

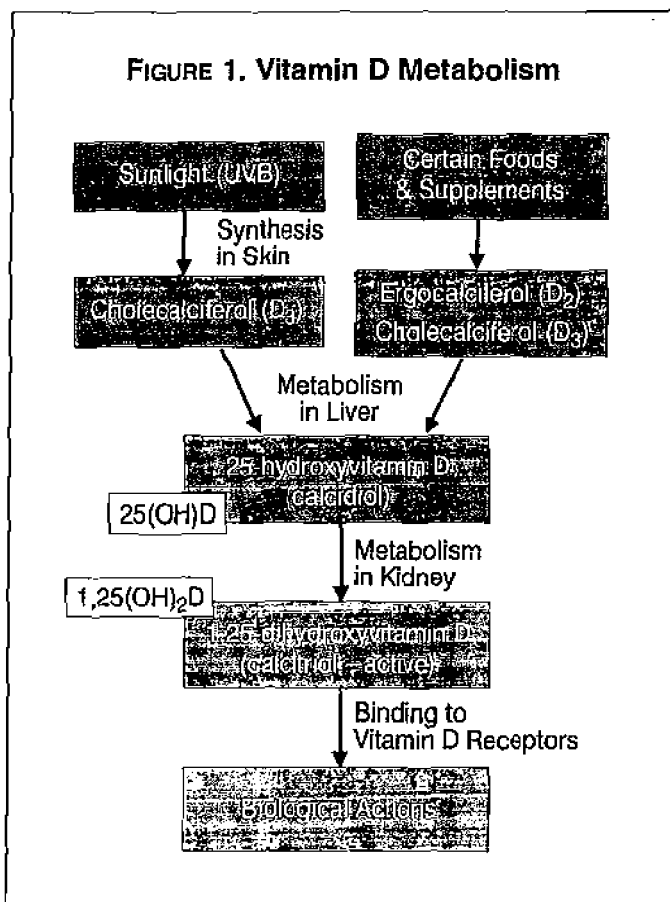
# VITAMIN D FOR CHRONIC PAIN

According to a comprehensive review of the clinical research evidence, helping certain patients overcome chronic musculoskeletal pain and fatigue syndromes may be as simple, well tolerated, and inexpensive as a daily supplement of vitamin D.

By Stewart B. Leavitt, MA, PhD.

*Editor's note: This article is adapted from the author's peer-reviewed research report, Vitamin D—A Neglected 'Analgesic' for Chronic Musculoskeletal Pain, from Pain Treatment Topics. The full report, along with a special brochure for patients, is available at [www.pain-topics.org/VitaminD](http://www.pain-topics.org/VitaminD).*

FIGURE 1. Vitamin D Metabolism



Standing apart from the various other essential nutrients, vitamin D was spotlighted recently as having special therapeutic potential. This has important implications for the management of chronic musculoskeletal pain and fatigue syndromes.

During this past June 2008, news-media headlines heralded recent clinical research that revealed benefits of vitamin D for preventing type 1 diabetes,<sup>1</sup> promoting survival from certain cancers,<sup>2</sup> and decreasing the risks of coronary heart disease.<sup>3</sup> Overlooked, however, was the traditional role of vitamin D in promoting musculoskeletal health and the considerable evidence demonstrating advantages of vitamin D therapy in helping to alleviate chronic muscle, bone and joint aches, and pains of various types.

Chronic pain—persisting more than 3 months—is a common problem leading patients to seek medical care.<sup>4,7</sup> In many cases, the causes are *nonspecific*, without evidence of injury, disease, or neurological or anatomical defect.<sup>4,9</sup> However, according to extensive clinical research examining adult patients of all ages, *inadequate concentrations of vitamin D* have been linked to nonspecific muscle, bone, or joint pain, muscle weakness or fatigue, fibromyalgia syndrome, rheumatic disorders, osteoarthritis, hyperesthesia, migraine headaches, and other chronic somatic complaints. It also has been implicated in the mood disturbances of chronic fatigue syndrome and seasonal affective disorder.

Although further research would be helpful, current best evidence demonstrates that supplemental vitamin D can help many patients who have been unresponsive to other therapies for pain. Vitamin D therapy is easy for patients to self-administer, well-tolerated, and very economical.

It must be emphasized that vitamin D is not pharmaceutical analgesic in the sense of fostering relatively immediate pain relief, and expectations along those lines would be unrealistic. Because Vitamin D supplementation addresses underlying processes, it may take months to facilitate pain relief, which can range from partial to complete. Furthermore, vitamin D supplementation is not proposed as a panacea or as a replacement for other pain treatment modalities that may benefit patient care.

### Vitamin D and 'D-ficiency'

**Pharmacology.** Vitamin D comprises a group of fat-soluble micronutrients with two major forms: D<sub>2</sub> (ergocalciferol) and D<sub>3</sub> (cholecalciferol)<sup>10,11</sup> (see Figure 1). Vitamin D<sub>3</sub> is synthesized in the skin via exposure of endogenous 7-dehydrocholesterol to direct ultraviolet B (UVB) radiation in sunlight and is also obtained to a small extent in the diet (see Table 1). In many countries, some foods are fortified with vitamin D<sub>3</sub>, which is the form used in most nutritional supplements.<sup>14,20</sup> Vitamin D<sub>2</sub>, on the other hand, is found in relatively few foods or supplements.<sup>14</sup>

Following vitamin D synthesis in the skin or other intake, some of it is stored in adipose tissue, skeletal muscle, and many organs,<sup>19</sup> while a relatively small portion undergoes a two-stage process of metabolism (see Figure 1). First, D<sub>2</sub> and/or D<sub>3</sub> are metabolized via hydroxylation in the liver to form 25-hydroxyvitamin D, abbreviated as 25(OH)D (also called calcidiol).<sup>10,14,18,21,22</sup> This has minimal biological activity and serum concentrations of 25(OH)D accumulate gradually, plateauing at steady-state levels by about 40 days<sup>19,23,24</sup> to 90 days.<sup>25,26</sup>

The 25(OH)D metabolite is converted primarily in the kidneys via further hydroxylation to 1,25-dihydroxyvitamin D, abbreviated as 1,25(OH)<sub>2</sub>D (also called calcitriol). It is the most important and biologically-active vitamin D metabolite with a short half-life of only 4 to 6 hours<sup>27</sup> but can remain active for 3 to 5 days.<sup>15,20</sup> A central role of vitamin D—via its active 1,25(OH)<sub>2</sub>D metabolite—is to facilitate the absorption of calcium from the intestine and help maintain normal concentrations of this vital agent. Equally important, 1,25(OH)<sub>2</sub>D sustains a wide range of metabolic and physiologic functions throughout the body.<sup>28</sup>

Vitamin D actually is misclassified as a vitamin; it may be more appropriately considered a prohormone and its active 1,25(OH)<sub>2</sub>D metabolite—with its own receptors found in practically every human tissue—functions as a hormone. These vitamin D receptors, or VDRs, affect the function of up to 1000 different genes<sup>16,22,29,30,31</sup> helping to control cell growth or differentiation. The VDRs themselves can differ

