

Effect of Vitamin D Replacement in Patients of Fibromyalgia

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ABSTRACT

Introduction: Fibromyalgia is a common condition characterized by long-term, body-wide pain and tender points in joints, muscles, tendons, and other soft tissues. It is a chronic pain disorder that is difficult to treat. Recently Vitamin D has shown promising impact in the treatment of this disorder.

Objective: To see the therapeutic role of vitamin D replacement in patients of fibromyalgia.

Study design: Prospective study.

Setting: Multicentre, Three private clinics.

Material and Methods. Out of 223 patients presenting with body aches and pains over the course of six months (January to June 2008), 100 patients (96 females and 4 males) between 20 to 50 years of age fulfilled the American College of Rheumatology (ACR) criteria of fibromyalgia and were included in the study. Using standard proforma, frequency of complaints other than ACR criteria were also documented. All of them were on some form of pain medication by various general practitioners/ consultants for more than three months but their symptoms were persistent. After informed consent, their serum vitamin D3 (25OH-D3) level was requested as the cost of investigation was to bear by patients themselves. Patients were then replaced with vitamin D with an expected target of > 50 ng/ml and followed for 6 months duration.

Supplementation with calcium in a dose of 1000mg/day was also done.

Results: In this study 83% of patients were having vitamin D between 11-20 ng/ml (mean = 13 ± 2), 11% between 5-10 ng/ml (mean = 7 ± 1) and 6% were below 5ng/ml (table-2). There were four male patients, all (100%) with age distribution of 41-50 year and all were deficient in vitamin D (<20ng/ml). Among 96 female patients 80(76.8%) were having level between 11-20 ng/ml, 10 (9.6%) between 5-10ng/ml and 6 (5.7%) were below 5 ng/ml. After replacement with vitamin D achieving expected target serum levels >50ng/ml. Improvement in ACR criteria of fibromyalgia syndrome consisting of widespread musculoskeletal pains and 11 out of 18 tender points was improved in more than 76 % of the patients. Improvement in the associated conditions was also observed e.g. restless legs in 91.3% chronic fatigue in 97.6%. Similarly 85% reported relief from muscle spasm and 65% from tingling. There was also improvement in neuropsychiatric conditions like depression (71%) and anxiety (46.8%). Moreover, improvement in cognitive function like concentration and forgetfulness was also reported by 69.8% and 67.7% respectively (Table-4).

Keywords: Vitamin D, Fibromyalgia, Generalized body aches, Fatigue, Tenderness.

INTRODUCTION

Pain is a condition that has spared no one in the world. Etiopathogenesis of many painful conditions have been well described, but some still remain elusive. Fibromyalgia is one of them. Fibromyalgia (new lat., fibro-, fibrous tissue, Gk. myo, muscle, Gk. *algos*, pain), meaning muscle and connective tissue pain (also referred to as FM or FMS), is a medically unexplained syndrome [1,2,3]

characterized by chronic persistent widespread pain that usually varies in intensity and a heightened painful response to pressure (allodynia) [4]. Other core symptoms are chronic debilitating fatigue (90% of the cases, often chief complaint), sleep disturbance, and joint stiffness [5,25]. Some patients may also report difficulty with swallowing [6], bowel and bladder abnormalities [7], numbness and tingling [8], and

cognitive dysfunction [9]. Many patients diagnosed with fibromyalgia also have psychiatric disorders like depression and anxiety [10,11]. Because fibromyalgia involves more than just pain, the term "fibromyalgia syndrome" is often used; not all affected persons experience all associated symptoms [12].

Over the past 20 years fibromyalgia (FM) has emerged as a leading cause of office visits to rheumatologists, both in its primary form and as an accompaniment of other rheumatic disorders. Epidemiological studies from western countries report a FM prevalence of between 2 and 7% in most nations, with a female to male ratio of approximately 9:1 [13,24]. Data is scarce from South Asia and a study in 1998 revealed prevalence of fibromyalgia in northern rural population of Pakistan to be 2.1%, however when prevalence of fibromyalgia, low back ache, soft tissue and unassessed rheumatism were combined, it turned to be 6.95% [26].

