STUDY OF THE ROLE OF MERCURY POISONING IN RHEUMATOID ARTHRITIS PATIENTS AND ITS RELATION WITH ZINC AND COPPER LEVELS

BY

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ABSTRACT

The present study aimed to evaluate role of increased blood levels of mercury on rheumatoid arthritis patients in Dakahlia governorate and to investigate the correlation between levels of zinc and copper in the blood with that of mercury and their relation to the disease activity. The present study included 32 patients (test group) suffering from rheumatoid arthritis (RA) attending the rheumatology and rehabilitation out patient clinic, Mansoura university hospital and 30 healthy volunteers (control group) matched according to age, sex, residence and occupation. All patients of the test group were evaluated by Disease Activity Score (DAS 28) and accordingly, the test group included 10 patients (31.3%) with mild to moderate DAS and 22 patients (68.7 %) with high DAS (6 patients were with dental filling amalgam and 16 were free from amalgam). Blood mercury, zinc and copper levels were determined using atomic absorption spectrophotometer. The present study observed significant increase in blood mercury levels while, blood zinc and copper levels were significantly decreased in the test group when compared to the control group. As regards the presence of dental amalgam, the present results revealed that the highest mercury levels (mean ±SD was 13.13±0.58 μg/dl), the lowest zinc levels (mean ±SD was 108.28±7.89 μg/dl) and relatively the lowest copper levels (mean ±SD was 7.26±0.73 μg/dl) were observed in severe RA activity score patients with dental filling amalgam. There were a significant negative correlation between blood mercury and zinc levels and DAS while, there was non-significant negative correlation was found between blood copper levels and DAS. In conclusion, the current study provided some support for the hypothesis that dietary intake or inhalation of toxic elements (mercury), most probably through dental filling amalgam, may increase the risk of rheumatoid arthritis.

Key words: *Mercury, Rheumatoid Arthritis, RA, DAS 28, Zinc, Copper.*

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic disease, usually manifesting as inflammation of multiple joints. It is characterized by a number of extra-articular manifestations, including rheumatoid nodules, vasculitis, heart or lung disease, anemia, and peripheral neuropathy (Yildirim et al., 2004).

The cause of RA is not known, but many possible etiologies have been identified. Important etiologic clues have been suggested by the identification of unique features of populations with a predilection for RA. The observation of geographic clustering of the disorder in ancient skeletons implies an important role for environmental factors, which are still poorly defined. In addition to environmental factors, hormonal, genetic, infectious, and other variables also contribute to RA in some manner (Cooper, 2008; Ala et al., 2009).

Hultman and Enestrom (1992) found that mercury elicited autoimmunity in genetically homogeneous, mercury-sensitive mice; at a body burden similar to that reported in some occupationally exposed humans; after given them oral mercuric chloride in drinking water for 10 weeks.

Autoimmune diseases may be induced by physical and/or chemical environmental factors. Yoshida and Gershwin (1993) indicated three general mechanisms that mercuric chloride may induce autoimmune disease. First, oxidative damage probably is a frequent process involved in disease induction and pathogenesis. Second, mercuric chloride generates antigen-specific immune responses that could then cross-react with self-tissues. Third, it may also modulate the immune system.

As acute mercury poisoning is uncommon, diagnosis is difficult if the exposure is not manifest. It has usually a slow onset and non-specific symptoms (Karata_ et al., 2002).

Mercury-containing compounds have historically been used in dental amalgams, Chinese traditional medicines, and skin-lightening creams (Liu et al., 2008). Dental amalgams are often called silver fillings, primarily as a marketing tool that describes their color. Mercury is the primary component, making up close to 50% of the content; copper is next, comprising almost 30%. The remaining 20% is divided among tin, silver, and zinc (Huggins, 2007). Other methods of exposure to mercury include consumption of sea food (Clarkson et al., 2003).

The dental amalgam controversy refers to the conflicting views over the use of it as a filling material mainly because it contains the element mercury. The accepted reference on absorbed dose of mercury from amalgam fillings comes from the World Health Organization proceedings (1991). The average person in the industrial world with an average number of amalgam fillings, and no occupational exposure to mercury would absorb between 3 - 17 μg per day, with an average of 10 μg, from the fillings; 2.3 μg from all dietary sources; and 0.3 μg from all other environmental sources.

