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Original Research

Serum boron concentration in rheumatoid arthritis: correlation with disease activity, functional class, and rheumatoid factor

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Trace elements

Abstract

Objectives: Rheumatoid arthritis (RA) is a common chronic inflammatory arthropathy of unknown etiology. Trace elements have a great role in a number of biological processes. The aim of this study was to assess the serum element boron in a sample of Iraqi patients with RA and to evaluate its relationship if present with disease activity, functional class of the disease, and rheumatoid factor (RF).

Methods: A cross sectional study enrolled 107 RA patients and 214 controls matched in age and sex. The American College of Rheumatology 1987 revised criteria was used for diagnosis of RA. Disease Activity Score index of 28 joints (DAS28), functional class of RA patients, RF, erythrocyte sedimentation rate (ESR) were measured in patients' group; serum boron levels were measured using a flame atomic absorption spectrophotometer in both patients and controls groups.

Results: RA patients had significantly lower serum boron level than controls ($P < 0.001$). Serum boron level was significantly negatively correlated with RF titer in RA patients ($r = –0.22$, $P = 0.001$). No significant correlation was found between serum boron with DAS28, disease functional class, and ESR ($P > 0.05$). Also, RF titer was a significant predictor of low serum boron level ($P = 0.023$, OR = –0.07, 95%CI –0.13-(–0.01)).

Conclusions: There was a significant low serum boron level in RA patients. RF titer was significant predictor of low serum boron level. This may suggest that boron element may play a role in pathophysiology of RA and its severity. Supplementation with boron element and diets rich in fruits, vegetables, nuts, and pulses may be useful.

INTRODUCTION

Rheumatoid arthritis (RA) is a common, systemic autoimmune disease of unknown cause that primarily affects the peripheral joints in a symmetric pattern [1]. The disease eventually leads to juxta-articular demineralization, joint space narrowing and erosion, resulting in reduced range of movement and deformity of joints. It is the most common inflammatory arthritis affecting approximately 1-2% of the general population worldwide [2].

Rheumatoid arthritis is characterized by chronic inflammation of the synovial joints which can lead to progressive joint destruction including symmetric joint swelling with stiffness, warmth, tenderness and pain [3]. The incidence of the disease increases with age, and women are affected more than men. Despite many years of intensive research, the exact etiology of RA is still unknown. Besides environmental influences like infectious agents, smoking and oral contraceptives, genetic factors are believed to be responsible for approximately 60% of the risk of developing RA [4].

Trace elements may play a critical role in the onset, progress and curing of the disease as manifested by different essential elements supplements, which are

used to decrease pain and increase joint mobility [5-7]. Trace elements are involved in various vital processes related to health, ranging from structural support, nerve conduction, muscle contraction, enzyme/hormones production and maintenance of mineral balance in human body [8, 9].

Boron is a water soluble, trace element mineral that is present in human and plant nutrition and critical to health. The biomolecules known to contain boron are either directly involved in immune defense mechanisms or affect components of the immune system [10]. Dietary boron influences the activity of many metabolic enzymes, as well as the metabolism of steroid hormones and several micronutrients, including calcium, magnesium, and vitamin D [11].

Previous studies have reported reduced serum selenium, magnesium, zinc, elevated serum copper in RA patients [12, 13]**.** However, serum boron levels have been rarely reported in RA patients and limited data are available. This study was designed to assess serum boron level in RA and to evaluate its relationship if present with rheumatoid factor (RF), disease activity, and functional class of the disease.

MATERIALS AND METHODS

Study design

This cross-sectional study was conducted in Rheumatology Unit at Baghdad Teaching Hospital, a tertiary referral center in Iraq between December 2011 and April 2012. We screened rheumatoid arthritis patients that are eligible to enter the study then compared with a convenient matched healthy controls and serum boron level was measured in both groups.

Sample selection

A total of 107 RA patients were diagnosed by rheumatologist according to the American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis [14] included in the study and compared with 214 healthy individuals recruited from the community matched in age and sex as a control group. Patients were excluded from the study if they had comorbid diseases that affect immunity, or overlapped with other connective tissue diseases, or were alcohol drinker, or received a systemic therapy which may interfere with the cellular immunity for the last 4 weeks before blood sample collecting, and pregnant women.

