

# Fibromyalgia, a disease or a subclinical presentation? A different perspective

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## Context

Fibromyalgia is a disease of exclusion. There is a huge overlap between symptoms of fibromyalgia and a lot of rheumatic, endocrinal, and metabolic diseases. Confirming the diagnosis of fibromyalgia might mask the diagnosis of a lot of conditions especially with the lack of periodic reevaluation to fibromyalgia patients.

## Objective

The aim was to evaluate the diagnosis of fibromyalgia in unresponsive patients after more than a year of diagnosis.

## Patients and methods

This is a cross-sectional observational study performed on 100 patients diagnosed with primary fibromyalgia for more than 1 year and that showed no response to two or three lines of treatments. Patients were investigated for erythrocyte sedimentation rate, rheumatoid factor, antinuclear antibody, in addition to serum vitamin D levels, total serum calcium, serum phosphorus, thyroid-stimulating hormone, parathormone hormone, and Dual energy Xray Absorptiometry (DEXA) scan. Patients were regrouped after laboratory investigations into two groups. Group I are patients who showed no abnormalities in their laboratory investigations. Group II are patients who showed abnormalities in their laboratory investigations. Functional assessment was performed for all patients by the fatigue assessment scale, insomnia severity index, and the visual analog scale for pain for patients in the beginning of the study and after 6 months.

## Results

Less than 20% of the patients remained with no abnormality in their laboratory investigations, while about 80% showed laboratory abnormalities for other associated conditions.

## Conclusion

Fibromyalgia patients showing response to treatment should be investigated on a regular basis even for markers that were shown to be normal. Treatment of any associated condition can improve symptoms of fibromyalgia dramatically.

## Keywords:

chronic fatigue syndrome, irritable bowel disease, subclinical hypothyroidism, vitamin D deficiency, widespread pain

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## Introduction

Fibromyalgia is a systemic disorder characterized by widespread musculoskeletal pain accompanied by fatigue, sleep, and mood disturbances. Fibromyalgia often coexists with other painful conditions, such as: irritable bowel syndrome, migraine, interstitial cystitis, and temporomandibular joint disorders [1–4].

The American College of Rheumatology (ACR) classification criteria require a specialized examination to quantify tender point distribution and number, which is not the case for the 2010 ACR diagnostic criteria that depend mainly on history [5,6].

Fibromyalgia is a diagnosis of exclusion so any disorder that mimics the manifestation of fibromyalgia must be

excluded first. These disorders have nearly the same musculoskeletal and psychological manifestations of fibromyalgia, for example, thyroid dysfunctions, vitamin D deficiency, and rheumatic and metabolic diseases [7].

Treatment of fibromyalgia includes lifestyle modifications, behavioral and psychological therapy, aerobic exercise, and pharmacological therapy to alleviate symptoms of anxiety, depression, sleep disturbance, musculoskeletal pain, and fatigue [8].

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## Patients and methods

### Patients

This is a cross-sectional, observational study, performed on 100 patients diagnosed with primary fibromyalgia for more than 1 year according to the 2010 ACR diagnostic criteria for fibromyalgia [6] and showed no response to two or three lines of treatments.

### Ethics, consent, and permission

The patients were collected from the outpatient clinic of Physical Medicine, Rheumatology and Rehabilitation Department, Faculty of Medicine, Tanta University. All the investigations were conducted at the Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Tanta University.

The study was approved by the Local Research Ethics Committee of Faculty of Medicine, Tanta University, approval code 31082/07. Written consents for publication were obtained from all patients.

An exclusion criterion was fibromyalgia secondary to any known chronic systemic disease.

### Methods

All patients were investigated for erythrocyte sedimentation rate, rheumatoid factor, antinuclear antibody, in addition to serum vitamin D level, total serum calcium, serum phosphorus, thyroid-stimulating hormone, parathormone hormone, and Dual energy Xray Absorptiometry (DEXA) scan. After investigations patients were regrouped into two groups.

Group I included patients who showed no abnormalities in their laboratory investigations. Group II included patients who showed abnormalities in their laboratory investigations. Functional assessment for all patients was by

- (1) Fatigue assessment scale [9].
- (2) Insomnia severity index [10].
- (3) Visual analog scale for pain [11].

Which were conducted at the beginning of the study and after 6 months of receiving treatment of any associated conditions that were detected.

### Statistical analysis

All statistical calculations and analysis were done using the computer program SPSS version 16 (SPSS 16 Inc., Chicago, IL). Frequency distribution, Student's *t*-test were used in analysis. A difference was considered to be statistically significant when the probability values or *P*

values were less than 0.05. *P* values less than 0.01 were considered highly significant. *P* values greater than 0.05 were considered statistically nonsignificant.

