Vitamin D Status in Chronic Myofascial Pain and Associated Neurological Disorders

As low levels of vitamin D are associated with multiple illnesses, new evidence suggests links to neurological diseases.

BY DHANPAT MOHNOT, MD; ALLAN V. KALUEFF, PHD; VJ DURAPAU, JR., PHD; SOPAN MOHNOT; GURDIAL ARORA, PHD; AND ADAM MICHAEL STEWART, MS

While the effects of vitamin D on the skeletal system are well documented, other tissues represent targets for multiple biological roles of this hormone.[1-3] Vitamin D deficiency has been linked to a higher risk of colon, prostate and breast cancers,[4-10] hypertension, congestive heart failure and myocardial infarction,[11-14] pulmonary dysfunctions, respiratory tract infection,[15-17] rheumatoid arthritis and osteoarthritis.[18] Moreover, there is mounting evidence of vitamin D's role in neurological and affective disorders,[19-20] such as multiple sclerosis, schizophrenia and depression.[21-30]

There is also a growing interest in the role of vitamin D in epilepsy, since neonatal hypocalcemic seizures have long been linked to hypovitaminosis D,[31-32] and is further supported by animal data.[33-35] For example, intra-hippocampal administration of vitamin D reduces chemically induced seizures in rodents.[36] Vitamin D receptor (VDR) knockout mice also display an increased susceptibility to pharmacogenetic seizures.[34] In line with this, subcutaneous vitamin D evokes rapid anti-seizure effects in mice,[33] whereas seizures elevate hippocampal VDR mRNA expression.[36]

Vitamin D is also implicated in pain,[37-41] given a frequent hypovitaminosis D in patients with chronic pain,[41] with more than 90 percent of U.S. patients with hypovitaminosis D exhibiting musculoskeletal pain.[42] Hypovitaminosis D also accompanies diffuse or non-specific migratory pain affecting several sites,[43] whereas patients with osteomalacia often complain of skeletal pain.[38,44] Hypovitaminosis D-induced pain may be due to a lack of calcium phosphate available to mineralize the collagen matrix of bone, with the matrix expanding under the innervated periosteum, leading to diffuse pain.[38,45]

Importantly, vitamin D therapy reduces pain caused by hypovitaminosis D.[37,39,44] Furthermore, where it was

TAKE-HOME TIPS

Vitamin D (25-hydroxyvitamin D) deficiency affects a wide range of physiological functions. However, the relationship between hypovitaminosis D and various neurological disorders, such as chronic pain, headaches, epilepsy, multiple sclerosis, cognition, etc. is poorly understood. We have evaluated the prevalence of vitamin D deficiency in patients diagnosed with chronic myofascial pain (CMP) with or without other neurological disorders in a large cohort of patients (n = 911). About 80 percent of patients had hypovitaminosis D. Males and females had similar mean 25-hydroxyvitamin D levels; although the females with epilepsy or diabetes had significantly lower vitamin D levels. Also, moderate to severe vitamin D deficiency was significantly higher in females as well as in the group with CMP and associated illnesses. This data is especially relevant in the evaluation of patients with CMP and other neurological disorders.

not sufficient to ameliorate pain, it significantly reduced the severity of pain,[40] supporting the use of vitamin D as potential treatment for pain.

Overall, the relationship between vitamin D deficiency, chronic pain, and epilepsy is poorly understood.[46] While there seems to be widespread effects of vitamin D deficiency, most data come from uncontrolled studies with small patient population. To further address this problem, we evaluated the vitamin D status in a large suburban population of patients with chronic myofascial pain (CMP), epilepsy and other neurological disorders.

METHODS

Background: Given data associating vitamin D deficiency with a number of neurological disorders, we began testing for blood 25-hydroxyvitamin D levels in these patients in January 2007. This study was approved by the Ochsner Clinic Foundation Institutional Review Board including waiver of informed consent due to the nature of the study. This data was collected over a 30-month period between February 2007 and July 2009, covering all seasons.

Patients: The patients were referred for a variety of neurological disorders including chronic pain, headache and epilepsy to an outpatient neurology clinic (New Orleans Headache and Neurology Clinic) in Southeast Louisiana. As per a standard protocol, patients were interviewed and examined. A history of pain in neck, back, paraspinal, supra and interscapular muscles, upper and lower extremities, numbness, fatigue, and insomnia was obtained. Patients with myofascial pain had neurological examinations including spinal range of motion, muscle spasm, and tender points. All patients had a complete blood count, comprehensive metabolic panel, 25-hydroxyvitamin D, thyroxine 4 and thyroid stimulating hormone as part of routine evaluation. Some patients also had their blood tested for phosphorus, magnesium, parathyroid hormone intact, antinuclear antibodies, erythrocyte sedimentation rate (Westergren), C-reactive protein and rheumatoid arthritis factor. 25-hydroxy-vitamin D level was analyzed by liquid chromatography-mass spectrometry (normal level >30 ng/ml). If clinically indicated, select patients also had spinal magnetic resonance imaging, electromyography and nerve conduction velocity studies. All patients' demographics, symptoms, signs, examination findings were recorded on a preformed data sheet. The data were handled in full compliance with the health information portability and accountability regulations.