All patients and controls included in the study signed an informed consent form according to the declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Baghdad University, College of Medicine, Department of Medicine.

Data collection

We used paper clinical research form through interview and questionnaires. We asked the patients about age, sex and disease activity was calculated according to Disease Activity Score 28 joints (DAS28). DAS28 is calculated from the number of tender and swollen joints (28-joint count), patient self-assessment of disease activity (visual analog scale), and erythrocyte sedimentation rate (ESR) by the following formula:

$$\text{DAS28} = (0.56 \times \sqrt{\text{tender-joint-count}}) + (0.28 \times \sqrt{\text{swollen-joint-count}}) + (0.7 \times \ln[\text{ESR}]) + (0.014 \times \text{VAS}) \text{ [15]}$$

Functional class of RA patients was measured using The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis [16].

Laboratory measurements

About 6 ml of whole blood were collected by standard clinical procedures. 1 ml whole blood in EDTA tube used for ESR measurements. 1 ml whole blood placed in ordinary tube to use its serum for RF measurements by latex fixation test. 4 ml whole blood to measure serum boron using special plastic trace element serum tubes were transferred to an acid-washed centrifuge tube and allowed to stand. After centrifugation (3,000g for 10 min), the serum was transferred to an acid-washed sample tube. Sample pre-treated consists only of dilution (x2) directly into auto sampler cup. Appropriate standards were prepared in 0.1 M nitric acid.

Blood Samples were analyzed at the Iraqi Ministry of Science and Technology Laboratories at daily basis. Trace element boron levels in serum was measured using the Phoenix-986 atomic absorbtion spectrophotometer (Biotech Engineering Management, UK). A flame atomic absorption spectrophotometer and flameless Graphite furnace with deuterium were background correction system to reduce the background to an acceptable level.

All reagents were of analytical reagent grade. The water used to dilute standards and samples was deionized and distilled. Glassware, pipettes, micropipettes tips, and auto sampler cups were acid wash before use.

Statistical analysis

Statistical software (IBM SPSS v20) was used for data input and analysis. Continuous variables were presented as mean ± standard deviation (SD) and categorical variables were presented as numbers and percentiles. Chi square test for independence was used to test the significance of association between categorical variables. Continuous variables were tested by Kolmogorov-Smirnov test to determine if they were

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normally or abnormally distributed. For continuous variables Student's t test was used to find the difference between the means of 2 groups. Pearson's linear correlation coefficient (r) was done between serum boron and each quantitative independent variable which is normally distributed and Spearman's linear correlation coefficient between serum boron and functional class because it is an ordered variable. Tertile categories are a statistically unbiased way to convert a quantitative variable into an ordered level categorical variable. A multiple linear regression model was used to assess the net and independent effect of a set of explanatory variables, including sociodemographic, disease severity measures and treatment used on serum boron concentration. All P values used were asymptotic and two-sided. Values with $P < 0.05$ were considered significant.

RESULTS

A total of 107 RA patients and 214 healthy controls were enrolled in this study without significant difference between both groups in age and sex (Fig.1, Table 1). Serum boron level was significantly lower in RA patients compared to controls (21.7 ± 8.6 ng/ml *vs* 43.5 ± 9.8 ng/ml; $P < 0.001$, 95%CI –23.9-(–19.5); Fig.2, Table 2).

Given in Table 3, the mean serum boron concentration significantly decrease from 25.1 ng/ml among subjects with lowest serum RF concentration (first tertile) to 20.4 ng/ml among those with highest RF concentration (third tertile)($r = –0.219$, $P = 0.023$). The mean serum boron was significantly higher among subjects with negative RF (26.6 ng/ml) compared to those with positive RF (mean = 19.6 ng/ml, $P < 0.001$).