The cause of fibromyalgia is currently unknown. However, several hypotheses have been developed. There is evidence that genetic factors may play a role in the development of fibromyalgia. For example, there is a high aggregation of fibromyalgia in families [27,28]. The mode of inheritance is currently unknown, but it is most probably polygenic [29]. Current research has revealed that fibromyalgia is associated with polymorphisms of genes in the serotonergic [30], dopaminergic [31] and catecholaminergic systems [32]. However, these polymorphisms are not specific for fibromyalgia and are associated with a variety of associated disorders (e.g. chronic fatigue syndrome[33], irritable bowel syndrome[34]) and with depression[35]. Stress may be an important precipitating factor in the development of fibromyalgia [36]. Hypothalamic-pituitary-adrenal (HPA) axis, dopamine, serotonin, growth hormone and psychosocial factors are also implicated in its development [37,44]. Recently vitamin D deficiency is linked to the development of fibromyalgia syndrome as its deficiency shares most of the conditions associated with fibromyalgia syndrome [46,50,52,53,54,55]. Above findings lead to the initiation of this study as Pakistani population was not investigated so far.

OBJECTIVES

To see the therapeutic role of vitamin D replacement in patients of fibromyalgia.

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MATERIAL AND METHODS

Out of 223 patients presenting with body aches and pains over the course of six months (January to June 2008), 100 patients (96 females and 4 males) between 20 to 50 years of age fulfilled the American College of Rheumatology criteria of fibromyalgia and were included in the study (Fig-1). Using standard proforma, frequency of complaints other than ACR criteria were also documented (Table-1). ACR criteria requires presence of widespread musculoskeletal pain and 11 tender points out of 18 (Fig-2). Digital pressure was used to elicit tender points. Patients with incomplete proformas, pregnant and lactating females and those with the diagnosis of rheumatoid arthritis, systemic lupus erythematosus were excluded.

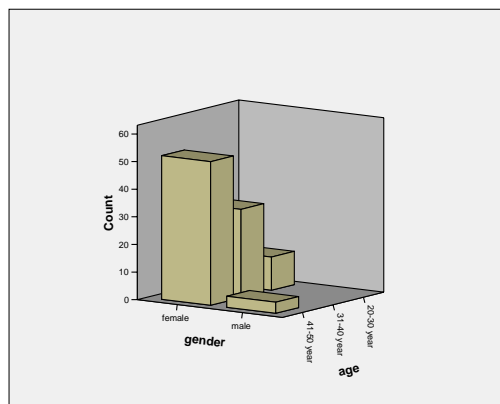


Fig-1: Age and Gender Distribution of the Study Population

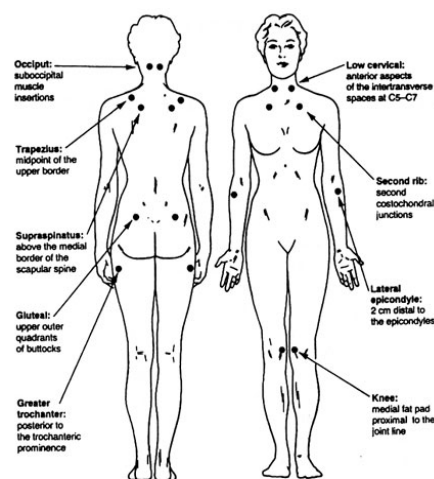


Fig-2: Fibromyalgia Tender Points

All of them were on some form of pain medication by various general practitioners/consultants for more than three months but their symptoms were persistent. After informed consent, their serum vitamin D3 (25OH-D3) level was requested as the cost of investigation was to bear by patients themselves. The method employed for measurement of serum vitamin D level was chemiluminescence assay. Patients were then replaced with vitamin D with an expected target of > 50 ng/ml (50,000 IU increase level by 2.5 ng/ml) and followed for 6 months duration. Supplementation with calcium in a dose of 1000mg/day was also done.

RESULTS

In this study 83% of patients were having vitamin D between 11-20 ng/ml (mean =13 ±2), 11% between 5-10 ng/ml (mean=7 ±1) and 6% were below 5ng/ml (Table-2). There were four male patients, all (100%) with age distribution of 41-50 year and among them 3(75%) were having vitamin D levels between 11-20 ng/ml and only one (25%) was having less than 10 ng/ml. Among 96 female patients 80(76.8%) were having level between 11-20 ng/ml, 10 (9.6%) between 5-10ng/ml and 6 (5.7%) were below 5 ng/ml. When adjusted for age, 54 (56%) were with age between 41-50 years and their vitamin D levels were 11- 20 ng/ml in 43(79.6%) , 5-10 ng/ml in 8(14.8%) and less than 5 ng/ml in 3(5.5%).

