ORIGINAL ARTICLE

Serum levels of serotonin as a biomarker of newly diagnosed fibromyalgia in women: Its relation to the platelet indices

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Background: This study aimed to assess the serum serotonin levels in the newly diagnosed fibromyalgia (FM) and to relate these levels to the presenting signs and symptoms. **Materials and Methods:** This case–control study included 35 healthy women (Group I) served as controls and 130 women with newly diagnosed FM (Group II). The diagnosis of FM was confirmed by the diagnostic criteria of the American College of Rheumatology-10. The assessment of pain using a revised fibromyalgia impact questionnaire and tender points scoring, blood platelet indices, and serum serotonin levels were determined. **Results:** Group II patients had significantly ($P < 0.001$) higher values of mean platelet volume (MPV) (10.60 ± 1.57fL) and platelet width distribution (16.25 ± 1.45%) than the corresponding values in Group I (8.73 ± 0.81fL and 15.0 ± 1.15%). Significant low-serum serotonin levels observed in Group II patients compared with Group I healthy individuals (187.3 ± 50.3 ng/ml vs. 219.5 ± 78.3 ng/ml, $P = 0.026$). Multiple linear regression analysis showed the nonsignificant correlations between serum serotonin levels and platelet indices in Group II patients. **Conclusion:** Newly diagnosed FM women have significantly low-serum serotonin levels, which does not correlate with a significant increment of the platelet activity expressed as increase MPV and platelet width distribution percentage. Therefore, this study highlighted that the correction of serum serotonin level by medicines could help the patients.

Key words: Fibromyalgia, mean platelet volume, platelet activation, serotonin

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INTRODUCTION

Fibromyalgia (FM) is a chronic, multisymptom complex of unknown etiology and with ineffective treatment.[1] It affects 2%–4% of the population worldwide and is predominately prevalent in women.[1,2] The patients presented clinically with chronic widespread pain, fatigue, sleep disturbances, impairment of the cognitive function, and effective.[3] It is related to the central sensitivity syndromes which including a wide variety of diseases and disorders, notably, chronic pelvic pain and endometriosis, irritable bowel syndrome, chronic fatigue syndrome, idiopathic low backache pain, migraine, interstitial cystitis, posttraumatic stress syndrome, restless leg, temporomandibular joint disorder, primary dysmenorrhea, myofascial pain syndrome, and multiple chemical sensitivity.[4-8] These disorders are characterized by a specific symptom which related to a particular painful sensation.[9] Some of these disorders are shared by the role of serotonin, as a central neurotransmitter, in their pathogenesis.[10,11] Moreover, drugs that used in the management of FM, migraine, and irritable bowel syndrome are partly acting on the central serotonin levels.[12,13] Walit *et al*.[14] highlighted the importance and the useful prescription of selective serotonin reuptake inhibitors in the management of FM and their usefulness in the modulation or alleviation the symptoms of pain, fatigue, and sleep disturbances. Blood platelets usually loaded with serotonin granules

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and an increase in the platelet activity is observed in patients with FM by the evidence of a significant high value of mean platelet volume (MPV).[15,16] Therefore, we hypothesize that FM is a disorder resulted from disturbances of the central serotonin, and this may reflect on the peripheral serum serotonin levels. This study aimed to assess the serum serotonin levels in the newly diagnosed FM and to relate these levels to the presenting signs and symptoms.

MATERIALS AND METHODS

Study design and participants

This case–control study conducted in the Departments of Pharmacology and Toxicity-Clinical Pharmacy, College of Pharmacy at Hawler Medical University in Erbil, Iraq. A consent form was obtained from each patient before the admission to the study (Harrison Middleton University-postgraduate studies N1-2016). The study was conducted according to the ethical guidelines constructed by the Institutional Scientific Committee in which the treatment or using device should not be harmful to the patient, and the patient is free to decline from the study or to refuse for study admission.