Studies have yet to fully appreciate the potential relationship between RA and the body's exposure to mercury from a variety of sources, including dental amalgams so the present study aimed to evaluate role of increased blood levels of mercury on rheumatoid arthritis patients in Dakahlia governorate and to investigate the correlation between levels of zinc and copper in the blood with that of mercury and their relation to the disease activity.

MATERIAL AND METHODS

Subjects:

The present study conducted on 32 patients suffering from rheumatoid arthritis (RA) attending the rheumatology and rehabilitation out patient clinic Mansoura University Hospital served as test group. Control group included 30 healthy volunteers who matched according to age, sex, residence and occupation. Written informed consent was obtained from the patients and control group.

Methods:

I. Disease activity in patients with rheumatoid arthritis was determined according to Disease Activity Score (DAS 28) Test:

The DAS includes the Ritchie Articular Index for joint tenderness (RAI), a 44-joint swollen joint count (SJC), erythrocyte sedimentation rate (ESR), and general health (GH) assessment on a visual analog scale (Van der Heijde et al., 1990; Van Riel and Schumacher, 2001).The DAS is most easily calculated using a programmed calculator.

DAS 28 score of higher than 5.1 is indicative of high disease activity, whereas a DAS 28 below 3.2 indicates low disease activity. A patient is considered to be in remission if they have a DAS 28 lower than 2.6.

II. Biochemical studies :

Analysis of the studied heavy metals and trace elements [mercury (Hg), zinc (Zn) and copper (Cu)] was done by Perkin Elmer 2380 Atomic Absorption Spectrophotometer after wet ashing using reagent-grade HNO_3 and $HClO_4$ according to Eads and Lambdin (1973) and Stockwell and Corns (1993). Instrument start- up and optimization were carried out as detailed in the operating manual. The source of the flame was an air- acetylene mixture. Hydride generation method was used for Hg. Wavelengths were set at 253.7, 213.9 and 324.8 nm for Hg, Zn and Cu respectively. Working standard solutions were prepared by appropriate dilution of stock solutions. Preparation of standards and samples was carried out under clean conditions using deionized water. All chemicals and reagents used were of ultra-pure reagent grade (BDH laboratory reagents, Ltd Poole England). All glassware were washed three times with deionized water, and then soaked in 20 % nitric acid over-

night. After soaking the glassware were rinsed three times with deionized water and dried. Quality assurance was achieved by measuring blank test solutions.

Statistical analysis:

Data were compared by using student's t-test (to compare two groups) and ANOVA test for multiple groups' comparison. Pearson Correlation was used to test association between variables. Significance was considered when P value is less than 0.05. These data were run on an IBM compatible personal computer by using MedCalc® program version 10.0.1 (Schonjians et al., 1995).

RESULTS

The age of the test and control groups was ranged between 28 to 62 years old with a mean ± SD of 44.87±12.1 and 43.79 ±13.5 years respectively. The ratio between male and female in the test group was 3:29 while, it was 3:27 in the control group. There were no differences between male and female results and these finding may be explained by the small male sample size included in the study.

According to rheumatoid arthritis disease activity score (DAS 28), the test group included 10 patients (31.3%) with mild to moderate disease activity score and 22 patients (68.7%) with high disease activity score [6 patients were with dental filling amalgam (27.3%) and 16 were with no dental filling amalgam (72.7%)] as shown in Table 1.

Blood mercury levels were significantly increased in the test group in comparison to the control group (P<0.001) while, blood zinc and copper levels were significantly low in the test group compared to the control group (P<0.001) (Table 2).

As regards the blood metals level, the highest mercury levels (mean ±SD was 13.13±0.58 µg/dl), the lowest zinc levels (mean ±SD was 108.28±7.89 µg/dl) and relatively the lowest copper levels (mean ±SD was 7.26±0.73 µg/dl) were observed in severe rheumatoid arthritis (RA) activity score patient with dental filling amalgam (Table 3 and Figures 1-3).

