# Measurement of serum trace elements levels in patients with juvenile idiopathic arthritis

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**Aim**
This study was designed to assess the serum levels boron (B), copper (Cu), and zinc (Zn) in patients with juvenile idiopathic arthritis (JIA), and to evaluate their relationships with the disease activity parameters.

**Patients and methods**
This study was conducted on 30 children with JIA and 20 apparently healthy children. Patients were subjected to a thorough history-taking, clinical examination, plain radiography of both hands, and laboratory investigations including erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, and antinuclear antibodies. Disease activity was measured using the Juvenile arthritis disease activity score 27 (JADAS-27 score). Serum B, Cu, and Zn levels were also measured.

**Results**
The mean serum B level was highly statistically significantly lower in the JIA patients' group than that in the control group. The mean serum Cu level was highly statistically significantly higher in the JIA patients' group than that in the control group. Finally, the mean serum Zn level was statistically insignificantly lower in the JIA patients group than that in the control group. There were significant negative correlations between serum B concentrations and tender joint count (TJC). There were significant positive correlations between serum Cu concentrations and TJC, erythrocyte sedimentation rate, and JADAS-27. There were significant negative correlations between serum Zn concentrations and TJC and JADAS-27.

**Conclusion**
B serum level may play a role in the pathophysiology of JIA and its severity. Serum levels of B, Cu, and Zn seem to be of fundamental importance in the assessment of a JIA patient.

**Keywords:**
juvenile idiopathic arthritis, serum, trace elements

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## Introduction

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of chronic arthritis diseases in childhood [1]. JIA is the most common chronic arthropathy of childhood and its pathogenesis is still poorly understood. It is also the most common inflammatory joint disease in pediatric patients [2]. JIA is divided into seven subtypes, defined by the International League Against Rheumatism (ILAR) classification, and includes systemic onset arthritis, oligoarthritis, seropositive polyarthritis, seronegative polyarthritis, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis on the basis of clinical and laboratorial data during the first 6 months of the disease and the family history features [3–6].

Trace elements such as zinc (Zn) and copper (Cu) are crucial catalytic cofactors for several enzymes, structural proteins, and transcription factors. In addition, they are essential elements for the immune system, and for the integrity of the articular tissues [7,8]. Cu and Zn are constituents of the superoxide-dismutase enzyme, which performs intracellular antioxidant functions. Furthermore, Cu is a constituent of ceruloplasmin, a powerful extracellular antioxidant enzyme. The anti-inflammatory effects of Cu and Zn have been documented in humans and animals. Moreover, Zn constitutes a structural element of alkaline phosphatase and stimulates its synthesis in osteoblasts, playing an important role in bone mineralization, and it is responsible for the latency of metalloproteinases [9].

Boron (B) is a water-soluble trace element and is directly involved in immune defense mechanisms or affects components of the immune system [10,11]. Moreover, it influences the activity of many metabolic enzymes, as well as the metabolism of steroid hormones and several micronutrients, including calcium, magnesium, and vitamin D [12]. Moreover, reported beneficial actions



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of B 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 [13–15].

## Patients and methods

This study was conducted on 30 children with JIA, diagnosed according to the ILAR classification of JIA [3] attending Rheumatology, Rehabilitation and Physical Medicine Department of Benha University Hospitals. A total of 20 apparently healthy children, age and sex matched to the patients' group, represented the control group. The cases were enrolled in the period between August 2014 and February 2015. Prior written consent was obtained from the parent of each patient, and from those of the controls included in the study. This study was approved by the Ethical Committee of Faculty of Medicine, Benha University. Patients were subjected to thorough history-taking, clinical examination including locomotor system examination, slit lamp examination, plain radiography of both hands, and laboratory investigations including erythrocyte sedimentation rate (ESR), C-reactive protein, rheumatoid factor (RF), and antinuclear antibodies (ANA). Disease activity was measured using the JADAS-27 score.

