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ORIGINAL ARTICLE

Efficacy of vitamin D replacement therapy on patients with chronic nonspecific widespread musculoskeletal pain with vitamin D deficiency

Ramazan YILMAZ,[1] Ali SALLI,[2] Havva Turac CINGOZ,[3] Sami KUCUKSEN[2] and Hatice UGURLU[2]

[1]*Department of Physical Medicine and Rehabilitation, Yoncali Physical Medicine and Rehabilitation Hospital, Kutahya,* [2]*Department of Physical Medicine and Rehabilitation, Meram Medical School, Necmettin Erbakan University, and* [3]*Department of Physical Medicine and Rehabilitation, Seydisehir State Hospital, Konya, Turkey*

Abstract

Aim: The objective of this study is the evaluation of the effect of vitamin D replacement treatment on musculoskeletal symptoms and quality of life in patients with chronic widespread musculoskeletal pain (CWP) including fibromyalgia (FM) and vitamin D deficiency.

Method: Patients with nonspecific CWP and vitamin D deficiency (25-OH D3 < 25 ng/mL) were included into the study. Replacement treatments of 50 000 IU/week oral vitamin D3 for 3 months were given to the patients. Patients were assessed pre- and post-treatment in terms of serum levels of Ca, P, alkaline phosphatase, 25-OH D3, severity of pain (visual analogue scale [VAS]-pain), severity of asthenia (VAS-asthenia), Beck Depression Inventory (BDI), quality of life scale (Short Form [SF]-36), tender point count (TPC), severity of waking unrefreshed, headache, tenderness on tibia, meeting the criteria of FM, and level of patient satisfaction.

Results: Fifty-eight patients with a mean age of 36.9 ± 9.2 years were included into the study. 25-OH D3 levels of patients elevated from 10.6 ± 5.1 ng/mL to 46.5 ± 24.0 ng/mL after replacement treatment ($P < 0.001$). Marked decrease in VAS-pain, VAS-asthenia, severity of waking unrefreshed, TPC, and BDI and an evident increase in subgroups of SF-36 were established in patients after treatment ($P < 0.001$). The number of FM+ patients was 30 (52%) before treatment and regressed to 20 (34%) after treatment ($P = 0.013$); 85% of patients stated satisfaction with the treatment.

Conclusions: Vitamin D replacement treatment in patients with nonspecific CWP has provided improvements in musculoskeletal symptoms, level of depression and quality of life of patients. Patients with CWP should be investigated for vitamin D deficiency.

Key words: chronic pain, depression, fibromyalgia, quality of life, vitamin D deficiency.

INTRODUCTION

Chronic widespread musculoskeletal pain (CWP) is one of the major global causes of disability and is very common (4.2–13.3%) in the general population.[1,2] In 1990, the American College of Rheumatology (ACR) defined CWP as pain lasting at least 3 months, both above and below the waist, on the right and left sides of body and in the axial skeleton.[3] CWP differs from localized pain not only in its distribution, but also with higher pain intensity, longer pain duration, greater disability, more common psychosocial problems and lower levels of life quality.[4]

Correspondence: Dr Ramazan Yilmaz, Department of Physical Medicine and Rehabilitation, Yoncali Physical Medicine and Rehabilitation Hospital, Yoncali, Kutahya 43250, Turkey.
Email: drramazanyilmaz@yahoo.com

Fibromyalgia (FM) has been classified as CWP with mechanical hyperalgesia at ≥ 11 tender points.[3] FM is the most common and best known disease in which the cardinal symptom is CWP. In studies comparing patients with CWP who met or did not meet the FM criteria,[5,6] it was shown that more severe clinical symptoms, increased frequency of depression and anxiety, and more negatively affected daily living activities were present with FM. Therefore, FM can be considered as an extreme form or presentation of disseminated pain. Nonspecific CWP including FM is a significant health matter with unilluminated etiology and no effective treatment.

