Rheumatoid arthritis (RA) is characterised by migration of activated phagocytes and other leukocytes into synovial and periarticular tissue. Activated oxygen species and other mediating substances from triggered phagocytes appear to exacerbate and perpetuate the rheumatoid condition. Iron excesses are capable of aggravating the arthritic inflammation, probably through their pro-oxidant potentials. In contrast, therapeutically given gold salts, through a lysosomal loading of the metal, inhibit the triggered cells, thereby reducing the toxic oxygen production. Pharmacological doses of zinc also may immobilise macrophages. Furthermore, the copper–zinc-containing enzyme SOD (superoxide dismutase) can act as a scavenger of toxic oxygen in the tissues. Therapeutic remission of RA has been obtained following intraarticular administration of SOD. Intramuscular administration of copper complexes has induced remission in about 60% of RA patients in open studies. Another drug, penicillamine, that protects cellular membranes against toxic oxygen in vitro, is presumed to act as an antirheumatic via the SOD mimetic activity of its copper complex. Thiomalate and other thiols may possess similar activities. Selenium compounds also may act as oxygen radical scavengers. A significant alleviation of articular pain and morning stiffness was obtained following selenium and vitamin E supplementation in a double-blind study on RA patients. The observations reviewed here indicate that metal compounds and other antioxidants can reduce the rheumatic inflammation by reducing the cellular production and/or concentration of toxic oxygen species.

Keywords: Copper; zinc; selenium; gold; thiols; trace elements; phagocytes; leukocytes; macrophages; rheumatoid arthritis

The pathological hallmark of rheumatoid arthritis (RA) is a persistent inflammation in synovial membranes of joints. This leads to a gradual destruction of the supporting structures of the joints, such as bone and cartilage, a process that ceases only if a remission occurs.

It is surprising that active RA can be brought to remission by treatment with metal compounds such as gold or copper complexes or with metal-complexing agents such as penicillamine or 5-aminosalicylate. In some way, the remission-inducing agents must interfere with crucial mechanisms underlying the chronicity of the disease. Recent research indicates that activated tissue macrophages and blood monocytes invading the synovial tissue play a central role in the early steps of pathogenesis and chronic nature of RA.1 Important signal substances derived from the activated macrophages are the free oxygen radicals (superoxide and hydrogen peroxide) and the cytokines such as tumour necrosis factor-α (TNF-α). Apparently, these mediating substances play key roles in the progression of the rheumatoid inflammation.2 Another possible source of free oxygen radicals is related to the anoxic reperfusion reactions that may accompany excessive motions of affected joints.3 The aim of this paper is to discuss traditional and new pharmacological approaches that makes use of metal compounds and chelators that are presumed to interact with the generation or toxicity of activated oxygen species.

Gold compounds

The first clinical tests of gold around 1925 were precipitated by in vitro studies of the bacteriostatic effect towards bacilli of gold and other metals. Since RA was assumed to be an infectious disease, some patients suffering from RA were included in a programme of clinical testing of the heavy metals. These open studies led to the introduction of gold complexes as remission inducing agents by a French physician, Forestier.4 However, it was not until over 30 years later, in a report of the British Rheumatism Council in 1960, that gold therapy was shown to be clinically efficient in a controlled study.5 Nevertheless, already in the early 1930s it was observed that the most applicable gold compounds consisted of gold and sulfur-containing complexing agents. The compound most used in clinical medicine has been gold thiomalate (Myocrisin) (Fig. 1).

Astonishingly, these gold(i) complexes have only a weak or negligible anti-inflammatory action in animal models, although their antirheumatic effect has now been documented. This indicates that gold has a specific action in RA, perhaps on some basic mechanism underlying the perpetuating nature of this disease. However, the clinical use of sulfur–gold has been limited, to some extent, by its toxic reactions. Further, it has to be given by weekly intramuscular injections, which may be inconvenient for patients. This has led to the introduction of the lipophilic gold compound auranofin, which can be administered orally.

After absorption the gold complex is not stable in vivo, the gold cation being released from the complexing agent. We have found that gold(i) thiomalate dissociates rapidly in blood plasma, gold being chelated by albumin and thiomalate being liberated in the free thiolate form.6

1 Presentated at The Sixth Nordic Symposium on Trace Elements in Human Health and Disease, Roskilde, Denmark, June 29–July 3, 1997.