TABLE 1: Sources of Vitamin D

Vitamin D <sub>2</sub> and D <sub>3</sub> Sources	
Source	Vitamin D Content
<b>Higher-Yield Natural Sources</b>	
Exposure to sunlight, ultraviolet B radiation (0.5 minimal erythral dose)*	3000–10,000 IU D <sub>3</sub>
Salmon fresh, wild (3.5 oz*)	600–1000 IU D <sub>3</sub>
Salmon fresh, farmed (3.5 oz)	100–250 IU D <sub>3</sub>
Salmon canned (3.5 oz)	300–600 IU D <sub>3</sub>
Herring, pickled (3.5 oz)	680 IU D <sub>3</sub>
Catfish, poached (3.5 oz)	500 IU D <sub>3</sub>
Sardines, canned (3.5 oz)	200–360 IU D <sub>3</sub>
Mackerel, canned (3.5 oz)	200–450 IU D <sub>3</sub>
Tuna, canned (3.6 oz)	200–360 IU D <sub>3</sub>
Cod liver oil (1 tsp / 0.17 oz)	400–1400 IU D <sub>3</sub>
Eastern oysters, steamed (3.5 oz)	642 IU D <sub>3</sub>
Shiitake mushrooms fresh (3.5 oz)	100 IU D <sub>2</sub>
Shiitake mushrooms sun-dried (3.5 oz)	1600 IU D <sub>2</sub>
Egg yolk, fresh	20–148 IU D <sub>3</sub>
<b>Fortified Foods</b>	
Fortified milk	60–100 IU/8 oz, usually D <sub>3</sub>
Fortified orange juice	60–100 IU/8 oz usually D <sub>3</sub>
Infant formulas	60–100 IU/8 oz usually D <sub>3</sub>
Fortified yogurts	100 IU/8 oz, usually D <sub>3</sub>
Fortified butter	50 IU/3.5 oz, usually D <sub>3</sub>
Fortified margarine	430 IU/3.5 oz, usually D <sub>3</sub>
Fortified cheeses	100 IU/3 oz, usually D <sub>3</sub>
Fortified breakfast cereals	60–100 IU/serving, usually D <sub>3</sub>
Food labels often express vitamin D content only as % of daily value, so it is usually unknown what the exact amount is in International Units (IU).	
<b>Supplements</b>	
<b>Over The Counter/Internet</b>	
Multivitamin (including vitamin D)	400–800 IU vitamin D <sub>2</sub> or D <sub>3</sub> *
Vitamin D (tablets, capsules)	Various doses 400–50,000 IU (primarily D <sub>3</sub> )
<b>Prescription/Pharmaceutical</b>	
Vitamin D <sub>2</sub> (ergocalciferol)	50,000 IU/capsule
Drisdol®, Calciferol®, others (vitamin D <sub>2</sub> ) liquid supplements	8000 IU/mL
Rocaltrol®, Calcigex®, others (1,25[OH] <sub>2</sub> D) available outside US	0.25–0.5 mcg capsules 1 mcg/mL solution
* 1 oz = 28.3 grams = 29.6 mL; 1 IU = 40 mcg (microgram) † A 0.5 minimal erythral dose of UVB radiation would be absorbed after about 10–15 minutes of exposure of arms and legs to direct sunlight (depending on time of day, season, latitude, and skin sensitivity). Dark-skinned persons would require longer. ‡ Ergocalciferol on product label signifies D <sub>2</sub> ; cholecalciferol signifies D <sub>3</sub> .	
References: Calcitriol <sup>12</sup> ; Ergocalciferol <sup>15</sup> ; Holick <sup>14</sup> ; Marcus <sup>16</sup> ; ODS <sup>18</sup> ; Singh <sup>17</sup> ; Tavera-Mendoza and White <sup>20</sup> ; and Vieth <sup>19</sup>	

**TABLE 2: DEFINING ADEQUATE 25(OH)D CONCENTRATIONS****25(OH)D Concentrations**  
*Major Metabolite of Vitamin D from D<sub>2</sub> or D<sub>3</sub>*

Deficient	<20 ng/mL
Insufficient	20–29 ng/mL
Optimal Range	30–50 ng/mL
Potentially Toxic	>150 ng/mL

In some literature 25(OH)D is expressed as nmol/L. The conversion formula is: 1 ng/mL = 2.5 nmol/L or 1 nmol/L = 0.4 ng/mL.

References: Heaney<sup>24</sup>; Heaney et al<sup>25</sup>; Holick<sup>26</sup>; Reginster et al<sup>27</sup>; Tavera-Mendoza and White<sup>28</sup>; Vieth<sup>29</sup>

in their genetic makeup (poly-morphism) and activity, which may account for varying individual responses to vitamin D therapy.<sup>32,33</sup>

The discovery of vitamin D receptors in many tissues besides intestine and bone—including heart, pancreas, breast, prostate, lymphocytes, and other tissues—implies that vitamin D supplementation might have applications for treating a number of disorders. These include autoimmune diseases, diabetes, cardiovascular disease, psoriasis, hypoparathyroidism, renal osteodystrophy, and possibly leukemia and cancers of the breast, prostate, or colon.<sup>3,30,34–37</sup> Research is ongoing in these areas.

If vitamin D production or intake is diminished, reabsorption of vitamin D from tissue-storage reservoirs can sustain conversion to 25(OH)D and the 1,25(OH)<sub>2</sub>D metabolite for several months. However, an abundant supply of vitamin D during certain times, such as from summer sun exposure, does not deter its complete depletion during periods of lean intake, such as during winter months.<sup>19</sup>

Numerous individual factors may affect the status of vitamin D and its metabolites in the body. Synthesis of vitamin D<sub>3</sub> in the skin in reaction to UVB exposure is a self-limiting reaction that achieves equilibrium within 20 to 25 minutes of exposure to strong sunlight in persons with white skin, with no net increase in D<sub>3</sub> production after that.<sup>19</sup> Persons with darker skin require longer sun exposure, but the total yield in D<sub>3</sub> is the same. Age is another limiting factor, and it is more difficult for older persons to acquire adequate vitamin D from UVB radiation.<sup>21,28</sup>

**Adequate 25(OH)D Concentration.** Most researchers agree that a minimum 25(OH)D serum level of about 30 ng/mL or more is necessary for favorable calcium absorption and good health.<sup>14,38–41</sup> Optimal 25(OH)D concentrations are considered to range from 30 ng/mL to 50 ng/mL (see Table 2).<sup>20,33,36,42–44</sup>

Most definitions of deficiency stress that circulating 25(OH)D concentrations of <20 ng/mL may be associated with increased parathyroid hormone (PTH) secretion and greater bone turnover—potentially engendering symptoms of osteomalacia.<sup>15,39,45</sup> Concentrations ≤8 ng/mL have been considered as highly predictive of fully-developed, or clinical, osteomalacia.<sup>15,22,50,46–48</sup>

Furthermore, levels of circulating 25(OH)D concentrations below an optimal range but above true deficiency status might also have a negative impact. This range—spanning 20 to 29 ng/mL of 25(OH)D—would constitute insufficiency.<sup>18,27</sup>

In cases of vitamin D toxicity—usually characterized by hypercalcemia and/or hyperphosphatemia—serum 25(OH)D levels are usually elevated to >150 ng/mL.<sup>14,20</sup> Some laboratories may indicate >100 ng/mL as possibly toxic, but this could be overly conservative and reported reference ranges are not always consistent from one laboratory to another.

