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Research Article

Determination of Some Essential & Non-Essential Metals in Patients with Fibromyalgia Syndrome (FMS)

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ABSTRACT

Fibromyalgia is a chronic condition causing pain, stiffness, and tenderness of the muscles, tendons, and joints accompanied by sleep abnormalities, anxiety & depression, pathophysiologic mechanism remains unknown, no structural, inflammatory, metabolic or endocrine abnormality has been identified. Toxic heavy metal exposure such as aluminum, lead, mercury, cadmium, and mercury are recognized as being a major cause of many illnesses and also plays a large role in many psychological conditions such that occur in fibromyalgia and chronic fatigue syndrome. Trace metals are metals in extremely small quantities in cells and tissue. They are a necessary part of nutrition and physiology, furthermore, several studies reported the importance of calcium & magnesium in biological functions especially in nerve and muscle functions, insufficient serum level or imbalance of these elements in human tissues and body fluids, has been suggested as a contributing factor for the development of fibromyalgia. The main objective of this study is to estimate & evaluate possible role of some toxic, non -essential heavy metals (Cadmium & Lead) and whether the change of serum essential metals (Zinc& copper ,Magnesium & Calcium) levels which may be involved as a possible causative factor in patients with fibromyalgia Syndrome (FMS) and their deleterious effect, in a group of patients as compared to healthy control individuals This clinical study was performed on 31 patients (25 females and 6 males) with age range of (40–65) years attending Rheumatology department / Baghdad Teaching Hospital / Iraq and 21 healthy individuals , who were age and sex matched were included in the study as control group . All patients diagnosed as having primary fibromyalgia syndrome (FMS) fulfill the criteria of the American College of Rheumatology (ACR) of FMS, in which whole blood levels of heavy metals for lead & cadmium, serum trace elements (zinc & copper) levels were measured in toxicological department laboratory, using Atomic Absorption spectrometry, while serum levels of calcium & magnesium were measured by traditional spectrophotometric methods. Fibromyalgia tender points and accompanying symptoms (fatigue, sleep disorders, headache, severity of pain and fatigue, and ability to perform daily activities were estimated by using clinical interview to fill Revised Fibromyalgia impact questionnaire (FIQR) was used for diagnosis & functional assessment, Statistical testing was carried by Student's t-test; All results were expressed as mean ± SD, $P < 0.05$ was considered statistically significant. For heavy metals, The results of this study found that there is a significant difference as elevation of blood lead (Pb) and cadmium (Cd) levels. On the other hand, Serum levels of essential metals show that, zinc (Zn) is significantly decreased in FMS patients group, Whereas there is a significant elevation in copper (Cu) of FMS Patients group compared to control group, whereas Serum levels of calcium (Ca) & magnesium (Mg) is significantly reduced in FMS Patients group compared to control group where ($P<0.05$) is considered significant. Conclusion from the study results, showed that there is significant disturbances and imbalance of essential & non-essential metals level, in FMS patients, that could be contributed to the pathogenesis of fibromyalgia syndrome, this may be based on mimicry metal theory, affecting certain trace metal -catalyzed antioxidant enzymes leading to some neurological signs of fibromyalgia.

Keywords: essential, heavy, trace, metals and FMS.

INTRODUCTION

Fibromyalgia syndrome (FMS) is multi-factorial disorder characterized by widespread musculoskeletal pain and hyperalgesic tender points with no single identified organic cause, Fibromyalgia is not simply related to pain, and patients often have stiffness, fatigue and sleep disturbance among other physical and psychological symptoms as anxiety and depression, affecting up to 12% of the population , There is a strong female predominance of around (9:1) and the women are more likely to have more tender points on examination than are their male counterparts similar to chronic fatigue syndrome[1]. Diagnosis of fibromyalgia based on the American College of Rheumatology developed criteria (ACR) in 1990, involves widespread musculoskeletal pain in all four quadrants of the body, Present for at least 3 months with Hyperalgesic points positive on digital pressure in 11 out of 18 points[2]. No single pathophysiological causative

