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PLASMA SELENIUM LEVELS IN RHEUMATOID ARTHRITIS

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In order to investigate whether selenium (Se) is an important factor in the pathogenesis of rheumatoid arthritis (RA), the plasma Se levels were determined in RA patients and healthy controls. Plasma Se levels in 60 patients were found to be significantly lower than those in 60 normal, healthy controls ($p<0.001$). Similar significant differences were determined in sex-matched comparisons between patients and controls ($p<0.001$); but, there was no significant difference in plasma Se levels in sex-matched comparisons in both groups ($p>0.05$). In conclusion, Se supplementation might lead to clinical improvement in patients with RA.

INTRODUCTION

The possibility of a relationship in human subjects between diet and chronic acute diseases has been a major preoccupation of nutritional and medical scientist through a long period of history (1).

Selenium (Se) is a trace element and an essential nutrient (2). The biological importance of Se is incompletely understood; but it is known to act as a component of the membrane protecting enzyme glutathione peroxidase (EC 1.11.1.9; GSH-px), which utilizes glutathione for the breakdown of peroxides (3). Additionally much evidence now exists that Se has anticancerogen, antiproliferative, antiinflammatory, antiviral and immune altering effects (1,2,4).

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A daily intake of 50-200 μg of Se per day has been recommended (5). Foods rich in Se are: liver, kidney, seafoods and mushrooms, but the main sources are meat and cereals, although their Se content in certain areas can be low. A risk for Se deficiency in certain populations is thus evident (2).

Deficiency of Se is particularly associated with the development of two diseases: Keshan disease is a cardiomyopathy of children and young women, and Kashin-Beck syndrome is an osteoarthropathy that occurs mainly in young people. Both diseases are only seen in China where acutely low soil levels of the element are reflected in very low blood levels; fortunately both of them are preventable by therapy with Se supplements (1,2).

On the other hand, abnormalities in the metabolism of Se have been implicated in the pathogenesis of rheumatoid arthritis (RA) (6). A low Se levels in the serum or plasma of RA patients have been reported in areas of relatively low (7-9) and high (4, 10) natural dietary Se intake; but also normal values have been reported (11).

In the present study, plasma Se levels was determined to provide clinical support to earlier data indicating that Se is an important factor in RA.

MATERIAL AND METHODS

Subjects. Patients with chronic RA who attended Physical Therapy and Rehabilition Department of Erciyes University Faculty of Medicine between 1990-1993 were included in the present study. There were 60 patients (44 female and 16 male), aged 21 to 75 years (mean age 51.1±12.2 years), with a mean disease duration of 9.62±6.0 years (range 1-24 years).

All the patients met the American Rheumatism Association (ARA 1987) criteria for diagnosis of RA (12) and they were in stable clinical condition (stage I-III). C-reactive protein (CRP) was positive in 60% of patients. Exclusion criteria included a history of regular vitamin consumption, excess alcohol consumption and a history of intercurrent infection. Patients with other major diseases and patients receiving systemic corticosteroid treatment were also excluded. All patients received nonsteroidal antiinflammatory drugs, and treatment with these drugs was withdrawn 3 to 4 days before the study commenced.

As a control group, 60 subjects (40 female and 20 male), age-matched, were selected from a healthy population and they had no rheumatoid symptoms when examined.

Biochemical procedure. For the determination of Se, venous blood was collected in acid washed tubes containing heparin. Plasma was separated after centrifugation. Plasma Se was measured by a direct graphite furnace atomic absorbtion spectrometry (Hittachi Z-8000), with a Zeeman background correction (13). Plasma Se values are expressed as μg of Se per liter (μg/L).

Differences between group means were determined by the Student'st test (14).

RESULTS

Table shows the plasma Se levels of RA patients and healthy controls.

Table 1: Plasma Selenium Levels in Patients with Rheumatoid Arthritis and Healthy Controls

	RA Patients		Healthy Controls		
Subjects	n	Se (μg/L)	n	Se (μg/L)	p value
Total	60	107.50±23.76 (50-150)	60	168.45±46.44 (100-250)	< 0.001
Female	44	105.45±23.27 (50-150)	40	170.30±47.21 (100-250)	< 0.001
Male	16	113.13±24.96 (50-150)	20	164.75±45.84 (110-250)	< 0.001

Se values are given as mean and standard deviation ($\bar{x}$±SD). The range values of each group are expressed in paranthesis.
n: number of subjects.

Plasma Se concentrations in patients with RA were found to be significantly lower than those in healthy conrtrols ($p<0.001$). Similar significant differences were determined in sex-matched comparisons between patients and controls ($p<0.001$); but there was no significant difference in plasma Se levels in sex-matched comparisons in both groups ($p>0.05$).