**General Prevalence of “D-ficiency.”**

There is a growing consensus that vitamin D inadequacies in the general population—or what Holick [2004a]<sup>112</sup> has broadly labeled “D-ficiency”—are much more common and severe than might be imagined. This has been extensively studied and, according to the research evidence, it may be assumed in almost any clinical practice that at least 50% of patients will have 25(OH)D concentrations below 30 ng/mL, the lower limit of the optimal range. In many instances, the percentage of patients with vitamin D insufficiency will be much greater, and a significant proportion of them may have more serious deficiencies of <20 ng/mL 25(OH)D.<sup>49</sup>

Otherwise healthy persons at special risk include darker-skinned individuals, the obese, the elderly, and those living in northern or southern latitudes greater than 42 degrees.<sup>20,30,51</sup> Numerous factors in modern society may also contribute to the problem, including diets devoid of the

relatively few foods naturally rich in, or fortified with, vitamin D; lifestyles of work or leisure spent predominantly indoors and concerns about sun exposure with the attendant use of clothing or lotions that almost completely block UVB radiation.<sup>3</sup>

Significant numbers of males and females of all ages and races, and in all parts of the world have been found lacking in vitamin D.<sup>14,18,32–38</sup> For example, an investigation of healthy adults (18–84 years of age) from a northern U.S. city in February found that 87% had insufficient 25(OH)D (<30 ng/mL) and 6 out of 10 were deficient (<20 ng/mL)—despite the fact that many of them (30%) took a daily multivitamin containing at least 400 IU of vitamin D and nearly half drank fortified milk each day.<sup>23</sup>

Surprisingly, even persons living in the sunniest regions are not exempt. A recent study in southern Arizona found that the mean serum 25(OH)D concentration in 637 randomly-selected subjects was about 26 ng/mL; half of them had concentrations <30 ng/mL and more than a quarter (27%) had levels <20 ng/mL.<sup>49</sup>

**Associations of Vitamin D and Pain**

**Vitamin D in Chronic Musculoskeletal Pain.** From the perspective of vitamin D involvement in musculoskeletal pain, the process is presumed to begin with a lack of circulating calcium (hypocalcemia) due to inadequate vitamin D, and this sets in motion a cascade of bio-chemical reactions negatively affecting bone metabolism and health. Even mild hypocalcemia results in an elevation of parathyroid hormone (PTH) that can diminish bone density (osteopenia) and/or more severely affect bone architecture (osteoporosis).<sup>53,56</sup>

The effect relating more closely to musculoskeletal aches and pains is that increased PTH levels also impair proper bone mineralization causing a spongy matrix to form under periosteal membranes covering the skeleton. This gelatin-like matrix can absorb fluid, expand, and cause outward pressure on periosteal tissues, which generates pain since these tissues are highly innervated with sensory pain fibers.<sup>27,44,59</sup>

This dysfunction of bone metabolism (osteomalacia) is proposed in the literature as an explanation of why many patients with vitamin D inadequacies may complain of dull, persistent, generalized musculoskeletal aches, pains, and

Table 3. Vitamin D Research in Musculoskeletal Pain &amp; Fatigue Syndromes

Researchers/Population	Subjects	Vitamin D Status	Comments
Turner et al <sup>60</sup> – Mayo Clinic – retrospective case series in patients with chronic musculoskeletal pain of diverse etiologies. Mean age 47.5 years. [Reported also by Hooten et al <sup>61</sup> ]	n=267 75% female 98% white	26% <20 ng/mL 25(OH)D mean = 15.7 ng/mL  Overall mean = 28.7 ng/mL (reflecting insufficiency)	Low back pain (n=77) and fibromyalgia (n=66) were the most prevalent diagnoses. More than half (52%) of all patients were using opioids (mean morphine equivalent 87 mg/day) for an average of 52 months. Patients with deficient vitamin D were taking opioids longer, and also reported poorer physical functioning and overall health perception.
Hicks et al <sup>62</sup> – Italy – prospective study in elderly persons, mean age 74.5, with pain in lower extremities or back, or both.	n=958 55% females	22% <10 ng/mL 25(OH)D 50+% <20 ng/mL  median = 19 ng/mL males median = 14 ng/mL females <i>(25(OH)D was significantly lower in older patients)</i>	A low threshold of <10 ng/mL 25(OH)D was defined as deficiency; although, more than half of all subjects were at <20 ng/mL. Pain was associated to a greater degree with inadequate 25(OH)D for lower back pain in women than in men. Lower 25(OH)D also was associated with more depressive symptoms, poorer cognition, and higher PTH levels.
Lotfi et al <sup>64</sup> – Egypt – female patients with chronic (>3 mo.) low back pain compared with a pain-free control group.	60 patients 20 controls	pts 82% <40 ng/mL 25(OH)D  ctls 60% <40 ng/mL  <i>(This is a much higher threshold for defining deficiency than used in other studies)</i>	25(OH)D was significantly lower (p < .05) and PTH higher (p < .05) in patients with pain. Alkaline phosphatase higher in patients with pain, no differences in calcium or phosphorus. Low sun exposure (duration and skin exposed) accounted for 88% of the variance between groups, even in this sunny climate.
Armstrong et al <sup>63</sup> – United States – patients with fibromyalgia syndrome.	n=75	56% = 10-20 ng/mL 25(OH)D +13% <10 ng/mL	86% of total considered deficient in 25(OH)D. There also was a correlation between deficient vitamin D and greater anxiety and depression.
Kealing <sup>64</sup> – Kansas – women with breast cancer experiencing joint pain prior to cancer treatment.	Not stated.	75% vitamin D deficient (levels not given)	In this pilot study, supplemental vitamin D (amount unknown) reduced joint pain as well as fatigue.
de la Jara et al <sup>65</sup> – Switzerland – females from various countries of origin with chronic back pain and/or multiple somatic pain symptoms (consistent with osteomalacia diagnosis).	n=33; mean age=39	97% <8 ng/mL 25(OH)D (mean=4.5 ng/mL)  43% had hypocalcemia 32% hypophosphatemia	With vitamin D supplementation, symptoms disappeared after 2.84 months in two-thirds (22/33) of patients; another 18% (6/33) had partial resolution. Mean number of Rx analgesic drugs taken declined from 3.27 to 0.85.
Gostline and Davis <sup>50</sup> – Michigan – randomly selected patients in a pain clinic with arthritis, pelvic pain, failed back surgery, and fibromyalgia.	n=56 84% female	96% <30 ng/mL 25(OH)D 84% = deficient (undefined) 50+% <17 ng/mL	Patients ranged in age from 26 to 84 years; no significant differences in 25(OH)D deficiencies across age groups or between female and males.
Benson et al <sup>66</sup> – Australia – Aboriginal patients with muscle pain, compared with a pain-free control group from the same population.	8 patients 8 controls	100% pts <20 ng/mL 25(OH)D 12% ctls = 20 ng/mL	Mean 25(OH)D in patients was 16 ng/mL vs 23.3 ng/mL in controls (p=.017). All subjects were urban dwelling and had left their prior outdoor lifestyle with its ample exposure to sunlight.
Helliwell et al <sup>67</sup> – England – South Asian patients with either unexplained widespread pain or specific rheumatic diagnosis.	n=160	73% = low 25(OH)D (undefined).	In 47% of patients for whom combined data were available, PTH was elevated and 25(OH)D was deficient – which are biomarkers of osteomalacia. Few had abnormal Ca, PO, or ALP.
Erkal et al <sup>68</sup> – Germany – comparison of German control group vs Turkish patients with bone/muscle pain living in Germany or Turkey.	893 patients 101 controls	pts. = mean 15.7 ng/mL 75% <20 ng/mL 25(OH)D  ctls = mean 27.4 ng/mL	Age range was 16-69 years; 41% females. There was a strong correlation between low 25(OH)D and higher rates and longer duration of generalized bone and/or muscle aches and pains (often diagnosed as fibromyalgia). Lack of sun exposure, higher latitude, and female sex were important predictors for low 25(OH)D.
Macfarlane et al <sup>69</sup> – Scotland – South Asian young women with widespread pain.	n=114	3.5 times greater risk of <10 ng/mL 25(OH)D in those with pain than without.	This was a subset of patients from a study of 3135 South Asian subjects who demonstrated a 60% greater rate of widespread pain than their non-Asian counterparts in the UK.

