Role of high sensitivity C - Reactive protein and some of heavy metals in patients with rheumatoid arthritis

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Abstract

Background: Rheumatoid arthritis a chronic auto-immune condition is characterized by inflammation that contributes to the deterioration of joints, bones, tendons and ligaments. hs-CRP is a systemic inflammatory marker which can be used to predict events such as rheumatoid arthritis. Toxic and trace elements are among the several contributing factors proposed to participate in the pathogenesis of this disease.  

Objective: To evaluate hs-CRP and some heavy metals, such as lead, nickel, cadmium, chromium, zinc and copper, in patients with rheumatoid arthritis and to compare it with healthy control and to identify any possible correlation between these parameters.  

Method: This study was conducted in various hospitals in Baghdad Medical City, Iraq, from October 2019 to February 2020. The study included 50 Iraqi patients with rheumatoid arthritis and 40 healthy subjects in the control group. Enzyme - linked immunosorbent assay (ELISA) used for determination of hs-CRP and Atomic Absorption Spectrophotometry (AAS) used for the determination of lead, zinc and copper cadmium, chromium and nickel.  

Results: This study found that the levels of hs-CRP, cadmium, lead, nickel and copper in patients with rheumatoid arthritis were significantly higher than in healthy controls. While zinc and chromium levels were significantly lower in patients with rheumatoid arthritis than in healthy control (P > 0.001). The study was found a positive correlation between hs-CRP and disease activity in rheumatoid arthritis patients. We also found a positive correlation between lead and disease activity (DAS-28) and also a statistically highly significant positive correlation exists between DAS-28 and Cadmium in rheumatoid arthritis patients (P > 0.01) in this study.  

Conclusion: High sensitivity C reactive protein can be considered an important parameter for early detection of rheumatoid arthritis and can also be used to determine the activity of rheumatoid arthritis. High levels of cadmium, lead, nickel, copper and deficiency levels of Zinc and chromium may play a role in the development of rheumatoid arthritis itself.

Keywords: sensitivity C, Reactive Protein, heavy metals, patients, rheumatoid arthritis
Introduction:

Rheumatoid arthritis a chronic auto-immune condition, is characterized by inflammation that contributes to the deterioration of joints, bones, tendons and ligaments [1]. Rheumatoid arthritis is a long-term condition that causes inflammation of the joints and tissues around it. Toxic and trace elements are among the several contributing factors proposed to participate in the pathogenesis of this disease [2]. The condition is characterized by symmetrical chronic synovitis, which primarily affects small peripheral joints but can include nearly all joints with a synovial membrane. While it is reversible, this inflammatory process can lead to irreversible damage to the joints if left untreated and loss of function [3].

Rheumatoid arthritis may be the most common type of inflammatory arthritis. Chronic synovitis is a basic feature of this disease, which causes discomfort, stiffness and swelling, which is gradually accompanied by deterioration of cartilage, bone loss, resulting joint defects and systemic complications [4]. One of the main factors for assessing the pathophysiology of rheumatoid arthritis patients is oxidative stress. The combination of cellular immune and endogenous or exogenous antigens in the body induces reactive oxygen species and reactive nitrogen species in autoimmune disorders such as rheumatoid arthritis [5].

High sensitive C-reactive protein (hs-CRP) is a systemic inflammatory marker which can be used to predict events such as rheumatoid arthritis, stroke and myocardial infarction. Several studies have shown that hs-CRP is a major predictor of systemic inflammation, such as rheumatoid arthritis, both when stable and during exacerbations [6]. High sensitivity C reactive protein is a secreted inflammatory agent of the liver. It may be related to obesity and insulin resistance [7]. CRP (C reactive protein) and high sensitivity C reactive protein (hs-CRP) have been shown to be more closely linked to disease activity variables than ESR (erythrocyte sedimentation rate) [8].