### Measurement of serum boron, zinc, and copper

About 5–6 ml of blood was collected into a clean, dry, labeled test tube and clear serum was harvested and kept in a deep freezer at −20°C before analysis. Serum samples of 1 ml were poured into 50-ml beakers, followed by the addition of 10 ml mixture of analytical grade acids $HNO_3$ : $HClO_4$ in a ratio of 5 : 1. The digestion was carried out at a temperature of about 190°C for 2–3 h. After cooling, the resulting solution was transferred to polypropylene bottles made up to a final volume (25 ml) with deionized water acidified with 3% nitric acid. Procedural blanks, submitted to the same steps described above for serum samples, were analyzed in parallel to each sample. The samples were analyzed using the Thermo Scientific iCap 7000 series ICP-QES spectrometer (Thermo Scientific, PerkinElmer, Waltham, MA, USA) in Laboratories Compound of Desert Research Center of Egyptian Ministry of Agriculture and Land Reclamation.

### Statistical analysis

Statistical analysis was carried out using statistical package for the social sciences (SPSS) program (version 22; SPSS Inc., Chicago, Illinois, USA) on an IBM compatible computer.

## Results

The present study included 21 (70%) girls and nine (30%) boys, whose ages ranged between 4 and 12 years (mean: 8.10 ± 2.67 years). A total of 20 apparently healthy children, age and sex matched with the patients' group, represented the control group. As regards the JIA patients' group, as shown in Table 1, the disease duration ranged between 1 and 8 years, with a mean of 4.05 ± 2.04 years. The number of tender/swollen joints ranged between one and nine joints, with a mean of 4.50 ± 2.76 joints. ESR ranged between 4 and 85 mm/h, with a mean of 28.25 ± 21.82 mm/h. Three (10%) cases were RF positive and the other 27 (90%) cases were RF negative. There were eight (26.7%) cases of the polyarticular subtype and 22 (73.3%) cases of the oligoarticular subtype. JADAS-27 score ranged between 1.70 and 14.50, with a mean of 7.24 ± 3.39. Moreover, hemoglobin (Hb) concentration ranged between 9.10 and 14.20 g/dl, with a mean of 11.24 ± 1.27 g/dl. Furthermore, red blood cell (RBC) count ranged between $3.70 \times 10^6$ and $5.80 \times 10^6$ cells/mm$^3$, with a mean of $4.84 \times 10^6 \pm 0.52 \times 10^6$ cells/mm$^3$, whereas the white blood cells (WBCs) count ranged between $4.30 \times 10^6$ and $13.80 \times 10^6$ cells/mm$^3$, with a mean of $7.93 \times 10^6 \pm 2.67 \times 10^6$ cells/mm$^3$. Only 12 out of 30 (40%) cases were positive for ANA. In addition, four (13.3%) cases had a history of uveitis. As regards disease activity grade (JADAS-27) of JIA patients' group, there were 18 (60%) patients with moderate disease activity and 12 (40%) patients with high disease activity. As regards the measured serum trace elements in this study, as

**Table 1 Clinical and laboratory data of juvenile idiopathic arthritis patients group**

| Variables (*n*=30) | Mean±SD | Minimum | Maximum |
|---|---|---|---|
| Duration of disease (years) | 4.05±2.04 | 1.00 | 8.00 |
| TJC | 4.50±2.76 | 1.00 | 9.00 |
| ESR (mm/h) | 28.25±21.82 | 4.00 | 85.00 |
| RF titer (*n*=3) | 33.4±17.99 | 8 | 64 |
| JADAS-27 score | 7.24±3.39 | 1.70 | 14.50 |
| Hb% (g/dl) | 11.24±1.27 | 9.10 | 14.20 |
| RBCs (×10$^6$ cells/mm$^3$) | 4.84±0.52 | 3.70 | 5.80 |
| WBCs (×10$^3$ cells/mm$^3$) | 7.93 ± 2.67 | 4.30 | 13.80 |

ESR, erythrocyte sedimentation rate; Hb, hemoglobin; RBC, red blood cell; RF, rheumatoid factor; TJC, tender joint count; WBC, white blood cell.