The disease activity score (DAS) was shown to have significant positive correlation with blood mercury levels (r= 0.65, p<0.001), significant negative correlation with blood zinc levels (r= -0.60, p<0.001) and non-significant negative correlation with blood copper levels (r= -0.09, P= 0.6) (Table 4).

Results of this study showed non-significant negative correlation between blood mercury and zinc levels in all studied groups while, there were also non-significant negative correlation between

blood mercury and copper levels in all studied group except the group of severe RA disease activity score having dental filling amalgam as there was a non-significant positive correlation between both metals levels (Table 5).

DISCUSSION

The aim of the present study was to evaluate role of increased blood levels of mercury on rheumatoid arthritis patients in Dakahlia governorate and to investigate the correlation between levels of zinc and copper in the blood with that of mercury and their relation to the disease activity.

The test group in the present study was classified according to rheumatoid arthritis disease activity score (DAS 28) into 10 patients (31.3%) with mild to moderate disease activity score and 22 patients (68.7%) with high disease activity score [6 patients were with dental filling amalgam (27.3%) and 16 were with no dental filling amalgam (72.7%)].

The DAS 28 score is used extensively to evaluate disease activity in patients with rheumatoid arthritis (RA). It is a composite index that provides clinicians with a simple and objective assessment of the patient's level of disease activity and progression (Prevoo et al., 1995).

In the present results, blood mercury levels were significantly higher in the test group (RA) than the control group while, blood zinc and copper levels were significantly lower in the test group than the control group.

Moreover, the correlation between the disease activity score (DAS) and the metals level showed a significant positive correlation with blood mercury levels, significant negative correlation with blood zinc levels and non-significant negative correlation with blood copper levels.

Inman and Chiu (2009) observed that mercury-exposed rats had a marked exacerbation of the histopathological severity of the arthritis, and the infiltration was predominantly neutrophilic.

In addition, Kim et al. (2002) stated that rheumatoid arthritis aggravated by mercury intoxication probably through increasing the production of inflammatory cytokines (TNFa) tumor necrosis factor alpha and increased oxidative stress and free O2 radicle production.

The participation of trace elements, especially copper, manganese and zinc, in the normal development and maintenance of the skeleton is, at least in part, related to their catalytic functions in organic bone matrix synthesis or in the functioning of cells of bone or cartilage (Grynpas, 1990).

Zinc is required for multiple cellular tasks, and especially the immune system depends on a sufficient availability of this essential trace element. During the last decades, many studies attempted to affect the outcome of various diseases by zinc supplementation. These efforts either aimed at supporting immunity by zinc administration or at correcting a loss of zinc secondary to the disease to restore the zinc-dependent functions of the immune system (Overbeck et al., 2008).

In agreement with the current results, Afridi et al. (2012) who stated that the deficiency of zinc may be a synergistic risk factors associated with rheumatoid arthritis.

Moreover, Mierzecki et al. (2011) observed that the mean hair zinc content was significantly lower in rheumatoid arthritis (RA) patients as compared to healthy individuals.

Accordingly, Evans and Halliwell (2001) concluded that zinc is a key component of the two major superoxide dismutase enzymes which has been shown to fight against the reactive intermediates that are linked to joint damage in arthritis.

Önal et al. (2011) explained the decrease in zinc levels and elevation in copper levels observed in the patients with rheumatoid arthritis relative to controls as probably due to the defense response of patient and is mediated by inflammatory-like substances.

In agreement with the current results, Mierzecki et al. (2011) as observed a negative correlation between the erythrocyte zinc levels and the activity score in the rheumatoid arthritis patients.

In agreement with the current study, Afridi et al. (2012) showed that the mean concentration of copper was found to be lower in the scalp hair samples of rheumatoid arthritis patients of both genders.

On the contrary, Yazar et al. (2005) found that copper levels were significantly higher in patients with RA than those of healthy subjects.

