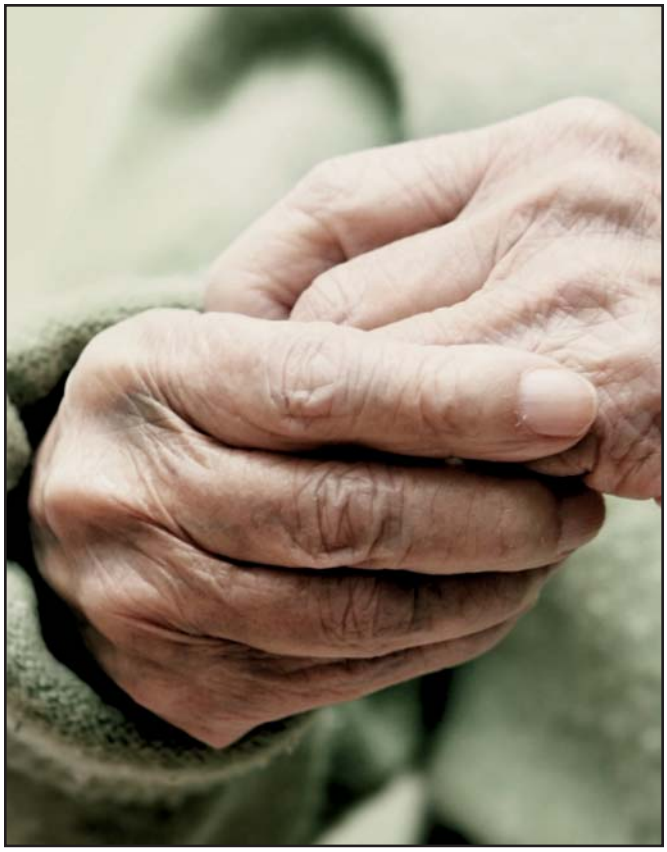

VITAMIN D DEFICIENCIES IN PAIN PATIENTS

This condition, associated with muscle weakness, myopathy, and consequently musculoskeletal pain, was found to be prevalent in the patient population studied.

By Mark L. Gostine, MD and Fred N. Davis, MD

Vitamin D's role in calcium metabolism is well known. In the last ten years, since the vitamin D receptor (VDR) was cloned and recognized, researchers realized the compound is more accurately categorized as a hormone with many activities unrelated to calcium physiology. Vitamin D modulates the immune system, is an important antiproliferative, and may help treat cancer.[1-3] Vitamin D receptors are present in blood forming elements, pancreatic islet cells, the nervous system, and muscle tissues.

Vitamin D technically refers to both vitamin D2 and vitamin D3. Vitamin D2 is the provitamin ergosterol found in plants, while vitamin D3, or cholecalciferol is found in animals. Either form can prevent osteomalacia and rickets, although vitamin D3 is more active.

Vitamin D deficiencies were once very common but were generally eliminated with the advent of vitamin D fortified foods. Unfortunately, the prevalence once again seems to be widespread in diverse populations. Dark skinned individuals, the obese, the elderly, and those in northern latitudes seem to be more at risk.[4-6]

The recurrence of hypovitaminosis D is related to a variety of factors in the modern lifestyle. These include the explosion of non dairy beverage consumption, a lifetime spent predominantly indoors, fear of sun exposure, and the widespread adoption of sun screens.

Although the recommended dietary allowance (RDA) for vitamin D is 400 units, there is no certainty that this is the proper amount for general health. The RDA was determined based on the average amount of vitamin D in a teaspoon of cod liver oil, the amount needed to generally prevent rickets in children.[7] This amount is inadequate in adults because it does not take into account their larger body mass. Inpatients who had taken 400 units of vitamin D remained vitamin D deficient.[8] Up to 10,000 units per day do not elevate blood levels above high normal limits.[9]

Bile is necessary for proper vitamin D absorption. Patients who have had gastric bypass surgery, or who have inflammatory bowel disease, are at higher risk of low vitamin D levels secondary to their gastrointestinal alterations or disease. Once vitamin D is absorbed from the GI tract it is modified with a sequence of two hydroxylations in the liver and kidneys to become calcitriol, or 1,25(OH)2D. Calcitriol is the most active form of vitamin D and is tightly regulated by enzymatic modification to ensure proper calcium homeostasis. Increased calcium and phosphate levels inhibit enzymatic conversion of provitamins to calcitriol. Conversely, low calcium and phosphate levels, parathyroid hormone and estrogen all raise blood levels of the most active form of vitamin D. Normal blood levels of vitamin D are reported as 25 to 80 ng/ml; however, parathyroid hormone activity can be increased to levels as high as 30 ng/ml resulting in increased bony turnover.[10]

Physiologic Activity of Vitamin D

Vitamin D's primary action is to enhance the absorption of both calcium and phosphate from the gastrointestinal tract, decrease the kidney's excretion of calcium, and to complement the activity of parathyroid hormone (PTH) to mobilize calcium from bone when calcium blood levels are low. Calcitriol exerts its effects on the vitamin D receptors (VDR) in the cell's cytosol. The calcitriol and vitamin D receptor complex migrate to the nucleus where they can induce gene transcription. The thyroid and steroid supergene family include the VDR[11] consistent with the

Decade (age)	Vitamin D Level	Number of Patients
20 to 39	18	5
40 to 49	17.6	13
50 to 59	17.5	11
60 to 69	15.3	16
70 to 89	19.8	11

idea that vitamin D is more accurately characterized as a hormone with many activities unrelated to its role in calcium homeostasis.