Analysis: We were prompted to conduct this study after reviewing various published data on the possible association of neuro-muscular disorders with vitamin D deficiency. We conducted a retrospective chart review and data were recorded in Microsoft Excel spreadsheet format. The patients were coded by numeric numbers starting from 1-911. All data were analyzed using the Statistical Package for Social Sciences software program (SPSS 19.0.0.1 for Windows). Comparisons were made with an analysis of variance (ANOVA) and proportions with a chi square test. Univariate analysis was performed for the individual variables likely to affect vitamin D levels, and multivariate analysis was performed utilizing principal component analysis.

RESULTS

Over the 30-month period, a total of 1142 patients were evaluated for various neurological disorders including CMP (pain more than 3 months duration with no obvious cause, several tender and trigger points), neck and back pain, paresthesia, muscle cramps, chronic fatigue, epilepsy, and headaches. Of these 1142 patients, 25-hydroxyvitamin D assays were performed in 911 patients. During analysis patients were divided into 2 groups, including the study group (comprised of patients with CMP and associated illnesses; n=426) and control (patients who had neurological illnesses other than CMP; n=485).

Table 1 provides data on the patient demographics, symptoms, associated illnesses and corresponding 25-hydroxyvitamin D levels. The two groups were comparable for racial/ethnic distribution although there were more females in both groups. As a group, the study patients were significantly older, shorter and had a higher body mass index ($p<0.05$). The body weights were comparable in both groups ($p>0.23$). Epilepsy was more prevalent in the control group ($p<0.05$), whereas other associated illnesses were comparable in both groups ($p>0.05$). All blood chemistry indices were similar in both groups ($p>0.05$), and there was no statistical difference between the two groups for the mean 25-hydroxyvitamin D levels or the distribution of 25-hydroxyvitamin D levels into normal (>30 ng/ml), mild (20-30 ng/ml), moderate (10-20 ng/ml), and severe (<10 ng/ml) deficiency ($p>0.05$). Overall, about 80 percent of patients in both groups had subnormal 25-hydroxyvitamin D levels. The analysis could not identify any single independent risk factors for 25-hydroxyvitamin D deficiency either in the study or the control group. The mean 25-hydroxyvitamin D levels in females were comparable to their male counterparts within the same group as well as compared to those in the other group ($p>0.05$ for all comparisons), although the combined factors of being female and having epilepsy or diabetes revealed significantly lower 25-hydroxyvitamin D levels, compared to the control cohort. Similarly, in the study group the proportion of females (58.1 percent) with moderate to severe vitamin D deficiency (25-hydroxyvitamin D levels < 20 ng/ml) was significantly higher ($p<0.02$) than in their male counter-

TABLE 1: PATIENT CHARACTERISTICS AND 25-HYDROXYVITAMIN D STATUS			
	Study Group	**Control Group**	**p value**
Group description	CMP + associated illnesses	Neurological illnesses other than CMP	
Number of patients	426	485	
Age in yrs (Mean + SD)	52.4 (13)	49.1 (16)	0.001
Sex (% of M:F)	19:81	28:72	0.03
Race/Ethnicity (% of group total):			
Caucasian	66	68	NS
African American	28	26	NS
Asian	03	02	NS
Hispanic	03	04	NS
Anthropometrics (Mean + SD):			
Weight in lbs	177 (47)	181 (49)	NS
Height in inches	64.9 (3.5)	65.4 (3.9)	.004
Body Mass Index	30.0 (7.1)	28.9 (6.8)	0.019
Associated Illnesses (% of group total):			
Epilepsy	8	25	0.001
Arthritis	36	26	NS
Anxiety	39	32	NS
Depression	46	36	NS
Hypertension	41	36	NS
Diabetes	19	11	NS
Hypercholesterolemia	25	21	NS
Coronary Artery Disease	15	13	NS
Associated Symptoms (% of group total):			
Paresthesia	79	32	0.002
Muscle Cramps	26	05	0.002
Fatigue	78	77	NS
Neck/back pain	86	55	0.04
Laboratory findings (Mean + SD):			
Serum albumin (g/dL)	4.2 (0.36)	4.2 (0.30)	NS
Serum Calcium (mg/dL)	9.5 (0.45)	9.5 (0.42)	NS
Serum Alkaline Phosphatase (IU/L)	81 (28)	79 (45)	NS
Serum Magnesium (mg/dL)	2.1 (0.25)	2.1 (0.24)	NS
Serum Phosphorus (mg/dL)	3.5 (0.55)	3.5 (0.48)	NS
25-hydroxyvitamin D level in ng/mL (Mean + SD)	20.73 (12.46)	21.56 (11.1)	NS
25-hydroxyvitamin D status (% of group total):			
Normal: (> 30 ng/mL)	21.4	19.6	NS
Mild Deficiency: (20-30 ng/mL)	22.1	31.3	0.051
Moderate Deficiency: (10-20 ng/mL)	36.9	35.3	NS
Severe Deficiency: (< 10 ng/mL)	19.7	13.8	NS
CMP: chronic myofascial pain.			

parts (50 percent). Similar differences could be seen in the control group.

