3	20.4±9.2[a]*	27.8±5.6	18.8±4.8[a]*
hsCRP (μg/ml)	6.9±5.2	6.2±3.1[a]	8.7±5.9	4.6±2.8[a]*	9.2±7.2	4.8±4.3[a]*
TNF-α (pg/ml)	195.9±60	194.7±77[a]	177.1±44.4	141.6±38.6[b]*	152.4±20.6	99.0±38.2[c]*
IL-1α (pg/ml)	12.4±3.4	10.4±1.8[a]*	10.4±3.2	7.8±2.5[b]*	11.6±2.5	7.3±1.9[b]*
IL-6 (pg/ml)	13.6±2.8	13.1±3.1[a]	17.3±8.0	13.0±4.8[a]*	18.7±10.9	10.7±4.7[a]*

Values are presented as mean±SD, n: Number of patients, *significantly different compared to pretreatment ($P<0.05$), posttreatment values with different superscripts [(a,b,c)]within each parameter are significantly different ($P<0.05$). SD: Standard deviation, NTB: Sodium tetraborate, CFB: Calcium fructoborate, IL: Interleukin, TNF: Tumor necrosis factor, ESR: Erythrocyte sedimentation rate, hsCRP: High-sensitivity C-reactive protein

They are commonly linked with the assessment of CRP and ESR. These two acute phase reactants (ESR and CRP) provide reliable tools to discriminate between drugs that produce symptomatic relief only and those with more profound effects in RA. This study shows that both types of boron significantly decreased serum CRP levels compared with baseline values. This finding was consistent with that reported in patients with primary OA [29]. The ACR recommended the use of disease activity indices that include multiple variables, such as DAS28 or SDAI for accurate measurement of RA severity [30]. We showed, for the first time, that both forms of boron significantly improved the DAS28 scores and their effects are comparable. This result can be explained on the bases that DAS28 depends on different factors, including TJC, SJC, VAS, and ESR; so the effect of boron will be the result of the effects of all the above factors, which are highly modified as shown in boron administered groups. These effects can be attributed to the influence of boron on multiple sites within the inflammatory cascades beyond the types of the inflammatory initiator or grade of the inflammatory response [16]. Moreover, this study shows that both types of boron supplements significantly decreased SDAI score compared with baseline values and placebo. This was the first trial that evaluates the effect of boron supplements, when used as adjuvant with etanercept against placebo on SDAI score of RA patients. The results can be explained on the bases that SDAI depends on different factors, including TJC, SJC, VAS, EGA, and CRP levels [31]. Accordingly, this effect may represent the influence of boron on the above factors, which showed a high percent of changes in boron-treated groups. Since SDAI was shown to be superior over DAS28 in assessment of remission in RA patients [32], and even easier than DAS28 to calculate, it can be concluded that the use of SDAI may be better than DAS28 not only to follow-up RA patients but also to monitor response to particular therapy in clinical trials. These modest benefits of boron in Iraqi patients with active RA may be attributed to its pleotropic effects that antagonize many pathophysiological processes of RA, including immunomodulatory, anti-inflammatory, and antioxidant activities [16]. Meanwhile, other studies reported the dose-dependent antioxidant and anti-inflammatory activities of boron, and most of the pleotropic effects were produced using a relatively higher daily doses than the daily required amounts, which was similar to that used in this study [27,33]. This may explain partly why treatment with boron in this study produced statistically significant benefits when compared to placebo. This study declared the decrease in morning stiffness in boron-treated and placebo groups. This finding was expected because boron could improve the markers of inflammation that morning stiffness was correlated with such as ESR, SJC, pain, fatigue, tender joint and patient and physician global assessment of disease activity [34]. Meanwhile, this finding is consistent with previous data that reported placebo effect in this regard [35]. Many experimental animal and clinical data have demonstrated that boron decreases production of many inflammatory mediators [36,37]. In this study, the influence of boron on the inflammatory markers seems to be relatively in tune with the previously reported data, although they differ in the etiology of inflammation and the experimental model that may predispose to some differences in the change pattern. However, it confirms the expected anti-inflammatory role of boron, and furthermore shows a novel finding in RA model. In this study, although CRP levels significantly decreased in boron-treated groups compared with baseline values, they are found to be comparable with those reported in placebo-treated group. This can be attributed to the differences in baseline values among groups and the multifactorial etiology of CRP elevation. Although the current results represents the first finding regarding the influence of boron on CRP levels in patients with active RA maintained of biological therapy, they seem to be comparable with many previous reports that utilize other disease models [9,38]. TNF-α is important mediator of inflammation and tissue damage in active RA [39]. This study showed that both boron significantly decrease serum TNF-α levels compared with placebo, and CFB shows greater effect than NTB in this regard. This finding was consistent with that reported by others, where boron could significantly decrease the elevated levels of TNF-α produced during many exaggerated inflammatory responses [29,40]. Moreover, Newnham reveals the antiarthritic effect of boric acid in animals and some forms of arthritis in humans [38]. Similarly, Hunt and Idso indicated that joint damage was remarkably attenuated in adjuvant-induced arthritic rats that received supplemental boron [41], and conclude that boron may decrease the inflammatory response due to attenuating pro-inflammatory cytokines production by the activated inflammatory cells. These marked anti-inflammatory effects of boron could be attributed to various mechanisms, including the suppression of serine proteases released by inflammation-activated white blood cells, inhibition of leukotriene synthesis, reduction of ROS generated during neutrophil's respiratory burst, and suppression of T-cell activity and antibody concentrations [8]. Although the current results are consistent with many previously reported ones in other models of inflammation, the influence in RA can be considered as a new insight in this regard. Many experimental animal models and clinical studies have proved the role of IL-1 type cytokine in the pathogenesis of synovial inflammation and destruction of articular tissue [42]. Serum concentration of IL-1α was found to be substantially higher in RA patients compared with that of healthy control, and may provide clinically useful markers for the diagnosis of disease activity. The response of this marker to antirheumatic agents may be of value in monitoring response to treatment, especially when DMARDs are used in this respect [43]. In this study, NTB and CFB comparably decreased serum IL-1α levels, and the effect was significantly greater than that reported in control group. A relatively similar outcome was observed regarding the effects of boron supplements on serum IL-6 levels. The anti-inflammatory effects of NTB and CFB can be related to many different mechanisms, including suppression of serine proteases released by inflammation-activated white blood cells, inhibition of leukotriene synthesis, reduction of ROS generated during neutrophil's respiratory burst, suppression of T-cell activity, and antibody concentrations [44]. Although the current results are clear within the limitations of the trial, previously reported data raises many doubts about the effect of boron in this regard, where supplementation with dietary boron increases production of cytokines following stress, which indicates a role for boron in the immune system [45]. Accordingly, a mechanism beyond boron-induced reduction of cytokines might explain

the alleviation in the inflammatory symptoms in RA patient supplemented with boron as adjuvant with etanercept.

CONCLUSION

The use of elemental and organic complex forms of boron, as adjuvant with etanercept, improves the clinical scores and significantly decreases the inflammatory markers in RA patients. This improvement in therapeutic outcome supports the idea of utilizing this new strategy to improve the treatment and to avoid the problems associated with biologics utilized in RA treatment.

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