Vitamin D that has substantial function in equilibrium of Ca and P and also in bone health, is a hormone with steroid structure. It has been established that vitamin D deficiency is considerably common with a prevalence of 25–50% among the general population.[7,8] It has been reported that vitamin D deficiency is related to musculoskeletal disturbances, neuromuscular function disorders, infections, autoimmune diseases, lung diseases, metabolic syndrome, diabetes, cardiovascular diseases, cognitive function disorders, psychiatric disorders and increased risk of many types of cancer.[8–12] The best known results of vitamin D deficiency include rickets in children, osteomalacia in adults, osteopenia/osteoporosis, and increased risk of fractures and falls.[11,13]

However, the relationship between CWP and vitamin D deficiency is controversial. Several studies have reported a 'positive association'[14–25] whereas others found 'no association'.[26–30] The effect of vitamin D replacement treatment on musculoskeletal symptoms and quality of life in patients having CWP including FM and vitamin D deficiency, were evaluated in the current study.

PATIENTS AND METHODS

Study population

The study was done at a Physical Therapy and Rehabilitation Clinic of Necmettin Erbakan University Meram Faculty of Medicine in Konya, Turkey (latitude: 37°52′ north; longitude: 32°31′ east). Patients with primary nonspecific CWP including FM and vitamin D deficiency (25-OH D3 < 25 ng/mL) were included into the study. The primary nonspecific CWP was diagnosed in patients with main complaint of 'having pain throughout the body' and otherwise unexplained widespread pain with a duration of at least 3 months in accordance with the criteria of the 1990 ACR CWP.[3] Patients were subjected to a detailed history taking, musculoskeletal and neurological physical examination and patients with an identifiable pain origin (such as tendinitis, disk hernia, osteoarthritis, carpal-tunnel syndrome, lumbar pain, knee pain, etc.) were excluded even though they had widespread pain. Patients with the following profiles were excluded from the study: radicular or discogenic pain, with thyroid or parathyroid function disorder, anemia (Hb < 11 mg/dL in women, Hb < 12 mg/dL in men), vitamin B12 deficiency, having diagnosis of any disease that might cause widespread pain (such as diseases of liver and kidney, inflammatory rheumatic diseases, infectious diseases, malignity, parkinsonism, multiple sclerosis), malabsorption and patients taking vitamin D or Ca supplementation. The study protocol was approved by the Ethics Committee of Meram Faculty of Medicine before onset of the study, and all the patients signed informed consent forms freely and the forms were collected.

Sixty-five patients were included to the study. Data of patients such as age, gender, occupation, body mass index (BMI), duration of symptom, comorbidities, accompanying medicines were noted. Out of 65 patients included in the study, four, two and one patients were excluded from the study due to loss of follow up, incompatibility with treatment and vitamin B12 deficiency, respectively, and the remaining 58 subjects completed the study.

Severity of pain, asthenia and morning symptoms

All patients were assessed in terms of pain and asthenia levels by means of a visual analogue scale of 0–10 cm (VAS). Severity of waking unrefreshed was assessed in accordance with 2010 ACR FM classification criteria[31] by a score in the range of 0–3.

Assessment of quality of life and level of depression

Quality of life was assessed in general scales by the Turkish version of the quality of life questionnaire of the Short Form-36 (SF-36) index[32] which is the most commonly used one and not specific to any age, disease or treatment group. SF-36, with proven validity and reliability in musculoskeletal disorder patients, consists totally of 36 items that can be answered by the patients. SF-36 includes eight different sub-dimensions related to health. These are physical function, social function, role limitations due to physical problems and emotional problems, mental health, vitality, bodily pain and general health perception. For each dimension, item scores

are coded from 0 (worst health status) to 100 (best health status) and transformed into a scale. In the assessment of depression severity, the Turkish version of the 21-item Beck Depression Inventory (BDI) was used, which is one of the most common psychometric tests used and a value of 0 to 3 is assigned for each answer to each item.[33]

Tender point counts and assessment of tibial tenderness

Eighteen defined tenderness points for the classification criteria of FM were assessed before and after treatment by a single physician as specified in the classification criteria of 1990 ACR FM[3] via applying pressure (approximately 4 kg) until the whitening of the thumb nail. As with the tender points, tibial tenderness was also assessed by applying pressure to the anterior of the tibia and statement of the pressure by the patient as 'pain' was approved as presence of tibial tenderness.

