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Original Article

Vitamin D supplementation for diffuse musculoskeletal pain: Results of a before-and-after study

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KEY MESSAGE:

- Serum 25 (OH) D deficiency should be explored in the context of diffuse musculoskeletal (DMS) pain in adults.
- Vitamin D supplementation seems to have a positive effect on DMS pain and quality of life.
- The causal relationship between vitamin D supplementation and DMS pain needs to be explored and confirmed in further studies.

ABSTRACT

Background: Several studies have shown that vitamin D supplementation could be useful for treating diffuse musculoskeletal (DMS) pain in adults.

Objectives: The aim of this study was to evaluate the effects of correcting a vitamin D deficiency ($\leq$ 50 nmol/l) on DMS pain and quality of life in adults.

Methods: A pragmatic prospective study was conducted in a general practice setting in the Rhone-Alps area between 1 February and 30 April 2009. Patients between the ages of 18 and 50 years old who consulted their general practitioner (GP) for DMS pain or chronic unexplained asthenia and had a deficient serum 25 (OH) D level with no signs of any other disease were enrolled in this study. The patients received high doses of vitamin D supplements (400 000 to 600 000 units). Mean pain evaluation scores were evaluated before and after vitamin D supplementation using mixed models and accounting for repeated measures.

Results: Before vitamin D supplementation, the adult study cohort ($n = 49$) had an adjusted mean serum 25 (OH) D level of 23.7 nmol/l, a mean pain evaluation score of 5.07 and a mean quality of life score of 3.55. After vitamin D supplementation, the adjusted mean serum 25 (OH) D level increased to 118.8 nmol/l ($P < 0.001$), the mean quality of life score increased to 2.8 nmol/l ($P < 0.001$) and the mean pain evaluation score decreased to 2.8 ($P < 0.001$).

Conclusion: In this small before-and-after study, vitamin D supplementation decreased pain scores in adult patients with diffuse musculoskeletal pain and vitamin D deficiency. These results must be confirmed by further studies.

Keywords: Vitamin D, musculoskeletal pain, quality of life, general practice

INTRODUCTION

25-hydroxyvitamin D – 25 (OH) D plays an important role in bone mineralization and muscle metabolism (1). Many studies have reported that hypovitaminosis D exists all over the world. In the UK, Hypponen reported that 87.4% of the studied population had vitamin D levels below 75 nmol/l, 46.6% had levels below 40 nmol/l and 15.5% had levels below 20 nmol/l in the winter and spring. In the summer, the proportions of the population at each of the three levels were 60.9%, 15.4% and 3.2%, respectively (2). In Germany, Erkal reported that 29% of the German population and 100% of immigrants had levels below 50 nmol/ l (3). In Saudi Arabia in 2011, Elsammak showed that 65% of 139 healthy persons had hypovitaminosis D (the mean serum level was 25.2 $\pm$ 11.5 nmol/l for men, and 24.7 $\pm$ 11.2 nmol/l for women)(4). Similar results were noted in Belgium by McFarlane, in Austria by Kaehler and in Norway by Knutsen (5–7). Pain related to hypovitaminosis D was also reported in these studies.

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Since infants and children have been supplemented with vitamin D, rickets has been eradicated in developed countries. Many studies have shown severe vitamin D deficiency in patients complaining of diffuse musculoskeletal (DMS) pain. DMS pain may be present many years before osteomalacia is diagnosed (3,8–11); chronic unexplained fatigue could also be a symptom of severe vitamin D deficiency (7). We previously reported that young women who consulted their general practitioners (GP) in late winter with very low vitamin D levels, frequently complained of pain or fatigue and had poor physical quality of life but unimpaired psychosocial quality of life (12). DMS pain is a frequent reason for repetitive consultations in primary care and can lead to multiple and costly drug prescriptions, X-ray examinations, and physiotherapy (13).

The current study was designed to evaluate blood 25 (OH) D levels in adult patients who consulted their GP for fatigue or unexplained DMS pain and to compare pain levels, quality of life and drug consumption before and after correcting the patients' vitamin D levels. We could not identify any similar studies in the literature.

