Serum 25-OH Vitamin D Levels in Patients with Fibromyalgia

Howard Tandeter MD[1,5], Mirta Grynbaum MD[1,5], Irene Zuili BSc[4], Shraga Shany PhD[3] and Pesach Shvartzman MD[1,2,5]

[1]Department of Family Medicine, Siaal Research Center for Family Medicine and Primary Care, [2]Pain and Palliative Care Unit, and [3]Department of Clinical Biochemistry, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel
[4]Toor Institute, Soroka University Medical Center, Beer Sheva, Israel
[5]Clalit Health Services-Southern District, Beer Sheva, Israel

ABSTRACT: **Background:** The association between low levels of 25-hydroxyvitamin D and non-specific musculoskeletal pain, including fibromyalgia syndrome, is controversial. Several studies have reported a "positive association" and two others found "no association."

Objectives: To test levels of 25OHD in patients with fibromyalgia syndrome and in matched controls.

Methods: The study population comprised 68 premenopausal women with a diagnosis of fibromyalgia and 82 age-matched premenopausal women without. The former were identified from the computerized medical databases of five primary care urban clinics in the south of Israel, and the control subjects were attending the participating clinics for regular periodic blood tests. For each patient, the matched control interview and blood test were performed within a week or two from the patient's interview and blood test, thus controlling for expected seasonal variations.

Results: Serum 25OHD was measured using different cutoff levels and compared between the groups (< 30 ng/ml, < 20 ng/ml and < 15 ng/ml). No statistically significant differences were found between the groups regardless of the cutoff level used. A logistic regression model for predicting women with 25OHD levels < 20 ng/ml showed that all the variables examined in both groups (age, country of birth, education) were not statistically significant. We found the expected seasonal variations of 25OHD levels, though these were not statistically significant.

Conclusions: We found no association between fibromyalgia and low 25OHD levels as previously suggested in other studies.

IMAJ 2009;11:339–342

KEY WORDS: fibromyalgia, 25-hydroxyvitamin D, primary care

For Editorial see page 371

The association between low levels of 25-hydroxyvitamin D and non-specific musculoskeletal pain, including fibromyalgia syndrome, is controversial. Several studies have reported a "positive association" [1-7]. One study that was especially striking showed a significantly higher prevalence of low 25OHD concentrations in women with fibromyalgia as compared to age-matched female controls (42.5% vs. 18.9%, respectively) [8]. In contrast, two other publications found "no association" [9-10]. We evaluated serum 25-OH vitamin D in premenopausal women with fibromyalgia and compared them to an age-matched control.

250HD = 25-hydroxyvitamin D

PATIENTS AND METHODS

Participating in the study were five Clalit Health Services primary care urban clinics in Beer Sheva, a city in southern Israel (latitude 31º, 15' North). Clalit is the largest health management organization in Israel, covering nearly 55% of the population.

STUDY POPULATION

The study group included 68 premenopausal women identified from the computerized medical databases with a diagnosis of fibromyalgia in accordance with the American College of Rheumatology criteria. The control group comprised 82 age-matched premenopausal women who did not have fibromyalgia and were attending the participating clinics for regular periodic blood tests. Patients with known calcium abnormalities, hyperparathyroidism, vitamin D deficiency or osteomalacia were excluded from the study.

DATA COLLECTION

The study protocol was approved by the Ethics Committee of Soroka University Medical Center and all participants signed an informed consent. For each patient, the matched control interview and blood test were performed within a week or two from the patient's interview and blood test, thus controlling for expected seasonal variations.

LABORATORY INVESTIGATIONS

Serum 25OHD levels were measured by the IDS OCTEIA 25OHD kit (IDS AC-57F1, Immunodiagnostic Systems, Boldon, UK). This assay is an enzyme immunoassay in which biotin-labeled 25OHD is bound to a specific sheep 25OHD antibody. This is followed by the addition of a horseradish peroxidase-labeled avidin that binds the biotin complexes.

Table 1. Sociodemographic characteristics of the study population

	Fibromyalgia group (N=68)		Control group (N=82)		*p* value
Age (yrs)					
Mean ± STD	43.83 ± 7.57		40.37 ± 9.85		< 0.02
Range	19–55		20–54		
Total	68		81	(mis=1)	
Country of birth					
Israel	29	42.6%	26	32.1%	NS*
Other	39	57.4%	55	67.9%	
Total	68		81	(mis=1)	
Marital status					
Married	52	76.5%	54	66.7%	NS
Single/Divorced/ Widowed/Separated	16	23.5%	27	33.3%	
Total	68		81	(mis=1)	
No. of children					
Mean ± STD	3.16 ± 1.38		2.54 ±1.26		< 0.01
Range	1–8		1–6		
Total	64		81	(mis=1)	
Years in Israel (for immigrants)					
Mean ± STD	26.62 ± 13.99		18.04 ± 12.59		< 0.01
Range	5–51		1–51		
Total	37	(mis=2)	55		
Years of education					
Mean ± STD	12.74 ± 3.12		12.56 ± 2.94		NS
Range	6–24		6–22		
Total	67	(mis=1)	77	(mis=5)	
Total	66	(mis=2)	80	(mis=2)	