The patients were recruited from Consultant Public Clinics and Private Clinics of Rheumatology in Baghdad, Iraq, and from the Rizgary Teaching Hospital in Erbil, Iraq. The eligible patients are of both genders aged <60 years. The criteria of inclusion are new cases of FM with a signs and symptoms suggestive of FM of at least 3 months of duration. The consultant rheumatologists and the researchers examined each patient thoroughly. The diagnosis of FM confirmed by the consultant of rheumatology using the American College of Rheumatology-10 diagnostic criteria.[17,18] Patients with a history of hypertension, diabetes mellitus, acute or chronic liver diseases (included viral hepatitis and chronic active hepatitis), renal disorders, autoimmune diseases, and drug intake, for example, nonsteroidal anti-inflammatory drugs were excluded from the study.

A total number of 35 healthy women served as a control (Group I), and 130 women patients diagnosed as FM (Group II) were included in this study.

The authors examined and interviewed each patient and an healthy individual taking the following considerations: The characteristics of the participants, assessment of pain using a revised fibromyalgia impact questionnaire (FIQR), and tender points (TPs) scoring.[19-21]

Measurements

Peripheral venous blood samples were drawn immediately into tubes with and without ethylenediaminetetraacetic acid anticoagulant on the day of admission, for determination of the hematological indices, and the serum serotonin and high-density lipoprotein, respectively. The hematological platelet indices, including platelet count, plateletcrit (%), MPV, and platelet distribution width (PDW), were determined using the Coulter machine. The blood samples without anticoagulant centrifuged at 2500 rpm for 10 min, and the sera were separated for the determination of serotonin level using the technique of enzyme-linked immunosorbent antibody technique.

Statistical analysis

Categorical and continuous data were presented as frequency (percentage) and mean ± standard deviation, respectively. Unpaired Student's (independent two samples) *t*-test was used to evaluate differences between Group I and Group II. For all tests, a two-tailed $P \leq 0.05$ was considered statistically significant. The multivariables linear regression (Pearson correlation) test with ANOVA was performed to assess correlations between these indices. All calculations were made using Excel 2003 (Microsoft Corporation, Redmond, WA, USA) and Statistical Package for the Social Sciences software (SPSS-20 programs for Windows, IBM Corp., Armonk, NY, USA).

RESULTS

The characteristics of the participants do not show differences between Group I and II in the mean of the age ($P = 0.406$) or the frequency (percentages) of the residency ($P = 0.566$), smoking habit ($P = 0.299$) [Table 1]. Group II patients showed significant differences ($P < 0.001$) in the marital, educational, and occupation status [Table 1]. Group II patients had a nonsignificantly high percentage of the positive family history of FM compared with Group I ($P = 0.351$). The percentage of active smokers in Group II is higher than the corresponding value of the Group I.

The assessment of participants revealed that the Group II patients have a significantly higher score of revised FIQR and TPs compared with Group I [Table 2]. The mean of the total function, global, and symptoms score in Group II was 2–3 folds of the corresponding value of Group I [Table 2]. Widespread pain that evaluated by scoring the number of TPs was significantly ($P < 0.001$) more in Group II by 2.9 folds of the corresponding value of Group I [Table 2]. The hematological platelets indices showed a significant high value of MPV and PDW in FM patients (Group II) compared with healthy individuals (Group I) [Table 3]. The patients with FM (Group II) did not show a significant difference in the number of blood platelet ($P = 0.188$) or plateletcrit (0.081) as compared with healthy individuals (Group I). The Group II patients have a significantly ($P = 0.026$) low-serum serotonin levels (187.3 ± 50.3) compared with Group I healthy individuals (219.5 ± 78.3) [Figure 1]. Analysis of

Table 1: Characteristics of the participants included in the study

Characteristics	Group I (*n*=35)	Group II (*n*=130)	*P*
Age (year)	42.7±7.7	41.5±7.6	0.406
Marital status			
Single	6 (17.1)	16 (12.3)	<0.001
Married	26 (74.3)	88 (67.7)	
Divorced	0	8 (6.2)	
Widow	3 (8.6)	18 (13.8)	
Residency			
Urban	27 (77.1)	94 (72.3)	0.566
Rural	8 (22.9)	36 (27.7)	
Education			
Illiterate	4 (11.4)	13 (10)	<0.001
Elementary	9 (25.7)	38 (29.2)	
Secondary	12 (34.3)	38 (29.2)	
Higher education	10 (28.6)	41 (31.6)	
Occupation			
Housewife	16 (45.7)	61 (46.9)	<0.001
Employee	18 (51.4)	67 (51.5)	
Retired	1 (2.9)	2 (1.6)	
Family history of FM	6 (17.1)	32 (24.6)	0.351
Smoking			
Active smokers	8 (22.9)	17 (13.1)	0.299
Ex-smokers	3 (8.6)	14 (10.8)	

