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Cadmium and Zinc in the Aetiology of Inflammatory Arthritis

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ABSTRACT

Background*: Autoimmune diseases is observed globally, with rheumatic diseases being the most prevalent among them. CD and Zn have their role in autoimmune diseases.* ***Objectives****: To investigate the role of cadmium (Cd) and zinc (Zn) in rheumatoid arthritis (RA) pathogenesis by comparing their serum levels in RA patients to healthy controls.* ***Materials and Methods****: Biochemical studies were conducted to measure Zn and Cd levels using atomic absorption spectrophotometry and evaluate rheumatoid factor & anti-CCP levels with ELISA.* ***Results:*** *Patient demographics showed no significant differences in sex, age, and smoking status between RA patients (n=50) and controls (n=50). Serum Zn levels were lower in RA patiets (0.66 ± 0.08 µg/L) compared to controls (0.72 ± 0.11 µg/L; p=0.017), Serum Cd levels were higher in RA patients (0.99 ± 0.28 ng/L) compared to controls (0.89 ± 0.21 ng/L; p=0.031).* ***Conclusion****: The study suggests an association between elevated serum cadmium and reduced serum zinc levels in RA patients, emphasizing the need for further research on environmental factors and autoimmune disease.*

Keywords: Cadmium, Zinc, Autoimmune Diseases, and Inflammatory Arthritis.

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INTRODUCTION

There has been a steady raise in the prevalence of autoimmune diseases over the world, particularly in the developed, industrialized western and northern countries. Rheumatic diseases is rising the most Among autoimmune diseases, followed by endocrine and gastrointestinal diseases.[1]. In daily clinical practice rheumatic diseases are an important issue where patients potentially suffer from severe chronic pain, joint damage, increasing disability, early retirement and even death [2] The three most common types of inflammatory arthritis (IA) are rheumatoid arthritis (RA) affects about 1%, psoriatic arthritis (PsA), and ankylosing spondylitis(AS). These are chronic, progressive autoimmune diseases whose pathogenesis is still not fully understood [3][4].

Inflammatory pathway for these diseases is the activation of T helper cells 17 (Th17), resulting in an increase in pro-inflammatory cytokines, tumour necrosis factor (TNF-α), and the joint inflammation process [5][6]. Genetic factors play an essential role in autoimmunity, but they do not explain all the differences in IA prevalence among populations [7]. As in many other disorders, unfavourable genetic factors are brought forth in specific environmental conditions. Inflammation and various environmental contaminants (immune adjuvants, immunotoxic substances) can induce or exacerbate autoimmunity. Numerous factors have been investigated in association with IA risk, including smoking, diet, physical activity, vitamin D deficiency, alcohol use, medications, and infections [8]. It is considered that tobacco smoking is significantly associated with RA and PsA risk in the general population; in turn, its impact on AS is linked mainly to disease progression [9] [10].The influence of smoking on the autoimmune process has been explained by several hypotheses, involving such factors as increased oxidative stress, general inflammation, and triggering autoantibody

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production [9][11][12]. As there is a well-documented link between cigarette smoking and arthritis, a growing interest also has been observed in the role of different environmental pollutants (especially cadmium compounds) in rheumatic diseases [13][14].

Cadmium is a major public health concern, as it is widespread and toxic and contributes to the development of numerous diseases [15], [16] . Both in work settings and in daily life, there are many potential sources of cadmium, such as smoking (including passive smoking), vehicle exhaust, low emissions from coal-fired furnaces, recycling of electronic waste, the manufacture of nickel-cadmium batteries, industry (dyeing, textiles ,plastics, mining…), as well as cosmetics or contaminated food [17][18]. The link between cadmium and IA however is not clear, having been studied mainly in patients with RA. A Korean cross-sectional study of 53,829 residents found a significant positive association between serum cadmium levels and the incidence of RA [19]. Similar relationships have been observed by other authors [20][21][22]. There is evidence that exposure to metals (including cadmium) may cause autoimmunity and epigenetic effects, thereby contributing to the incidence and prevalence of autoimmune diseases [23][24]. Some metal compounds modify cytokine production, leading to an imbalance between CD4 Th1 and Th2 cell activation and altering the pro- and anti-inflammatory cytokine profiles. This immune dysregulation can result in impaired cell-mediated immunity and /or aberrant humoral immunity, and, consequently, an autoimmune disease [23]. The influence of cadmium on the development of IA may, therefore, be related to the toxic effect on the immune system and its dysregulation, this impact on the development of IA can be linked to an anti-pro-oxidative imbalance and the subsequent induction of oxidative stress and inflammatory processes [25].

Also, Cadmium inhibits absorption of iron by the suppression of iron transport in duodenal enterocytes [26].Iron deficiency and anaemia of chronic disease are often found in patients with autoimmune diseases and chronic inflammation (including joint diseases) [27]. These conditions increase cadmium absorption and accumulation in the body [26].Low haemoglobin levels are associated with disease activity, joint damage, pain, and functional impairment; they may predict worse outcomes in RA patients [28].

Low zinc levels in the blood are reported in patients with RA. Zinc is a cofactor for more than 3000 proteins and, as a signalling ion, affects many pathways relevant to joint disease [29].