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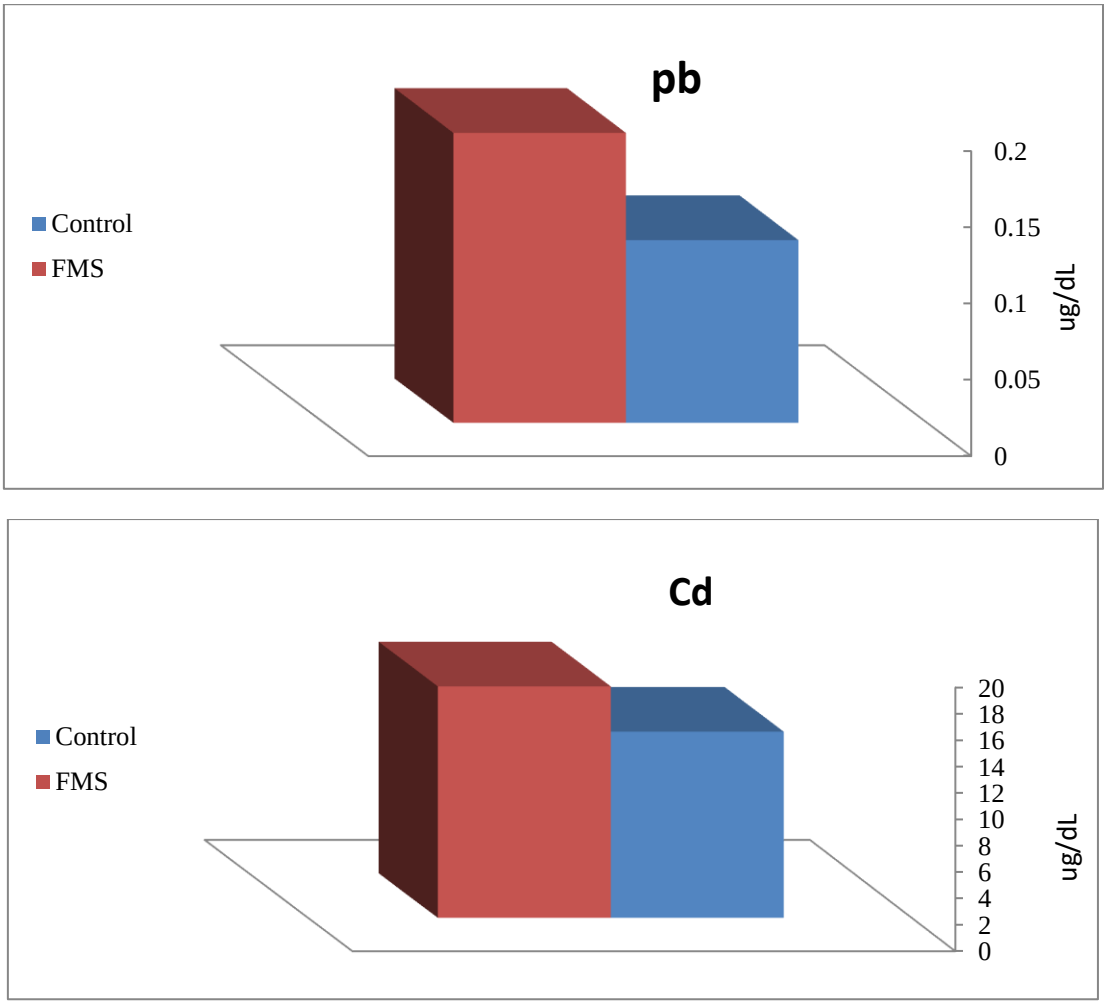

Figure 1: Blood Lead & Cadmium Levels in FMS Patients compared to Control Groups.

Table 1: Study groups characteristics for disease (FMS)and healthy subjects.

Parameter	Control N = 21	Patients N =31
Age (years) Mean ± S.D	36.5±11.46	40.21±13.27
Weight (kg) Mean ± S.D	78.27±4.97	75.50±3.39
Sex	%9.10 ♂ %90.9♀	♂ 8.3 % ♀ 91.7%

Values are presented as mean ± S.D.
N= Number of individuals in study groups
* Significantly different (P<0.05) compared to control group.