Table 3. Vitamin D Research in Musculoskeletal Pain &amp; Fatigue Syndromes (continued)

Researchers/Population	Subjects	Vitamin D Status	Comments
Baker et al <sup>70</sup> – Boston VA Medical Center – patients with painful and radiographically confirmed knee osteoarthritis.	n=221; mean age=67	48% • 20 ng/mL 25(OH)D	Subjects with lower vitamin D had more pain and disability and were weaker. In patients with increasing vitamin D levels during a 30 mo. monitoring period there were corresponding improvements in disability and pain scores.
Haque et al <sup>71</sup> – Johns Hopkins, Baltimore – general rheumatology patients with pain.	n=48; 87% female; mean age=59	58% = 10-20 ng/mL 25(OH)D +25% <10 ng/mL	A total 83% were vitamin D deficient. The most common diagnoses were rheumatoid arthritis, inflammatory polyarthritis, chronic musculoskeletal pains, and polymyalgia rheumatica.
van der Heyden et al <sup>72</sup> – Netherlands – females with progressive muscle weakness and pain >6 mo. [case report].	n=3	Low 25(OH)D (undefined)	Also had decreased phosphate, increased alkaline phosphatase. After vitamin D supplementation, pain resolved and muscle strength improved "within a week."
Block <sup>73</sup> – Maine – white patients with chronic widespread musculoskeletal pain, 69% diagnosed as fibromyalgia.	n=101 85% female	47% <20 ng/mL 25(OH)D 9% <10 ng/mL	The author alleged that these levels were not sufficiently deficient to account for the pain syndromes in these patients, but this belief is not consistent with other research. PTH levels were not measured.
Plotnikoff and Quigley <sup>48</sup> – Minnesota – patients with chronic, nonspecific musculoskeletal pain (excluded fibromyalgia, complex regional pain syndrome, other disorders)	n=150	93% <13 ng/mL 25(OH)D 100% <20 ng/mL 28% <8 ng/mL	Age range up to 65 years, with all age groups affected. Overall, no significant differences between males and females. Darker-skinned patients had greater 25(OH)D deficiencies and deficits in all patients were more pronounced in winter.
Al Faraj and Al Mutairi <sup>74</sup> – Saudi Arabia patients with idiopathic, chronic (>6 mo.) back pain (probable osteomalacia, as patients with diagnosed anatomical, neuropathic, or mechanical causes were excluded).	n=360 90% female	83% = <9 ng/mL 25(OH)D (Low threshold for 'normal' defined as 9-38 ng/mL)	Age range up to 52 years. After vitamin D supplementation for 3 months symptom improvement was seen in 95% of all patients and in 100% of those who would be considered as severely 25(OH)D deficient pretreatment.
Huisman et al <sup>75</sup> – Canada – female patients with fibromyalgia.	n=25	48% <20 ng/mL 25(OH)D (Group mean = 20.5 ng/mL)	PTH elevation also was evident in those with deficient 25(OH)D.
Glerup et al <sup>76</sup> – Denmark – female Arab patients with bone pain and muscle pain and weakness compared with pain-free female Danish controls.	55 patients 22 controls	pts 85% <3 ng/mL 25(OH)D 96% <8 ng/mL ctls = mean 19 ng/mL	High-dose vitamin D supplementation increased 25(OH)D 5-fold in 3 months and was paralleled by significant reductions in muscle and bone discomfort. Pretreatment, patients had elevated PTH but only 6% had subnormal calcium; alkaline phosphatase was normal. Note: most symptom-free controls had 25(OH)D levels that could be considered inadequate.
Prabhala et al <sup>77</sup> – SUNY, New York – aches, pains, and severe myopathy in patients confined to wheelchairs [case report].	n=5	Confirmed low 25(OH)D (undefined). PTH elevated.	Weakness had been attributed to old age, diabetic neuropathy, or general debility. Vitamin D supplementation resolved body aches and pains, and restored normal muscle strength in 4-6 weeks – 4 patients became fully mobile and had normal 25(OH)D.
McAlindon et al <sup>78</sup> – United States – osteoarthritis of the knee recorded in persons participating in the Framingham Study.	n=75 knees (82% progressively worsening)	33% <24 ng/mL 25(OH)D 33% <33 ng/mL	79% of cases involved vitamin D intake <347 IU/day. Low intake and low 25(OH)D resulted in a 3-fold risk of progressive osteoarthritis; although, there was no evidence of low intake/low 25(OH)D as causing osteoarthritis in normal knees. Conclusion was that persons with osteoarthritis and 25(OH)D <30 ng/mL should have increased vitamin D intake.
Loth et al <sup>79</sup> – Johns Hopkins, Baltimore – hyperesthesia (nonspecific oversensitivity to physical stimuli) unresponsive to analgesics [case report].	n=5	Range 3.2 - 41 ng/mL 25(OH)D	Pain resolved in 5-7 days after high-dose vitamin D supplementation. In 1 patient, 25(OH)D again became deficient and pain returned, but was relieved with further supplementation.

weakness.<sup>20</sup> Therefore, experts recommend that vitamin D deficiency and its potential for associated osteomalacia should be considered in the differential diagnosis of all patients with chronic musculoskeletal pain, muscle weakness or fatigue, fibromyalgia, or chronic fatigue syndrome.<sup>27</sup>

Table 3 summarizes 22 clinical investigations of vitamin D in patients with chronic musculoskeletal-related pain. These studies were conducted in various countries and included approximately 3,670 patients representing diverse populations and age groups.