As regards the blood metals level, the current work observed the highest mercury levels (mean 13.13±0.58 μg/dl), the lowest zinc levels (mean 108.28±7.89 μg/dl) and relatively the lowest copper levels (mean 7.26±0.73 μg/dl) were observed in severe rheumatoid arthritis (RA) activity score patients with dental filling amalgam.

In accordance, Mutter et al. (2005) agree that dental amalgam fillings leach mercury into the mouth, but studies vary widely in the amount and whether such amount presents significant health risks. Estimations run from 1-3 μg per day up to 27

μg/day. The effects of that amount of exposure are also disputed and currently dental amalgam is approved for use in most countries, although Norway, Denmark, and Sweden are notable exceptions.

Besides, Gleissner et al. (1998) indicated that silver amalgam fillings increased the risk of autoimmunity, multiple sclerosis, and impaired immune responses.

In addition, Clarkson et al. (2003) who stated that patients with rheumatoid arthritis particularly those with multi-dental filling amalgam demonstrated highly significant increase in blood mercury level with concomitant elevation of disease activity score. Dental filling amalgam is known to be a major source of chronic mercury intoxication.

The present study observed non-significant negative correlation between blood mercury and zinc levels in all studied groups while, there were also non-significant negative correlation between blood mercury and copper levels in all studied group except the group of severe rheumatoid arthritis disease activity with dental filling amalgam as it was found non-significant positive correlation between both metals levels. These findings may be explained by the fact that mercury is the primary component of dental amalgam, making up close to 50% of the content and copper formed the second component as comprising almost 30%.

Noor et al. (2002) observed that mercury intoxication affect zinc levels leading to deficiency of principal antioxidant enzyme, CuZn-Super oxide dismutase which has a role in various diseases.

CONCLUSION

The results of this study provided guidance to clinicians and other professionals investigating deficiency of essential trace elements and level of toxic elements (mercury) in healthy and arthritis patients. This study also provides some support for the hypothesis that dietary intake of toxic elements (mercury), most probably through dental filling amalgam, may increase the risk of rheumatoid arthritis and related disorders. These results propose that essential and toxic elemental measurements may be performed on patients to test whether their concentration may serve not only as markers of rheumatoid arthritis and their remedies but also as predictors of adverse outcomes.

RECOMMENDATION

The current study recommends the governments of respective countries to ensure mercury free air, water and food by making strict laws regarding contaminating industrial units, ensuring proper disposal of mercury garbage and encouraging proce-

dures without use of mercury. Media also should raise an attention against any negligence on part of government besides educating the population about mercury hygiene. Scientists should work towards making vaccines in which mercury is not a preservative and dental filling free from mercury.

Table (1): Classification of the test group patients according to disease activity score (DAS 28).

DAS 28		Number (n=32)	Percentage (%)	Total (100%)
Mild to moderate disease activity		10	31.3	31.3%
Severe disease activity	Patients with dental filling amalgam	6	27.3	68.7%
	Patients with no dental filling amalgam	16	72.7	

Table (2): Comparison between blood metals level in the studied groups.

Blood metals level (µg/dl)	Control group (n=30) Mean± SD	Test (RA) group (n=32) Mean ± SD	t test	*p*
Mercury (Hg)	3.7 ± 0.30	11.12 ± 1.54	16.54	0.001
Zinc	250.83 ± 105.18	115.38 ± 10.17	7.33	0.001
Copper (Cu)	11.58 ± 1.20	7.32 ± 0.65	15.10	0.001

RA: rheumatoid arthritis.
$p \leq 0.05$ was considered as significant.

Table (3): Comparison between blood metals level and disease activity score (DAS 28) in studied groups.

Variables		Control group (n=30)	Mild to moderate RA disease activity score (n=10)	High RA disease activity score (n=22)		ANOVA	p
				RA patient with dental filling amalgam (n=6)	RA patient with no dental filling amalgam (n=16)		
		Mean ± SD	Mean ± SD	Mean± SD	Mean ± SD		
Blood metals level (µg/dl)	Mercury	3.7 ± 0.30	9.73±1.15	13.13±0.58	11.24±1.04	227.7	<0.001
	Zinc	250.83 ± 105.18	123.63±10.27	108.28±7.89	112.88±7.60	17.4	<0.001
	Copper	11.58 ± 1.20	7.40±0.38	7.26±0.73	7.29±0.77	72.7	<0.001
Disease activity score (DAS 28)		----------	3.53±0.12	5.79±0.17	5.62±0.19	518.3	<0.001

p≤ 0.05 was considered as significant.