Shown in Table 4, a multiple linear regression model was used to assess the net and independent effect of a set of explanatory variables, including sociodemographic, disease severity measures and treatment used on serum boron concentration. The concentration of RF was the only variable that had a statistically significant association on serum boron after adjusting for the remaining explanatory variables included in the model. For each one unit increase in RF concentration, it is expected for serum boron to decrease by 0.08 ng/ml. This measure of disease severity (RF concentration) had the strongest effect on serum boron. Age and gender ranked second in their association with serum Boron, but their effect was not significant statistically. The resulting model was not statistically significant and able to explain 11% of observed variation in the dependent variable.

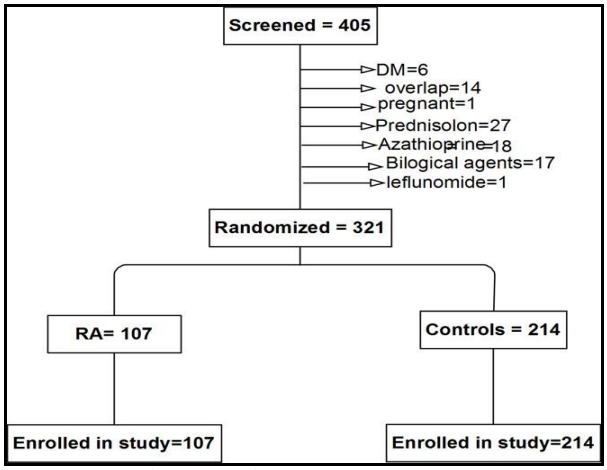

Figure 1. Study flow chart of patients and controls

Table 1. Baseline characteristic of RA patients and controls.

Variables	Patients (n=107)	Controls (n=214)	P
Age (years, mean ± SD)	45.5 ± 4	44.3 ± 5	0.06
Female n (%)	88 (82.2%)	168 (78.5%)	0.43
Duration of RA (years, mean ± SD)	8.7 ± 6.6		
DAS28 (mean ± SD)	5.7 ± 0.14		
Functional class (median)	Class-II		
BMI (kg/m², mean ± SD)	29.6 ± 6.2		
Smoker n (%)	13 (11.6%)		
NSAIDS n (%)	63 (56.3%)		
HCQ n (%)	31 (27.7%)		
ESR (mm/h, mean ± SD)	58 ± 33.2		
Positive RF n (%)	73 (65.2%)		

SD, Standard Deviation; n, number; BMI, body mass index; NSAIDS, nonsteroidal anti-inflammatory drugs; HCQ; hydroxychloroquine; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor

Table 2. Comparison of serum boron between cases with RA patients and apparently healthy controls (mean ± SD)

Elements	RA cases (n=107)	Controls (n=214)	95% Confidence interval for difference between 2 means)
Boron (ng/ml)	21.8 ± 8.6*****	43.5 ± 9.8*****	–23.9 to –19.5[#]

*P < 0.001 between RA cases and controls; [#]the negative sign indicates that the mean in RA cases is lower than controls

Table 3. The mean serum boron concentration by selected explanatory (independent) variables

	Serum Boron concentration (ng/ml)			P
	Mean	SD	n	
Age group (years)				0.35 [NS]
< 30	24.8	6.5	13	
30-49	21.8	8.9	49	
≥ 50	20.8	9.0	44	
r = –0.158 P=0.11[NS]				
Gender				0.57 [NS]
Female	21.6	8.7	88	
Male	22.8	8.3	19	
Functional class				0.78 [NS]
Class-I	20.2	10.5	6	
Class-II	21.7	8.9	49	
Class-III	22.6	8.4	42	
Class-IV	19.8	8.4	10	
*r = –0.032 P = 0.74 [NS]				
Disease Activity Score 28 joints (DAS28)				0.98 [NS]
First tertile (≤ 5.5)	22	9.4	36	
Second tertile (5.6-6.6)	21.8	8	36	
Third tertile (> 6.6)	21.6	8.7	35	
r = 0.003, P = 0.97 [NS]				
Duration of the disease (years)				0.84 [NS]
First tertile (≤ 4)	22.2	8.9	36	
Second tertile (5-10)	22.1	8.5	37	
Third tertile (≥ 11)	21.1	8.8	34	
r = –0.03, P = 0.76 [NS]				
Body mass index categories (kg/m^2)				0.99 [NS]
Acceptable (< 25)	22.1	9.4	22	
Overweight (25-29.9)	21.7	8.8	38	
Obese (> 30)	21.8	8.4	47	
r =0.037, P=0.71[NS]				
Erythrocyte sedimentation rate (mm/h)				0.45 [NS]
First tertile (≤ 40)	22.7	8.4	39	
Second tertile (41-65)	22.3	8.4	33	
Third tertile (≥ 66)	20.3	9.1	35	
r = –0.09, P = 0.36 [NS]				
Rheumatoid factor concentration-categories based on tertiles				0.018
First tertile (≤ 23)	25.1	6.8	36	
Second tertile (24-45)	19.9	9.4	39	
Third tertile (≥ 46)	20.4	8.7	32	
r = –0.219, P = 0.023				
Rheumatoid factor				< 0.001
Negative	26.6	4.9	34	
Positive	19.6	9.1	73	
Smoking History				0.83 [NS]
Negative	21.9	8.5	94	
Positive	21.3	10.1	13	
Nonsteroidal anti-inflammatory drugs				0.76 [NS]
Negative	21.5	9.4	44	
Positive	22	8.1	63	
Hydroxychloroquine				0.28 [NS]
Negative	21.2	9.0	76	
Positive	23.2	7.8	31	