The percentage of patients with pain having inadequate vitamin D concentrations ranged from 48% to 100%, depending on patient selection and the definition of 25(OH)D "deficiency." In most cases, <20 ng/mL was used as the threshold of deficiency, although deficiencies were very severe (<10 ng/mL) in many patients. Considering the studies in total, approximately 70% of patients with pain, on average, were found to have 25(OH)D concentrations <20 ng/mL. While this percentage is a high rate of deficiency, some of the reported 25(OH)D deficits in patients with pain might be suspected as merely reflecting the background prevalence of vitamin D inadequacy in the general population. However, the several investigations that included a control group of pain-free subjects from the same population for comparison purposes demonstrated that patients with pain do have significantly greater rates of 25(OH)D deficiencies.<sup>54,66,68,76</sup>

An interesting feature is that many of the control-group patients also had 25(OH)D concentrations that would be considered at the least as insufficient. This would more genuinely reflect the background prevalence of vitamin D inadequacy in the various populations studied, and it also confirms that vitamin D deficits do not always result in musculoskeletal pain in all persons.

Researchers also reported results of vitamin D supplementation therapy in response to the symptoms putatively related to the 25(OH)D deficiencies that they detected:

- In one large study of 360 female patients with chronic back pain, vitamin D therapy produced symptomatic improvement in 96% of all patients and in 100% of those with the most severe 25(OH)D deficiencies.<sup>74</sup> This study was of interest because only cases of idiopathic pain probably associated with osteomalacia were included; patients with pain diagnosed as due to anatomical, neuropathic, or injury-related causes were excluded.
- In a study of 33 patients with chronic back pain and/or multiple somatic pain symptoms, researchers reported that vitamin D therapy led to a resolution of all symptoms in two-thirds of the subjects.<sup>65</sup> Partial pain relief was achieved in 18% of patients and 16% were not helped.
- A case-series report noted that aches, pains, and extreme muscle weakness were resolved by vitamin D supplementation in five patients who had been confined to wheelchairs.<sup>77</sup> Four of the patients reportedly became fully mobile upon normalization of their 25(OH)D concentrations.
- An earlier case report of five patients by Gloth and colleagues<sup>79</sup> noted that vitamin D supplementation produced significant and rapid improvements of hyperesthesias (nonspecific oversensitivity to physical stimuli) that had been unresponsive to analgesic therapy.

Taken as a whole, the research evidence supports vitamin D

supplementation as a potentially important therapy for helping to ameliorate chronic, nonspecific musculoskeletal pain, and fatigue syndromes. In fair balance, however, it must be noted that randomized controlled trials (RCTs) have not been conducted to assess vitamin D therapy for pain. Such investigations would be helpful and could be important for defining which disorders are relieved most by vitamin D and the dosing regimens that are optimal for particular groups of patients. Furthermore, it is evident that not all persons with inadequate 25(OH)D levels develop musculoskeletal maladies and the specific predisposing factors affecting some persons but not others are unknown.

**Beyond Musculoskeletal Pain.** Since vitamin D receptors have been identified in skeletal muscle, myopathy—presenting as decreased muscle strength, usually in lower limbs, or merely as fatigue—is also part of the D-ficiency/osteomalacic symptom complex and may appear prior to any pain.<sup>51,76,80-83</sup> Vitamin D deficiency also has correlated with increased body sway<sup>84</sup> and an increased risk of falls that often result in painful fractures.<sup>85-89</sup> Various investigations have demonstrated benefits of vitamin D supplementation for reversing myopathy and increasing physical endurance.<sup>87,90</sup>

Clinical researchers have also found that the role of vitamin D extends beyond bone and muscle involvement in chronic pain syndromes. For example, vitamin D receptors have been identified in various brain structures, the spinal cord, and sensory ganglia.<sup>91</sup> Accordingly, results of some studies suggest non-muscu-

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musculoskeletal benefits of vitamin D supplementation, as follows:

- **Neuropathy.** A recently reported prospective study of 51 patients with type 2 diabetes and associated chronic, painful neuropathy found that conservative vitamin D supplementation (about 2000 IU/day) for 3 months resulted in nearly a 50% decrease in pain scores.<sup>51</sup>
- **Inflammation.** Clinical research indicates that vitamin D supplementation modulates or decreases pro-inflammatory cytokines (eg, C-reactive protein, interleukin 6 and 12, and tumor necrosis factor-alpha) while increasing anti-inflammatory cytokines (eg, interleukin-10).<sup>90,92-94</sup> Investigators have further suggested that vitamin D may help to moderate painful chronic inflammatory autoimmune conditions that are influenced by excessive cytokine activity, such as inflammatory bowel disease.<sup>16</sup>
- **Migraine Headaches.** There have been case reports of vitamin D combined with calcium supplementation to alleviate migraine headaches in postmenopausal<sup>95</sup> and premenopausal<sup>96</sup> women. Reductions in both frequency and intensity of migraines were achieved within 2 months.
- **Affective (Mood) Disturbances.** In patients with fibromyalgia syndrome, pain, depression, and anxiety were found to be strongly associated with insufficient vitamin D.<sup>61</sup> Furthermore, large studies examining older persons (aged  $\geq 65$  years) found significant associations between 25(OH)D deficiencies and depressive disorders.<sup>55,62</sup> In one of the studies, inadequate 25(OH)D and depression also were highly correlated with chronic lower-back pain specifically in female patients.<sup>62</sup>

There is some evidence that seasonal affective disorder (SAD) is influenced by diminished stores of vitamin D, which would be expected to occur most commonly during winter months. In a study of supplemental vitamin D versus broad-spectrum light therapy (phototherapy), which is often recommended for patients with SAD, vitamin D produced significant improvements in all outcome measures of depression, whereas the phototherapy group showed no significant changes.<sup>97</sup>

In a randomized, placebo-controlled study that included patients with clinical depression, those administered supplemental vitamin D had significantly enhanced mood and a reduction in negative-affect symptoms.<sup>98</sup> In similar investigations, more adequate vitamin D concentrations were associated with better physical, social, and mental functioning as measured by quality-of-life assessment instruments,<sup>99</sup> and improved scores on an assessment of well-being.<sup>100</sup>

