

The Role of Vitamins A, C and E with Zinc and Copper Elements in the Etiology and Pathogenesis of Fibromyalgia Syndrome

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Abstract:

Fibromyalgia is one of the rheumatological disorder syndromes. It is characterized by generalized musculo-skeletal pain, fatigue with nervous system involvement such as memory disturbance, difficulty in concentration and depression. However, its etiology and pathogenesis is still obscured. Besides, its diagnosis has been done according to its clinical feature and by exclusion of other systemic diseases. Some studies found that serum level of vitamins like A, C and E, besides, Zinc and Copper elements would be altered during the affection by this disorder. **Aim of study:** to demonstrate the role of vitamins A, C and E together with Zinc and Copper in the etiology and pathogenesis of fibromyalgia syndrome. **Subjects and methods:** this study included forty patients (male and female) with fibromyalgia syndrome. In addition, nineteen healthy individuals were involved in this study. In both groups, vitamins A, C and E serum level were examined. Besides zinc and copper levels also were measured in the serum of the subjects of both groups involved in this study. **Results:** the results showed obvious reduction in the level of vitamins A and E with minimal decreament in the level of vitamin C in the serum of fibromyalgia patients. In the contrary, the Copper serum level revealed significant increase in the fibromyalgia patients while Zinc level in the serum of both groups remained almost unaltered. **Conclusion:** the serum levels of vitamins A, C and E, in addition to the Copper and Zinc could play an important role in the etiology and pathogenesis of fibromyalgia syndrome. Besides, it could be helpful in the laboratory investigation for the diagnosis of this disorder.

Keywords: fibromyalgia, vitamin A, C and E, Copper and Zinc.

1. Introduction

Fibromyalgia (FM) is one of the syndromes that belongs to the rheumatic disorders family. It is common, chronic and widely distributed syndrome, affected people in almost all countries and of most ethnic groups. ⁽¹⁾

This disorder is multi-systemic disease; the musculo-skeletal system gains the major percentage of its signs and symptoms. It is characterized by wide spread severe pain and tenderness in multiple specific sites of muscles and bones, mainly the prominent bony areas (which is about 17 tender points), besides easy fatigability and feeling of tiredness all over the body. The nervous system stays no far from this disease. The patients have many neurological and psychological symptoms including sleep disturbances, memory problems, and difficulty in concentration, besides mood changes. ⁽¹⁾⁽²⁾

Fibromyalgia affects both males and females. Yet, the females are predominantly suffered more than males. The ratio of female to male is 9:1. ⁽²⁾⁽³⁾ FM syndrome rarely affects young women, and if present, their ages usually range between 30-50 years old. However, this disease is mostly prevalent among women around the age of 50 years old or more. Besides, the clinical features of this disorder increase in severity with aging till reaching 20% more than that of other affected younger women. ⁽¹⁾⁽²⁾⁽⁴⁾

The etiology and pathogenesis of FM syndrome is still unclearly understood, since so many factors and causes are interfering with each other's, making its diagnosis still not easy. ⁽¹⁾⁽⁴⁾⁽⁵⁾

The diagnosis of this syndrome has been done according to the clinical features and exclusion of other diseases, since there are no diagnostic biochemical investigations to base on it in the diagnosis of this syndrome.

The complex defense mechanism activity has been strongly controlled the concentration of reactive oxygen species (ROS). Many vitamins play an important role as powerful non-enzymatic anti-oxidant factors. These vitamins are vitamin A, C and E which are involved in a complex defense mechanism. ⁽⁶⁾

Vitamins A and E, fat soluble vitamins, play an essential role in protection of cell membrane at an early stage through their free radicals quenching capability. Therefore, these two vitamins are considered to be the principle line in the defense mechanism against lipid peroxidation and one of the main anti-oxidants agents against breaking of protein and DNA chains in the different tissues of the body. Vitamin A acts as a Pro-hormone for retinoid. It promotes signal transduction through cytoplasm and cytoplasmic membrane during organogenesis. ⁽⁷⁾

Vitamin C is a water soluble vitamin. Its free radicals act as a scavenger, besides, it transforms vitamin E from inactive form into active one. ⁽⁸⁾

In spite of antagonistic effect of Zinc against Copper, yet, adequate level of Zinc will balance Copper level in the serum of the individuals. Therefore, Zinc deficiency permits Copper accumulation in excessive pattern and this imbalance could play an important role in the etiology and pathogenesis of FM. ⁽⁹⁾

2. Aim of study

1. Elicit the serum level of vitamin A, C and E in control healthy individuals and FM patients.
2. Evaluate the serum level of Zinc and Copper in healthy people and FM patients.
 Both tests will be analyzed to find an acceptable explanation for the etiology and pathogenesis of FM syndrome and possible treatment, if present.