**Table 2 Comparison between the juvenile idiopathic arthritis patients and the control groups regarding measured serum elements**

| Variables | Mean±SD | | *t*-test | |
|---|---|---|---|---|
| | Patients (*n*=30) | Control (*n*=20) | *t* | *P* |
| B (ng/ml) | 17.64±4.78 | 31.64±4.82 | 9.23 | <0.001* |
| Cu (μg/dl) | 156.45±23.98 | 114.45±23.99 | 5.54 | <0.001* |
| Zn (μg/dl) | 111.65±28.99 | 128.10±27.62 | 1.84 | 0.06 |

B, boron; Cu, copper; Zn, zinc; *means significant.

shown in Table 2 and Figs. 1a and 2a, first, the mean serum B level was highly statistically significantly lower in the JIA patients' group (17.64 ± 4.78 ng/ml) than in the control group (31.64 ± 4.82 ng/ml) ($P < 0.001$). Second, the mean serum Cu level was highly statistically significantly higher in the JIA patients' group (156.45 ± 23.82 µg/dl) than in the control group (114.45 ± 23.99 µg/dl) ($P < 0.001$). Finally, the mean serum Zn level was statistically insignificantly lower in the JIA patients' group (111.65 ± 28.99 µg/dl) than in the control group (128.10 ± 27.62 µg/dl) ($P > 0.05$). The mean serum B concentration was statistically significantly higher in oligoarticular JIA patients (21.30 ± 4.16 ng/ml) than in polyarticular JIA patients (14.64 ± 2.75 ng/ml) ($P < 0.001$), as shown in Table 3 and Fig. 1b. The mean serum Cu concentration was lower in oligoarticular JIA patients (132.22 ± 8.39 µg/dl) than in polyarticular JIA patients (176.27 ± 8.72 µg/dl), with a highly statistically significant difference ($P < 0.001$). The mean serum Zn concentration was higher in oligoarticular JIA patients (137.22 ± 11.56 µg/dl) than in polyarticular JIA patients (90.73 ± 20.50 µg/dl), with a highly statistically significant difference ($P < 0.001$).

There were significant negative correlations between serum B concentrations and tender joint count (TJC) ($P = 0.004$). In addition, there were insignificant correlations between serum B concentrations and age ($P = 0.84$), the disease duration ($P = 0.70$), ESR ($P = 0.35$), JADAS-27 ($P = 0.18$), ANA ($P = 0.56$), Hb ($P = 0.91$), WBCs ($P = 0.46$), and RBCs ($P = 0.05$), as shown in Table 4 and Fig. 2. There were significant positive correlations between serum Cu concentrations and the following studied parameters: TJC ($P < 0.001$), ESR ($P = 0.03$), and JADAS-27 ($P = 0.006$). In addition, there were insignificant correlations between serum Cu concentrations and the patients' age ($P = 0.55$), the disease duration ($P = 0.33$), ANA ($P = 0.58$), Hb ($P = 0.90$), WBCs ($P = 0.16$), and RBCs ($P = 0.30$), as shown in Table 4 and Fig. 3. There were significant negative correlations between serum Zn concentrations and TJC ($P < 0.001$) and JADAS-27 ($P = 0.04$). In addition, there were insignificant correlations between serum Zn concentrations and the patient's age ($P = 0.26$), the disease duration ($P = 0.22$), ESR ($P = 0.44$),

**Table 3 Comparison between oligoarthritis and polyarthritis juvenile idiopathic arthritis patients regarding measured serum elements**

| Variables | Mean±SD | | *t*-test | |
|---|---|---|---|---|
| | Oligoarthritis JIA (*n*=20) | Polyarthritis JIA (*n*=6) | *t* | *P* |
| B (ng/ml) | 21.30±4.16 | 14.64±2.75 | 4.29 | <0.001* |
| Cu (µg/dl) | 132.22±8.39 | 176.27±8.72 | 11.43 | <0.001* |
| Zn (µg/dl) | 137.22±11.56 | 90.73±20.50 | 6.04 | <0.001* |