Assessment of patient satisfaction

Satisfaction levels of patients were questioned. In the assessment consisting of five clauses with Likert-type scales, clauses were described as follows: 1, 'no satisfaction at all'; 2, 'no satisfaction'; 3, neutral (no + or − effect); 4, 'satisfied'; and 5, 'very satisfied'.[34]

Vitamin D measurement

Pre- and post-treatment levels of serum Ca, P, alkaline phosphatase (ALP) and vitamin D were measured in all patients. For vitamin D analysis, serum samples were separated immediately after phlebotomy, and stored at −20°C and analyzed in the same laboratory (laboratory of Meram Faculty of Medicine) by melting within 1 week at the latest. 25-OH D3 was used to determine vitamin D level as measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) methodology on a Tandem GOLD Triple Quadrupole LC/MS/MS system (Zivak Technologies, Kocaeli, Turkey). Results were expressed as ng 25-OH D3 per 1 mL serum with analytical sensitivity of 1 ng/mL and interassay coefficient of variation was 93% and 104%. The lower detection limit was 0.4 ng/mL. For the description of vitamin D deficiency, 25 ng/mL was taken as the reference threshold value in accordance with optimal levels of 25-OH D reported in many updated trials (< 25 ng/mL = vitamin D deficiency).[7,11,30,35,36] Two different cut off points for defining hypovitaminosis D were used (< 10 ng/mL as severe deficiency, 10–24 ng/mL as mild to moderate deficiency).[30]

Study protocol

Oral vitamin D3 (cholecalciferol) treatment of 50 000 IU weekly, with total dose of 600 000 IU and elemental calcium of 1000 mg/day were given to patients for 3 months in our study which is similar to previous studies.[7,24,29,30,37] We selected a 3-month interval for reassessment after treatment, based on the studies which reported that regression of symptoms, possibly related to vitamin D deficiency, including osteomalacia, frequently occurs within 2–3 months of treatment.[29,38–40]

No analgesic treatment was recommended to the patients for a period of 3 months; however, it was stated that paracetemol 500 mg tablet (tb) could be used up to 2 g/day in case of need and no analgesic should be taken less than 24 h before the assessment.

Patients were evaluated before and 3 months after the end of treatment in regard to laboratory parameters (Ca, P, ALP and 25-OH D3), pain and asthenia levels with VAS, severity of waking unrefreshed, tender point counts (TPC), presence of depressive mood with BDI, quality of life with SF-36, patient satisfaction scoring with a Likert scale of 0–5 and whether 1990 ACR FM criteria were completed or not. Furthermore, presence of tibial tenderness and chronic headache (> 3 months) were also assessed as present or not and patients with headache were noted with questioning of whether there was a 50% reduction or not.

Statistical analysis

Data were analyzed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Data were given as percentage (%), mean ± standard deviation (SD), median (quarters inter interval) and range. Pre- and post-treatment comparison of paired two groups with dependency, Paired-Samples test for numeric data, Wilcoxon marked sequence test for ordinary data, McNemar test for comparison of dicotomous data were used. Independent *t*-test for comparison of independent parametric variables, Mann–Whitney *U*-test for comparison of non-parametric variables and Chi-square test for comparison of categorical (dicotomous) variables were used. To assess the correlation between two variables, Pearson analysis and Spearman rho test were applied for the parametric and non-parametric variables, respectively. *P*-values ≤ 0.05 were considered statistically significant.

RESULTS

Basic characteristics of 58 patients who completed the study are presented in Table 1. Mean age of patients

was 36.9 ± 9.2 years. Median value of duration of CWP was 24.0 months (range, 3–96 months); 51.7% (30) of 58 patients with non-specific CWP fulfilled the 1990 ACR classification criteria for FM.