An analysis within the CMP group (n=426) divided patients into subgroups A (CMP with no other associated disorders, n=54) and B (CMP with other associated disorders, n=372). The mean 25-hydroxyvitamin D levels were similar in both subgroups (22.3 + 10.8 vs. 20.5 + 12.7, respectively). However the proportion of patients with moderate to severe deficiency (< 20ng/ml) was higher in subgroup B (58.3 percent) as compared to subgroup A (44.4 percent), which favored a tendency toward significance (p=0.057).

DISCUSSION

Overall, the prevalence of hypovitaminosis D in patients with CMP, epilepsy and other neurological disorders was about 80 percent in this study. There was no difference in mean vitamin D levels between males and females, although a higher proportion of females had a more profound vitamin D deficiency (compared to corresponding males). Since this study did not use normal healthy control patients, it was not possible to conclude whether this high prevalence reflects the general population, or is due to the referral pattern in our study.

The fact that about 80 percent of our patients had vitamin D deficiency is striking, given data from other parts of the country showing vitamin D deficiency in 40-50 percent of cases.[38, 47-50] Whereas females have a higher risk of vitamin D deficiency, our study also found more severe hypovitaminosis in females. There was a higher prevalence of 25-hydroxyvitamin D deficiency in patients with epilepsy, supporting previous studies.[1,51-58] Moreover, with the increased use of antiepileptic drugs (largely associated with altered vitamin D metabolism) for the treatment of non-epileptic neurological conditions, an increased risk for vitamin D deficiency becomes likely.[58-61] Since older age and higher body mass indices have been linked to vitamin D deficiency,62-65 this may also have an effect on our results. However, patients with CMP, but without an associated illness, still had 25-hydroxyvitamin D deficiency, similar to patients with CMP and concomitant illnesses. Collectively, this implies that CMP per se is associated with 25-hydroxyvitamin D deficiency, and is even higher if associated with other symptoms (see Table 1).

Various clinical studies have explored the relationship between vitamin D and chronic pain, including the middle aged British population,[41] a South Asian ethnic group[66] and young females in Urmia.[67] Vitamin D deficiency has been implicated in impaired neuromuscular functioning among patients with chronic pain, poor physical performance and reduced exercise tolerance.[68-70] There is also a high prevalence of hypovitaminosis D in patients with chronic nonspecific musculoskeletal pain[42,71-74] and unusual pain,[75] likely to involve both central and peripheral mechanisms.[76-78]

While there are several reports of hypovitaminosis D in patients with CMP,[42-79] it remains unclear whether this deficiency is the cause, effect or simply an epiphenomenon. For example, a recent study did not find significant improvement in diffuse musculoskeletal pain,[80] and a placebo-controlled study showed no improvement in the elderly bedridden patients with pain81 after vitamin D supplementation. Clearly, methodological problems, such as small sample sizes, poorly defined pain states, lack of randomized double blind placebo controlled groups, lack of control for associated illnesses and concomitant medications,[46,82] complicate the analysis of the role of vitamin D in pain.

CONCLUSIONS

Vitamin D is a neurosteroid hormone and hypovitaminosis D can induce various neurological deficits. Our study is an observational retrospective analysis which primarily focuses on prevalence of hypovitaminosis D in 911 patients over a span of 30 months. Overall about 80 percent of patients had subnormal 25-hydroxyvitamin D levels. Moderate to severe vitamin D deficiency was significantly higher in females as well as in patients who had CMP with other associated symptoms. There was a higher prevalence of hypovitaminosis D in patients with epilepsy. These data suggest a need for additional consideration of vitamin D status in patients with neurological disorders. Furthermore, the role of vitamin D treatment in the amelioration of chronic pain needs to be defined and can only be clarified by well-designed prospective randomized double blind placebo controlled studies. ■

The authors declare no conflicts of interest associated with this study. This paper is dedicated to the memory of Dr. Vikram Khoshoo, MD, PhD.

Dr. Mohnot is on staff at the New Orleans Headache and Neurology Clinic in Gretna, LA.

Dr. Kalueff and Mr. Stewart are in the Department of Pharmacology at Tulane University School of Medicine in New Orleans, LA.

Dr. DuRapau and Dr. Arora are in the Department of Mathematics at Xavier University in New Orleans, LA. Sopan Mohnot is in the Neuroscience Program at Tulane University in New Orleans, LA.

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