3. Subjects and methods

The current study had been lasted for 8 months, started from August 2014 till April 2015. The patients had been selected from outpatient clinic of Rheumatology center in the Medical City Teaching Hospital in Baghdad.

These patients had been diagnosed as FM patients by Rheumatologist consultants in this center. The criteria of diagnosis had been categorized according to the criteria of diagnosis of American College of Rheumatology (ACR) 1990. ⁽¹⁰⁾

The total numbers of FM patients,involved in this study , were forty patients, while the control group was included nineteen healthy individuals.

The average age, of both patients and control groups subjects, was ranged between 45-55 years old.

The grouping of the involved subjects, regarding sex, age and number could be summarized in table 1:

Table (1): grouping of subjects examined.

Subjects	Total number	Sex		Age (years)
		female	male	
Controls	19	16	3	45-55year
Patients	40	35	5	45-55year

All the subjects (controls and patients) had been exposed to the following clinical investigations:

1. Estimation of serum level of vitamin A, C and E:-
 These measures had been done using high performance liquid chromatography (HPLC) system (Agilent Technologies, Waldbornn, Germany).
 The fat soluble vitamins (A and E) were separated using NH₂ column under standard optimal conditions (regarding temperature, flow rate and elutriated composition).While vitamin C (water soluble one) was separated via using reversed phasec-18 column. ⁽¹¹⁾ These tests had been performed in the research labs of the Department of Clinical Biochemistry, College of Medicine, University of Baghdad.
2. Evaluation of serum level of Zinc and Copper:-
 This test had been performed using atomic absorption spectrophotometer (A.A.S.) [A Shimadzu Atomic Absorption (670A),Germany]. In this procedure the serum samples of the involved examined subjects had been diluted 10 times with de-ionized water and aspirated, for examination, directly ⁽¹¹⁾. These tests of Zinc and Copper had been examined in the Toxicology Center in the Specialized Surgical Hospital within Medical City Teaching Hospital ,Baghdad .

Statistical analysis

The results obtained from the current study had been analyzed statistically according to Daniel (2005) ⁽¹²⁾ using SPSS-18" PASW statistics software.

The degree of significance, of data collected, was assessed using t- test for two independent means+_ standard error of mean at 95% confidence.

The significance of the data had been categorized as the following:

- P-value \leq 0.001 highly significant (***)
- P-value \leq 0.01 moderately significant (**)
- P-value \leq 0.05 significant (*)

4. Results

The biochemical results, obtained from the current study, had been elicited an obvious reduction in the serum

level of vitamin A and E among FM patients group in comparison with those of control group, although the degree of reduction was different ($p < 0.01$, $p < 0.001$) respectively. However, vitamin C serum level demonstrated not significant decrement in FM patients ($p < 0.098$)

The detailed results could be summarized in table 2.

Table (2): serum level of vitamin A, C and E in FM patients and control group with their significance.

Studied parameters	Control(n=19) mean±SD	Patients(n=40) mean±SD	P-value	Significancy
Vitamin A	5.3 ± 0.4	3.0 ± 0.6	p<0.01	**
Vitamin E	9.0 ± 1.0	3.9 ± 0.9	p<0.001	***
Vitamin C	7.5 ± 0.6	7.0 ± 0.4	P<0.098	Non-significant

Regarding laboratory tests of serum Zinc and Copper in both groups, the FM patients had demonstrated clear increment in serum level of Copper when compared with healthy control subjects ($p < 0.004$). However serum level of Zinc had elicited slightly reduction in FM patients comparing with control serum level ($p < 0.609$) as shown in table 3.

Table (3): serum level of Zinc and Copper in healthy control group and FM patients with their significance.