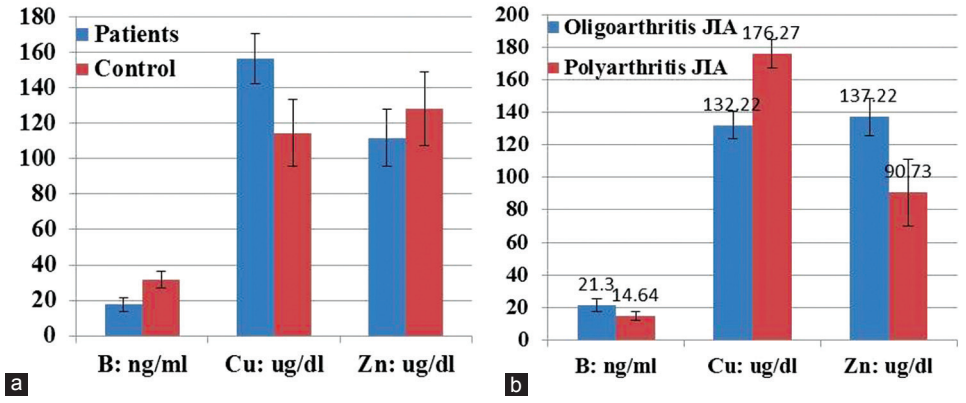
B, boron; Cu, copper; JIA, juvenile idiopathic arthritis; Zn, zinc.

**Table 4 Correlations between serum boron, copper and zinc and the juvenile idiopathic arthritis patients studied parameters**

| Studied variables | B | | Cu | | Zn | |
|---|---|---|---|---|---|---|
| | *r* | *P* value | *r* | *P* value | *r* | *P* value |
| Age | 0.05 | 0.84 | −0.14 | 0.55 | 0.27 | 0.26 |
| Disease duration | 0.09 | 0.70 | −0.23 | 0.33 | 0.30 | 0.22 |
| TJC | −0.61 | 0.004* | 0.86 | <0.001* | −0.72 | <0.001* |
| ESR | 0.22 | 0.35 | 0.40 | 0.03* | 0.18 | 0.44 |
| JADAS-27 | −0.31 | 0.18 | 0.60 | 0.006* | −0.46 | 0.04* |
| ANA | −0.03 | 0.91 | −0.11 | 0.58 | −0.03 | 0.88 |
| Hb | −0.03 | 0.91 | 0.03 | 0.90 | −0.07 | 0.77 |
| WBCs | −0.18 | 0.46 | 0.33 | 0.16 | −0.14 | 0.55 |
| RBCs | −0.44 | 0.05 | 0.25 | 0.30 | −0.38 | 0.10 |