Table -1
Frequency of associated complaints in Fibromyalgia.

No	Complaints	N
1	Muscle spasm	41
2	Tingling	23
3	Bloating	43
4	Depression	52
5	Anxiety	64
6	Irritable bowel syndrome	28
7	Restless legs	23
8	Chronic fatigue	86
9	Bladder problems	27
10	Forgetfulness	59
11	Poor concentration	73

N= no of patients

31 (32%) females were of age 31-40 years and levels among 28(90.4%) were between 11-20 ng/ml whereas one (3.2%) was between 5-10ng/ml and 2 (6.4%) were

below 5ng/ml.11 (12%) female were having age range 20-30 years with vitamin D distribution as 11-20 ng/ml in 9 (81.8%), 5-10 ng/ml in one (9.1%), less than 5 ng/ml in one (9.1%) (Table-3).

Table-2
Serum vitamin D levels in 100 study subjects

No	%age	25OH-D3 level	Mean
1	83%	11-20 ng/ml	13 ±2
2	11%	<10 ng/ml	7 ±1
3	6%	<5 ng/ml	

Table-3
Serum vitamin D levels versus Age and Gender in fibromyalgia patients.

	M		F		Total Patients
Patients	4		96		100
Age ranges	41-50	41-50	31-40	20-30	
Number (%ages)	4(100)	54(56)	31(32)	11(12)	
Vitamin D Level*					
11-20 ng/ml	3(75)	43(79.6)	28(90.4)	9(81.8)	83
5-10 ng/ml	1(25)	8(14.8)	1(3.2)	1(9.1)	11
<5ng/ml	0	3(5.6)	2(6.4)	1(9.1)	6

F= female, M= male.

* Vitamin D level ranges and in no of patients

Frequency of associated complaints in fibromyalgia is shown in table No-1 and after replacement with vitamin D achieving expected target serum levels >50ng/ml. Improvement in ACR criteria of fibromyalgia syndrome consisting of widespread musculoskeletal pains and 11 out 18 tender points was improved in more than 76 % of the patients. Improvement in the associated conditions was also observed. Notably, out of 23 patients with restless legs and 86 patients with chronic fatigue, 21 (91.3%) and 84(97.6%) reported marked improvement respectively (Table-4). Similarly, 35 out of 41 (85%) reported relief from muscle spasm and 15 out of 23 (65%) from tingling. There was also improvement in neuropsychiatric conditions like depression in 37 out of 52 (71%) and anxiety in 30 out of 64 (46.8%).

Moreover, improvement in cognitive function like concentration and forgetfulness was also reported by 51 out of 73 (69.8%) and 40 out of 59 (67.7%) respectively (Table-4).

Table -4
Improvement of Fibromyalgia Complaints after vitamin D replacement.*

No	Complaints	N	n	%age
1	Muscle spasm	41	35	85
2	Tingling	23	15	65
3	Bloating	43	2	4.6
4	Depression	52	37	71
5	Anxiety	64	30	46.8
6	Irritable bowel syndrome	28	03	10.7
7	Restless legs	23	21	91.3
8	Chronic fatigue	86	84	97.6
9	Bladder problems	27	03	11
10	Forgetfulness	59	40	67.7
11	Poor concentration	73	51	69.8

N= no of patients, n= patients improved.

* Based on subjective improvement compared with history proforma at beginning of study.

CONCLUSION

All patients with fibromyalgia were deficient in vitamin D. Replacement with vitamin D had significant beneficial effect on fibromyalgia. Such findings warrant larger double blind placebo controlled studies in future.

DISCUSSION

The findings of our study were consistent with other studies. A prospective study (Al Faraj et al) involving 360 patients in Saudi population with chronic low back pain showed that 83% of the study patients (n = 299) had an abnormally low level of vitamin D before treatment with vitamin D supplements. After treatment, clinical improvement in symptoms was seen in all the groups that had a low level of vitamin D, and in 95% of all the patients[53]. Another study (Huisman AM, et al) revealed that about 50% of systemic lupus erythematosus (SLE) and FM patients had 25(OH)-vitamin D levels < 50 nmol/l, a level at which PTH stimulation occurs[52]. One study (Plotnikoff GA et al) showed that 93% of persons 10 to 65 years of age who were admitted to a hospital emergency department with muscle aches and

bone pain and who had a wide variety of diagnoses, including fibromyalgia, chronic fatigue syndrome, and depression, were deficient in vitamin D[50]. In a recent large study (Atherton K et al), a significant association between 25-OH vitamin D levels and increased pain was found in only one of the several analyses for 3495 women but not for 3365 men[56]. This also supports the results of our study as our study population consisted of only female population.