Heavy metals influence the development of autoimmunity and one of most important autoimmune disorder is rheumatoid arthritis. Mercury (Hg), cadmium (Cd), arsenic (As), lead (Pb), cobalt (Co), nickel (Ni) and copper (Cu) exposure has been considered important in the development of rheumatoid arthritis. Although the toxicity of metal ions is not well known, but reactive oxygen species (ROS), such as hydrogen peroxide (H2O2), superoxide ions (O2-), nitrogen oxide (NO) and hydroxyl radical (OH) can be produced. The production of ROS play role in many human diseases including degenerative lung and heart conditions, rheumatoid arthritis, aging and Alzheimer disease [9].

Chromium is one of the most important elements in the human body. Have a major role to play in the maintenance of good health; Chromium may have a role in the regulation of glucose and lipid metabolism [10].
Zinc is an essential component for proteins that are involved in cell structures and cell membranes’ stabilization and is important biological feature for the human body and involved in many aspects of cellular metabolism. It plays an important role in (immune function, cell respiration, wound repair, protein synthesis, cell division, and DNA synthesis). Zinc nutritional deficiency or over absorption is also associated with many diseases, in particular immune disorders, such as rheumatoid arthritis [11]. Zinc prevents free radicals from occurring in the body, activates metallothion synthesis, promotes proliferation and osteoblast differentiation, and controls vitamin D activity. It also stops the parathyroid hormone that causes bone resorption [12].

The study aimed to test heavy metals such as lead, nickel, cadmium, chromium, zinc and copper in patients with rheumatoid arthritis and to compare them with healthy control

Method:

This study was conducted at Baghdad Teaching Hospital and at Ghazi Al-hariri Hospital in the Medical City of Bagdad, Iraq, from October 2019 to February 2020. It included 50 Iraqi patients with rheumatoid arthritis and 40 healthy subjects as a control. Eight milliliters of blood was aspirated from each control and patient subject, divided into two parts. The first one (4 ml) transferred into plain tube, allows 30 minutes to clot, at 2500 rpm, the serum was then isolated by centrifugation for 10 minutes used for measurements of the hs-CRP, nickel, chromium, copper and zinc. While, the second part (4 ml) was transferred into citrate containing tube to be used for determination of erythrocyte sedimentation rate (ESR), lead and cadmium. Enzyme linked immunosorbent assay (ELISA), Flam Atomic Absorption Spectrophotometry (FAAS) and Grafite Furnace Atomic Absorption Spectrophotometry (GFAAS) were used to determine these parameters. All statistical analysis and data reporting were performed using SPSS version 24. Difference of means that is significant according to t-test at p < 0.05.

Results:

Table 1: show mean levels of hs-CRP and heavy metals (μg/dl) in control and rheumatoid arthritis patients groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sample</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>Calculated t</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>hs-CRP</td>
<td>Control</td>
<td>0.582</td>
<td>0.195</td>
<td>-22.042</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>8.972</td>
<td>2.709</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lead</td>
<td>Control</td>
<td>14.48</td>
<td>2.953</td>
<td>-12.953</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>24.51</td>
<td>4.415</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cadmium</td>
<td>Control</td>
<td>0.161</td>
<td>0.028</td>
<td>-21.864</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>0.365</td>
<td>0.058</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromium</td>
<td>Control</td>
<td>0.169</td>
<td>0.028</td>
<td>10.897</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>0.103</td>
<td>0.028</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nickel</td>
<td>Control</td>
<td>0.015</td>
<td>0.004</td>
<td>-9.301</td>
<td>0.000</td>
</tr>
</tbody>
</table>
Patients | 0.024 | 0.005
---|---|---
**Zinc**
Control | 103.25 | 18.235 | 11.044 | 0.000
Patients | 69.24 | 7.735
**Copper**
Control | 103.25 | 18.235 | -17.510 | 0.000
Patients | 158.16 | 8.805

Figure 1: correlation between hs-CRP and DAS-28 in rheumatoid arthritis patients.