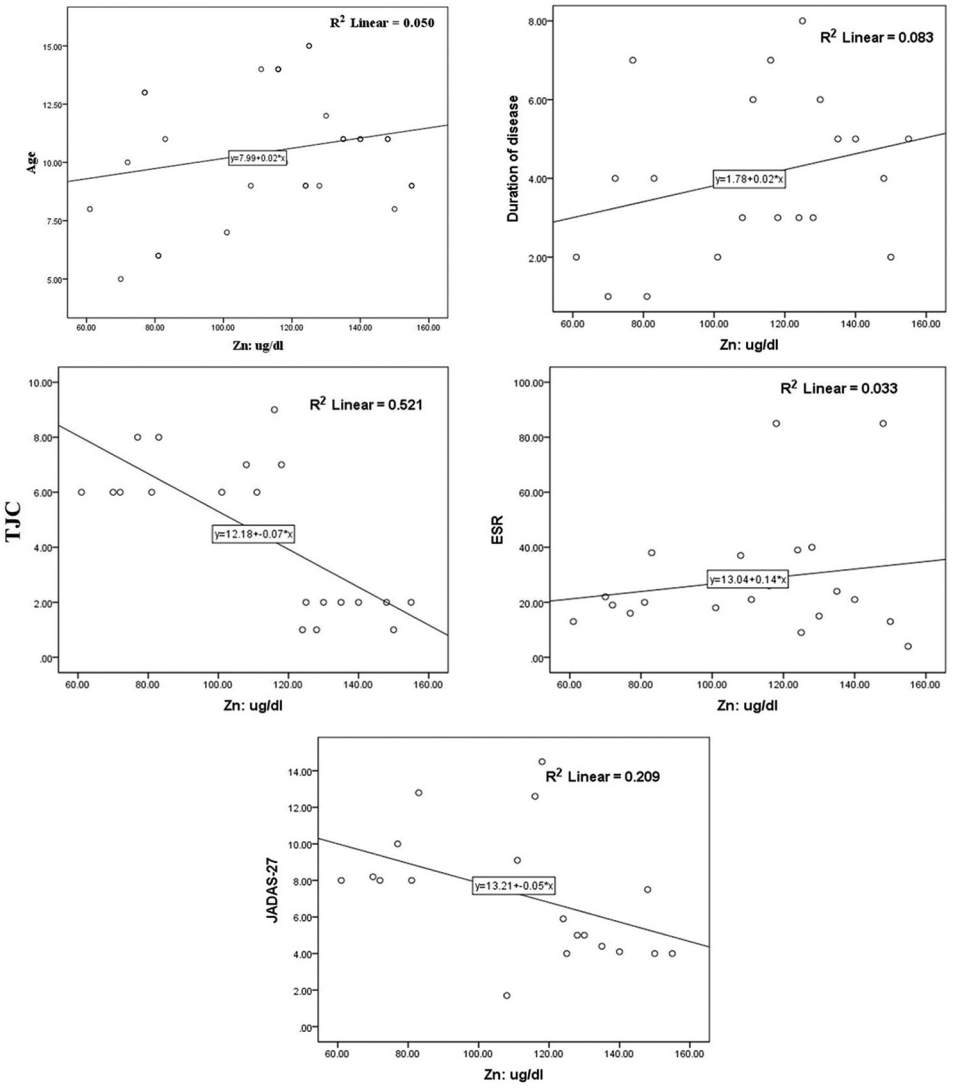
ANA, antinuclear antibodies; B, boron; Cu, copper; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; RBC, red blood cell; TJC, tender joint count; WBC, white blood cell; Zn, zinc; *means significant.

**Figure 1**




The bar graph (a) shows the comparison between the juvenile idiopathic arthritis (JIA) patients and the controls regarding measured serum elements, whereas the bar graph (b) shows the comparison between oligoarthritis and polyarthritis JIA patients regarding measured serum elements.

**Figure 2**




Correlations between serum boron concentrations and the studied variables among the juvenile idiopathic arthritis patients' group. ESR, erythrocyte sedimentation rate; TJC, tender joint count.

ANA ($P$ = 0.88), Hb ($P$ = 0.77), WBCs ($P$ = 0.55), and RBCs ($P$ = 0.110), as shown in Table 4 and Fig. 4.