Studied parameters	Control(n=19) mean±SD	Patients(n=40) mean±SD	P-value	Significancy
Copper(µg/dl)	99 ± 20.1	160.2 ± 12.0	p<0.004	**/**
Zinc(µg/dl)	100.2 ± 9.2	90.4 ± 5	P<0.609	Non-significat

Note: since p –value of serum Copper was higher than 0.01 (moderately significant) and less than 0.001 (highly significant), therefore its significance was referred to as **/**

5. Discussion

The etiology and pathogenesis behind FM disorder are still not clear enough. Besides, the diagnosis of the disease still depends mainly on the clinical features with exclusion of other pathology. For these reasons, so many researches and studies had been performed to explain the etiology and pathogenesis of this disease and a trial to find biochemical laboratory investigations to confirm the clinical diagnosis of this disorder.

The antioxidant role of vitamin A in protection of cells against inflammatory process was proved by Rao and Rao (2007).⁽¹³⁾

The stability of cellular membrane could be obtained by the antioxidant effect of vitamin E. This fact was proved by many studies.⁽¹⁴⁾

In this study, the serum levels of vitamin A and E were significantly decreased in FM patients in comparison with healthy subjects. These findings supported the above explanation, particularly, the same findings were reported in other inflammatory diseases like Behget's disease⁽¹⁵⁾ and Rheumatoid arthritis.⁽¹⁶⁾

The findings of the current study were supported by those of Akkus *et al* (2009).⁽¹⁷⁾ However, laboratory investigations found by Eisinger *et al* (1998)⁽¹⁸⁾ disagree with the results of this study and with those of Akkus *et al* (2009).⁽¹⁷⁾

The insignificant decrease in the serum level of vitamin C in FM patients could be satisfactorily explained. Since, vitamin C is needed for transforming the inactive form of vitamin E into active one. As shown previously, vitamin E serum level was revealed significant reduction in FM patients. This transformation of vitamin E from inactive to its active form needs only a small amount of vitamin C which is enough, although in a small amount. This transformation explains this significant reduction of vitamin E in FM patients.⁽⁸⁾ This significant reduction of vitamin E in FM patient was associated with reduction in the serum level of vitamin C in

FM patient, although, this reduction is insignificant.

The imbalance of some elements like Copper and Zinc in the human tissue and their fluids may have a causative factor in the etiology and pathogenesis of this disorder. ⁽¹⁹⁾

The antioxidant role of Zinc is very well known. ⁽²⁰⁾ Besides, there is an intimate correlation between Zinc level and severity of clinical feature of FM syndrome, mainly the number of the tender points of muscle and bone. ⁽²¹⁾ In addition, Zinc has principle effect in some neurological and psychological features like stress and diurnal rhythm. ⁽²²⁾ This reflects the importance of Zinc in pathogenesis of FM syndrome.

However, this study revealed non-significant reduction in level of serum Zinc in FM patients, in contrary to the finding of Eisingar *et al* (1998). ⁽¹⁸⁾

This controversy in the role of Zinc in the development of FM disease and the result obtained in this study could be attributed to the fact that the major quantity of the Zinc, in the body, is present mainly intracellularly, while the remaining small amount could be detected mainly bounding to the serum protein. ⁽²²⁾

The role of Copper in bone formation is well known, since it has an important contribution in fixation of calcium inside the bone, building and repairing of all connective tissue inside the body. Therefore, the Copper imbalance has principle effect in bone ache and tenderness of soft tissue. ⁽²³⁾ The controversy among the important role of copper in repairing and rebuilding of musculo-skeletal system (including bones, muscles and connective tissue) and the clinical features of bone ache, tenderness and increase in number of tender points in FM patients, in spite of moderate-high significant increase in copper serum level in those patients, could be attributed to the concept that the copper needs zinc to elicit its building action of the musculo-skeletal system. Therefore copper/zinc balance disturbance in FM patients is responsible for these clinical features ⁽²³⁾.

From the above explanation, it is obvious that the imbalance and disturbance in serum level of vitamin A and E mainly with imbalance of the elements like Copper and Zinc could share in the highlight on the etiology and pathogenesis of the questionable FM disorder.

Therefore these laboratory investigations could help to make the clinical diagnosis of FM syndrome more accurate. Besides, maintaining the normal balance of the mentioned vitamins and minerals may be effective in the treatment of this syndrome.

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