## Results

This study examined 100 adult patients (14 men and 86 women) with primary fibromyalgia. The mean age of our patients was 43.5±9.1 years with mean disease duration of 4.2±1.1 years. Symptom frequency among our patients is illustrated in Table 1. Laboratory investigations are illustrated in Table 2. Classification of patients according to the presence or absence of associated conditions are given in Table 3. Symptom frequency among patients after 6 months of treatment of the associated conditions is given in Table 4. Comparison between functional assessment of patients without any associated conditions and patients with associated conditions after 6 months of treatment is given in Table 5.

## Discussion

Fibromyalgia has been proven to have neurophysiological abnormalities that result in abnormal pain processing and abnormal levels of chemical transmitters that are responsible for central sensitization and whole-body hypersensitivity to pain also, a neuroendocrinal abnormalities and abnormal hypothalamic-pituitary adrenocortical axis were detected in fibromyalgia patients [12,13]. These changes resemble exactly what happens to the body in stressful conditions or any other chronic diseases and these changes are responsible for the symptoms in fibromyalgia patients. Unfortunately, these changes are undetectable by ordinary laboratory workup or clinical assessments [14–16].

The highly frequent symptoms in our patients were fatigue, widespread pain, and sleep disturbance (Table 1), which was also reported in a German study by Häuser *et al.* [17] These are the same vague symptoms that patients with vitamin D

**Table 1 Frequency of symptoms among all patients**

Symptoms	N=100 [n (%)]
Fatigue	100 (100)
Widespread pain	98 (98)
Sleep disturbance	87 (87)
Irritable bowel disease	8 (8)
Interstitial cystitis	4 (4)
Myalgia	33 (33)
Arthralgia	12 (12)
Mood swings	35 (35)
Headache	27 (27)

deficiency, endocrinal abnormalities especially hyperthyroidism or hypothyroidism or osteoporosis

**Table 2 The distribution of mean values of ESR, RF, ANA, serum calcium, serum phosphorus, serum vitamin D, TSH, T3, T4, parathormone hormone, bone mineral density of hip and lumber spine**

Laboratory investigation	Mean±SD of all patients	Mean±SD of abnormal results
ESR	16.05±3.89	–
RF	Negative	–
ANA	Negative	–
Serum calcium (8.5–10.5 mg/dl)	8.94±0.74 mg/dl	10.4±0.45 mg/dl
Serum phosphorus (3.5–5.5 mg/dl)	3.58±0.47 mg/dl	–
25(OH) vitamin D (30–100 ng/ml)	21.8±13.16 ng/ml	11.27±7.12 ng/ml
TSH (0.2–5.5 mIU/ml)	1.97±2.27 mIU/ml	6.14±1.4 mIU/ml
T3 (12–22 mol/L)	14±2.1 mol/L	–
T4 (3.0–7.8 mol/L)	4±1.8 mol/L	–
Parathormone hormone (10–65 pg/ml)	57.9±21.72 pg/ml	153.75±52.81 pg/ml
Bonemineral density of L1–L5	–0.91±0.9	–2.93±0.23
Bone mineral density of HIP	–1.0±0.2	–2.3±0.45

ANA, antinuclear antibody; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; TSH, thyroid-stimulating hormone.

complain of. These diseases are slowly progressive and sometimes their abnormalities are on the level of receptors, which make it more difficult to detect by ordinary laboratory workup.

The laboratory assessment of erythrocyte sedimentation rate, rheumatoid factor, and antinuclear antibody showed normal parameters while serum 25(OH) vitamin D showed deficiency in 55 patients with a mean±SD of 11.27±7.12 (Tables 2 and 3). The same results were obtained from Matthana [18] and Abokrysha [19] while Tandeter *et al.* [20] found no relation between vitamin D and fibromyalgia. Actually, we are not talking here about fibromyalgia patients being at risk of developing other conditions, rather we want to clarify that a lot of conditions among them,

**Table 3 Classification of patients according to the presence or absence of associated conditions**

Diagnosis	Number of patients
Vitamin D deficiency	55
No associated conditions	19
Subclinical hypothyroidism	12
Osteoporosis	10
Primary hyperparathyroidism	4