*NS = not significant

Table 2. Vitamin D levels

	Fibromyalgia group (N=68)		Control group (N=82)			
25OHD levels	**n**	**%**	**n**	**%**	**Total**	***P* value**
< 30	56	82.4	75	91.5	131 87.3	NS
< 20	30	44.1	42	51.2	72 48.0	NS
< 15	21	30.9	26	31.7	47 31.3	NS
< 10	11	16.2	11	13.4	22 14.7	NS
Mean ± STD	21.75 ± 10.20		19.43 ± 7.81		20.48 ± 9.01	
Median	20.5		19.0		20.0	
Range	7–47		6–38		6–47	

A characteristic color is developed after the addition of a chromogenic substrate. The absorbance was determined in a 96-well micro-plate by using an enzyme-linked immunosorbent assay reader (Molecular Devices Corp., Menlo Park, CA, USA) at 450 nm wavelength. The intensity developed is inversely proportional to the 25OHD concentration. Results are expressed as ng 25OHD per 1 ml serum. Each serum sample was tested in duplicate.

STATISTICAL ANALYSIS

Results of continuous variables are shown as means ± standard deviation. Results of categorical variables are described as frequencies. Fisher's exact tests were used to analyze statistically significant differences of categorical variables. Logistic regression was used for multivariate analyses. *P* values ≤ 0.05 were considered statistically significant. Three different cutoff points for defining hypovitaminosis D were used, in accordance with data from the literature (< 15 ng/ml, < 20 ng/ml and < 30 ng/ml) [11].

RESULTS

Table 1 presents the sociodemographic characteristics of the study population. Fibromyalgia patients were slightly older than controls (43.8 ± 7.6 vs. 40.4 ± 9.8, $P < 0.02$), had more children (3.2 ± 1.4 vs. 2.5 ± 1.3, $P < 0.01$), and immigrants in the patient group had lived in Israel longer (26.62 ± 13.99 vs. 18.04 ± 12.59, $P < 0.01$). No significant differences were found between the groups with regard to country of birth, marital status, education, employment, and religiosity.

Table 2 depicts the 25OHD levels by study group. Serum levels of 25OHD were examined using different cutoff levels and compared between the groups. The cutoff serum levels used were < 30 ng/ml, < 20 ng/ml, < 15 ng/ml and 10 ng/ml. No statistical significant differences were found between the groups in 25OHD levels regardless of the cutoff level used.

A logistic regression model for predicting women with 25OHD levels < 20 ng/ml showed that all the variables examined (age, country of birth, education) were not statistically significant between the two groups.

We found the expected seasonal variations of 25OHD levels (71.8% of the total population had levels < 20 ng/ml in winter, 52.4% in spring, 17.6 % in summer and 45.7% in autumn), though these were not statistically significant between the study group and the controls. The tests performed were evenly distributed between the seasons.

DISCUSSION

This study shows that a low 25OHD level (< 20 ng/ml) is not more common in premenopausal women with fibromyalgia than in controls without the disorder. This is further emphasized by the fact that different cutoff points of 25OHD levels did not affect the findings and that none of the variables examined were found to be statistically significant predictors of low levels of vitamin D.

The literature regarding the correlation between low blood levels of 25OHD and non-specific musculoskeletal pain is controversial. Reports from Europe [1,2] and the United States [3,4] found a positive association. It has been suggested that up to 50% of Caucasian fibromyalgia patients may have low levels of 25OHD, and these lower levels were observed more frequently in patients with anxiety and depression [5]. Low levels of 25OHD have also been shown more often in chronic pain/fibromyalgia patients than in other "general rheumatology outpatients" [6]. Plotnikof and Quigley [4] found that 89% of subjects with chronic musculoskeletal pain were deficient in 25OHD [4]. In contrast, Block [9] did not confirm these findings and did not find a difference in 25OHD levels between patients with chronic musculoskeletal pain who fit the ACR criteria for fibromyalgia and those who did not. Warner and Arnspiger [10], as well, found no association between low 25OHD levels and diffuse musculoskeletal pain, and no reduction of pain in patients who had low vitamin D levels after treatment with vitamin D.

In 2003, a significantly higher prevalence of low 25OHD concentrations in women with fibromyalgia as compared to age-matched female controls (42.5% vs. 18.9%) was reported by Al-Allaf and colleagues [8]. If confirmed, these findings would have a significant impact on the investigation and management of this syndrome in the future. However, the findings of our study did not confirm those of Al-Allaf and team. Their study group was small (40 fibromyalgia patients), and despite the known seasonal variation in 25OHD levels, all measurements were taken in March and for the controls in May. Our sample size was larger – 68 fibromyalgia patients, and we compared the study group with the controls throughout the four seasons of the year and described the latitude where the samples were taken, being aware of its effect on 25OHD plasma concentrations [12].