In sum, while further research is needed, the potential benefits of vitamin D supplementation may be expanded from its role in supporting bone and muscle health to that of a complex hormonal system benefiting other conditions often associated with chronic pain.<sup>51</sup>

### Assessing Vitamin D Status

**Clinical Indicators.** From a clinical perspective, a number of factors may suggest that chronic musculoskeletal pain and related problems may be due to inadequate vitamin D intake. Researchers have stressed that the "gold standard" for a presumptive diagnosis of inadequate vitamin D is a review of patient history, lifestyle, and dietary habits that might pose risks for deficiency.<sup>101</sup> Along with this, indicators of defects in bone metabolism may include chronic muscle, bone, or joint pain, as

well as persistent muscle weakness, fatigue, and possibly difficulty walking.<sup>20,101,102</sup> Radiological changes potentially associated with osteomalacia are seen only in advanced stages.<sup>20,103</sup>

Signs/symptoms of calcium deficiency (hypocalcemia) due to vitamin D deficiencies relate to neuromuscular irritability. Patients sometimes complain of paresthesias (numbness, tingling, prickling, or burning) in their lips, tongue, fingertips, and/or toes, along with fatigue and anxiety. Muscles can be painfully aching, progressing to cramps or spasms.<sup>104-107</sup> Lethargy, poor appetite, and mental confusion may be part of the syndrome.<sup>104</sup>

The diverse signs and symptoms may be erroneously attributed to other causes. Holick<sup>14,44</sup> and others<sup>21,76</sup> caution that osteomalacia due to vitamin D deficiency can be misdiagnosed as chronic fatigue syndrome, arthritis or rheumatic disease, depression, or fibromyalgia.

**Biochemical Markers.** Laboratory assessments usually pertain to the measurement of biomarkers that could denote osteomalacic processes, including:<sup>108</sup>

- Serum 25(OH)D, total serum calcium (Ca), and phosphate (PO) are decreased to below normal ranges;
- Parathyroid hormone (PTH) and total alkaline phosphatase (ALP) are elevated.

It must be understood that there are limitations to the various laboratory assays in terms of their accuracy and/or helpfulness in making or confirming a diagnosis. Assessing ALP (a surrogate marker for bone turnover), PO, or Ca are not reliable predictors of inadequate 25(OH)D concentrations or underlying osteomalacic processes.<sup>28,101</sup> Up to 20% of patients with 25(OH)D deficiency and elevated PTH may have normal Ca, PO, and ALP levels.<sup>74,108</sup>

It is generally believed that elevations of PTH may be a suitable biomarker of histological osteomalacia since, at the least, secondary hyperparathyroidism seeks to correct calcium deficits via bone resorption. A diagnosis of inadequate vitamin D with osteomalacic involvement to some extent could be presumed if PTH is elevated in association with low calcium levels, which also would serve to exclude patients with primary hyperparathyroidism due to other causes.<sup>108</sup>

Various assays for determining 25(OH)D concentrations in serum have relatively recently become available from commercial laboratories.<sup>39,109</sup> Circulating 25(OH)D reflects both D<sub>2</sub> plus D<sub>3</sub> intake, but not 1,25(OH)<sub>2</sub>D concentrations. Measuring 1,25(OH)<sub>2</sub>D is not recommended because it can be a poor or misleading indicator of overall vitamin D status.<sup>14,28,107</sup>

There are some concerns about the validity and utility of 25(OH)D assays, which also can be relatively expensive.<sup>108</sup> Several testing methods are available and there can be significantly large differences in results from one laboratory to the next, as well as stark variations across types of assays.<sup>21,39,46,110</sup> Error rates can be high and the reference ranges reported may be confusing or unhelpful. These concerns should not completely deter testing for biomarkers related to vitamin D deficiency. Rather, informed healthcare providers need to consider test limitations and their objectives in using such measures, keeping in mind that patient-centered care focuses on individual needs rather than relying solely on laboratory values for guidance.

While severe deficiencies in 25(OH)D and unambiguous clinical signs of osteomalacia relate most clearly to musculoskeletal pain, less severe vitamin D inadequacies are often unrecognized

but nevertheless contributing sources of nociception in patients with chronic pain.<sup>60</sup> This has been proposed as a "subclinical" effect of vitamin D inadequacy, since subjective musculoskeletal pain or weakness develops prior to the emergence of more objective clinical indicators.<sup>54,76,111</sup>

Lotfi et al<sup>54</sup> proposed that in some persons even slight deficits of 25(OH)D can produce secondary hyperparathyroidism to a degree that manifests as musculoskeletal pain and/or weakness. Although vitamin D inadequacy may not be extreme enough to produce clinically diagnosable osteomalacia, it can still cause enough PTH elevation to generate increased bone turnover and loss, increased risk of microfractures, and pain or myalgia.

As Holick<sup>112</sup> has suggested, either the level of 25(OH)D is adequate for the individual patient, or it is not. If it is inadequate, subclinical osteomalacia along with multiple forms of chronic pain and myopathy may emerge and the extent of the 25(OH)D deficit in nanograms-per-milliliter may not matter – as long as the shortfall is corrected to the extent necessary.

### Vitamin D Therapy

**Vitamin D Intake in Healthy Persons.** In 1997, the U.S. Institute of Medicine determined that there was insufficient data to specify a Recommended Daily Allowance (RDA) for vitamin D. Instead, the organization developed very conservative Adequate Intake (AI) values of 200 IU to 600 IU per day of vitamin D, based on an assumption that as people age they would need extra vitamin D supplementation<sup>16,113</sup> (see Table 4).

According to the most recent 2005 Dietary Guidelines for Americans from the U.S. government,<sup>114</sup> and expert recommendations,<sup>14,18,24,42,68</sup> healthy children and adults of any age should consume no less than 1000 IU/day of vitamin D<sub>3</sub> to reach and maintain minimum serum 25(OH)D concentrations of at least 30 to 32 ng/mL. However, this may be inadequate.

Clinical research trials have demonstrated that 1000 IU/day of vitamin D<sub>3</sub> produces only modest increases in 25(OH)D that can be inconsequential for achieving and maintaining optimal concentrations of 30 ng/mL or more in some persons.<sup>36,39</sup> Vieth and colleagues<sup>25</sup> demonstrated that 4000 IU/day D<sub>3</sub> could be safe and more effective in producing desired outcomes. Several general principles emerge from the accumulated research to date<sup>19,21,23,25,26,39,46,100,115,116,117,118</sup>:

- Concentrations of 25(OH)D are not increased in direct proportion to the amount of supplementation increase. For example, tripling the D<sub>3</sub> dose—such as going from 600 IU/day to 1800 IU/day—does not increase the concentration of 25(OH)D by threefold.
- Any increase in 25(OH)D is also dependent on the concentration of this metabolite at the start of treatment. At equivalent vitamin D doses, patients with more severe baseline inadequacies will have larger, more rapid increases in 25(OH)D concentrations.
- What might be considered large doses of vitamin D<sub>3</sub> by some practitioners do not produce proportionately large increases in 25(OH)D concentrations, depending on the amount of dose and duration of administration. For example, a single 50,000 IU dose of D<sub>3</sub> may produce a significantly smaller increase in 25(OH)D than 2000 IU given daily over time, and the increases from either of these could be modest.
- However, it must be noted that continuous megadoses of

**TABLE 4. Recommended Vitamin D Intake in Healthy Persons**

#### 1997 — Institute of Medicine

200 IU/d – children and adults to age 50 years

400 IU/d – men and women aged 50-70 years

600 IU/d – those older than 70 years

#### 2005 — Dietary Guidelines for Americans

1000 IU/d – children and adults

*Note: In some of the literature International Units are expressed as micrograms. The conversion formula is 1 IU = 0.025 mcg or 1 mcg = 40 IU.*

vitamin D (eg, >50,000 IU) could produce robust, possibly toxic, increases in 25(OH)D concentrations over time.