**Table 4 Symptoms frequency among patients after 6 months of receiving treatment to the associated conditions**

Symptoms	Vitamin D deficiency (n=55) [n (%)]	Fibromyalgia without association (n=19) [n (%)]	Subclinical hypothyroidism (n=12) [n (%)]	Osteoporosis (n=10) [n (%)]	Primary hyperparathyroidism (n=4) [n (%)]
Fatigue	7 (13)	19 (100)	3 (25)	3 (30)	–
Widespread pain	4 (7)	19 (100)	2 (16)	–	–
Sleep disturbance	–	15 (79)	1 (8)	2 (20)	–
Irritable bowel disease	–	4 (21)	2 (16)	–	–
Interstitial cystitis	–	–	–	–	–
Myalgia	4 (7)	9 (47)	1 (8)	–	–
Arthralgia	–	2 (10)	–	4 (40)	–
Mood swings	2 (3)	14 (73)	2 (16)	–	–
Headache	2 (3)	10 (52)	–	1 (10)	–

**Table 5 Functional assessment of fibromyalgia patients without associated conditions and fibromyalgia patients with associated conditions after 6 months of receiving treatment for the associated conditions**

	Fibromyalgia without association (mean±SD)	Fibromyalgia with association (mean±SD)	t test P value
Fatigue assessment scale	N=19 36.6±0.69	N=13 13.5±0.27	t=131.91 P=0.00098*
Insomnia severity index	N=15 19.75±1.73	N=3 7.5±0.29	t=25.68 P=0.02*
VAS for pain	N=19 7.85±1.7	N=6 2.05±0.53	t=13.00 P=0.0085*

VAS, visual analog scale. \*Significant.

vit. D deficiency, are having the exact same symptoms we rely on to diagnose fibromyalgia. Vitamin D might be the primary cause for the symptoms and having the highest frequency among our patients might be related to other epidemiological factors.

Subclinical hypothyroidism with a thyroid-stimulating hormone of more than 5.5 was found in 12 patients with a mean±SD of 6.14±1.4 (Tables 2 and 3). The same was reported in a study of Suk *et al.* [21] John [22] *et al.* studied the effectiveness of eltroxin therapy in the treatment of euthyroid fibromyalgia and suggested in his results that patients with fibromyalgia might have resistance to thyroid hormones and needs a higher level of eltroxin therapy. So, having resistance to thyroid hormones might be the cause for musculoskeletal symptoms.

We found 10 osteoporotic patients with a mean of -2.93±0.23 in the lumbar region by DEXA scan (Tables 2 and 3). Upala [23] reported that fibromyalgia patients are at risk for osteoporosis. Though fibromyalgia is a disease that has a lot of co-morbidities that might be higher than the general population, treatment of these associated conditions resulted in nearly full improvement of fibromyalgia symptoms which raises our question: Can fibromyalgia be a clinical presentation rather than be a separate entity in these patients? We also found four patients with primary hyperparathyroidism. Among our patients the diagnosis was based on the level of their parathyroid hormone 153.75±52.81 and confirmed with the parathyroid scan (Tables 2 and 3). The results of Freitas [24] were compatible with ours. Our patients reported full improvement pain and myalgia from the following day after parathyroidectomy operation.

After comparison of the functional assessment of the 19 fibromyalgia patients without associated conditions and the 81 fibromyalgia patients with associated conditions after 6 months of their treatment each according to their condition (Tables 4 and 5), we found that the most frequent symptoms showed significant improvement in fibromyalgia patients with associated conditions after treatment regardless of their different conditions and methods of treatment in comparison to fibromyalgia without association. In our study we did not analyze the use of pain medications because of their diversity with different mechanism of action but of our patients some remained on their regular medications, others became nonadherent to therapy and some stopped treatment except for NSAIDS when required.

In our opinion, stress conditions that arise from undiagnosed and untreated medical conditions can cause the same impact and same symptoms of fibromyalgia which might be misdiagnosed as fibromyalgia.

The wide range of hormonal assays and vitamin deficiencies takes long time before reaching the detectable laboratory levels and their clinical manifestations are vague enough to lead physicians to early diagnosis of fibromyalgia.

Our study and the many studies mentioned here found a great number of patients that are misdiagnosed or at least suffered from a treatable disease masked by the diagnosis of fibromyalgia. This raises our question: can fibromyalgia be a clinical presentation of these associated conditions rather than be a diagnosis of its own. We cannot generalize our results to all fibromyalgia patients because we performed our study on a subgroup of patients that were not responding to treatment.

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## Conclusion

This study proves that fibromyalgia is a disease of exclusion even after the diagnosis has been made. Periodic evaluation of unresponsive fibromyalgia patients is mandatory even for markers that were shown to be normal.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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