Tertile categories are a statistically unbiased way to convert a quantitative variable into an ordered level categorical variable. As shown in the table above the mean serum boron concentration significantly decrease from 25.1 ng/ml among subjects with lowest serum RF concentration (first tertile) to 20.4 ng/ml among those with highest RF concentration (third tertile). The mean serum boron was significantly higher among subjects with negative RF (26.6 ng/ml) compared to those with positive RF (mean=19.6 ng/ml).

r, Pearson's linear correlation coefficient between serum boron and each quantitative independent variable; *****The linear correlation coefficient here is Spearman's linear correlation coefficient because functional class is an ordered variable; NS, not statistically significant (P > 0.05).

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Table 4. Multiple linear regression model with serum boron as the dependent (outcome) variable and selected explanatory variables

	Partial regression coefficient	P	Standardized coefficient
(Constant)	29.31	< 0.001	
Age in years	–0.13	0.11 [NS]	–0.169
Male gender compared to females	3.07	0.23 [NS]	0.136
Duration of the disease (years)	–0.004	0.98 [NS]	–0.003
DAS28	0.19	0.81 [NS]	0.032
BMI (kg/m^2)	–0.07	0.67 [NS]	–0.047
ESR (mm/h)	–0.03	0.39 [NS]	–0.104
Being a smoker compared to non-smokers	–1.18	0.69 [NS]	–0.045
Using NSAID compared to non-users	1.11	0.55 [NS]	0.063
Using hydroxychloroquine compared to non-users	2.22	0.25 [NS]	0.116
Functional class	0.84	0.55 [NS]	0.073
RF concentration	–0.08	0.013	–0.259

A multiple linear regression model was used to assess the net and independent effect of a set of explanatory variables, including sociodemographic, disease severity measures and treatment used on serum boron concentration. The concentration of RF was the only variable that had a statistically significant association on serum boron after adjusting for the remaining explanatory variables included in the model. For each one unit increase in RF concentration, it is expected for serum boron to decrease by 0.08 ng/ml. This measure of disease severity (RF concentration) had the strongest effect on serum boron. Age and gender ranked second in their association with serum boron, but their effect was not significant statistically. The resulting model was not significant statistically and able to explain 11% of observed variation in the dependent variable; P (model) = 0.37, r^2 = 0.11.

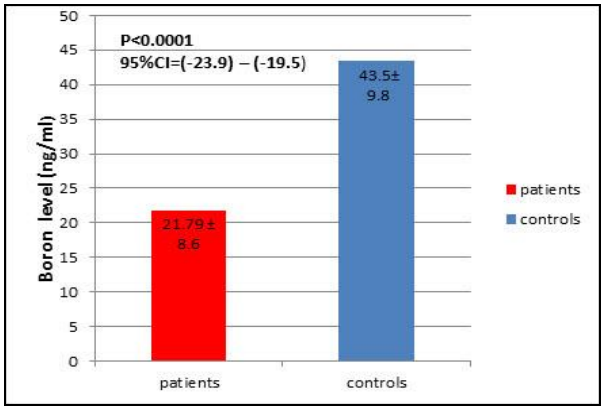

Figure 2. Serum boron levels RA patients and controls

DISCUSSION

The importance of trace elements in chronic inflammatory diseases is related to their cofactor role in immune system functions and in different metabolic processes in articular tissues [17].