Table (4): Correlation between blood metals level and disease activity score (DAS 28).

Blood metals level (µg/dl)	Disease activity score (DAS 28)		
	r	p	95% confidence interval
Mercury	0.65	<0.001	0.39 to 0.82
Zinc	-0.60	<0.001	-0.78 to -0.32
Copper	-0.09	0.6	-0.42 to – 0.26

p≤ 0.05 was considered as significant.

Table (5): Correlation between blood mercury and zinc and copper levels in studied groups.

Variables		Blood mercury level (µg/dl)			
		Control group (n=30)	Mild to moderate RA disease activity score (n=10)	High RA disease activity score (n=22)	
				RA patient with dental filling amalgam (n=6)	RA patient with no dental filling amalgam (n=16)
Blood Zinc level (µg/dl)	r p 95% confidence interval	-0.3 0.3 -0.75 to 0.31	-0.5 0.1 -0.87 to 0.18	-0.2 0.6 -0.87 to 0.72	-0.2 0.4 -0.63 to 0.33
Blood Copper level (µg/dl)	r p 95% confidence interval	-0.02 0.9 -0.58 to 0.55	-0.3 0.3 -0.81 to 0.34	0.7 0.08 -0.15 to 0.97	-0.05 0.8 -0.54 to 0.45

RA: rheumatoid arthritis.
p≤ 0.05 was considered as significant.
r : correlation coefficient.

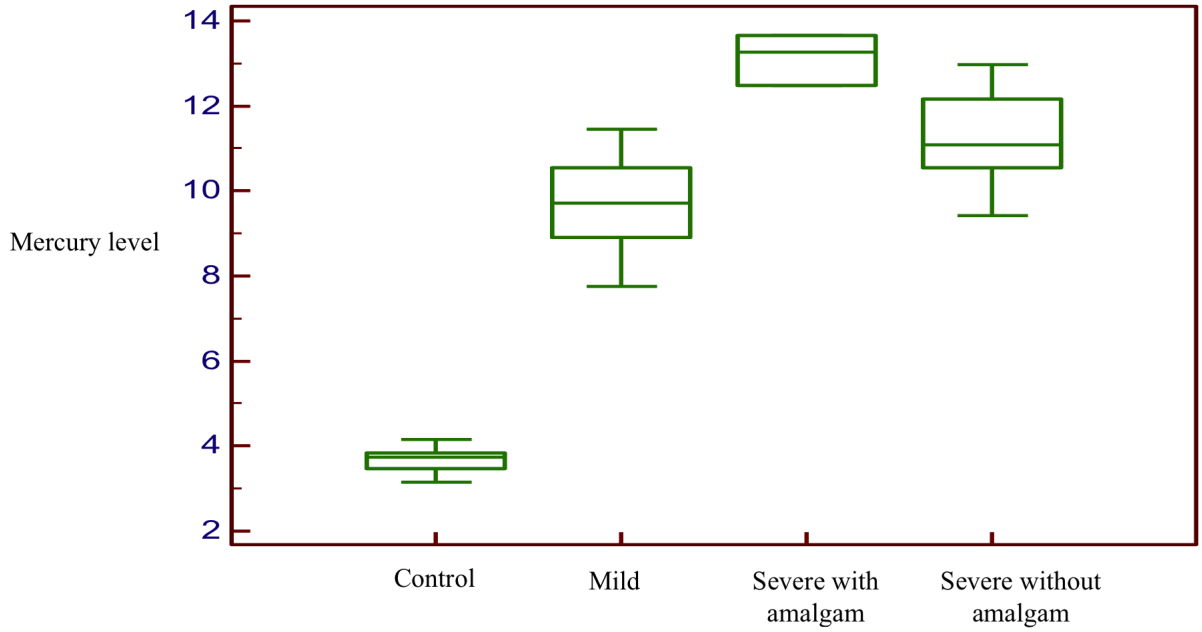

Figure (1): Blood mercury level in relation to disease activity score in the studied groups.