DISCUSSION

Rheumatoid arthritis (RA) is a chronic inflammation with cellular immun reactions in synovial tissue and a continuous interaction of granulocytes with immun complex in synovial fluid (15). The pathogenesis of RA is not completely understood, but it is almost certanly multifactorial and may well include altered immune mechanism, genetically determined disease susceptibility, and common environmental exposures. Further,

synovial proliferation and inflammation play a central part in disease expression (4).

Oxygen radicals are thought to play a part in the disease process by acting as mediators of oxidative damage (16). Several studies have suggested a state of increased oxidative stress and reduced ability to resist attack by radicals in RA (17). Hydrogen peroxide and lipoperoxides have been shown to have inflammatory properties, and each (or its products) has been detected in tissues of RA patients (6). Indeed, in RA synovial tissue, great amounts of toxic oxygen derivatives are generated (16, 18), and high levels of products of lipid peroxidation are found in synovial fluid and plasma of these patients (17,19).

The fact that low Se status may be a factor in the etiology of RA is a plausible hypothesis if one assumes that RA is caused by overproduction of peroxides (6). The enhancement of adjuvant arthritis observed in rats fed with a Se deficient diet supported a role for this essential element in RA (20). Therefore the antiproliferative, anti-inflammatory, and immune modulating effects of Se are of interest (4).

The firmly established metabolic role of Se in humans is as an essential constituent of the enzyme GSH-px (2), which protects cells from oxidative damage by destroying peroxides (21). At the active center of this selenoenzyme, Se serves to catalyze the reduction of hydroperoxides produced from oxidized species such as superoxide and lipoperoxides (22). Therefore, a defective regulation of this Se containing GSH-px together with Se could account for some pathological features of the disease.

Several investigators have found depressed plasma or serum Se values in patients with RA, both in adults (4,7-10,13,23,24) and in juveniles (25); and it is speculated that Se levels might modulate the effects of viral or other types of infections in subjects with the appropriate genetic background. Thus, Se deficiency might enhance the development or progression of RA (4). In contrast, Peretz et al (11) have reported normal plasma Se levels in RA. In the peresent study, we confirmed that plasma Se levels in patients with RA are lower than in controls; therefore our findings are in agreement with most other studies previously published, except that of Peretz et al (11). Although the decrease in Se levels is related to nutritional changes or inflammatory activity remains unclear in these studies; among factors liable to modify plazma Se levels, nutritional status must be considered first in patients with RA. Patients might be prone to malnutrition and

therefore exposed to inadequate dietary Se intake. Unfortunately, nutritional status is diffucult to assess in RA, because plasma proteins and other commonly used test are modified by the inflammatory reaction (12). Therefore, the reason for these changes might well be inadequate dietary intake, however the prevalance of RA is similar in areas of high or low Se intake (4).

Se supplementation within a nutritional range has been shown to increase the concentration of Se in plasma and red blood cells (3,9); further, some clinical improvement has been reported for RA patients treated with Se (17); but the others reported that plasma Se values can be normalized after supplementation without convincing clinical improvement (3). On the other hand, patients with RA had a reduced Se concentration in polymorphonuclear (PMN) leucocytes which was unaffected by selenium supplementation (9); it suggests that the Se metabolism is affected in the PMN leucocytes, probably as a result of impaired uptake of selenium during the formation of cells in the bone marrow. Thus a lack of antioxidative response to selenium supplementation in PMN could have a pathogenetic role in joint destruction in patients with RA (9).

CONCLUSION

It is possible that the low Se values in RA are not just an unspecific consequence of inflammation, but a sign of depletion of stores of redistribution of the total body Se. Therefore, in RA cases, Se supplementation should be considered.

ÖZET

ROMATOİD ARTRİTLİ HASTALARDA PLAZMA SELENYUM SEVİYELERİ

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Romatoid artrit (RA)'in patogenezinde selenyum (Se)'un önemli bir faktör olup olmadığını araştırmak için, RA hastalarında ve sağlıklı kontrol gruplarında plazma Se seviyeleri tayin edildi. 60 hastanın plazma Se seviyeleri, normal, sağlıklı kontrol grubu olan 60 kişininkine nazaran önemli düşüklük gösterdi ($p<0.001$). Kontrol ve hasta grubundaki kadınlar birbiriyle karşılaştırıldığında, hasta grubunda Se seviyelerinde önemli bir düşme gözlendi; aynı durum erkeklerde de tespit edildi ($p<0.005$). Fakat, hasta grubunda cinsler arasında Se seviyeleri açısından bir fark yoktu; kontrol

grubunda da benzer sonuçlar elde edildi ($p>0.05$). Sonuç olarak, RA hastalarında Se takviyesinin klinik iyileşmeyi hızlandırabileceği kanaatine varıldı.

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