

Plasma zinc and its relationship to clinical symptoms and drug treatment in rheumatoid arthritis

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SUMMARY Total plasma zinc levels in patients with rheumatoid arthritis on different therapeutic treatments were determined in conjunction with total serum proteins, serum albumin and globulin, and articular index of joint tenderness, erythrocyte sedimentation rate, rheumatoid factor, serum copper, and serum iron. There were significantly lower zinc levels in patients with rheumatoid arthritis on nonsteroidal anti-inflammatory drugs than in patients on levamisole and penicillamine. Zinc levels correlated positively with serum albumin, and there was an inverse correlation between zinc levels and both ESR and globulin concentration in all rheumatoid patients. However, the correlation coefficient varied in the different treatment groups. The results of this study support the hypothesis that low plasma zinc level in rheumatoid arthritis is one of the nonspecific features of inflammation.

Strangely, considerably less attention has been paid to divalent as opposed to monovalent cation metabolism in medicine. This may be attributable to the earlier appearance of simple methods of measurement for the alkali metals (Na⁺, K⁺) rather than to their relative biological importance. Elevation of serum copper and ceruloplasmin has long been associated with rheumatoid arthritis, and we have recently reported a relationship between serum copper, serum iron, articular index of joint tenderness, and erythrocyte sedimentation rate.¹

Zinc is intimately involved in numerous biological systems of relevance to patients with arthritis ranging over collagen and bone metabolism,^{2, 3} complement system,⁴ lysosomal enzyme release,⁵ and macrophage functions.⁶ Zinc deficiency in chickens is associated with an arthropathy,⁷ and in man alteration of zinc metabolism may be associated with wound healing,⁸ cutaneous ulceration,⁹ severe burns,¹⁰ liver disease,¹¹ and hypogonadal dwarfism.^{12, 13} Drug treatment, particularly with corticosteroid drugs¹⁴ or penicillamine,¹⁵ may influence zinc levels, and it has been reported that administration of zinc sulphate improves the clinical status of patients with rheumatoid arthritis.¹⁶

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Zinc in plasma is mainly bound to proteins, both albumin (about 60%) and globulins (α 2 macroglobulin about 35%), and the biologically active fraction is partly complexed to amino acids, in particular histidine (about 5%).^{17, 18} Histidine concentrations are low in patients with rheumatoid arthritis,¹⁹ but plasma zinc has been variously reported to be raised,²⁰ normal,^{21, 22} or depressed,^{3, 23} possibly due to differences in the patients studied and to differences in treatment.^{1, 24} We have reported a reduction in plasma zinc in some patients with rheumatoid arthritis and have pointed out that total body zinc is not accurately reflected by measurements of plasma zinc,²⁵ since, like potassium²⁶ zinc exists mainly in the intracellular compartment.

In the present study we have focused attention on different drug treatments and their effect on total plasma zinc, and we have also examined some inter-relationships between zinc and rheumatoid factor, clinical indices of activity, various plasma proteins, and other divalent cations.

Materials and methods

One hundred and forty patients (mean age 54.1 years, \pm SEM 4.9 years), of whom 45 were males, were studied. All the patients had classical or definite rheumatoid arthritis²⁷ with a mean disease duration

of 8.6 years (\pm SEM 0.9 years). All patients had radiological evidence of articular erosions, and in 104 patients serological tests for IgM rheumatoid factor were positive. The mean articular index of joint tenderness²⁴ was 11.4 score points (\pm SEM 1.7) and ESR in the first hour 26.7 mm (\pm SEM 2.7). Seventy-three patients were treated with levamisole, 15 patients with penicillamine, and the other 52 were receiving a number of nonsteroidal anti-inflammatory drugs (NSAI). None of these patients were receiving corticosteroid drugs, and no patient had clinical signs of any of the seronegative spondylarthritides.

In all the patients plasma zinc was estimated by atomic absorption spectrophotometry,²⁸ care being taken to avoid contamination of specimens by the use of appropriate syringes, needles, and specimen tubes. The blood from all patients was withdrawn after breakfast at the same time of the day, between 9 and 12 a.m. Rheumatoid factor was measured by the R3 titration test.²⁹ Total serum copper was estimated by atomic absorption spectrophotometry with carbon furnace atomisation,³⁰ again with considerable care being taken to avoid contamination.

Results

The mean plasma zinc concentration in all patients studied was 11.74 \pm SEM 0.21 μ mol/l, which was significantly lower than that of the normal values (mean: 15.1 \pm SEM 0.17 μ mol/l = 99 \pm SEM 11 μ g/100 cc) taken from 100 subjects obtained in this laboratory.²⁸

Table 1 Plasma zinc values in different treatment groups of patients with rheumatoid arthritis

Treatment	Number of patients	Plasma zinc in μ mol/l (mean \pm SEM)
Levamisole	73	12.62 \pm 0.277
Penicillamine	15	11.86 \pm 0.674
NSAI	52	10.47 \pm 0.282
Total	140	11.74 \pm 0.209

Significance: Levamisole—NSAI, $t=5.28$, $P<0.001$. Penicillamine—NSAI, $t=2.17$, $P<0.05$. Levamisole—penicillamine, $t=1.10$, P not significant.