Table 2: Blood Lead & Cadmium Levels in FMS Patients compared to Control Groups.

Groups	N	Mean (FIQR) score	Blood Lead level (µg /dL)	Blood Cadmium level (µg /dL)
Control	21	32.38	14.12 ± 3.15	0.12 ± 0.011
Patients	31	78.58*	17.55 ± 4.15*	0.19 ±. 044*

Values are presented as mean ± S.D.
N= Number of individuals in study groups
* Significantly different (P<0.05) compared to control group.
FIQR=Revised Fibromyalgia Impact Questionnaire for Disease Severity Score.

mechanism has been identified, but the most acceptable theory to date suggests that fibromyalgia is a multifactorial syndrome characterized by abnormal processing of pain[3]. Abnormalities in pain processing have been identified at various levels in the peripheral, central, and sympathetic nervous systems, as well as the hypothalamic -pituitary-adrenal (HPA) axis and its role in stress[4]. Familial studies point to some genetic predisposition with up to 26% of relatives of patients with FMS reporting chronic widespread pain diagnosed in women[5]. Various

Table 3: Serum Zinc & Copper Levels in FMS patients compared to Control Group.

Groups	N	Mean (FIQR) score	Serum Zinc level (µg /dL)	Serum Copper level (µg /dL)
Control	21	32.38	93.21 ± 11.94	116.50 ± 14.35
Patients	31	78.58*	75.87 ± 5.5 *	145.80 ± 17.34 *

Values are presented as mean ± S.D..
N= Number of individuals in study groups
* Significantly different (P<0.05) compared to control group.
FIQR=Revised Fibromyalgia Impact Questionnaire for Disease Severity Score.

Table 4: Serum Calcium &Magnesium level in FMS patients compared to Control Groups.

Groups	N	Mean (FIQR) score	Serum Magnesium level (mg /dL)	Serum Calcium level (mg /dL)
Control	21	32.38	1.56 ± 0.23	9.18± 0.72
Patients	31	78.58*	1.12 ± 0.18 *	7.90± 0.55*

Values are presented as mean ± S.D..
N= Number of individuals in study groups
* Significantly different (P<0.05) compared to control group.
FIQR=Revised Fibromyalgia Impact Questionnaire for Disease Severity Score.

neurotransmitters seem to be involved in the central sensitization. Serotonin (5-HT) has a significant role in the modulation of pain and several studies have been carried out looking for modified levels of this molecule in the serum and in the cerebrospinal fluid (CSF). Serotonin is involved also in the regulation of mood and sleep and this could explain the association between fibromyalgia, sleep and mental disorders[6,7]. Other neurotransmitters also play a role. There are data from previous studies suggesting the involvement of norepinephrine, dopamine and substance P[8]. Psychosocial distress has been shown to predict onset of chronic widespread pain in population studies conducted with greater frequency in FMS patients than controls[9]. These numerous interacting factors may be the setting in which a stressful or psychological factors, can lead to a vulnerable health status and may be a trigger for FMS as reported for nearly a quarter to a third of persons with FM S[10]. Metal toxicity is documented and there are several studies in toxic interaction of metals in humans. Heavy or toxic non-essential metals comprise a group of metals human exposure occurs from environmental pollution arise from highest levels of these metals or due to their industrial use; considered to be harmful to human & have become a major cause of illness, aging and even genetic defects[11]. Long-term observations show that pollution by heavy metals occurs not only in anthropogenic areas but also in the distance from the sources of pollution[12]. A characteristic feature of heavy metals as beryllium, mercury, lead, cadmium, aluminum, antimony, bismuth, barium, uranium and others, that increases danger is due to their accumulation and very slow excretion[13] Chronic metal poisoning usually presents with symptoms affecting multiple systems, but is associated with three main types of symptoms: gastrointestinal, neuromuscular, and neurological. Signs include loss of short-term memory, depression, loss of coordination, numbness and tingling in the extremities, Fatigue, problems with sleep, headaches, stupor, slurred speech[14], Many key symptoms of fibromyalgia and chronic fatigue resemble classic signs of heavy metal toxicity, including fatigue, neuromuscular pain, depression/anxiety, and sleep disturbances[14] that may be shared by FMS symptoms.