The results expressed as a *n* (%) and mean±SD. *P* value was calculated by using independent two samples *t*-test for continuous data and Chi-square test for category data. SD=Standard deviation; FM=Fibromyalgia

Table 2: Clinical assessment of participants

Variables	Group I (*n*=35)	Group II (*n*=130)	*P**
Duration of FM (weeks)	-	19.5±2.5	
Scoring of FIQR			
Total function	24.14±3.10 (24)	52.85±5.11 (53)	<0.001
Total global	4.91±1.63 (5)	13.43±1.58 (53)	<0.001
Total symptoms	24.77±3.42 (24)	64.19±4.86 (64)	<0.001
Overall total	53.83±6.21 (55)	130.47±8.67 (131)	<0.001
Tender points (*n*)	4.86±1.44 (5)	14.28±1.71 (14)	<0.001

*Unpaired (independent two samples) *t*-test. FIQR=Fibromyalgia impact questionnaire revised; FM=Fibromyalgia

Table 3: Hematological platelet indices and serum serotonin level

Variables	Group I (*n*=35)	Group II (*n*=130)	*P**
Platelet count per mm^3	276,171.4±55,317.5 (295,000)	290,201.9±55,410.5 (300,500)	0.188
Plateletcrit (%)	0.172±0.019 (0.17)	0.180±0.037 (0.18)	0.081
MPV (fL)	8.73±0.81 (8.7)	10.60±1.57 (10.6)	<0.001
Platelet width distribution (%)	15.0±1.15 (14.9)	16.25±1.45 (16.5)	<0.001
Serum serotonin level (ng/ml)	219.5±78.3 (187)	187.3±50.3 (182)	0.026

*Unpaired (independent two samples) *t*-test. MPV=Mean platelet volume

multivariables linear regression (using Pearson correlation) between serum serotonin levels and platelet indices does not show significant correlation (R = 0.113, F = 0.403, P = 0.806) with a variability of 13% (R^2 = 0.013) [Figure 2] in

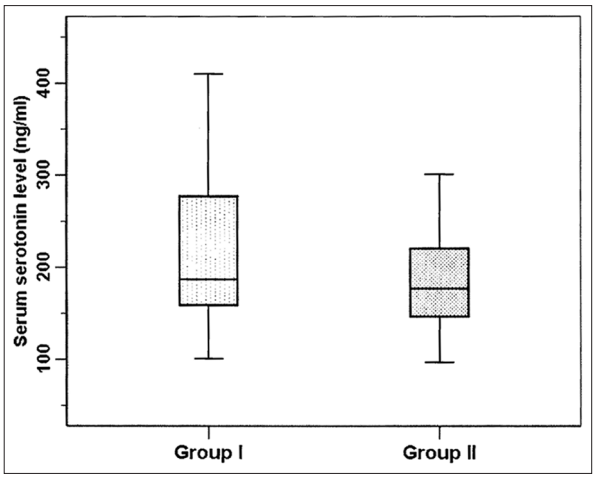

Figure 1: Boxplot showed significant (P = 0.026) low-serum serotonin level (ug/ml) of fibromyalgia patients (Group II) compare with healthy individuals (Group I)

FM patients (Group II). There is no significant correlation between the serum serotonin levels with the scores of the FIQR including function, global, and symptoms of FIQR, and the TPs score as predictors (R = 0.240, F = 1.908, P = 0.113) with a variability of 5.8% (R^2 = 0.058) in FM patients (Group II). The beta coefficient of TPs is 6.667 with a corresponding value of 0.227 beta coefficient of serotonin level indicated a positive significant (P = 0.013) Pearson correlation [Figure 3].