METHODS

Study design and selection of study subjects

A pragmatic prospective study was conducted in accordance with articles L.1121–1 and R1121–2 of the French Code of Public Health. All patients gave oral consent for the anonymous use of their personal data.

Between 1 February and 30 April 2009, a group of 13 GPs in the Rhone-Alps area agreed to collect data from patients' records. The GPs selected men and women 18 to 50 years old who sought a consultation for DMS pain or fatigue that had been present for several weeks without any apparent reason and clinical features compatible with a specific pathology. They were informed that data collected in this study was being used to understand the possible link between a severe vitamin D deficiency and pain.

Measurements

Subject characteristics. The following patient data were collected: age, gender, phototype (according to the Fitzpatrick classification scheme), body mass index (BMI), the use of body-covering clothes (e.g. burqa, niqab, or hijab), and whether the patient received CMU (Couverture Maladie Universelle; a system allowing low-income patients to access free health care). The questionnaire also asked patients about their diet, sun exposure, pain, fatigue, and the impact of pain on their daily life and quality of life.

Sunlight exposure, dietary intake of vitamin D and calcium were assessed using questions previously validated by Garabedian et al. for estimating the risk of vitamin D deficiency in adolescents (14).

Biology. Serum 25 (OH) D concentration was measured in the patient's usual laboratory, and the physicians were free to prescribe any additional tests they deemed useful for determining a diagnosis. The patients were considered vitamin D deficient if their 25 (OH) D level was below 50 nmol/l. The patients with very low vitamin D levels were invited to measure their parathyroid hormone (PTH).

Mean pain evaluation score. DMS pain was evaluated according to four criteria: location, duration, intensity, and the use of analgesics. The impact on instrumental activities of daily living was measured using the Lawton Scale. Fatigue intensity, with or without pain, was measured on a numerical scale from 1 (lowest) to 10 (highest).

Quality of life. Quality of life was assessed using the Dartmouth Primary Care Cooperative Information Project/ World Organization of National Colleges, Academies, and Academic Associations (COOP-Wonca) charts, which are easy to use on an outpatient basis and show good consistency and reliability. The six components of the COOP-Wonca assessment are physical condition, emotional state, activities of daily living, social activities, change in health status, and overall health. The answers are scored from 1 (best) to 5 (worst) (15).

Vitamin D supplementation

Based on a review of the literature (6,15–19), we asked the GPs to prescribe one, two, or three doses of 200 000 units of vitamin D per dose, depending on the severity of the deficit. The doses were separated by an inter-treatment interval of 10 days. A clinical and biological follow-up examination was conducted 45 to 60 days after the administration of the last dose of vitamin D.

Statistical analysis

The analyses were performed using SAS software (version 9.3, SAS institute Inc., Cary, NC, USA). A two-sided *P*-value less than 0.05 was considered significant. The baseline data was analysed using the chi-square test or the Wilcoxon Rank test for paired data; for continuous quantitative data, an analysis of variance (ANOVA) was conducted. The evolution of the mean scores was analysed using a mixed model analysis with a spatial power covariance structure, taking into account the individual repeated measures over time. The final models for mean serum 25 (OH) D levels, mean pain scores and mean quality of life scores were adjusted for age, gender and BMI, and the *P*-values presented correspond to the before/after effect.

RESULTS

Baseline characteristics

Initially, 69 adults participated in the first survey. Of these participants, 20 (29.0%) were considered lost to follow-up. No differences were found between individuals who were lost to follow-up and individuals in the final cohort (Table 1).

Ultimately, 49 adults participated in this study: 33 females (71.4%) and 14 males (28.6%). The females' mean age was 33.7 years (SD = 8.4). No significant differences were observed between the men and the women (Table 2). Symptoms of fatigue had been present for several months for 35 (71.4%) patients and had been present for several years for six (12.2%) patients. Patients reported pain in multiple locations, including arms, shoulders, legs, and hips, but they most frequently reported pain in the back.