Table 2 Correlation between plasma zinc values and ESR, serum albumin, and serum globulin in different treatment groups of patients with rheumatoid arthritis

	Treatment groups											
	Levamisole			Penicillamine			NSAI			Total		
	No.	r	P	No.	r	P	No.	r	P	No.	r	P
ESR	50	-0.406	0.01	11	-0.536	NS	17	-0.440	NS	78	-0.448	0.001
Albumin	37	0.414	0.02	8	0.817	0.02	25	0.112	NS	70	0.419	0.001
Globulin	37	-0.175	NS	8	-0.534	NS	25	-0.427	0.05	70	-0.305	0.01

Patients treated with NSAI drugs had a mean plasma zinc concentration (μ , 10.47 \pm SEM 0.28 μ mol/l), which was significantly lower than were the results obtained in patients treated with levamisole (μ , 12.62 \pm SEM 0.28 μ mol/l, $P<0.001$) or with penicillamine (μ , 11.86 \pm SEM 0.67 μ mol/l, $P<0.05$). There was no significant difference between the results with levamisole and penicillamine (Table 1).

The results for ESR in the patients receiving NSAI drugs (μ , 40.1 \pm SEM 7.2 mm/h) were significantly higher than those obtained in patients receiving levamisole (μ , 21.8 \pm SEM 2.9 mm/h; $t=2.81$, $P<0.01$), but there was no significant difference between the results obtained with penicillamine (μ , 29.0 \pm SEM 7.9 mm/h) and either the results with NSAI drugs ($t=1.01$, NS) or those with levamisole ($t=0.99$, NS).

There were a significant inverse correlation between plasma zinc concentration and the ESR in all patients studied ($r=-0.448$, $P<0.001$) and in the patients treated with levamisole ($r=-0.406$, $P<0.01$), but no significant correlation in the patients receiving either NSAI drugs or penicillamine (Table 2).

The plasma zinc concentration in those patients with an ESR of less than 50 mm/h (μ , 12.12 \pm SEM 0.26 μ mol/l) differed significantly ($t=4.59$, $P<0.001$) from the result in those patients with an ESR in excess of 51 mm/h (μ , 9.46 \pm SEM 0.52 μ mol/l).

There was a significant correlation between plasma zinc concentration and serum albumin in the total group ($r=0.419$, $P<0.001$) in the patients treated with levamisole ($r=0.414$, $P<0.02$) and in the patients receiving penicillamine ($r=0.817$, $P<0.02$), but no significant correlation in those receiving NSAI drugs. There was a significant inverse correlation between plasma zinc and serum globulin concentrations in the total group ($r=-0.305$, $P<0.01$) and in those treated with NSAI drugs ($r=-0.427$, $P<0.05$), but no significant correlation in the other treatment groups (Table 2).

No significant relationship was recorded between total serum protein concentration, rheumatoid

factor titre, serum copper or iron concentration, or articular index of joint tenderness and plasma zinc concentration.

Discussion

Early literature on this subject was bedevilled by methodological problems which could go some way towards explaining the apparent discrepancies.^{20, 22, 23, 31} The results of this study confirm and extend our previous observation³ that the plasma zinc concentration in patients with rheumatoid arthritis receiving NSAID drugs is low. In that study we looked at patients receiving NSAID drugs and corticosteroids. In the present study we have compared the former group with patients receiving 'second line' antirheumatic drugs³² such as penicillamine and levamisole. It has been suggested that such regimens may alter the rate of progression of the underlying disease,^{33, 34} and this effect may be reflected in reduction in acute-phase protein concentrations and ESR.³⁵ Certainly in the present study plasma zinc concentrations, ESR, and globulin concentrations were lower in those patients receiving levamisole, and serum albumin concentrations were higher. The results for patients receiving penicillamine were intermediate. In particular the results in all patients for plasma zinc concentrations were lower in those subjects with the highest ESRs'

We have demonstrated a significant relationship between the ESR and plasma zinc concentrations, and the inter-relationships extend in much the direction one would expect, since low plasma zinc concentrations are also related to high globulin and low albumin concentrations. It is relevant in this context that, although α_2 macroglobulin is particularly associated with plasma zinc, as much as 60% of zinc is bound to albumin and a small but highly significant amount to amino acids, especially histidine.^{36, 37} It is interesting that plasma zinc concentrations were significantly related to serum albumin but not globulin concentrations in those patients receiving second line drugs (penicillamine and levamisole) but not in those patients receiving NSAID drugs. On the other hand plasma zinc concentrations were significantly related to serum globulin concentrations only in those patients receiving NSAID drugs.

It is possible that changes in plasma zinc in chronic inflammatory diseases may reflect changes in leucocyte endogenous mediator (LEM). It is suggested that this is released from polymorphonuclear leucocytes during phagocytosis as a result of a wide variety of nonspecific stimuli.³⁸ LEM subsequently exerts an effect on the hepatocyte which results in enhanced uptake of amino acids such as histidine,

which are thereafter used as the building blocks for acute phase proteins. Zinc both independently and in association with histidine is thus concentrated from plasma into the hepatocyte, with consequent reduction in plasma concentration.³⁹⁻⁴¹ This may account for the reduction in plasma but not in total body zinc concentrations in patients receiving NSAID drugs for rheumatoid arthritis. The subsequent increase in synthesis of acute phase proteins may explain the elevation of plasma ceruloplasmin and kininogen^{39, 42} and through this the elevated copper concentrations in rheumatoid arthritis. Second line drugs such as gold, penicillamine, or levamisole produce the reverse effect whether primarily or through intermediate mechanisms. If this is correct, then it seems likely that most of these phenomena are entirely nonspecific and may not be common to other chronic inflammatory diseases. Furthermore, if this is correct, such interrelated biochemical mechanisms are probably in dynamic equilibrium, and results obtained at any single time must be interpreted in perspective.

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