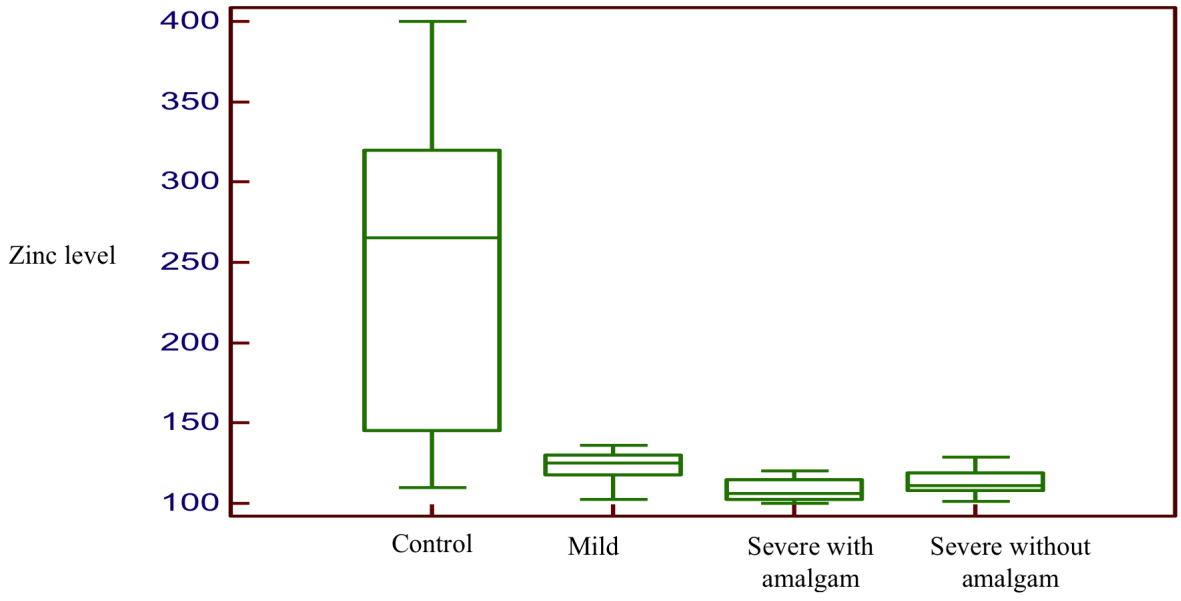

Figure (2): Blood zinc level in relation to disease activity score in the studied groups.