![Fig. 1 Formulæ of gold thiomalate and thiomalate.](image-url)
Selenium

Low selenium levels have previously been reported in blood plasma and cells from patients with RA. The most important biological function of selenium is attributed to its presence in the enzyme glutathione peroxidase (GSH-Px), which is a crucial factor in the cellular defence against toxic free radicals. Although oxygen radical formation may be of significance in the pathogenesis of RA, no significant clinical improvement was obtained when using nutritionally adequate or moderate doses of selenium supplementation, up to about 250 μg d⁻¹. We have undertaken a double blind clinical study to test if higher doses of selenium might exert disease-modifying efficacy in RA.

Forty-seven patients with classical or definite RA (ARA criteria) were randomly allocated to a treatment or placebo group (Table 1). The study was double-blind. In the treatment group all patients received 600 μg d⁻¹ of selenium, as a selenomethionine-containing yeast, for 8 months. The control group received placebo tablets for the first 4 months, and the following 4 months they received 600 μg d⁻¹ of selenium, the same as in the selenium group. All tablets were enriched with vitamin E because this vitamin has been reported to protect against toxicity of high selenium doses. The patients were examined at the start of the study and after 4 and 8 months of treatment.

To assess the disease activity, the following clinical variables were measured: articular index, grip strength in right and left hands, morning stiffness in minutes, number of swollen joints and ESR.

The Wilcoxon two-sided paired test was used for longitudinal intra-group comparisons and Wilcoxon rank sum test for inter-group comparisons.

**Table 1 Patients’ characteristics at inclusion**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Selenium group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>Female/male</td>
<td>20/5</td>
<td>17/5</td>
</tr>
<tr>
<td>Age/years (mean and range)</td>
<td>51.9 (20–66)</td>
<td>52.1 (21–77)</td>
</tr>
<tr>
<td>Disease duration/months</td>
<td>80 (3–360)</td>
<td>142 (6–480)</td>
</tr>
</tbody>
</table>

Table 2 Clinical and laboratory variables recorded at inclusion and after 8 months of treatment [mean and (in parentheses) SEM]

<table>
<thead>
<tr>
<th>Variable</th>
<th>Selenium group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Articular index</td>
<td>At inclusion</td>
<td>17.2 (1.8)</td>
</tr>
<tr>
<td></td>
<td>8 months</td>
<td>9.8* (1.7)</td>
</tr>
<tr>
<td>Grip strength, right hand</td>
<td>At inclusion</td>
<td>57 (7)</td>
</tr>
<tr>
<td></td>
<td>8 months</td>
<td>80 (9)</td>
</tr>
<tr>
<td>mmHg</td>
<td>Grip strength, left hand</td>
<td>50 (7)</td>
</tr>
<tr>
<td></td>
<td>mmHg</td>
<td>66 (9)</td>
</tr>
<tr>
<td>Morning stiffness/min</td>
<td>At inclusion</td>
<td>76 (10)</td>
</tr>
<tr>
<td></td>
<td>8 months</td>
<td>38 (8)</td>
</tr>
<tr>
<td>Number of swollen joints</td>
<td></td>
<td>8.8 (1.2)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation</td>
<td></td>
<td>7.3 (1.3)</td>
</tr>
<tr>
<td>rate</td>
<td></td>
<td>38 (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44 (6)</td>
</tr>
</tbody>
</table>

* Compared with the value at the start of the study, p < 0.01.

**Fig. 2** Selenium concentrations (mean values) in A, whole blood; B, serum; and C, placebo, during the study.
Copper

Forestier\(^2\) was among the first to report that a copper complex, Cupralene, was effective in the treatment of rheumatoid arthritis. Based on open studies, he concluded in 1949 that ‘Copper salts are effective in the treatment of rheumatoid arthritis. They give better results than gold salts in the early stages of the disease. In cases of longer standing, they must be used if there is gold intolerance or gold resistance, but whenever gold salts are tolerated they are to be preferred’.

These positive results with copper complexes were supported by the studies of other workers.\(^21\)\(^,\)\(^22\) Hangarter and Lubke\(^22\) treated more than 600 patients suffering from RA with copper salicylate and reported that 65% became symptom free, 23% improved and 12% of the patients remained unchanged. No serious toxic disturbances were recorded in association with the treatment. Their studies were not controlled, however, and their reports are difficult to evaluate. Although extensive evaluations of copper complexes in animal models have been undertaken,\(^23\) double-blind clinical studies on copper complexes in rheumatoid arthritis are still lacking.