Patients' baseline level of 25-OH D3 was 10.6 ± 5.1 ng/mL (range, 3.5–2.2). Severe and mild to moderate vitamin D deficiency was present in 32 (55.2%) and 26 cases (44.8%), respectively.

Baseline mean serum levels of Ca, P and ALP of patients were within the normal reference values and no patients had reduction of Ca, P or elevation of ALP. In the investigation of correlation across the baseline level of 25-OH D3 and assessed clinical parameters, a significant correlation was found only with SF-36 subscale of social function ($r = 0.30$, $P = 0.02$). Frequency of meeting the 1990 ACR FM criteria was seen more in the patients with severe vitamin D deficiency compared to patients with mild to moderate vitamin D deficiency (65.5% *vs*. 34.6%, $P = 0.034$); no significant difference was observed across the other assessed parameters ($P > 0.05$).

25-OH D3 levels increased to 46.5 ± 24.0 ng/mL (range 13–157) ($P < 0.001$ after replacement (Table 2). Levels of 25-OH D3 above the range of 100–150 ng/mL, which was accepted as the safe upper limit,[7,41] were detected in two patients (108 and 157 ng/mL). No significant change was determined in the post-treatment level of Ca and P ($P > 0.05$), whereas a statistically significant reduction in the level of ALP was ascertained ($P < 0.001$) (Table 2). Findings of hypercalcemia or signs of vitamin D intoxication were not observed in any patient.

Table 1 Baseline demographic and clinical characteristics of patients ($n = 58$)

Age (years)	
Mean ± SD	36.9 ± 9.2
Median (interquartile range)	35.5 (29, 45)
Gender *n* (%)	
Female	52 (89.7%)
Male	6 (10.3%)
Occupation	
House wife	42 (72.4%)
Working	16 (27.6%)
BMI (kg/m²)	26.4 ± 5.3
Duration of pain (month)	
Mean ± SD	28.9 ± 22.7
Median with range	24 (3–96)
Patients who fulfilled with classification criteria of 1990 ACR FM: 30 (51.7%)	

ACR, American College of Rheumatology; BMI, body mass index; FM, fibromiyalgia.

Table 2 Pre- and post-treatment comparison of assessment parameters ($n = 58$)

	Pre-treatment	Post-treatment	*P*
Ca (8.4–10.2 mg/dL)†	9.3 ± 0.4	9.4 ± 0.3	0.78
P (2.3–4.7 mg/dL)†	3.6 ± 0.6	3.6 ± 0.6	0.89
ALP (40–150 U/L)†	59.1 ± 16.3	54.0 ± 14.4	< 0.001*
25-OH D3 (ng/mL)	10.6 ± 5.1	46.5 ± 24.0	< 0.001*
VAS-pain	7.4 ± 1.4	3.9 ± 2.3	< 0.001*
VAS-asthenia	7.3 ± 1.6	4.2 ± 2.6	< 0.001*
Tender point count	10.4 ± 5.2	7.5 ± 5.4	< 0.001*
Severity of waking unrefreshed	2.3 ± 0.8	1.2 ± 1.1	< 0.001*
Beck Depression Inventory	19.7 ± 8.8	12.7 ± 7.5	< 0.001*
SF-36 Physical function	51.6 ± 22.8	66.0 ± 23.6	< 0.001*
SF-36 Limitation of physical role	21.6 ± 34.0	53.5 ± 39.7	< 0.001*
SF-36 Bodily pain	30.0 ± 13.3	51.2 ± 19.7	< 0.001*
SF-36 Perception of general health	41.5 ± 23.4	52.1 ± 23.1	< 0.001*
SF-36 Vitality	26.4 ± 15.4	46.8 ± 21.6	< 0.001 *
SF-36 Social function	47.6 ± 23.4	64.2 ± 22.1	< 0.001*
SF-36 Limitation of emotional role	25.9 ± 36.4	51.5 ± 39.0	< 0.001*
SF-36 Mental health	43.3 ± 16.8	57.4 ± 19.1	< 0.001*

ALP, alkaline phosphatase; VAS, visual analogue scale. †Normal reference range. *Statistically significant.