Baseline 25 (OH) D deficiency levels

Of the 49 adults, six (12.2%) had a mean serum 25 (OH) D level ≤ 10 nmol/l, 27 (55.1%) had a level between 11 nmol/l and 30 nmol/l, and 16 (32.7%) had a level between 31 nmol/l and 50 nmol/l. No differences in the general characteristics or anthropometric data were found between these three sub-groups (Table 3).

Patients with the greatest deficiency were those who did not expose themselves to the sun in summer and those who ate small amounts of dairy products; only four of the 33 patients with severe hypovitaminosis D consumed milk fortified with vitamin D. The Lawton questionnaire measured whether the symptoms commonly limited the patients' abilities to perform day-to-day activities: household tasks (19/49, 38.8%), vacuuming (17/49, 34.7%), cooking (8/49, 16.3%), making beds (15/49, 30.6%), and walking distances more than a kilometre (14/49; 28.6%).

Pain evaluation and quality of life before and after vitamin D supplementation

After vitamin D supplementation, the adjusted mean serum level of the 49 adults increased significantly from 25.2 nmol/l (SD = 4.5) at the first observation point to 118.8 nmol/l (SD = 4.5) at the second observation point ($P < 0.0001$), and their quality of life increased from 3.5 (SD = 0.1 to 2.8 (SD = 0.1) ($P < 0.0001$). Meanwhile, their adjusted mean pain evaluation scores decreased significantly from 5.1 to 2.8 ($P < 0.0001$), and the proportion of adults reporting the use of analgesic drugs decreased from 20 (SD = 40.8) to 12.2 (SD = 12.2) ($P = 0.03$).

The highest 25 (OH) D level observed was 195 nmol/l, and six patients (12.2%) did not reach a level above the normal threshold of 75 nmol/l. The most severely deficient patient, whose initial level was less than 10 nmol/l, still had a serum vitamin D level below 50 nmol/l after treatment.

After treatment, the patient group reported significantly different experiences, including less discomfort while performing activities such as shopping, household chores, walking and dressing. They also reported improvements in their fitness, emotional status and social life. Nevertheless, their discomfort while climbing

Table 1. Baseline subject characteristics by follow up status.

Characteristic	Follow-up (*n* = 49)	Lost to follow-up (*n* = 20)	*P*-value
Mean age (SD), years	34.7 (9.0)	35.4 (10.6)	0.80
Female, *n* (%)	35 (71.4)	17 (85.0)	0.36
Mean BMI (SD), kg/m²	25.2 (5.5)	25.4 (7.1)	0.94
Normal weight, *n* (%)	24 (55.8)	5 (71.4)	0.86
Overweight, *n* (%)	11 (25.6)	1 (14.3)	
Obesity, *n* (%)	8 (18.6)	1 (14.3)	
Phototype, *n* (%)			
I and II	12 (24.5)	2 (16.7)	0.96
III	19 (38.8)	5 (41.7)	
IV and V	15 (30.6)	5 (41.7)	
VI	3 (6.1)	0 (0)	
Covering clothes, *n* (%)	4 (8.2)	2 (11.8)	0.64
Mean serum 25 (OH) D level (SD), nmol/l	25.1 (11.1)	30.0 (10.9)	0.99
Mean pain evaluation score (SD)	4.8 (2.6)	3.8 (2.7)	0.28
Median pain evaluation score (min–max)	6 (0–8)	3 (0–10)	0.18
Mean quality of life score (SD)	3.6 (0.7)	3.7 (0.7)	0.59
Median quality of life score (min–max)	4 (2–5)	4 (2–5)	0.51

Table 2. Baseline subject characteristics by gender.