When reviewing the literature we found several potentially problematic methodological issues that may have affected the results. First, the lack of a control group was apparent in both studies reporting a positive association [1,4,7] and no association [9]. Second, in studies with a control group, the composition of the group was problematic (choosing patients with osteoarthritis or other rheumatologic problems, instead of healthy populations [6,10]). Third, the main problem in designing a single study to resolve this controversy worldwide is that assessing "normal" circulating 25OHD levels based on a Gaussian distribution of these values is now considered a grossly inaccurate method of identifying the normal range for vitamin D [11]. Levels of 25OHD vary between countries and these variations are due not only to latitude but also to time, season, total ozone, clouds, pollution, aerosols, surface reflectivity and altitude, skin pigmentation and exposure of the skin (affected by dress codes) [10-13]. Thus, a comparison of subpopulations only according to latitude and season may be misleading.

Although Israel is a sunny country, we found a very high prevalence of low 25OHD levels in our study population (48% had levels < 20 ng/ml). Although this has been previously described in specific subpopulations in this country [14], the prevalence of "hypovitaminosis D" in our study was much higher than that found in previous studies [10,15].

Some limitations of our study are the lack of data regarding our population's religious status, the dress code, sun exposure, and use of medications and supplements. Nevertheless, both the control and the study group were matched at the clinic level, representing very similar homogenous populations, and we believe that this lack of data will not affect the findings.

Comparing results of studies on the relationship between vitamin D levels and musculoskeletal symptoms performed in different areas of the world may be difficult due to local variations in the prevalence of hypovitaminosis D. We do not know if the high prevalence of low 25OHD levels found in our study will affect the comparison with studies performed in countries with a lower prevalence of low 25OHD levels.

In summary, we found no association between fibromyalgia and low 25OHD levels in our study (shifting the controversy to the "no association" side). Further research should take into account the possibility that differences between countries and populations in their local prevalence of low 25OHD levels may affect comparison between studies performed in different parts of the world.

ACR = American College of Rheumatology

Correspondence:
Dr. H. Tandeter
Dept. of Family Medicine, Siaal Research Center for Family Medicine and Primary Care, Ben-Gurion University of the Negev, P.O. Box 653, Beer Sheva 84105, Israel
Phone: (972-8) 647-7436
Fax: (972-8) 647-7636
email: howard@bgu.ac.il

References

1. Nellen JF, Smulders YM, Jos Frissen PH, Slaats EH, Silberbusch J. Hypovitaminosis D in immigrant women: slow to be diagnosed. *BMJ* 1996; 312(7030): 570-2.
2. Erkal MZ, Wilde J, Bilgin Y, et al. High prevalence of vitamin D deficiency, secondary hyperparathyroidism and generalized bone pain in Turkish immigrants in Germany: identification of risk factors. *Osteoporos Int* 2006; 17(8): 1133-40.
3. Reed SD, Laya MB, Melville J, Ismail SY, Mitchell CM, Ackerman DR. Prevalence of vitamin D insufficiency and clinical associations among veiled East African women in Washington State. *J Womens Health (Larchmt)* 2007; 16(2): 206-13.
4. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. *Mayo Clin Proc* 2003; 78(12): 1463-70.
5. Armstrong DJ, Meenagh GK, Bickle I, Lee AS, Curran ES, Finch MB. Vitamin D deficiency is associated with anxiety and depression in fibromyalgia. *Clin Rheumatol* 2007; 26(4): 551-4.
6. Mouyis M, Ostor AJ, Crisp AJ, et al. Hypovitaminosis D among rheumatology

outpatients in clinical practice. *Rheumatology (Oxford)* 2008; 47(9): 1267-8.

7. Atherton K, Berry DJ, Parsons T, Macfarlane GJ, Power C, Hypponen E. Vitamin D and chronic widespread pain in a white middle-aged British population: evidence from a cross-sectional population survey. *Ann Rheum Dis* 2009; 68(6): 817-22
8. Al-Allaf AW, Mole PA, Paterson CR, Pullar T. Bone health in patients with fibromyalgia. *Rheumatology (Oxford)* 2003; 42(10):1202-6.
9. Block SR. Vitamin D deficiency is not associated with nonspecific musculoskeletal pain syndromes including fibromyalgia. *Mayo Clin Proc* 2004; 79(12): 1585-6.
10. Warner AE, Arnspiger SA. Diffuse musculoskeletal pain is not associated with low vitamin D levels or improved by treatment with vitamin D. *J Clin Rheumatol* 2008; 14(1): 12-16.
11. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. *J Nutr* 2005; 135(2): 317-22.
12. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; 357(3): 266-81.
13. Engelsen O, Brustad M, Aksnes L, Lund E. Daily duration of vitamin D synthesis in human skin with relation to latitude, total ozone, altitude, ground cover, aerosols and cloud thickness. *Photochem Photobiol* 2005; 81(6): 1287-90.
14. Weisman Y. Vitamin D deficiency rickets and osteomalacia in Israel. *Isr Med Assoc J* 2003; 5(4): 289-90.
15. van dM, I, Ponsonby AL, Engelsen O, et al. The high prevalence of vitamin D insufficiency across Australian populations is only partly explained by season and latitude. *Environ Health Perspect* 2007; 115(8): 1132-9.