DISCUSSION

The results of this study showed that the serum levels of serotonin are low in patients with FM compared with healthy individuals, and these levels are not correlated with the indices of the clinical symptoms or blood platelet. The characteristic features of the FM patients are in agreement with other studies that showed a positive family history and smoking.[22,23] These observations indicate that FM is a disease that related to the genetic disorder, and the smoking behavior is a reaction to stress. The values of MPV and platelet width distribution were significantly higher in FM patients than healthy individuals. This observation is in agreement with other study[15] indicating that the patients are at risk of developing premature atherosclerosis and they are in the state of active disease. Tecer *et al*.[24] showed that the MPV is an indicator of the inflammation similar to C-reactive protein and erythrocyte sedimentation rate in the patients with rheumatoid arthritis. Literature review did not reveal any study on the PDW (%) that increased in FM and reflected a prothrombotic state.[25] The significant low-serum serotonin levels that observed in this study was also observed in other rheumatic conditions, for example, ankylosing spondylitis and rheumatoid arthritis as well as in a known case of treated FM.[26,27] Atasever *et al*. suggested that the low-serum serotonin levels may contribute to the development of FM in pregnant women.[28] Our results are in agreement with other studies

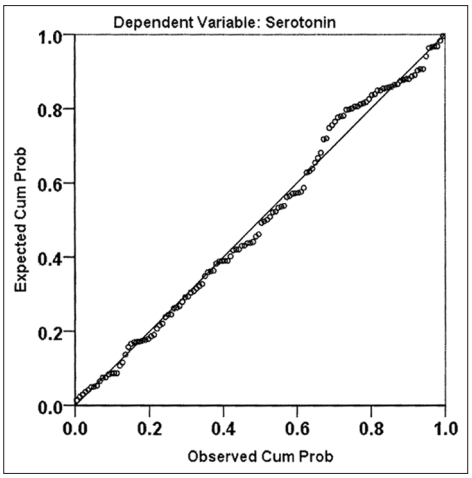

Figure 2: Multiple linear regression analysis showed nonsignificant correlation (R = 0.113, F = 0.403, P = 0.805) between serum serotonin level (as dependent variable) and platelet indices as predictor in fibromyalgia patients

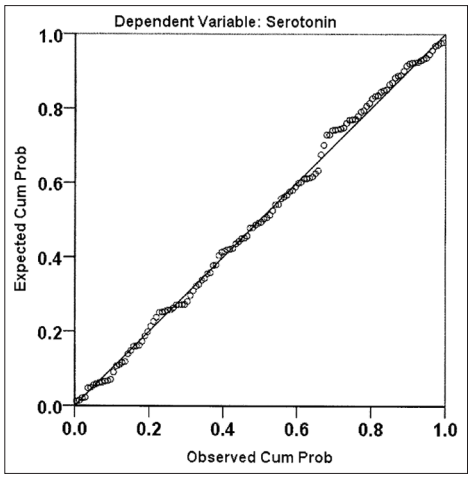

Figure 3: Multiple linear regression analysis showed nonsignificant correlation (R = 0.240, F = 1.908, P = 0.113) between serum serotonin level (as dependent variable) and the scores of fibromyalgia impact questionnaire revised as predictor in fibromyalgia patients

and indicating that there is an impairment in the metabolism of serotonin in women with FM and it does not relate to the drug therapy that acts on the serotonin as our patients are newly cases of FM.[29] There are no significant correlations between the serum levels of serotonin with the platelet indices or with the scores of the FIQR and TPs. This is indicating that the serum serotonin level is not a useful predictor of the FM taking into considerations the clinical symptoms (assessed by FIQR and TPs scores) and the platelet indices (as markers of disease activity). Therefore, the results point out that the determination of serum serotonin level and the platelet indices are helpful in the diagnosis of FM; however, these biomarkers do not serve good predictors of disease severity. Moreover, the nonsignificant correlation between serum serotonin levels and the platelet indices indicated that there are disturbances in the serotonin metabolic pathways. Limitation of the study is the measurement of serotonin levels in the platelets, platelet-rich, and poor plasma was not done.

CONCLUSION

We conclude that newly diagnosed FM women have significantly low-serum levels of serotonin, which does not correlate with a significant increment of the platelet activity expressed by increased MPV and platelet width distribution percentage. Therefore, this study highlighted that the correction of serum serotonin level by medicines can help the patients.

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Conflicts of interest

There are no conflicts of interest.

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