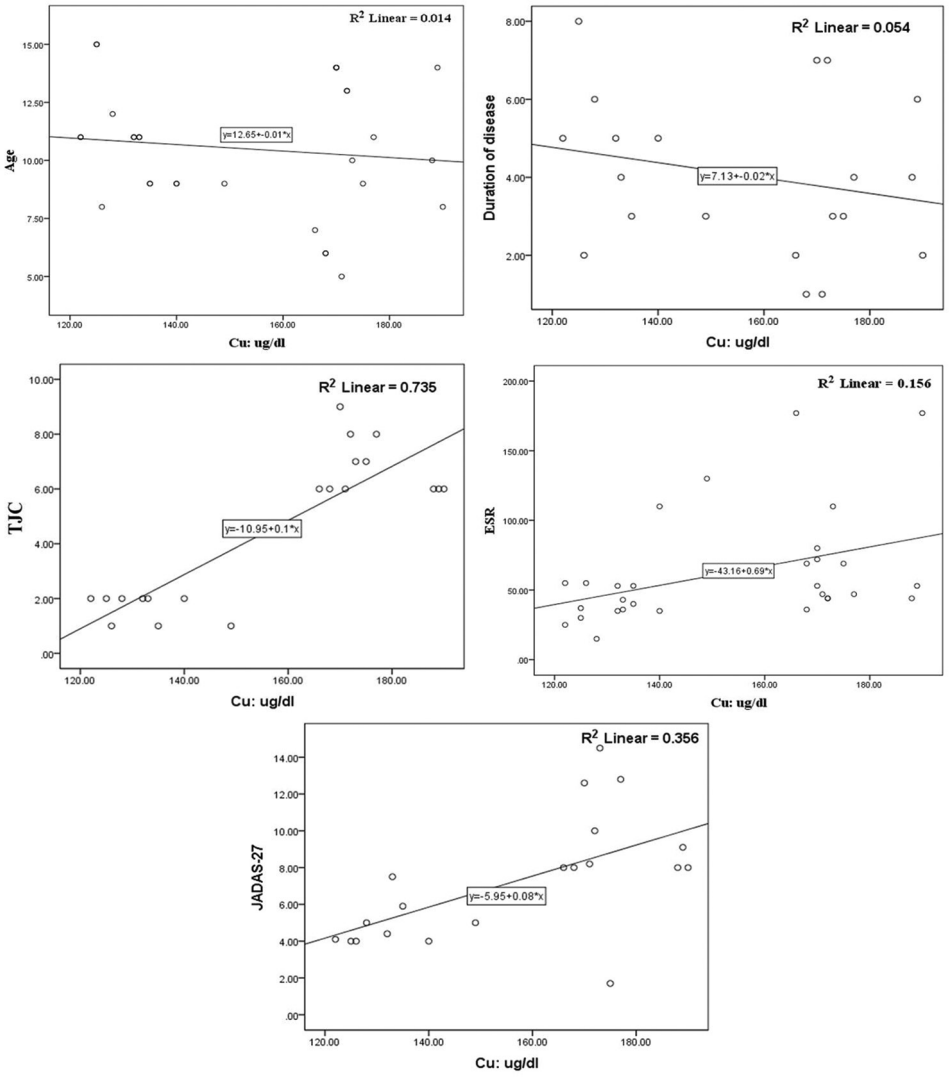
## Discussion

JIA is the most common chronic arthropathy of childhood, whose pathogenesis is still poorly understood. It is also the most common inflammatory joint disease in pediatric patients and it is divided into seven subtypes defined by the ILAR classification [3]. Trace elements are involved in various vital processes related to health, ranging from structural support, nerve conduction, muscle contraction, enzymes and hormones production, and maintenance of mineral balance in human body [16]. The importance of trace elements in chronic inflammatory arthritis is related to their cofactor role in the functions of the immune system and in different metabolic processes in the articular tissues [17].

Zn is involved in several biochemical processes and plays an important role in the growth and in the immune function. Alternatively, Cu metabolism is significantly affected by inflammation. Cu is bound to ceruloplasmin and its level is increased as part of the acute phase response [2]. The role of B is particularly important because it controls the inflammatory process in arthritic conditions by downregulating specific enzymatic activities typically elevated during inflammation at the inflammatory site, inhibiting the inflammatory stress and affecting the production of inflammatory cytokines by cartilage cells and cells involved in the inflammatory response [13].

Previous studies have reported reduced serum selenium, magnesium, Zn, and elevated serum Cu in