When discussing clinical treatment with copper-containing agents, the clinical use of the anti-inflammatory copper-dependent metalloenzyme superoxide dismutase (SOD), should also be commented upon. Bovine SOD has been shown to reduce inflammation when given intra-articularly into the joints of RA patients. The discovery and evaluation of this agent may provide insights into the biochemical mechanisms of actions for all copper compounds.\(^24\) It is found that RA is usually associated with decreased intracellular SOD activity.\(^25\) This is interesting since SOD has anti-inflammatory activity. It is known that the cytosolic SOD is a copper/zinc-containing enzyme. Ceruloplasmin and therapeutic copper complexes have been shown to possess SOD-like activity.\(^23\)\(^,\)\(^26\) Hence the demonstrated physiological rise of ceruloplasmin in RA is suggested to represent a protective response. Consistent with this, a lack of rise of ceruloplasmin may increase the risk of chronic disease, as seen in copper-deficient animals with adjuvant arthritis.\(^23\)\(^,\)\(^26\) Biochemically, SOD can act protectively by detoxifying superoxide radicals discharged from activated phagocytes. The less toxic product H\(_2\)O\(_2\) thus formed can be further degraded by glutathione peroxidase in the presence of glutathione. The clinical use of bovine SOD has, however, been abandoned because it is considered to induce antibody formation.

Other metal complexes

The well documented antirheumatic efficacy of the chelating agent penicillamine\(^27\) is still of theoretical interest, although the practical usefulness of this drug is limited by its pronounced tendency to induce toxic side reactions. It is noteworthy that the chemical structure of penicillamine, and also its clinical effect profile, resemble those of gold thiomalate. Selenomethionine, which was used in our clinical study described above, is structurally related to penicillamine (Fig. 3).

Penicillamine is also presumed to mediate its anti-inflammatory effects via an inhibiting effect on synovial tissue macrophages, analogues to the proposed mechanism of action of gold complexes. It inhibits macrophage migration and stabilises the lysosomal membrane,\(^28\)\(^,\)\(^29\) thus reducing the induction of pro-inflammatory cytokines and oxygen free radicals. Being a strong copper chelator, it rapidly ties up free copper ions, forming a complex that acts as an efficient superoxide dismutating catalyst.\(^23\)

Another strong copper-binding agent with anti-inflammatory properties is 5-aminosalicylate, which is delivered into tissues on the degradation of the anti-inflammatory drug sulfasalazine. Again, the superoxide dismutase mimetic activity of the copper chelate may contribute to its therapeutic potency.\(^23\) In addition, aminosalicylate is capable of chelating free iron(III) cations. This property is relevant since the presence of catalytic amounts of free metal ions in an extracellular mixture of H\(_2\)O\(_2\) and superoxide leads to a spontaneous interaction that gives rise to the extremely reactive hydroxyl radical. Thus, the ultimate consequences of the radical release accompanying respiratory bursts of invading leukocytes depend on the iron status in the tissue.

High doses of zinc salts led to significant improvements in symptoms of rheumatoid arthritis in a clinical trial,\(^30\) but controversial results have been reported.\(^31\) When reaching into the intracellular space, zinc is a potent inductor of metallothionein, which is a protein tying up both copper and zinc, and which is also reported to act as an oxygen radical scavenger in biological systems.\(^23\)

Conclusion

Rheumatoid arthritis is characterised by increased activity of macrophages, which in cooperation with other inflammatory cells infiltrates the synovial tissue. The activated macrophages, monocytes and granulocytes generate reactive forms of oxygen which have been suggested to be mediators of inflammation, together with the pro-inflammatory cytokines, particularly TNF-\(\alpha\). It is tempting to hypothesise that TNF-\(\alpha\) is an enzyme inhibitor acting on SOD and GSH-Px in RA. Recently, administration of TNF-\(\alpha\) antibodies has been used therapeutically with good results.\(^2\) Gold is accumulated in the lysosomes of the macrophages, which are thereby immobilised, causing an arrest of the pro-inflammatory signaling. Zinc in high doses can also immobilise macrophages. Gold, zinc and copper can induce synthesis of the sulfhydryl-rich protein metallothionein. Copper is a component of the cytosolic enzyme SOD, and several copper-containing molecules including ceruloplasmin possess SOD activity. The anti-inflammatory activity of pharmacological copper complexes is attributed to their SOD activity. The therapeutic effects of penicillamine, may also be related to an antioxidative or membrane-protecting action. Increased intracellular levels of the selenium-containing enzyme GSH-Px can also accelerate the breakdown of reactive oxygen. Further research to evaluate the possible therapeutic effects of oxygen radical detoxification and of selenium supplementation in high doses in RA is of interest.

References


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