In comparison of post-treatment with pre-treatment, statistically significant reduction was detected in VAS-pain, VAS-asthenia, severity of waking unrefreshed, TPC and BDI ($P < 0.001$) and a significant increase was also determined in all of the SF-36 subscales ($P < 0.001$) (Table 2). As the 30 patients in the pre-treatment assessment met the 1990 ACR classification criteria for FM, this number regressed to 20 (34.5%) in post-treatment assessment ($P = 0.013$) (Table 3). Forty-two (72.4%) patients had tibial tenderness before treatment; it regressed to 22 after treatment ($P < 0.001$) (Table 3). Pre-treatment complaint of headache was available in 29 patients and at least 50% of post-treatment decrease in the severity and frequency of the headache was reported in 20 (69%) ($P = 0.004$) (Table 3).

No significant difference was detected in terms of level of change (Δ) in pre- and post-treatment assessment parameters across the patients at baseline with severe levels of vitamin D deficiency and the ones with mild to moderate levels ($P > 0.05$).

Table 3 Post-treatment change in the dicotomous parameters (n = 58)

	Yes (n)	No (n)	P
BT FM†	30	28	0.013*
AT FM†	20	38	
BT tibial tenderness	42	16	< 0.001*
AT tibial tenderness	22	36	
BT headache	29	29	0.004*
AT > 50% reduction in headache	20	9	

AT, after treatment; BT, before treatment; FM, fibromyalgia. †In accordance with the 1990 American College of Rheumatism classification criteria. *Statistically significant.

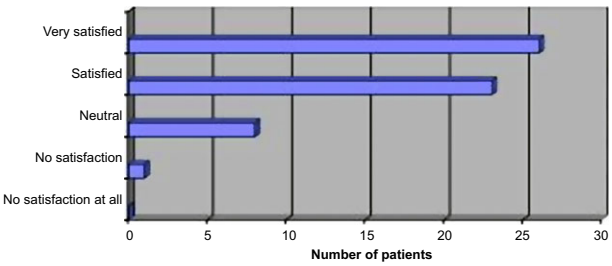

Figure 1 Post-treatment level of patient satisfaction.

In post-treatment assessment of patient satisfaction levels, no patient has stated 'no satisfaction at all'. Patient satisfaction levels were denoted as follows: 'not satisfied' one (1.7%) patient, 'neutral' eight patients (13.8%), 'satisfied' 23 (39.7%) patients, 'very satisfied' 26 (44.8%) patients (Fig. 1). A statistically significant correlation was found between the decrease in pain level and level of satisfaction ($r = -0.76$, $P < 0.001$).

DISCUSSION

The efficacy of vitamin D replacement treatment was evaluated in this study by means of laboratory and distinct clinical parameters in patients with nonspecific CWP, including FM and low levels of vitamin D. On the upshot, marked improvement was established by vitamin D3 replacement treatment in vitamin D3 levels, pain, asthenia, severity of morning symptoms, quality of life, depressed mood, headache and availability of tibial tenderness. Furthermore, prominent reduction was displayed after treatment as per before treatment in the ratio of meeting the classification criteria of FM and TPC.

Despite 55% of patients in this study having severe vitamin D deficiency, there was no patient with reduced Ca and P or elevated ALP, as expected in osteomalacia. The differential diagnosis might not be easy since osteomalacia may have similar symptoms to FM. Although osteomalacia is a well-known disease with its specific symptoms and findings, it is actually a histopathological diagnosis and final diagnosis can be done by biopsy.[36,42] Patients in the study had symptoms and findings observed in osteomalacia such as disseminated musculoskeletal pain, asthenia and bone tenderness. However, no patients had laboratory parameters[42] or clinical features specific for osteomalacia, such as proximal muscle weakness or difficulty in walking.