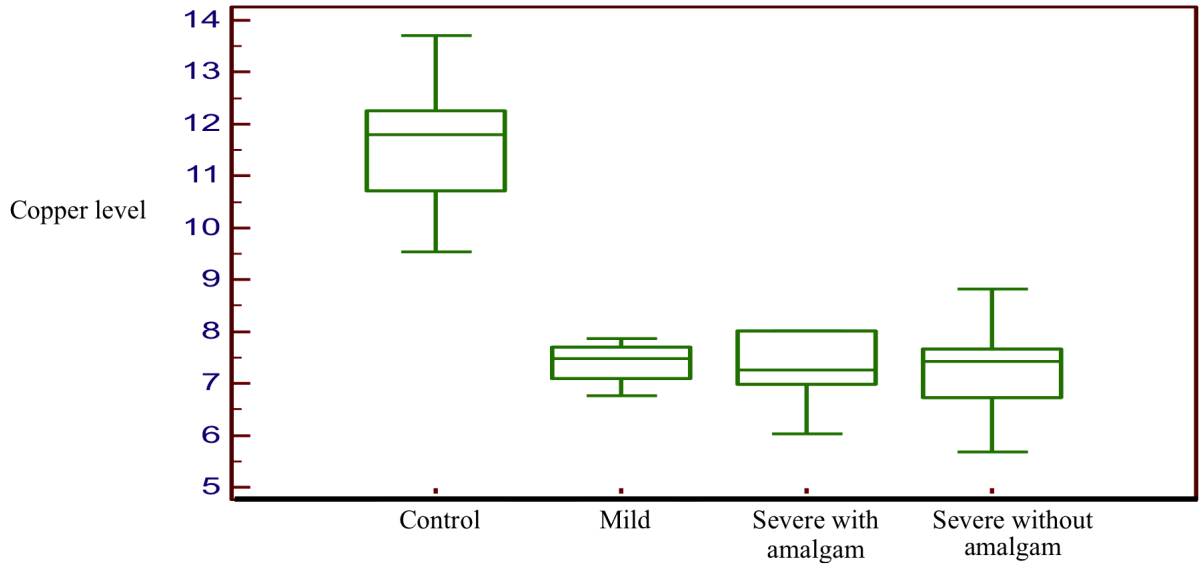

Figure (3): Blood copper level in relation to disease activity score in the studied groups.

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دراسة دور التسمم بالزئبق فى مرضى إلتهاب المفاصل الروماتيدى وعلاقته بمستوى الزنك والنحاس

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تهدف هذه الدراسة الى تقييم دور التسمم بالزئبق على المرضى الذين يعانون من التهاب المفاصل الروماتيدي في محافظة الدقهلية، والتحقق من العلاقة بين الزنك والنحاس من جهة والزئبق من الجهة الاخري وعلاقتها بنشاط المرض. وشملت هذه الدراسة ٣٢ مريضا (مجموعة الاختبار) الذين يعانون من التهاب المفاصل الروماتيدي المترددين علي العيادة الخارجية لقسم أمراض الروماتيزم والتأهيل ، مستشفى المنصورة الجامعي ، و ٣٠ متطوعا من الأصحاء (المجموعة الضابطة) المتطابقين وفقا للسن والجنس والإقامة والوظيفة. وجرى تقييم جميع المرضى بإختبار درجة نشاط المرض (DAS 28) وبناء على ذلك، شملت مجموعة الاختبار علي ١٠ مريضا (٣١,٣٪) كانت درجة نشاط المرض لديهم خفيفة الي متوسطة ، و ٢٢ مريضا (٦٨,٧٪) يعانون من ارتفاع درجة نشاط المرض منهم (٦ مرضى لديهم حشو الأسنان المملغم و ١٦ لا يوجد لديهم حشو اسنان). وتم تحديد مستويات الزئبق والزنك والنحاس في الدم باستخدام الامتصاص الذري. وقد لاحظت الدراسة زيادة ذات دلالة احصائية في مستوى الزئبق في الدم في حين انخفض مستوى الزنك والنحاس في الدم بقيمه ذات دلاله احصائية في مجموعة الاختبار بالمقارنة بالمجموعة الضابطة. وفيما يتعلق بوجود المملغم السني، فإن النتائج الحالية كشفت عن أن أعلى مستويات الزئبق (متوسط ١٣,١٣ +٥٨,٠ ميكروغرام / ديسيلتر)، وأدنى مستويات الزنك (متوسط ١٠٨,٢٨±٧,٨٩ ميكروغرام / ديسيلتر) وأدنى مستويات النحاس نسبيا (متوسط ٧,٢٦ ±٧٣,٠ ميكروغرام / ديسيلتر) كان في الحالات شديدة الالتهاب المفاصلي الروماتيدي التي لديها حشوة الأسنان المملغم. وكان هناك ارتباط إيجابي ذو دلالة احصائية بين مستوي الزئبق في الدم ودرجة نشاط المرض وارتباط سلبي ذو دلالة احصائية ايضا بين مستويات الزنك في الدم ودرجة نشاط المرض في حين، كان هناك علاقة عكسية ليس لها دلالة احصائية بين مستوى النحاس في الدم ودرجة نشاط المرض. وفي الختام، قدمت الدراسة الحالية بعض الدعم لفرضية أن المدخل الغذائي للعناصر السامة (الزئبق) على الأرجح من خلال حشو الأسنان المملغم، قد تزيد من خطر الاصابة بالتهاب المفاصل الروماتيدي.