Figure 2: correlation between Lead and DAS28 in rheumatoid arthritis patients.
Current results showed that levels of hs-CRP, cadmium, lead, nickel and copper were significantly higher in rheumatoid arthritis patients than in healthy controls. While zinc and chromium levels were significantly lower in patients with rheumatoid arthritis than in healthy controls (P < 0.001) as shown in Table1. The study found a positive correlation between hs-CRP and disease activity in RA, this result is in agreement with Dessein et al, Figure1. Also a positive correlation exists between lead and disease activity (DAS-28) as shown in Figure2 and also a statistically highly significant positive correlation exists between DAS-28 and Cadmium in rheumatoid arthritis patients (P < 0.01) as shown in Figure3.

Discussion:

Figure3: correlation between Cadmium and DAS28 in rheumatoid arthritis patients.

Figure4: correlation between Copper and DAS28 in rheumatoid arthritis patients.

Figure1: correlation between Copper and DAS28 in rheumatoid arthritis patients.
Lead and cadmium stimulate the development of cytokines and lead can interfere with antigen presentation by inhibiting specific stimulation of Th1 lymphocytes while promoting Th2 lymphocyte presentation [13]. Chronic exposure to heavy metals, especially lead and Cd affects the immune system as a result immune system attacks on its self-molecules, which can lead to rheumatoid arthritis and other joint diseases [14].

Chromium is widely distributed throughout the body; infants have a higher Chromium concentration than adults [15]. On this basis we believe that the deficiency of chromium in the adults may have a role in the development of rheumatoid arthritis. The rationale for suggesting that chromium may help to prevent rheumatoid arthritis is that women after menopause taking a chromium supplement had increased plasma dehydro epiaandrosterone, a precursor to oestrogen which inhibits bone loss, and reduced urinary calcium and hydroxy proline excretion [16].

Nickel plays some important role in biological system such as in enzyme activity, hormonal control also in structure or function of RNA, DNA and protein [17]. however, nickel may be toxic at high concentrations that may reduce glutathione and protein-bound sulphhydryl groups, leading to the development of reactive oxygen species, including hydroxyl radicals, superoxide anion and hydrogen peroxide and this may lead to development of rheumatoid arthritis [18]

Zinc is an essential trace element in the body and a key factor in the immune response [19]. Zinc is the cofactor for many antioxidant enzymes that prevent cellular damage from free radicals including superoxide anion, hydrogen peroxide and superoxide radicals [20]. Zinc deficiency is therefore correlated with the inappropriate maturation and function of B and T cells, the imbalanced ratio between Th2 and Th1 cells, and the weakening of natural killer cells function [21]. Deficiency of zinc in rheumatoid arthritis patients may contribute to the development of rheumatoid arthritis and the progression of the disease itself, Zoli et al.,

Copper (Cu) is an important human element; however, a high-copper diet will encourage the development of IL 2 and IL-6 and alter the composition of white blood cells (WBCs), including an increase in lymphocyte counts and a decrease in neutrophil counts [22]. In addition, Copper may also increase the production of proinmformational cytokines, including tumor necrosis factor-a and IL-1b, in several different cell types [23]. The copper level in patients with rheumatoid arthritis is correlated with disease activity markers such as ERS, C-reactive protein, and DAS-28. [24]. The copper levels in rheumatoid arthritis patients are high when compared with healthy control group and also found positive correlation between Copper and DAS-28 as show in Figure4. These findings show that copper can be significant in the determination of inflammation levels in rheumatoid arthritis patients [25].

Conclusion:

High sensitivity C reactive protein can be considered an important parameter for early detection of rheumatoid arthritis and can also be used to determine the activity of rheumatoid arthritis. High levels of cadmium, lead, nickel, copper and deficiency levels of Zinc and chromium may play a role in the development of rheumatoid arthritis itself.
References:


