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ORIGINAL ARTICLE

Vitamin D status in patients with musculoskeletal pain, fatigue and headache: A cross-sectional descriptive study in a multi-ethnic general practice in Norway

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Abstract

Objective. To investigate vitamin D levels in patients with non-specific musculoskeletal pain, headache, and fatigue. *Design*. A cross-sectional descriptive study. *Setting*. A health center in Oslo, Norway, with a multi-ethnic population. *Subjects*. A total of 572 patients referred by a general practitioner (GP) for an examination of hypovitaminosis D who reported musculoskeletal pain, headache, or fatigue. The patients' native countries were: Norway (n = 249), Europe, America, and South-East Asia (n = 83), and the Middle East, Africa, and South Asia (n = 240). Both genders and all ages were included. *Main outcome measures*. Vitamin D levels (25-hydroxyvitamin D) in nmol/L. *Results*. Hypovitaminosis D (25-hydroxyvitamin D < 50 nmol/L) was found in 58% of patients. One-third of ethnic Norwegians had hypovitaminosis D, while 83% of patients from the Middle East, Africa, and South Asia had hypovitaminosis D with minimal seasonal variation of levels. One in two women from these countries had a vitamin D level below 25 nmol/L. Mean vitamin D level was lower in patients with headaches compared with patients with other symptoms. Some 15% of patients with low (< 50 nmol/L) vitamin D levels reported headaches, compared with 5% of those with normal vitamin D levels. *Conclusion*. Our study shows a high prevalence of hypovitaminosis D in patients with non-specific musculoskeletal pain, headache, or fatigue for whom the GP had suspected a low vitamin D level. Hypovitaminosis D was not restricted to immigrant patients. These results indicate that GPs should maintain awareness of hypovitaminosis D and refer patients who report headaches, fatigue, and musculoskeletal pain with minimal sun exposure and a low dietary vitamin D intake for assessment.

Key Words: *Family practice, fatigue, headache, musculoskeletal pain, primary health care, vitamin D*

Muscular pain, fatigue, and headache are common symptoms in general practice and have numerous and often non-specific etiologies. Hypovitaminosis D is a health problem worldwide and is frequently seen among immigrants in Norway [1,2]. Although few systematic studies have been conducted regarding the relationships between vitamin D deficiency and muscular pain, fatigue, and headache, these symptoms are found to be accompanied by vitamin D deficiency in multi-ethnic patient populations and are amenable to treatment by vitamin D substitution [3–5].

Humans receive 80–90% of their vitamin D supply through ultraviolet B sunlight exposure of the skin and the rest through vitamin D-containing foods [6–8]. Only a few foods naturally contain vitamin D and vitamin D photoproduction is influenced by season, latitude of residence, and skin pigmentation. The elderly and people with dark skin need increased sunlight exposure time (twofold to 10-fold) for vitamin D synthesis compared with fair-skinned young individuals [8,9]. Norway lies above the latitude that permits solar skin synthesis of vitamin D during the winter (4–6 months) [9,10]. In Norway, the consumption of cod liver oil during the winter months has been a decades-long tradition, as is enjoying sun exposure during the summer [11]. Many immigrants to Norway do not share these traditions, and therefore run a higher risk of vitamin D deficiency [12]. Hypovitaminosis D is more common

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Hypovitaminosis D (25-hydroxyvitamin D < 50 nmol/L) was examined in a multi-ethnic patient population with musculoskeletal pain, headache, fatigue, and other clinical indications for referral.

- Hypovitaminosis D was found in over half of the patients.
- Patients with headaches had the lowest mean vitamin D levels.
- 83% of patients from the Middle East, Africa, and South Asia had hypovitaminosis D, and immigrant women had lower mean levels compared with men.
- 35% of the Norwegian patients had hypovitaminosis D.

among people who cover the body with protective clothing, those with dark skin pigmentation, who stay indoors and avoid direct sunlight, and among those with a low intake of fatty fish and cod liver oil [2,8].

Ultraviolet radiation (UV-B 290–315nm) of the vitamin D precursor (7-dehyrocholesterol) in the skin photolyses it to previtamin D which is rapidly converted to vitamin D. Vitamin D becomes a steroid hormone after conversion to $25(OH)D_3$ in the liver and is metabolized to the active $1,25(OH)_2D_3$ (calcitriol). This occurs mainly in the kidneys but also in various other tissues by 1α-hydroxylase. Calcitriol is tightly regulated and shows only minimal variation. Activated vitamin D leads to multiple biological responses and regulates cell differentiation by binding to vitamin D receptors (VDR) in several body tissues [1,6,7,13]. The finding of vitamin D receptors in human muscle in 2001 provides evidence of the importance of vitamin D for musculoskeletal function [14]. Treatment with vitamin D improved muscular function among patients with hypovitaminosis by increasing the cross-sectional area of fast-twitch type II A fibers and improving proximal muscle strength [15,16]. Correction of hypovitaminosis D reduced postural body sway and decreased the number of falls and fractures among geriatric patients [17].

The best way to assess vitamin D status is to measure 25-hydroxyvitamin D [25(OH)D] in serum. The adequate range of 25(OH)D in Norway has been established at 50–150 nmol/L. The optimal range of vitamin D is 75–150 nmol/L and the amount of oral vitamin D intake needed to maintain a health-protective effect remain, however, a matter of debate [1,8,9,18].

The aim of this cross-sectional descriptive study was to investigate levels of vitamin D among patients suffering from musculoskeletal pain, fatigue, or headache in a multi-ethnic population from a general practice in Norway. We hypothesized that a substantial proportion of patients with these symptoms would also have hypovitaminosis D, especially individuals with dark skin, a tradition of low sun exposure, and a low intake of food rich in vitamin D. We believe that our findings will help inform the design and implementation of future intervention studies for hypovitaminosis D.

Material and methods

The study was conducted in a health center in which seven GPs serve 6200 registered patients in a multi-ethnic area in the north-eastern part of Oslo, Norway, at the latitude of 60ºN. In 2006, 33% of the population and 50% of children 0–5 years in this part of Oslo were non-Western immigrants (Statistics Norway). In 2005–2007, vitamin D levels were analyzed for 1729 patients, based on the doctors' suspicion of low vitamin D intake and/or sun exposure. In 572 of these 1729 patients, the main reason for contact had been either headaches, local or general musculoskeletal pain, or fatigue. These 572 patients were included in the study. Vitamin D level was measured within two months of presentation, and had not been tested previously. Inclusion criteria were the following ICPC-2 (International Classification of Primary Care, Second edition) diagnoses: headache (N01 and N95), local musculoskeletal pain (L01–05, L08–17, L83–84, and L92), and general pain/fatigue (A01, A04, A29, L18–20). Patients with osteoporosis, injury, intervertebral disc herniation, rheumatic disease, and migraine were not included.

Patient records were fully computerized. Automatic extracting procedures were applied to select patients into the study according to the inclusion criteria. Results of the selection process were manually verified. Patient records for all 572 patients contained information on age, gender, ethnicity, serum vitamin D level (25(OH)D), and the time of year for the vitamin D test. The patients originated from 51 different countries (country of birth of the individual or their parents/mother) and were divided into three main geographic regions: (1) Norway, (2) Europe, America, and Southeast Asia, and (3) the Middle East, Africa, and South Asia. The geographic regions were selected based on the following major risk factors for vitamin D deficiency: ethnic habits of covering the body, cultural food traditions, and the degree of skin pigmentation [8,19]. Fasting blood samples were taken. Serums were consecutively sent to the same laboratory (Fürst Medisinsk Laboratorium) for analysis by high-pressure liquid chromatography mass spectrometry (HPLC-MS). Assay results were received by modem. The assay laboratory is accredited by the International Organisation for Standardization.

Statistics and ethics

Bivariate comparisons were performed using independent sample t-tests (continuous variables) and chi-squared tests (categorical variables). Logistic regression analyses were performed to assess the impact of season, vitamin D level, gender, age, and region of origin (independent variables) on headache (dependent variable). Level of statistical significance was set at 5% ($p < 0.05$).

This study was approved by the Norwegian Social Science Data Service. The Directorate for Health and Social Affairs allowed a dispensation from the Health-Professional Secrecy regulations. The Regional Committee for Research Ethics in Norway considered the study a quality assurance project not requiring formal approval because the study guaranteed the anonymity of patients.

Results

Descriptive characteristics of the 572 patients are illustrated in Table I. As seen from Table I, 71% of the patients were female. Patients from all geographic regions reported fatigue, widespread, general pain, or local pain more frequently than headache.

A total of 58% (334/572) patients had low vitamin D levels (< 50 nmol/L, Table II). According to region of origin, we found low vitamin D levels for 83% of patients from the Middle East, Africa, and South Asia, 58% for patients from Europe, America, and South-East Asia, and 35% for Norwegian patients. Among patients from the Middle East, Africa, and South Asia, women had a higher degree of hypovitaminosis D than men (less than 30 nmol/L: $p = 0.0005$ and less than 25 nmol/L: $p = 0.021$), and half of the women from this region had vitamin D levels below 25 nmol/L. Table III shows a significant difference in mean vitamin D level between the three geographic regions, with the lowest level (32 nmol/L) in patients from the Middle East, Africa, and South Asia. Vitamin D levels were lower among patients presenting with headaches compared with other symptoms (Table III). This finding was statistically significant both in the total study population and in patients from Norway. Headache was still significantly associated with hypovitaminosis D ($p = 0.008$, OR 2.6) after adjustment for gender, season, geographic region of origin, and age, as indicated by the logistic regression (data not shown). Some 15% (50/334) of patients with low (< 50 nmol/L) vitamin D levels reported headache, compared with 5% (13/238) of those with adequate (≥ 50 nmol/L) vitamin D levels ($p < 0.001$). Vitamin D levels showed a significant correlation to age in the whole study population, but this result was affected by the lower mean age in the immigrant population (data not shown in table).

Table IV shows the variation in vitamin D level throughout the year, with the lowest level in winter and early spring. Norwegians showed a higher increase in vitamin D level during summer and fall compared with patients from the Middle East, Africa, and South Asia.

Discussion

In this multi-ethnic patient population with musculoskeletal pain, headache, fatigue, and other clinical indicators warranting the examination of vitamin D level, 58% had vitamin D levels below the recommended level. Thus, results suggest that the GPs' suspicion of hypovitaminosis D was frequently confirmed. The lowest levels of vitamin D were found among patients complaining of headaches.

Our study is an exploratory, descriptive study, using existing data from a group general practice. It was therefore not specifically designed to investigate the relationships between the reported symptoms and vitamin D level, and results must be interpreted with caution. It is possible that the use of ICPC diagnostic labels may vary to some extent among the seven GPs. Headaches, however, are arguably less affected by such a bias than other types of diagnoses.

Table I. Number (%) of patients according to gender, location of pain, and region of origin.

	Norway[a] (n = 249)	Europe, America, Southeast Asia[b] (n = 83)	Middle East, Africa, and South Asia[c] (n = 240)
Gender			
Male	61 (24)	27 (32)	78 (32)
Female	188 (76)	56 (68)	162 (68)
Headache	19 (8)	9 (11)	35 (15)
Local pain	110 (44)	40 (48)	120 (50)
Fatigue, general pain	120 (48)	34 (41)	85 (35)

Notes: [a]Norwegians for more than two generations. [b]Europe, North and South America, Southeast Asia with Vietnam, the Philippines, Thailand, and China. [c]The Middle East with Turkey, South Asia with Pakistan, Sri Lanka and India, and Africa.

Table II. Number (%) of patients with and without hypovitaminosis D according to region of origin and gender.

	Norway (n = 249)		Europe, America, Southeast Asia (n = 83)		Middle East, Africa and South Asia (n = 240)	
	Male	Female	Male	Female	Male	Female
Adeqate vitamin D						
25(OH)D ≥ 50 nmol/L	35 (57)	128 (68)	13 (48)	22 (39)	13 (17)	27 (17)
Hypovitaminosis D						
25(OH)D < 50nmol/L	26 (43)	60 (32)	14 (52)	34 (61)	65 (83)	135 (83)
< 30nmol/L	7 (12)	13 (7)	6 (22)	11 (20)	35 (45)	105 (65)
< 25nmol/L	3 (5)	11 (6)	5 (19)	5 (9)	25 (32)	79 (49)

To ensure a temporal link between the measured level of vitamin D and presenting complaint, a time-frame of two months or less was allotted. This time span was pragmatic, and a shorter time span may have enabled a stronger relationship, but fewer patients. A large decrease in vitamin D levels within the chosen time span was not expected, however, owing to the long half-life of vitamin D [15].

Our findings suggested an inverse relationship between headache and vitamin D, such that the frequency of headaches decreased with an increasing level of vitamin D. This association was equally present among men and women, indicating the significance for both genders. Moreover, the association was not eliminated in a regression model adjusting for age, gender, geographical region, and whether the analysis took place during winter or summer. Despite the limitations in our study design, we believe that the significant relationship found between headache and vitamin D levels deserves further investigation. Existing literature on headache and hypovitaminosis D is sparse. However, a newly published case report showed substantial improvement in headaches within 4–6 weeks following daily treatment with 1000–1500IU cholecalciferol (D3) and calcium 1000 mg among eight patients with chronic tension headaches and a high degree of hypovitaminosis D [21].