A variety of trace elements are found in bones including iron (Fe), copper (Cu), zinc (Zn), manganese (Mn), fluoride (F), strontium (Sr), and boron (B) [18]. Although they are present in only minute amounts, trace elements influence normal metabolic processes through interaction with -or incorporation into- proteins, particularly enzymes [19].

Growing evidence from a variety of experimental models shows that boron is a bioactive and beneficial element for humans. Reported beneficial actions of boron include arthritis alleviation or risk reduction, bone growth and maintenance, central nervous system function, cancer risk reduction, hormone facilitation, and immune response, inflammation, and oxidative stress modulation. Formation of boroesters with the ribose moiety of compounds involved in numerous reactions, such as S-adenosylmethionine and oxidized nicotinamide adenine dinucleotide (NAD^+) might be the reason for boron bioactivity [20].

The role of boron is particularly important because it controls the inflammatory process in arthritic conditions by down-regulating specific enzymatic activities typically elevated during inflammation at the inflammatory site [21], inhibiting the inflammatory stress [22], and affecting the production of inflammatory cytokines by cartilage cells and cells involved in the inflammatory response [23].

This study showed that serum boron level was significantly lower in RA patients (21.79 ± 8.6) compared to controls (43.5 ± 9.8). Havercroft and Ward [24] reported that boron concentrations in bone and synovial fluid were lower in RA patients than in healthy controls.

Newnham [25] reported that the occurrence of arthritis is negatively correlated with the amount of boron in the soil and in the food and water supply. In areas where daily boron intakes were typically 1 mg, the estimated incidence of arthritis ranged from 20% to 70%. In areas where daily boron intakes ranged from 3 to >10 mg, the estimated incidence of arthritis ranged from 0% to 10%.

A recent study of 20 patients with mild, moderate, or severe osteoarthritis also found that boron supplementation alleviated subjective measures of arthritis [26]. Patients with mild to moderate arthritis supplemented daily with 6 mg of boron as calcium fructoborate (a naturally occurring boron complex commonly found in fruits and vegetables) reported markedly reduced pain. By week 8, 80% of the test participants reduced or eliminated their use of painkillers. In addition, joint rigidity essentially disappeared, and mobility was markedly increased at 8 weeks. Patients with severe arthritis, who were supplemented daily with 12 mg of boron as calcium fructoborate, exhibited a more subdued improvement in mobility and rigidity but still reported a significant reduction in the use of painkillers. These findings, however, are weakened by the non-blinding to treatment and lack of placebo controls.

Additionally, another study in juvenile idiopathic arthritis (JIA) reported that boron supplementation at 3-9 mg per day may be beneficial [27]. A finding of note in this study was that serum boron level was not significantly correlated with disease activity, functional class, and ESR of RA patients; this may be explained by medications used in RA that control disease activity and subsequently improves activity and functional class.

Interestingly, the current study showed significant negative correlation between serum boron level and RF, a predictive of more aggressive and erosive articular disease and poorer long-term function in RA patients [28]; this may suggest that boron deficiency can be associated with the severity of RA disease.

The small size of the studied sample and short period of the study were the main limitations of the present study and these can be increased in larger scales, multicenter prospective studies, with longer period of follow up to support the reported data. Yet, in spite of that, this study has points of strength like strict inclusion and exclusion criteria, and defined data measurement and collection.

In conclusion, serum boron level was significantly lower in RA patients compared to controls and significantly negatively correlated with RF in RA patients. This may indicate that B element may play a role in pathophysiology of RA and its severity which is clinically relevant and suggest the importance of boron element supplementation to RA patients and even more important to individuals who are at high risk of developing RA.

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COMPETING INTERESTS

None were declared.

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