Characteristic	Female (*n* = 35)	Male (*n* = 14)	*P*-value
Mean age (SD), years	33.7 (8.4)	37.2 (10.2)	0.26
Mean BMI (SD), kg/m²	25.6 (6.3)	25.9 (6.6)	0.89
Normal weight, *n* (%)	16 (53.3)	6 (46.1)	0.19
Overweight, *n* (%)	6 (20.0)	6 (46.1)	
Obesity, *n* (%)	8 (26.7)	1 (7.8)	
Phototype, *n* (%)			
I and II	9 (25.7)	3 (21.4)	0.96
III	14 (40)	5 (35.7)	
IV and V	10 (28.6)	5 (36.7)	
VI	2 (5.7)	1 (7.2)	
Covering clothes, *n* (%)	4 (11.4)	0 (0)	0.31
Mean serum 25 (OH) D level (SD), nmol/l	25.7 (9.8)	24.8 (13.3)	0.82
Mean pain evaluation score (SD)	4.8 (2.6)	5.4 (2.3)	0.43
Median pain evaluation score (min-max)	6 (0–8)	6 (2–8)	0.51
Mean quality of life score (SD)	3.7 (0.7)	3.3 (0.7)	0.12
Median quality of life score (min–max)	4 (2–5)	3 (2–5)	0.08

Table 3. Characteristics by vitamin D deficiency level.

Characteristics	Vitamin D level ≤ 10 nmol/l (*n* = 6)	Vitamin D level 11–30 nmol/l (*n* = 27)	Vitamin D level 31–50 nmol/l (*n* = 16)	*P*-value
Female, *n* (%)	3 (50)	22 (81.5)	10 (62.5)	0.17
Mean age (SD), years	35.5 (8.5)	34.5 (8.7)	34.8 (10.1)	0.97
Mean BMI (SD), kg/m²	23.4 (3.9)	25.8 (4.9)	26.5 (8.9)	0.65
Normal weight, *n* (%)	4 (66.7)	10 (43.5)	8 (57.2)	0.72
Overweight, *n* (%)	2 (33.3)	7 (30.4)	3 (21.4)	
Obesity, *n* (%)	0 (0)	6 (26.1)	3 (21.4)	
Phototype, *n* (%)				
I and II	0 (0)	5 (18.5)	7 (43.7)	0.25
III	3 (50)	10 (37)	6 (37.5)	
IV and V	3 (50)	10 (37)	2 (12.5)	
VI	0 (0)	2 (7.4)	1 (6.3)	
Covering clothes, *n* (%)	0 (0)	3 (11.1)	1 (6.3)	1
Mean pain evaluation score (SD)	5.2 (2.7)	4.3 (2.4)	6.2 (2.3)	0.046
Median pain evaluation score (min–max)	6 (0–8)	5 (0–8)	7.5 (2–8)	0.02
Mean quality of life score (SD)	3.8 (1)	3.5 (0.8)	3.5 (0.6)	0.61
Median quality of life score (min–max)	3.5 (3–5)	4 (2–5)	4 (2–4)	0.80

staircases and performing general daily activities remained similar to the pre-treatment state, as did their general health status.

After adjusting for gender, age and BMI, the patients' pain decreased significantly, and quality of life increased significantly after treatment.

Before treatment, 20 (40.8%) patients reported consuming analgesics, such as paracetamol, anti-inflammatory drugs, and/or muscle relaxants, either daily or curative. Consumption of these substances decreased significantly after treatment: only six patients reported consuming paracetamol (12.2%; $P = 0.003$) (Table 4).

Parathyroid hormone (PTH)

PTH was measured in 33 patients with severe hypovitaminosis D. The mean serum PTH level was 63.9 ± 30.7 ng/l (range: 27 to 150 ng/l). It decreased after treatment to 50.2 ± 27.8 ng/l.

DISCUSSION

Main findings

Severe hypovitaminosis D affected 67.7% of the 49 young patients included in the study. Of the participants, 71.4% had symptoms for several months and pain in multiple locations. Large doses of vitamin D were employed to correct the patients' deficiencies without incident.

The most interesting results for general practice are the improvement in the patients' quality of life, the improvement in daily activities and the reduction in the consumption of analgesics.