In the small intestine, calcium absorption channels appear to be up regulated in the presence of vitamin D. Most of the absorption takes place in the proximal small intestine but a limited amount takes place in the distal ileum and can be negatively impacted by inflammatory bowel disease. Vitamin D does not appear to have a direct effect on bone mineralization; rather it exerts its effect primarily by increasing the absorption of intestinal calcium. Children with rickets caused by mutations of the VDR, can have their bone mineralization restored with intravenous calcium and phosphate, indicating that calcitriol exerts its primary influence on bones via calcium absorption and not directly on the bones itself. Indeed, super high doses of vitamin D increases bone mobilization of calcium.

Vitamin D also has significant physiologic activity outside the area of calcium metabolism. Calcitriol is a potent antiproliferative and analogs, stripped of their calcium activity, are being investigated for their antineoplastic properties.[1] Because of its ability to facilitate differentiation of the epidermis, vitamin D is being investigated as a therapeutic agent in psoriasis. It is also an important immune modulator affecting both mononuclear cell and cytokine production. Low levels of calcitriol are found in relation to a variety of common diseases such as multiple sclerosis, diabetes, arthritis, and heart disease.[12]

Vitamin D deficiencies are associated with muscle weakness,[13] myopathy,[14] and consequently muscle pain. Plotnikoff and Quigley reported that 100% of African American, East African, Hispanic, and American Indian patients with persistent, nonspecific musculoskeletal pain presenting to the Community University Health Care Center, a university-affiliated inner city primary care clinic, were vitamin D deficient.[15]

> "We found that 84 percent of our patients...suffered from hypovitaminosis D. This can contribute significantly to musculoskeletal complaints in the form of osteomalacia and accelerated osteoarthritis in the pain management patient population."

Study Population

The purpose of the study was to investigate to what extent hypovitaminosis D exists in a predominantly Caucasian population of patients presenting with a variety of musculoskeletal complaints to a Midwestern community based pain management center. Over a period of twelve weeks, three patients a day were selected from the clinic schedule at a designated appointment slot. This method was used because it facilitated patient flow, could be delegated to clinic staff and randomized the patients selected. There were 56 patients in the study. They ranged in age from 26 through 84. The average age was 57. There were 47 females and 8 males. Patients' diagnoses included spinal arthritis, fibromyalgia, pelvic pain, headaches, and failed back surgery. Many of the patients had a past medical history including obesity, hypertension and hyperlipidemia. None of the patients suffered from inflammatory bowel disease.

Methods

After informed consent, blood was drawn from patients from the middle of January 2006 to the beginning of April 2006. Tests were performed by Mayo Medical Laboratories Rochester MN. Vitamin D2 levels, vitamin D3 levels, and total vitamin D were assessed. The normal reference range for total vitamin D is 25 to 80 ng/ml.

Results

Of the 56 patients in the study, 46 were diagnosed with hypovitaminosis D. The average total vitamin D level was 17.43. Over half the patients qualified as having a moderately severe deficiency (less than 17 ng/ml.) Vitamin D levels were analyzed by decade with the two patients in their 20's included with patients in their 30's and patients in their 70's and 80's also included together. In essence we had five groups to consider, 20's and 30's, 40's, 50's, 60's, 70's and 80's.

There is no evident trend comparing age to vitamin D level. Males had a level on average of 16.3 ng/ml. and women had an average of 17.6 ng/ml.

Discussion

Thomas et. al.[16] looked at the incidence of vitamin D deficiencies in the inpatient population and found that 57 percent were vitamin D deficient. What is striking in our population is that neither light skin nor outpatient status conferred any protection against hypovitaminosis D. Indeed our prevalence of vitamin D deficiency is 84 percent. This may reflect that hypovitaminosis D is wide spread in the chronic pain population or may indicate that the problem has worsened in the population at large since 1998. Osteoporosis is widespread in the elderly. It is also difficult to distinguish from osteomalacia by radiographic studies although looser fractures are unique to osteomalacia. Laboratory studies are helpful—including vitamin D levels—and should be drawn in patients suspected of either diagnosis.

What constitutes vitamin D deficiency is open for debate. Vitamin D appears to protect against cancer and multiple sclerosis. The dose necessary for vitamin D's antiproliferative and immune modulating activity may be greater than the dose necessary to prevent rickets and osteomalacia. In mice, a dose equivalent to 3600 IU's per day in humans reverses symptoms of experimental allergic encephalomyelitis, the cell-mediated autoimmune disease model of multiple sclerosis.[2]

Parathyroid hormone can start to rise when vitamin D levels fall below 30 ng/ml. Increased levels of PTH accelerate bony turnover. In the Framingham Study patients with levels below 32 ng/ml. were at increased risk of knee osteoarthritis and pain.[17] By this standard, virtually all patients in our study, except two, were vitamin D deficient.

There are multiple ways to correct vitamin D deficiencies. In older adults, with potential problems of malabsorption, up to 4000 IU/D orally or prescription amounts of 50,000 units twice a week, also orally, are appropriate for up to twelve weeks. Calcium consumption of at least 800 mg per day is necessary. Follow blood levels of both vitamin D and calcium during the correction phase. Maintain patients on 2000 IU/D after the correction period.

Conclusions

Vitamin D deficiencies are very common even in lighter skinned individuals. We found that 84 percent of our patients presenting to our pain management center suffered from hypovitaminosis D. This can contribute significantly to musculoskeletal complaints in the form of osteomalacia and accelerated osteoarthritis in the pain management patient population. Future research should examine if the correction of hypovitaminosis D leads to improvement in reported pain. ■

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