In everyday practice, exceptionally large daily doses of vitamin D would rarely be recommended to patients. Researchers have noted that raising 25(OH)D from 20 ng/mL to the more optimal 30+ ng/mL range in otherwise healthy patients would require ongoing daily supplementation of only about 1300 IU<sup>39</sup> to 1700 IU<sup>119</sup> of vitamin D<sub>3</sub>. However, it should be noted that the daily adequate intake of vitamin D for maintaining health is, in most cases, lower than the amount needed as therapy for patients with chronic pain.

**Putting "D" Into Clinical Practice.** In patients with pain, researchers have examined daily vitamin D supplementation ranging from 600 IU to 50,000 IU,<sup>39,27,116</sup> as well as much larger amounts. Because vitamin D has a long half-life and can take several months to reach steady-state levels, one approach to supplementation has been to administer oral or intramuscular megadoses on an infrequent basis. For example, single doses of 300,000 IU D<sub>2</sub> have been used in the expectation that they might suffice for many months.<sup>120</sup> Hathcock et al<sup>121</sup> and others<sup>122</sup> noted that amounts of vitamin D up to 100,000 IU would not be toxic if restricted to one administration every four months, or daily for a single period of four days.

In one study of patients with chronic back pain, subjects were treated for 3 months with either 5000 IU/day or 10,000 IU/day of vitamin D<sub>3</sub> (heavier patients >50 kg received the larger dose).<sup>74</sup> There were no adverse effects reported, and pain symptoms were relieved in 95% of the patients.

Despite the reported successes of larger-dose vitamin D supplementation, many healthcare providers may be uncomfortable with recommending such doses for their patients. And, unless pathways of vitamin D metabolism are impeded (eg, due to liver or renal disease or an interacting drug), such high doses could be unnecessary, at least as initial therapy.

In patients with chronic pain, Glöth and colleagues<sup>79</sup> observed that symptom relief often can be achieved with relatively modest increases in 25(OH)D and 1,25(OH)<sub>2</sub>D concentrations. This is possibly because the vitamin D metabolites are being rapidly consumed at tissue sites and also becoming depleted in storage depots, so they cannot accumulate in needed quantities and so any added amount is beneficial. These researchers also suggested that pain syndromes may affect vitamin D receptors, causing them to become altered in function or increased in

**TABLE 5. Vitamin D Supplementation for Chronic Pain**  
**PROPOSED CONSERVATIVE DOSING PROTOCOL**

- In patients with chronic, nonspecific musculoskeletal pain and fatigue syndromes, it usually can be expected that vitamin D intake from combined sources is inadequate and concentrations of serum 25(OH)D are insufficient or deficient.
- All patients should take a multivitamin to ensure at least minimal daily values of essential nutrients, including calcium and 400 IU to 800 IU of vitamin D.
- Recommend a daily 2000 IU vitamin D<sub>3</sub> supplement, bringing total supplement intake to 2400 to 2800 IU/day (incl. from multivitamin). *Extra calcium may not be necessary unless diet is insufficient and/or there are concerns about osteoporosis (e.g., in postmenopausal women or the elderly).*
- Monitor patient compliance and results for up to 3 months. Other therapies for pain already in progress do not necessarily need to be discontinued.
- If results are still lacking after 3 months, or persistent 25(OH)D deficiency or osteomalacia are verified, consider a brief course of prescribed high-dose vitamin D<sub>3</sub> with, or without, added calcium as appropriate, followed by ongoing supplementation as maintenance.

quantity (upregulated) and, thereby, physiologically requiring extra amounts of the 1,25(OH)<sub>2</sub>D hormone.

A proposed conservative dosing protocol is outlined in Table 5. This involves adding a daily supplement of 2000 IU of vitamin D<sub>3</sub> to a daily multivitamin regimen, bringing the total daily vitamin D<sub>3</sub> intake to 2400 IU to 2800 IU. This is a convenient supplement dose, since inexpensive 1000 IU D<sub>3</sub> tablets or capsules are readily available and some outlets are now stocking 2000 IU/dose tablets. The daily cost of the supplement is typically US \$ 0.10 or less.

Vitamin D<sub>3</sub> products are preferred since they cost no more than D<sub>2</sub> and most research indicates that D<sub>3</sub> is more effective.<sup>19,115,118,123</sup> Vieth<sup>19</sup> has strongly urged that "all use of vitamin D for nutritional and clinical purposes should specify cholecalciferol, vitamin D<sub>3</sub>."

Vitamin D therapy would be contraindicated in patients with pre-existing excessive levels of calcium (hypercalcemia or hypercalcuria), and special caution might be advised in those prone to forming kidney stones or other calcifications.<sup>12,13,121</sup> Besides renal or hepatic dysfunction, intestinal malabsorption due to age, irritable bowel syndrome, Crohn's disease, or celiac disease also may limit response to vitamin D therapy.<sup>20,51,124</sup>

Current therapies for chronic pain, started prior to initiating vitamin D<sub>3</sub> therapy, do not need to be discontinued; however, it must be accepted that it could be difficult to attribute improvements to one therapy over another. This would be confounded further if new therapies for pain are started during vitamin D<sub>3</sub> supplementation and before enough time has elapsed to evaluate its effectiveness.

If there are no improvements after several months of the proposed conservative vitamin D<sub>3</sub> dosing protocol, more time

rather than increased doses may be necessary for vitamin D<sub>3</sub> therapy to effectively raise 25(OH)D concentrations, lower PTH levels, and/or saturate vitamin D receptors with the 1,25(OH)<sub>2</sub>D metabolite. In some cases, the patient might benefit from a course of high-dose vitamin D<sub>3</sub> supplementation followed by more conservative doses for ongoing maintenance.

There is always the possibility that a particular chronic pain condition cannot be alleviated by vitamin D<sub>3</sub> supplementation alone. For example, there may be a previously undetected anatomic defect, disease, or other pathology that would benefit from another type of therapeutic intervention in addition to vitamin D therapy.