Research suggests that low vitamin D status may be more than just an incidental finding in people with fibromyalgia. According to one report (Prabhala A et al), correction of vitamin D deficiency can ameliorate symptoms of fibromyalgia, chronic fatigue, and depression[51]. Although vitamin D status is almost never assessed in patients presenting with these conditions, it should be suspected in people with inadequate sun exposure, in those who do not consume vitamin D-fortified foods (such as milk), and in people with malabsorption, malnutrition, or chronic renal failure.

The understanding of fibromyalgia syndrome is quite vague. Vitamin D hypothesis may solve this puzzle in future. It was not until recent years we paid attention to vitamin D deficiency as an emerging epidemic. The vitamin D receptor (VDR) is nearly ubiquitously expressed, and almost all cells respond to 1,25-(OH)₂D exposure; about 3% of the mice and human genome is regulated, directly and/or indirectly, by the vitamin D endocrine system, suggesting a more widespread function[45]. Studies have shown that vitamin D apart from Calcium, Phosphorus, and bone metabolism, has a role in osteomalacia, osteoporosis, prevention of falls and fractures, improving muscle strength, cardiovascular health. Moreover, brain, prostate, breast, and colon tissues, among others, as well as immune cells have a vitamin D receptor and respond to 1,25-dihydroxyvitamin D, the active form of vitamin D. 1,25-Dihydroxyvitamin D is also a potent immunomodulator. It prevents various cancers, autoimmune disease like rheumatoid arthritis, multiple sclerosis, and diabetes mellitus. Vitamin D deficiency is linked to psychiatric illnesses like depression and schizophrenia[46]. It has also been reported that along with fibromyalgia, its associated conditions like anxiety and depression might be due to vitamin D deficiency[54].

As we speak of fibromyalgia, let's not forget osteoporosis and osteomalacia. It is noteworthy that osteoporosis is unassociated with bone pain, whereas

osteomalacia has been associated with isolated or generalized bone pain[47,48]. The cause is thought to be hydration of the demineralized gelatin matrix beneath the periosteum; the hydrated matrix pushes outward on the periosteum, causing throbbing, aching pain[49]. Osteomalacia can often be diagnosed by using moderate force to press the thumb on the sternum or anterior tibia, which can elicit bone pain[49,48] Exposure to stressful conditions can alter the function of the hypothalamic-pituitary-adrenal (HPA) axis, This is supported by a prospective epidemiology study which found that variations in HPA function characterized by high levels of circulating cortisol following dexamethasone suppression testing, low levels of morning salivary cortisol and high levels of evening salivary cortisol are all associated with the development of chronic widespread pain[37]. Some fibromyalgia patients responded in controlled trials to pramipexole, a dopamine agonist that selectively stimulates dopamine D2/D3 receptors and is used to treat both Parkinson's disease and restless leg syndrome[38], a finding formed basis of Central Dopamine Dysfunction Hypothesis. Psychosocial factors are also implicated in the the development of fibromyalgia but nature of the association is controversial [39]. A comprehensive review into the relationship between fibromyalgia and major depressive disorder (MDD) found substantial similarities in neuroendocrine abnormalities, psychological characteristics, physical symptoms and treatments between fibromyalgia and MDD, but currently available findings do not support the assumption that MDD and fibromyalgia refer to the same underlying construct or can be seen as subsidiaries of one disease concept[39]. Similarly, hypotheses suggesting deficiency of serotonin [40] and growth hormone[41,42,43,44] are controversial. However, a study(Darryl W. Eyles et al) on vitamin D receptors in brain showed that the strongest immunohistochemical staining for both the receptor and enzyme was in the hypothalamus and in the large (presumably dopaminergic) neurons within the substantia nigra. The observed distribution of the VDR is consistent with the proposal that Vitamin D operates in a similar fashion to the known neurosteroids. The widespread distribution of 1 α -OHase and the VDR suggests that Vitamin D may have autocrine/paracrine properties in the human brain[55]. This finding may open new ways in our understanding of fibromyalgia syndrome.

Limitation of Our Study: It was a pilot study to see the impact of vitamin D replacement on very small number (n=50) of patients.

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