Currently, more interest is shown in trace element interaction with plants, microorganism, and animals due to the established link of theses biological systems with human life. An essential trace element is an element in a sample that has an average concentration of less than 100 parts per million (ppm) atoms, or less than 100 micrograms per gram. In biochemistry, a trace element sometimes is also referred to as a micronutrient that is needed in minute quantities for the proper growth, development, and physiology of the organism[15]. Trace metals include iron, magnesium, zinc, copper, chromium, arsenic, molybdenum, manganese, selenium generally regarded as essential for human health in trace amounts, essential because they form an integral part of one or more enzymes involved in a metabolic or biochemical process. The primary role of such elements is as a catalyst, and only trace amounts are necessary for cellular function[16]. Trace metals are depleted through the expenditure of energy by various metabolic processes in living organisms. They are replenished through diet as well as environmental exposure[17]. Trace metals are metals in extremely small quantities that are present in animal and plant cells and tissue. They are a necessary part of nutrition and physiology. Ingestion of, or exposure to, excess quantities is often toxic. However, insufficient plasma or tissue levels of certain trace metals can cause pathology as well; as is the case with iron[18]. The Aim of this Study is to estimate & evaluate possible role of non-essential toxic heavy metals (Cadmium & Lead) and whether the change of serum essential trace elements (Zinc& copper, Magnesium & Calcium) levels may be involved as a possible causative factor in the pathogenesis of fibromyalgia Syndrome (FMS) and their deleterious effect, in a group of patients as compared to healthy control individuals.

Patients and methods

This clinical study was performed on 31 patients (25 females and 6 males) with age range of (40–65) years attending Rheumatology department / Baghdad Teaching

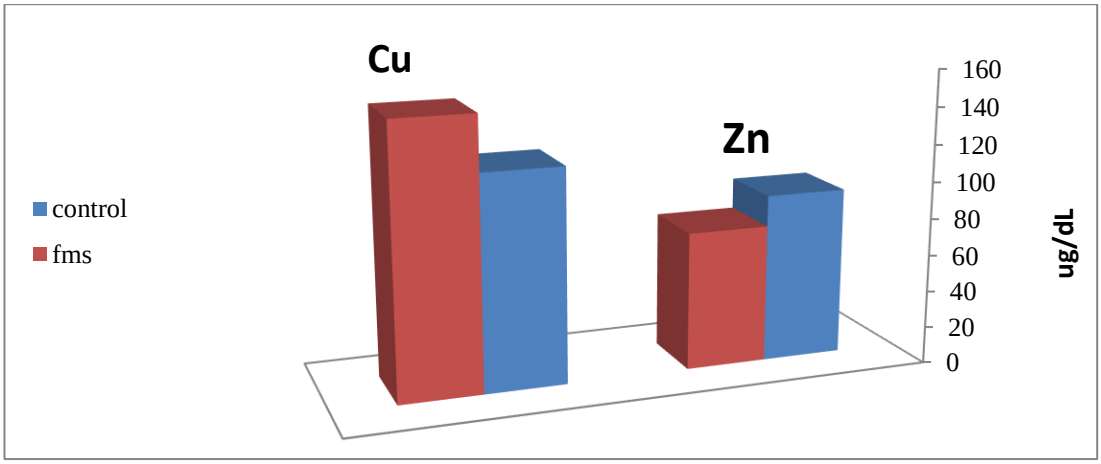

Figure 2: Serum Copper & Zinc level in FMS patients compared to control Group.