In our sample, a blood test was ordered by a GP due to suspected hypovitaminosis D. It was surprising to find that the GPs' suspicion was frequently confirmed and, in particular, that 35% of ethnic Norwegians had hypovitaminosis D. Existing data suggest that vitamin D status is sufficient among ethnic Norwegians [2]. In the Oslo Health Study 2000–2001, only 14% of Norwegians aged 45–75 years had vitamin D levels below 50 nmol/L, and the mean 25(OH)D was 75 nmol/L [22]. Based on our findings, therefore, it appears that hypovitaminosis D among ethnic Norwegians is more frequent in our symptomatic study population than the general public. The high frequency of hypovitaminosis D among immigrants in our study corresponds with other studies [12]. Immigrants living in Norway report musculoskeletal pain more frequently than ethnic Norwegians, with immigrant women presenting with a higher frequency of complaints than men [23,24].

Vitamin D has an anti-inflammatory effect through regulation of interleukin, tumor necrosis factor, and the activity of macrophages [1]. Thus, the supplementation of vitamin D might theoretically have a beneficial effect on inflammatory induced pain. Treatment with vitamin D is shown to reduce pain among patients with diabetic polyneuropathies [25]. Data are as yet insufficient to support the hypothesis that vitamin D supplementation is useful in the treatment of chronic pain [26]. One study found, however, that musculoskeletal pain among Arab and Indo-Pakistani patients with hypovitaminosis D decreased

Table III. Mean (95% CI) vitamin D (25(OH)D in nmol/L) levels in patients according to region of origin, gender, and symptoms.

	All (n = 572)	Norway (n = 249)	Europe, America, Southeast Asia (n = 83)	Middle East, Africa and South Asia (n = 240)
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
All	47 (45–50)	63 (60–63)	46 (41–50)	32 (30–35)
Male	46 (42–50)	61 (54–68)	46 (38–54)	34 (30–37)
Female	48 (46–51)	64 (60–67)	45 (40–51)	31 (28–34)
Headache	35 (30–40)[1]	51 (39–63)[2]	36 (25–47)[3]	27 (22–31)[4]
Local musculoskeletal pain	49 (45–52)	65 (60–70)	49 (42–56)	33 (30–37)
Fatigue and general musculoskeletal pain	50 (46–53)	63 (58–68)	44 (38–51)	32 (28–37)

Notes: Differences in mean level of vitamin D between patients with headache and local pain were [1]$p < 0.001$, [2]$p = 0.030$, [3]$p = 0.094$, [4]$p = 0.060$. The corresponding differences between vitamin D levels in patients with headache and general pain were $p < 0.001$, $p = 0.054$, $p = 0.092$, and $p = 0.095$.

Table IV. Mean (95% CI) vitamin D (25(OH)D in nmol/L) levels during two seasons among patients from different geographical regions.

	Norway n = 249	Europe, America, Southeast Asia n = 83	Middle East, Africa and South Asia n = 240
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Summer–fall June 1–Nov 30 (n = 256)	72 (67–77)[1]	50 (44–57)[2]	35 (31–39)[3]
Winter–spring Dec 1–May 31 (n = 316)	56 (53–60)	41 (36–47)	29 (27–32)

Note: Differences in mean vitamin D level between seasons were: [1]$p < 0.001$, [2]$p = 0.047$, [3]$p = 0.021$.

or disappeared in 90% of patients when treated with vitamin D [4]. A study from the UK reported that chronic widespread pain among 3297 women was significantly associated with vitamin D status. However, this association was not found among men [3]. A Danish study showed reduced muscular power in the proximal lower limb among Arab women with hypovitaminosis D compared with Danish controls. After treatment with vitamin D, however, their muscular power normalized [15].

The mean level of vitamin D in our study population varied significantly during the year, as expected in a country located as far north as Norway [10,27]. This variation was most prominent among Norwegian patients, while most patients from the Middle East, Africa, and South Asia had low vitamin D levels throughout the entire year. The minimal increase in vitamin D during the summer may be explained by avoidance of sun exposure and traditions of covering the body. The health consequences of a variable versus a chronically low vitamin D level remain unknown. However, recent studies have shown increased survival rates among cancer patients diagnosed in the seasons when vitamin D level is high [1,28,29]. Vitamin D inhibits tumor proliferation and promotes differentiation and apoptosis in numerous cell lines [28]. Several other health problems, such as cardiovascular disease, diabetes, and autoimmune diseases, have also recently been associated with vitamin D insufficiency [1,6,7,8,18].

Findings from this study may alert doctors to the importance of inquiring about nutrition and sun exposure among patients reporting headache, musculoskeletal pain, and fatigue, and the value of referring these patients for the assessment of vitamin D levels. Whether the correction of vitamin D deficiency reduces symptom load is not fully established. Further studies are needed to examine whether correction of hypovitaminosis D increases the threshold for pain and fatigue and reduces headache.

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Conflict of interest: None.

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