Cadmium absorption increases under zinc deficiency conditions, similar to iron. Cadmium dust inhalation can cause macrophage activation, inflammation, and IA development [30][31] conclude that a genetic variation in zinc transporters influences blood cadmium concentrations (Cd-B), individuals with a certain genotype of these transporters have higher Cd-B. It seems likely that people with this genetic condition are more susceptible to developing the diseases to which cadmium exposure may contribute. Zn is a crucial element in a series of cellular functions as normal growth, protein metabolism, membrane stability, and metalloenzyme functions [32]. Zn, has several other effects on immune response, complement system, lysosomal enzyme release, and macrophage functions [33]. Zn is also indispensable in many steps of the inflammatory reactions. Among these are prostaglandin biosynthesis, stimulation of lymphocytes and immune response, and scavenging of toxic free oxygen radicals [34][35] Zn is likewise an important element in collagen tissue formation and bone metabolism [36]

Aim of study

This study aimed to explore the possible role of Cd and Zn in the pathogenesis of rheumatoid arthritis (RA) by comparing serum levels of these elements in patients with RA to those individuals without the RA.

MATERIALS AND METHODS

Biochemical studies

Determination of Zn levels

The serum levels of Zn were determined at the Chemical Analysis by flameless atomic absorption spectrophotometry using an atomic absorption spectrophotometer (Shimadzu, GFA-7000f, Japan).

Zn was measured at wavelength 213.9 nm using a slit width of 0.5 nm and lamp current 5 mA. The levels of Zn were gained by extrapolation of the criterion curve followed by multiplication with the dilution Factor.

Determination of Cd levels

The serum levels of Cd were determined at the Chemical Analysis by flameless atomic absorption spectrophotometry using an atomic absorption spectrophotometer (Shimadzu, GFA-7000f, Japan).

Cd was measured at wavelength 228.8 nm using a slit width of 0.7 nm and lamp current 8 mA. The levels of Cd were gained by extrapolation of the criterion curve followed by multiplication with the dilution Factor.

Rheumatoid factor & Anti-CCP

Rheumatoid factor & Anti-CCP hs® (high sensitive) is an ELISA-based, automated, in-vitro test system for the quantitative determination of IgG antibodies against cyclic citrullinated peptides (CCP) in human serum or plasma.

Statistical Analysis

Quantitative variables were expressed as means ± standard deviation. Parametric data were analysed by the t-test, while the Mann–Whitney U test was applied for non-parametric data. Correlations between disease and cadmium and zinc levels. All statistical analyses were conducted with the SPSS v26. Statistical significance was set at $p < 0.05$.

RESULTS

Table (1) shows a non- significant difference in sex, age and smoking between OA patients and control groups.

Table (1): Described and the demographic characteristics in the OA patients and control groups.

Variable		Patients(OA) (*n=50*)	Controls (*n=50*)	P.value
Sex	**Male**	38	37	0.818
	Female	12	13	
Smoking	**Smoker**	25	17	0.107
	Non-smoker	25	33	
Age(year)		Mean± SD	Mean± SD	0.32
		42.88 ± 14.22	44.81 ± 13.33	

In comparing the mean levels of Zn,Cd & Anti ccp between the control group and RA patients, Zn levels were decreased in the RA group (0.66 ± 0.08 µg/L) compared to (0.72 ± 0.11 µg/L) in the control group (P.value =0.017).while increase in levels of Cd & Anti ccp (0.99 ± 0.28 ng/L)&(84.40 ± 53.17 U/ml) in RA group compared to (0.89 ± 0.21 ng/L)&(13.64 ± 4.55 U/ml) in control group (P.value = 0.031,0.001) respectively, Table 2.

Table (2): Relationship of Zn, Cd & Anti ccp with OA patients and controls.

Parameters	Patients (*n*=50) Mean± SD	Controls (*n*=50) Mean± SD	P.value
Zinc	0.66 ± 0.08	0.72 ± 0.11	0.017
Cadmium	0.99 ± 0.28	0.89 ± 0.21	0.031
Anti ccp	84.40 ± 53.17	13.64 ± 4.55	0.001

DISCUSSION

We noticed the non- significant statistical differences in sex, age and smoking between OA patients and control groups.as in table (1). But ,we observed that Zn levels were decreased in patients with RA compared to non-RA individuals (0.66 + 0.08 vs 0.72 + 0.11) and p value (0.017) while there were increase in Cd levels in RA patient in compare with non RA individuals (0.99 + 0.28vs0.89 + 0.21) and p value(0.031). Previous reports have indicated that the serum zinc concentration is lower in patients with RA than in healthy individuals [37] .Zinc has a major influence on the inflammatory process which occurs in patients with rheumatoid arthritis, the enzyme superoxide dismutase which is often deficient in zinc , zinc is also required to improve the scavenger process of oxygen free radicals generated during phagocytosis by increasing the bioavailability of enzyme superoxide dismutase [38].So, the treatment with zinc supplements were suggested and optimizing the zinc supply along with other standard medications in order to reduce RA activity[39]. The results of decrease levels of Zn in RA patients were agree with those studies of Ullah et al [40] Ali H et al [41],Sahebari M et al [42]and Farid Y et al [43].

Our study showing that patients with RA have markedly elevated serum Cd levels compared with control group(0.99 + 0.28vs0.89 + 0.21) and p value(0.031). Cigarette smoking, which is an established risk factor for RA[44] is also a source of cadmium exposure, with serum levels raised three-fold in current smokers [45], A few reports, higher concentrations of cadmium have been found in the blood, independent of smoking habits [46] .Nanoparticles of cadmium in dust and cigarette smoke are believed capable of inducing a lung process which could play a part in the initiation of RA; further, in a commonly used animal model of RA (collagen-induced arthritis), cadmium chloride in drinking water can potentially exacerbate some of the biological features that may occur during the disease's induction phase [47].

CONCLUSION

The study suggests an association between elevated serum cadmium and reduced serum zinc levels in RA patients, emphasizing the need for further research on environmental factors and autoimmune disease.

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