**Figure 3**

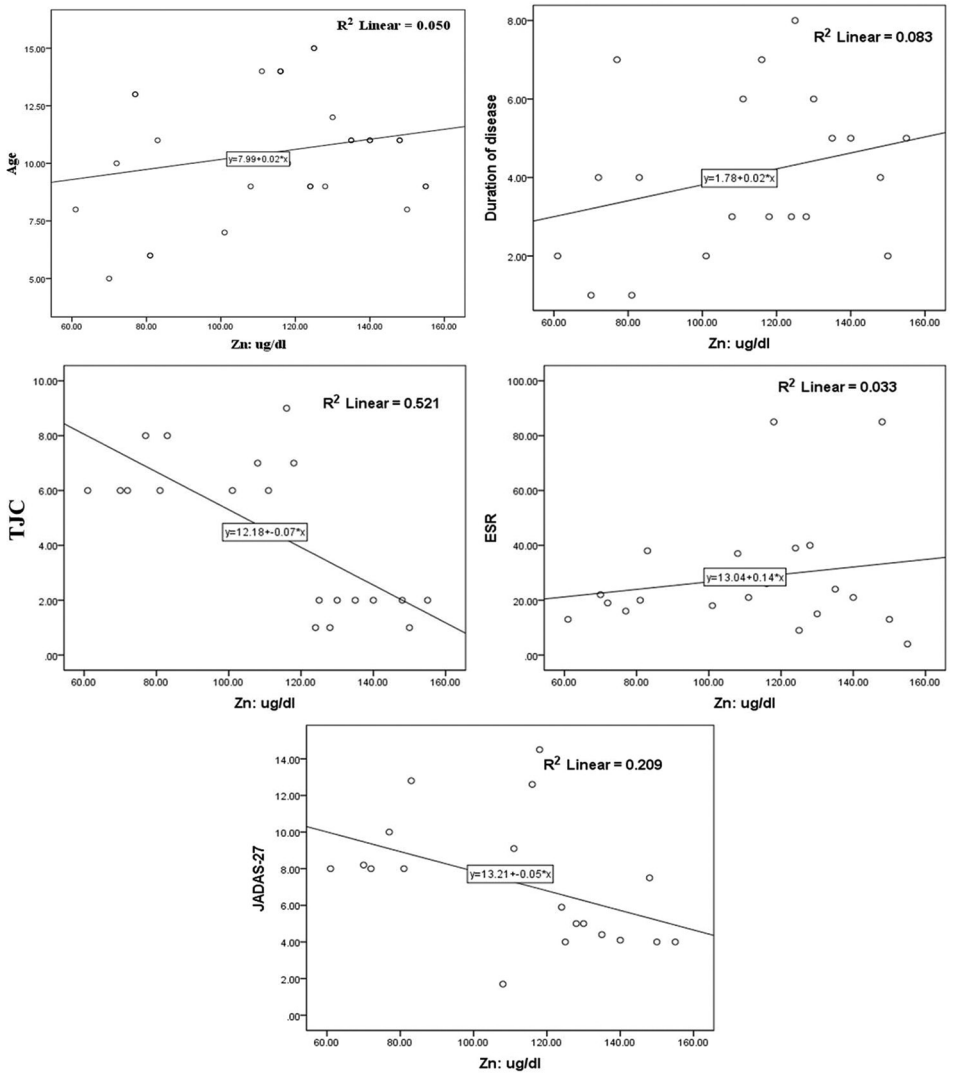



Correlations between serum copper concentrations and the studied variables among the juvenile idiopathic arthritis patients' group. ESR, erythrocyte sedimentation rate; TJC, tender joint count.

patients with rheumatoid arthritis (RA). To date, our knowledge about the serum level of these molecules in JIA and its correlation with clinicopathologic features is still incomplete [18]. To accomplish our goals, this study was conducted on a group of 30 patients suffering from JIA diagnosed according to the ILAR classification of JIA, attending the Rheumatology, Rehabilitation and Physical Medicine Outpatient Clinic and Inpatient Department of Benha University Hospitals. In addition, 20 apparently healthy children, age and sex matched with patients, were included in this study as controls.

This study showed that the mean serum B concentration was lower in the JIA patients' group (17.64 ± 4.78 ng/ml) than in the control group (31.64 ± 4.82 ng/ml), with a highly statistically significant difference ($P < 0.001$), and this was in agreement with Al-Rawi *et al.* [11], who reported that serum B levels were significantly lower in RA patients than in controls. Moreover, our results showed that serum B levels were highly statistically significantly higher in JIA patients with oligoarticular than in those with polyarticular pattern ($P < 0.001$) [11]. Our findings are also supported by those of a study by Newnham [19], who reported that the occurrence of arthritis is negatively correlated with the amount of B in the soil and in the water supply, and emphasized that in areas where daily B intakes were typically 1 mg, the estimated incidence of arthritis ranged from 20 to 70%. In areas where daily B intakes ranged from 3 to greater than 10 mg, the estimated incidence of arthritis ranged from 0 to 10% [19]. Moreover, it has been found that B concentrations in bone and synovial fluid were lower in RA patients than in healthy controls [20]. In addition, a recent study of 20 patients with osteoarthritis has also found that B supplementation alleviated subjective