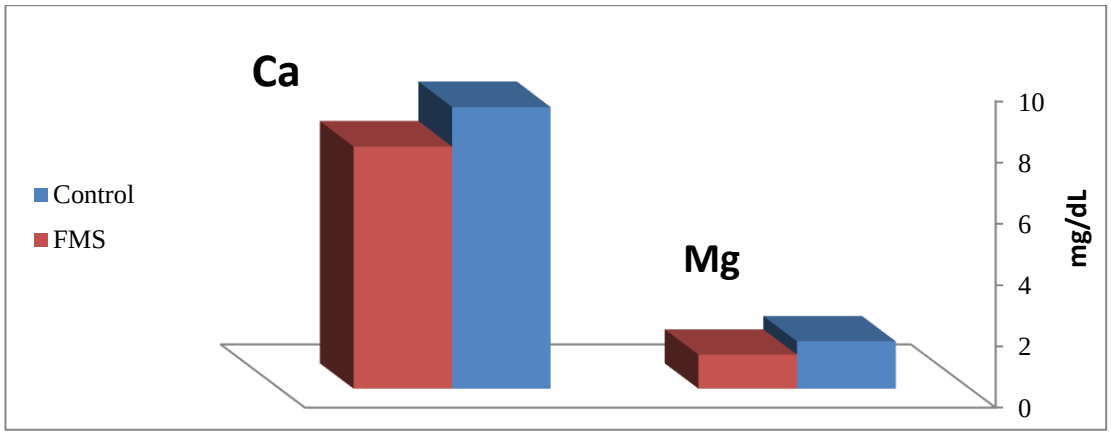

Figure 3: Serum Calcium & Magnesium level in FMS patients compared to control Group.

Hospital / Iraq and 21 healthy individuals, who were age and sex matched were included in the study as control group. All patients diagnosed as having primary fibromyalgia syndrome (FMS) fulfill the criteria of the American College of Rheumatology (ACR) of FMS[19]. The study protocol was approved by the scientific and ethic committee for clinical research in college of pharmacy, Baghdad University. All of the selected patients had no other marked pathologic disorders that may interfere with the outcome of the study protocol. Whole blood levels of heavy metals for lead & cadmium, serum level for Trace metals (zinc & copper) were measured in toxicological department laboratory, using Atomic Absorption spectrometer, calibrated from standard calibration curve for each metal in which, calibration curve for lead has formed using 3 stock solutions of 10,20 and 30 µg/dl read at 283 nm wavelength while, calibration curve for cadmium has formed using 0.1,0.2, and 0.3µg/dl read at 220 nm wavelength. Calibration curve for zinc has formed using 10, 20 and 30µg/dl standard solutions read at 213 nm wavelengths and calibration curve for copper has formed using 10, 20, and 30 µg/dl standard solutions read at 324 nm wavelengths. on the other hand, serum levels of calcium & magnesium were measured by traditional spectrophotometric methods. The demographic data of both patients and control groups are shown in table (1-1). Disease duration, number of tender points and accompanying symptoms (fatigue, sleep disorders, headache, severity of pain and fatigue, and ability to perform daily activities were estimated by using clinical interview to fill Revised Fibromyalgia impact questionnaire (FIQR) was used for diagnosis & functional assessment[20]. All results were expressed as mean ± SD. Statistical testing was carried by Student's t-test; $P < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Fibromyalgia Syndrome (FMS) is one of the least understood pain syndrome in medicine today, Metal-induced inflammation may be involved in the pathology of various chronic pain diseases, where abnormal fatigue, joint and muscle pain, cognitive impairment and other non-specific symptoms are often present. These symptoms can be explained by the deregulation of the Hypothalamic - Pituitary- Adrenal (HPA) axis by inflammatory cytokines affecting the brain resulting in neuromuscular symptoms shared with FMS[21]. From Table (1- 1), All FMS patients demonstrated poor symptoms parameters control which include (pain, fatigue, altered sleep, stiffness, anxiety, depression) and reduced ability to perform daily activities[20], these symptoms are manifested by high (FIQR) score in disease group which indicates severe or extreme symptoms of FMS, that is significantly different from healthy control group ($P< 0.05$). Toxic metals trigger