Strengths and limitations

Some limitations are worth noting. In pragmatic studies, such as this one, it is difficult to maintain a full study cohort because many individuals may decide to stop participating at any time. All patients who sought a consul-

Table 4. Serum 25 (OH),D level, pain evaluation score, quality of life score and analgesic consumption before and after vitamin D supplementation.

Variables	Before supplementation (*n* = 49)	After supplementation (*n* = 49)	*P*-value
Mean serum 25 (OH) D level, nmol/L[a] (SE)	25.2 (4.5)	118.8 (4.5)	< 0.001
Mean pain evaluation score (SE)[a]	5.1 (0.4)	2.8 (0.4)	< 0.001
Median pain evaluation score (min–max)	6 (0–8)	3 (0–7)	< 0.001
Mean quality of life score (SE)[a]	3.5 (0.1)	2.8 (0.1)	< 0.001
Median quality of life score (min–max)	4 (2–5)	3 (1–4)	< 0.001
Usual analgesic consumption, *n* (%)	20 (40.8)	6 (12.2)	0.003

*Adjusted on gender, age and BMI, SE, standard error.

tation for DMS pain were included in the study and agreed to participate in the treatment and complete the first questionnaires. However, 22 patients did not present for the follow-up visit. The GPs questioned these patients and determined that they had not returned mostly out of negligence or lack of interest. None mentioned worsening symptoms that led them to seek care elsewhere. The dropout rate observed (28.9%) was not surprising for an open study. Other researchers have reported losses of more than 50% (20,34).

The biochemical tests were performed in the patients' usual laboratories, which had typical quality control practices. Binkley et al. have shown that the differences in dosages were not large enough to skew the results (35).

This study was a before-and-after survey, which is not the best design to demonstrate a causal link between vitamin D deficiency and DMS pain; a randomized controlled trial with a placebo arm would have been better for this purpose. Studies with placebo groups exist and have not identified a causal relationship, but they did not include people with a serum 25 (OH) D level below 25 nmol/l (25,36).

The strengths of this study are the homogeneity of this young population and the lack of rheumatic or any other chronic diseases in the population. The only complaint was DMS pain or fatigue. Correcting a severe vitamin D deficit leads to a significant improvement in quality of life without sophisticated paramedical examinations.

Prevalence of vitamin D deficiency

In the present study, all patients who consulted their GPs for chronic DMS pain had serum 25 (OH) D levels below 50 nmol/l, and 67.7% had severe hypovitaminosis D (<30 nmol/l). Plotnikof et al., De Torrente et al., and Mytton et al., made similar observations with mean 25 (OH) D levels of 36 ± 2.2, 11.3 ± 4.5, and 17 ± 9 nmol/l, respectively (9–11).

Vitamin D deficiency supplementation

The vitamin D treatment in this study (1 to 3 doses of 200 000 units) was based on prior studies that have demonstrated success with a similar dose range. Several decades ago, Al Faraj gave women with severe hypovitaminosis D 10 000 units per day of vitamin D for three months (i.e. a cumulative dose of 900 000 units) and observed good results (16). In 2004, De Torrente et al. observed a decrease in MSD pain with two injections of 300 000 units of vitamin D (10). Badsha treated patients with 400 000 or 600 000 units (17). In his review, Holick advised that 800 000 units are required to bring the plasma 25 (OH) D level into the normal range of 75 to 125 nmol/l for severe deficiencies (<25 nmol/l) (18). Toxic thresholds were never reached nor were side effects observed with these doses. The safety of doses in this range has also been confirmed in other studies (19,20).

The Endocrine Society Clinical Practice Guidelines published in 2011 suggest doses up to 6000 units per day for eight weeks to correct severe deficits and maintenance doses of 600 to 2000 units/day, depending on risk factors, for persons aged 18 to 50 years (21). Oral doses of 200 000 units were chosen because they can be adapted somewhat to the severity of hypovitaminosis and did not impose a burden that could interfere with the patients' adherence to treatment. Nevertheless, several patients in our cohort were still vitamin D deficient after treatment; thus, our scheme may be insufficient in some cases.