Investigations in recent years demonstrated that vitamin D receptors (VDR) were available in almost all cells. So, it is considered that vitamin D deficiency can occur in association with many diseases.[11,43] VDR was detected in human muscle tissue for the first time in 2001,[44] and the possible relationship of vitamin D deficiency with symptoms such as musculoskeletal pain, asthenia and weakness were also suggested at the same time. Theoretically, the function of 1,25-OH D in the regulation of the immune system can explain musculoskeletal pain related to vitamin D deficiency and it was considered that inflammatory cytokines activated by infections may play a role in the etiopathogenesis of FM by modulating perception of central and peripheral pain.[17,45–47] On the other hand, secondary vitamin D deficiency can develop in patients with FM as a result of spending little time in the open-air due to pain, depression and restricted mobility or increased fat tissue.

In a cross-sectional study conducted by Plotnikoff and Quigley among different ethnic groups; vitamin D deficiency was present in 93% of 150 patients with persistent non-specific musculoskeletal pain and they recommended investigation of patients with treatment-resistant and non-specific pain in terms of vitamin D deficiency.[14] A relationship between vitamin D deficiency and non-specific musculoskeletal pain was also reported by other studies performed collinear with this study.[15–22]

In contrast, in a study performed by Block *et al.*[26] that were substantiated by two other controlled studies[27,28] in succeeding years, vitamin D deficiency was not found to be more frequent in patients with FM.

Recently, three studies found a high rate of vitamin D deficiency among patients with FM and a marked improvement was observed after replacement.[23–25] The major deficit of these studies that revealed the efficacy of the replacement treatment was the lack of control groups. Conversely, in two randomized, placebo-controlled trials, CWP was not found to be associated with

vitamin D deficiency and no improvement in musculoskeletal symptoms were seen in CWP after treatment with vitamin D.[29,30]

As described above, conflicting results were obtained in the studies investigating the relationship between vitamin D deficiency and CWP and by analyzing the currently available data, it was not possible to make a comment on the relationship between them.[46,47]

Detecting substantially efficient elevations in levels of vitamin D in patients following replacement treatment for 3 months and no observation of findings of hypercalcemia or vitamin D intoxication in any patient, demonstrates that treatment of oral vitamin D3 of 50 000 IU/week for 3 months is a relatively efficient and safe replacement protocol. Significant post-treatment reduction of tibial tenderness, TPC and the frequency of FM were noted in patients in the present study. Since FM and its specific signs, tender points, are considered as characterizing disease severity[48] and increased mechanical hyperalgesia, these findings could support the relationship between vitamin D deficiency and musculoskeletal hypersensitivity. And, supporting previous study results, a prominent increase in quality of life[22,49] of patients and a pronounced reduction in BDI[9,16] and headache[20,39] were noticed in this study.

The foremost limitations of our study were the absence of a control group and short follow-up period. Although 3 months seems a sufficient period of time for regression of symptoms related to vitamin D deficiency, if it were re-evaluated after maintenance treatment of vitamin D for 6–12 months, a stronger outcome could be reached supporting the relationship between the symptoms and vitamin D deficiency. Parathyroid hormone and urinary calcium of patients were also not assessed in the present study. However, despite these limitations, selective inclusion of the cases in this study and getting benefit of treatment to the patients clearly in terms of many symptoms were important results that were obtained in our study.

CONCLUSION

A 3-month replacement treatment has provided reductions in musculoskeletal symptoms, level of depression and an increase in quality of life of patients with nonspecific CWP and vitamin D deficiency. Patients with FM or CWP should be investigated in regard to deficiency of vitamin D. Oral vitamin D3 of 50 000 IU/week for 3 months is substantially efficacious and safe replacement treatment in vitamin D deficiency. Prospective, double-blind, randomized, placebo-controlled studies are required in order to reveal clearly the cause and outcome relationship between vitamin D deficiency and CWP.

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CONFLICTS OF INTEREST

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