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## Letters to the Editor

# Inappropriate serum levels of IGF-I and IGFBP-3 in patients with rheumatoid arthritis

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SIR, insulin-like growth factor (IGF)-I promotes the growth and differentiation of the bone and cartilage tissue [1] and also plays a role in the regulation of immunity and inflammation [2]. For instance, proinflammatory mediators such as tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) and prostaglandin E<sub>2</sub> have been shown to induce IGF-I production in macrophages [3]. Although rheumatoid arthritis (RA) is a disease that is representative of immune disorder and inflammation, little is known about the involvement of the IGF system in RA. The bioactivity of IGF-I is modulated by six binding proteins [IGF binding proteins (IGFBP)-1 to -6], and IGFBP-3 is a predominant carrier protein in serum [4]. Previously, we have found increased levels of IGF-I and IGFBP-3 in the synovial fluids of patients with RA [5]. These results suggested the local participation of IGF-I and IGFBP-3 in the development of cartilage destruction. To investigate the involvement of the IGF system in RA, we evaluated the serum levels of IGF-I and IGFBP-3 in patients with RA and related them to some serum markers.

Forty-eight women with RA who fulfilled the American College of Rheumatology criteria for diagnosis of RA [6] were included in this study. Their mean age was 52 yr (range 21–76 yr) and the median disease duration was 6 yr (range 6 months to 33 yr). All patients had been taking non-steroidal anti-inflammatory drugs and disease-modifying anti-rheumatic drugs. Twenty-nine of the 48 patients had received treatment with low-dose corticosteroids (prednisolone 2.5–5 mg/day). Control serum was obtained from 27 age-matched healthy women. Serum IGF-I and IGFBP-3 levels were determined using commercial enzyme-linked immunosorbent assay (ELISA) kits from Fujisawa (Osaka, Japan) and DSL (Webster, TX, USA) respectively. The other cytokines were also determined using ELISA kits, from Amersham Pharmacia Biotech (Little Chalfont, UK) (IL-6, TNF- $\alpha$ ) and Biomedical Technologies (Stoughton, MA, USA) (intact osteocalcin). For statistical analysis, we used the Mann–Whitney *U*-test and the Spearman rank correlation coefficient.

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The IGF-I levels in RA serum were significantly lower than those of controls ( $P=0.03$ ) and the IGFBP-3 levels were significantly higher in RA than in controls ( $P<0.0001$ ). The ratio of IGF-I to IGFBP-3 levels in serum was significantly lower in RA than in the controls ( $P<0.0001$ ) (Table 1). The IGFBP-3 level, but not the IGF-I level, showed a weak positive correlation with the levels of osteocalcin ( $r=0.316$ ,  $P=0.030$ ) and TNF- $\alpha$  ( $r=0.376$ ,  $P=0.012$ ). Neither IGF-I nor IGFBP-3 was related to the level of C-reactive protein (CRP) or IL-6. The IGF-I level did not correlate with the other clinical findings, such as radiological joint damage and joint swelling or pain, but was closely and negatively correlated with the age of the patients ( $r=-0.655$ ,  $P<0.0001$ ). The concentrations of IGF-I and IGFBP-3 showed no significant difference between patients who were treated and those who were not treated with steroids.

**View this table:** TABLE 1. Concentrations of IGF-I and IGFBP-3 in serum of patients with RA and controls  
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As IGF-I plays an important role in modulating the metabolism of bone and cartilage tissue, there is a possibility that some disturbance in the utilization of IGF-I may occur in pathological states. In this study, we have shown that IGF-I levels in sera of patients with RA were significantly lower than those in healthy controls. Similar findings have been reported in other inflammatory diseases, such as juvenile RA (JRA) [7] and ankylosing spondylitis (AS) [8]. It is interesting that these results were contrary to those obtained in the synovial fluid of patients with RA [5]. This discrepancy might be explained by the fact that IGF-I in synovial fluid reflects the local metabolism of cartilage tissue and that IGF-I in serum reflects the systemic metabolism of tissue including bone and cartilage. It is known that 80–95% of circulating IGF-I is bound to IGFBP-3, which regulates the availability of free IGF-I [4]. In contrast to the patients with JRA or AS, increased levels of IGFBP-3 in the serum of patients with RA were found in this study. Similar or conflicting findings are reported in the literature [9]. These discrepancies might be caused in part by differences in ages of the patients, in the methods of treatment, in the activity of the disease or in habitual exercise. Proinflammatory cytokines such as IL-1 and TNF- $\alpha$  have been reported to induce IGFBP-3 in chondrocytes *in vitro* [10]. In view of the positive correlation between serum levels of IGFBP-3 and TNF- $\alpha$ , the increased concentrations of IGFBP-3 might have been due to increased levels of TNF- $\alpha$ . Unexpectedly, the IL-6 and CRP levels did not correlate with IGF-I or IGFBP-3 levels, showing that neither IGF-I nor IGFBP-3 seems to be a good marker of inflammation. On the contrary, IGFBP-3 was slightly correlated with the osteocalcin level, suggesting some relationship with the activity of osteoblasts. In this study, we found that the ratio of IGF-I to IGFBP-3 in RA patients was significantly lower than that in controls. These findings suggest that an inappropriate balance of IGF-I and IGFBP-3 levels may reduce the availability of IGF-I and be involved in pathogenesis of RA.

## Notes

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