the production of free radicals, leading to oxidative stress and depletion of antioxidant as well as toxic metals are also known to stimulate the production of inflammatory messengers known as cytokines in the immune system causing immense pain[22]. On the other hand, Toxic metals replace nutrient minerals in enzyme binding sites. When this occurs, the metals inhibit, or alter thousands of enzymes, Lead & cadmium as type of heavy metal exposure were chosen to be studied in this study, toxicity from chronic exposure is much more common than from acute one, usually presents with symptoms affecting neuromuscular, and central nervous system Signs include loss of short-term memory, depression, Fatigue, problems with sleep, that may be shared by FMS symptoms[23]. For heavy metals , The results of this study found that there is a significant difference as elevation of blood lead (Pb) and cadmium (Cd) levels between fibromyalgia syndrome (FMS) compared to healthy control groups ($P< 0.05$) as shown in(table 1-2, fig.1-1) , these results are consistent with some previous studies as that of (Klinghardt D. study, 2004)[24] & that of (Lamb J. et al 2011)[25] which can be explained according to mimicry metal theory , since the metal binding with a variety of enzymes**,** results from its ability to mimic other metals that take part in biological processes, as cofactors in many enzymatic reactions, thus interfering with the enzyme's ability to catalyze its normal reaction or reactions. Among the metals with which lead interacts are calcium, iron, and zinc[23]. while the possible explanation for cadmium toxicity role in fibromyalgia is that it can affect cellular Oxidative & Antioxidant balance, oxidative stress caused by ROS leads to lipid peroxidation, protein denaturation and DNA damage. This, in turn, leads to change, inhibition and a variety of enzymatic activations, causing cellular damage and metabolic imbalance,[26]. Moreover, Cadmium may block the influx of Calcium through membrane channels would be associated with an altered transmitter release[27]. Although Cadmium is not accumulated in significant quantities into the brain following exposure, it disturbs the metabolism of Copper and Zinc. Because zinc and Cadmium are cat ions of similar size and charge, and Cadmium has been shown to inhibit Zinc uptake in a variety of systems, Cadmium is using transport systems that normally function to regulate Zinc levels in brain[28]. Competitive interference with the physiologic action of Magnesium, cadmium from the environment seems to replace the Magnesium in the body. probably because it replaces Magnesium especially in enzyme functioning in CNS may lead to symptoms shared with FMS, they do not realize their fatigue and other symptoms are due to the presence of incorrect "replacement parts" in their biological engine compartments[29]. The other accepted hypothesis of FMS that FMS represent a hypodopaminergic condition resulting from changes in limbic function after exposure to stress, the rationale informing a dopaminergic is Biogenic amines namely serotonin and dopamine are known to be involved in the regulation of cognitive behavior, aggression and motor control, FMS has shown a reduction in the CSF level of biogenic amine metabolites including dopamine, norepiephrine, and serotonin. Dopamine plays a dominant role in natural analgesia within multiple brain centers, most of which fall into the domain of the limbic system[30]. On the other hand, From (Table1-3, figure 1-2), Serum levels of trace elements zinc (Zn) is significantly decreased in FMS patients group, Whereas there is a significant elevation in copper (Cu) of FMS Patients group compared to control group, whereas Serum levels of calcium & magnesium is significantly reduced in FMS Patients group compared to control group where ($P<0.05$) is considered significant as shown in (table 1-4, figure 1-3). Since the core symptoms seen in individuals with fibromyalgia is sever musculoskeletal pain, Calcium & Magnesium elements are required for muscular contraction, any deficiency or imbalance promotes excessive muscle tension, leading to muscle spasms, & pain, furthermore, Previous studies showed that magnesium loss can be increased by emotional. Stress as depression and anxiety disorders which are clear symptoms in Fibromyalgia, so there is an excellent chance that deficiency of these elements may be involved in the pathogenesis of fibromyalgia.

CONCLUSION

This study results showed that there is some disturbance or imbalance in the levels of some essential & non-essential metals in FMS patients that could be contributed to the pathogenesis of fibromyalgia syndrome, this may be based on mimicry metal theory, affecting certain trace metal - catalyzed antioxidant enzymes leading to some neurological signs of fibromyalgia.

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