Vitamin D deficiency, pain and quality of life

The patients were young and had chronic DMS pain and/or fatigue without meeting the criteria for fibromyalgia or any other disease, particularly arthritis.

Pain is a common reason for consultations in primary and urgent care; it can lead to absenteeism and has been reported to occur at frequencies ranging from 13.5% to 47% (22). The French Society of General Medicine estimated that approximately 5% of consultations in France are related to unexplained musculoskeletal pain; excluding neck pain, back pain, and low back pain. Several studies have been conducted in different countries over many years, and they have demonstrated an association between MSD pain and severe vitamin D deficiency in adults (3,7,9,23,24).

In 2008, Warner published a study with a placebo group: he included patients with rheumatic diseases who were older than 50 years old and excluded patients with 25 (OH) D levels below 20 nmol/l (25). In this study, as in most others, the patients with the lowest pretreatment 25(OH) D levels benefitted most from the treatment.

Chronic DMS pain may be related to the sensitivity of vitamin D receptors to variations in vitamin D levels. Hypovitaminosis D can lead to hypersensitivity of the nerve fibres connected to muscles, causing pain (26). Vitamin D is thought to exert beneficial effects on muscle physiology by balancing hyperparathyroidism (27).

Other authors have described a link between hypovitaminosis D and muscle weakness (28). In a study involving 12- to 14-year-old peri-pubescent girls, Ward et al. found that girls with hypovitaminosis D (mean serum vitamin D level of 21.3 nmol/l; range, 2.5 to 88.5 nmol/l) had impaired speed, jump height, muscle power, and muscle strength compared with the control subjects with normal vitamin D levels (29). A similar form of muscle weakness is well known in the elderly, and supplementation has been shown to decrease falls and improve muscle strength. In their recent review, Bischoff-Ferrari

et al. reported evidence for an association between higher vitamin D levels and better muscle health (30).

In our study, after correcting the deficiency, the patients could more freely climb stairs, put their coats on, vacuum and run errands without pain.

The follow-up evaluation occurred only 45 to 60 days after the last dose of vitamin D; perhaps our results for pain would have been better if the follow-up evaluation had been later. In a study involving 55 veiled women of Arab origin living in Denmark and 22 Danish women treated for vitamin D deficiency, Glerup et al. observed that muscular strength recovered within three to six months after the patients received vitamin D treatments for severe hypovitaminosis D associated with pain (31).

Vitamin D deficiency and drugs

After the Vitamin D treatment, drug consumption decreased among our patients, as De Torrente (10) and Turner (32) also reported. Hypovitaminosis D represents a significant financial burden. Grant et al. estimated that widespread vitamin D supplementation aimed at bringing the mean serum levels of the population to 110 nmol/l could save 187 000 million Euros in health care costs in Europe (33). This target might be quite ambitious, but it is reasonable to think that most of the population could meet a more conservative goal of 75 nmol/l, which should be sufficient to alleviate symptoms and improve overall health and quality of life in young to middle-aged adults (32).

Implications

Chronic musculoskeletal pain in adults should prompt the measurement of the 25 (OH) D level before more complicated investigations are conducted. Patients' levels should be tested to ensure proper dosing because large doses of vitamin D are necessary to correct severe deficiencies. Notably, high doses of vitamin D can be given without causing eminent side effects in adult patients. Patients should be followed over time so that they do not develop a severe deficiency again, especially in places such as France, where vitamin D is commonly lacking in the diet and where the sunlight is insufficient to ensure a proper serum vitamin D level throughout the year.

This study revealed a significant improvement in pain and quality of life after vitamin D supplementation, but other investigations are needed to explain the link between hypovitaminosis D and DMS pain.

Conclusion

Curative treatment for severe 25 (OH) D deficiency associated with DMS pain (with or without chronic fatigue) improved the health status of a cohort of 49 patients who consulted their GPs. Their reported DMS pain decreased, and their quality of life improved after vitamin D supplementation as other studies have shown. To confirm the relationship between vitamin D deficiency and DMS pain in adults, further studies are necessary.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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