**Figure 4**




Correlations between serum zinc concentrations and the studied variables among the juvenile idiopathic arthritis patients' group. ESR, erythrocyte sedimentation rate; TJC, tender joint count.

measures of arthritis. Patients with mild to moderate arthritis supplemented daily with 6 mg of B as calcium fructoborate, naturally occurring B complex commonly found in fruits and vegetables, reported marked reduction in pain. By week 8, 80% of the test participants reduced or eliminated their use of pain killers. 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 B as calcium fructoborate, exhibited a more subdued improvement in mobility and rigidity but still reported a significant reduction in the use of pain killers [21]. Meanwhile, serum B level in our study was statistically significantly correlated with TJC ($P$ = 0.004); there were insignificant correlations between serum B level and ESR ($P$ > 0.05) and JADAS-27 ($P$ > 0.05), and these findings were consistent with a study by Al-Rawi *et al.* [11], who concluded that serum B levels in RA patients were lower than that of controls, without significant correlation with ESR or DAS-28. These findings suggested that serum B level has a role in the pathophysiology of chronic arthritis in children and did not correlate with disease activity because these patients were under drugs controlling disease activity parameters [11].

Our study found that serum Cu level was higher (156.45 μg/dl) in JIA patients than in controls (114.45 μg/dl), with a highly statistically significant difference ($P$ < 0.001). These findings were in agreement with that of a study by Taneja and Mandal [18] in Chandigarh, India, who emphasized that serum Cu, as well as urinary excretion, were increased in RA patients compared with healthy controls. Our study was in agreement with theirs regarding the positive significant correlations between

serum Cu level and TJC ($P < 0.001$), ESR ($P = 0.04$), and JADAS-27 ($P < 0.01$) [18]. In addition, our data were the same as that of Strecker *et al.* [22], who demonstrated significant correlation between serum Cu and disease activity parameters in RA patients. The increase of serum Cu may be because of the rise in ceruloplasmin, which is an acute phase protein, and whose role in adjuvant arthritis is to neutralize free oxygen radicals, mainly anion superoxide, in an attempt to stop the process of turning chronic [22].

Surprisingly, we found that the serum levels of Zn were lower (111 μg/dl) in JIA patients than in controls (128 μg/dl), and that there were statistically significant correlations between serum Zn level and TJC ($P < 0.001$) and JADAS-27 ($P < 0.001$). On the contrary, we agree with a study by Mierzecki *et al.* [23], who demonstrated that Zn level was reduced in the serum and hair of RA patients; there was a point of disparity where they documented significant correlation between serum Zn level and disease duration [23]. We found polyarticular subtype affecting six (20%) patients, oligoarticular subtype affecting 20 (66.7%) patients, and other subtypes affecting four (13.3%) patients. These results were nearly similar to that a study by Hyrich *et al.* [24], who documented the same percentages for the polyarticular subtype. Moreover, the current study disagrees with the study by Şen *et al.* [25], conducted on disease characteristics in children in southwestern Turkey ($n = 213$ patients), in which they reported that the polyarticular subtype affected 42.3% patients and oligoarticular subtype affected 37.1% patients. This can be attributed to the greater number of patients ($n = 213$) included in their study, so that other subtypes were represented [25]. In addition, the current study showed positive ANA in 12 (40%) patients and this was in accordance with a study by Cassidy and Petty [26]. Furthermore, Weiss and Ilowite [27] documented the same percentage of positive ANA. Moreover, the two studies were in agreement with the percentage of positive RF reported in the current study [27]. Furthermore, BenEzra *et al.* [28] reported that 11.6% of the 172 patients with JIA enrolled in their study had uveitis, which was nearly similar to the percentage reported in the current study. In addition, our results were consistent with that of a study by Heiligenhaus *et al.* [29], who demonstrated that uveitis prevalence was 12% for all JIA patients.

## Conclusion and recommendations

The pathogenesis of JIA could involve the trace element changes as they are part of both intracellular and extracellular antioxidant functions. Serum Zn, Cu, and B should be included in the routine assessment of children with JIA, and B should be supplemented in cases with JIA with high inflammatory disease activity.

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**Conflicts of interest**

There are no conflicts of interest.

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