At the doses recommended in Table 5, excessive accumulation of 25(OH)D or toxicity over time would not be expected and this supplementation might be continued indefinitely. It must be noted, however, that clinical investigations have largely observed subjects during months rather than years of ongoing supplementation, and long-term effects of vitamin D therapy on functions at the cellular level are still under investigation.<sup>50</sup> If there are concerns, after a year or longer the supplement might be continued at a reduced dose; it can always be increased again if pain symptoms return.

**How Long Until Improvement?** In anecdotal case reports, vitamin D supplementation provided complete relief within a week in some patients having widespread, nonspecific pain that was unresponsive to analgesics, including opioids.<sup>79</sup> In other cases, pain and muscle weakness reportedly resolved "within weeks" of beginning supplementation.<sup>73</sup>

In one study, pain relief from neuralgia was achieved at 3 months after beginning vitamin D supplementation.<sup>91</sup> In many cases, bone-related pain may require approximately 3 months of adequate vitamin D supplementation for its relief,<sup>47,65</sup> while muscle pain may need 6 months, and muscle weakness or fatigue may require even longer to resolve.<sup>47,65,76</sup>

Overall, Vasquez and colleagues<sup>77</sup> recommended that at least 5 to 9 months should be allowed for fully assessing either the benefits or ineffectiveness of vitamin D supplementation. Likewise, Vieth et al<sup>100</sup> suggested that the greatest physiologic responses may occur after 6 months of supplementation. Therefore, the timeframe recommended in Table 5 – monitoring results for up to 3 months – should be considered a minimum period of watchful waiting.

Complete pain relief would be easy for patients to detect, but in most cases this could be an unrealistic expectation. The evidence is suggestive of a potential range of improvements with vitamin D therapy, some more obvious than others. For example, instead of complete pain relief, patients may experience partial relief, reduced intensity or frequency of pain, less soreness or stiffness in muscles, increased stamina or strength, reductions in NSAID or opioid use, and/or improvements in mood or overall quality of life. These results are less spectacular than complete pain relief, but are still important and worthwhile outcomes to monitor.

#### Vitamin D Safety Considerations

The highly favorable safety profile of vitamin D is evidenced by its lack of significant adverse effects, even at relatively high doses, and the absence of harmful interactions with other drugs. While vitamin D is potentially toxic, reports of associated

overdoses and deaths have been relatively rare.

**Tolerance & Toxicity.** Excessive intake and accumulation of vitamin D is sometimes referred to as "hypervitaminosis D," however this is poorly defined. Because a primary role of vitamin D is facilitating absorption of calcium from the intestine, the main signs/symptoms of vitamin D toxicity result from excessive serum calcium, or hypercalcemia (see Table 6).

The rather diverse signs/symptoms of hypercalcemia in patients with pain may be difficult to attribute to vitamin D intoxication, since they might mimic those of opioid side effects, neuropathy, or other conditions. Paradoxically, some symptoms match those of hypocalcemia. In some cases, patients with serum 25(OH)D at toxic levels can be clinically asymptomatic.<sup>126</sup>

Since full exposure to sunlight can provide the vitamin D<sub>3</sub> equivalent of up to 20,000 IU/day, the human body can obviously tolerate and safely manage relatively large daily doses. Toxicity has not been reported from repetitive daily exposure to sunlight.<sup>25</sup>

Still, supplementation via commercially manufactured vitamin D products would circumvent natural mechanisms in human skin that prevent excess D<sub>3</sub> production and accumulation resulting from sun exposure. A Tolerable Upper Intake Level, or UL, for oral vitamin D<sub>3</sub> supplementation—which is the long-term dose expected to pose no risk of observed adverse effects—currently is defined in the United States as 1000 IU/day in infants up to 12 months of age and 2000 IU/day for all other ages.<sup>16</sup> However, many experts assert that the 2000 IU/day UL is far too low.<sup>19,55-57,59,62</sup> An extensive review by Hathcock et al,<sup>121</sup> applying risk-assessment techniques, concluded that the UL for vitamin D consumption by adults actually could be 10,000 IU/day of D<sub>3</sub>, without risks of hypercalcemia.

However, the duration of high vitamin D intake may be the more critical factor. Taking 10,000 IU of D<sub>3</sub> daily for six months has been implicated as toxic,<sup>22,128</sup> whereas Holick [2007]<sup>14</sup> noted that this daily amount in adults can be well tolerated for five months. And, this 10,000 IU/day dose was used successfully and safely during three months in one study for relieving back pain.<sup>74</sup>

Vieth et al<sup>100</sup> demonstrated that 4000 IU of D<sub>3</sub> per day was well tolerated during 15 months of therapy. Concentrations of 25(OH)D were increased to more optimal levels and parathyroid hormone was reduced, while calcium levels remained normal.

Some researchers have proposed that long-term daily consumption of 40,000 IU of vitamin D would be needed to cause hypercalcemia.<sup>18,19</sup> The US Office of Dietary Supplements<sup>153</sup> notes that hypercalcemia can result from 50,000 IU/day or more taken for an extended period of time.

There have not been any reports in the literature of a single, one-time excessive dose of vitamin D (D<sub>2</sub> or D<sub>3</sub>) being toxic or fatal in humans. However, a number of incident reports of vitamin D toxicity involving very high doses, and including 6 fatalities, have appeared in the literature. In the incident reports, encompassing 77 cases of toxicity, amounts of vitamin D taken for periods ranging from days to years included daily doses from 160,000 IU up to an astounding 2.6 million IU.<sup>125,126,128,129,130,131,154,155</sup> The relatively few fatalities resulted from secondary causes during treatment for hypercalcemia. A common feature of all incidents was that victims were not knowingly or intentionally taking excessive amounts of vitamin D, and no one was taking vitamin D under practitioner supervision. In almost all cases, toxic overdoses could have been

**TABLE 6. Signs/Symptoms of D Toxicity (Hypercalcemia)**

• abdominal pain	• muscle weakness
• achy muscles/joints	• nausea
• anorexia	• nervousness
• azotemia	• polyuria
• calcifications	• proteinuria
• constipation	• pruritus
• disorientation/confusion	• excessive thirst
• fatigue/lethargy	• urinary casts
• fever/chills	• vomiting
• GI upset	• weight loss
• hypertension	

References: Barrueto et al<sup>125</sup>; Blank et al<sup>126</sup>; Calcitriol<sup>127</sup>; Carroll and Schade<sup>128</sup>; Ergocalciferol<sup>129</sup>; Johnson<sup>130</sup>; Klontz and Acheson<sup>131</sup>; Koutkia et al<sup>132</sup>; Todd et al<sup>133</sup>; Vieth et al<sup>134</sup>

avoided with better quality control in product manufacture and/or education of patients in the proper use of supplements.

As another measure of safety, consolidated data for 2006 were examined (the most recently reported year) from 61 poison control centers serving 300 million persons in the United States.<sup>156</sup> There were only 516 mentions of incidents involving vitamin D which, by comparison, were roughly one-fourth the number for vitamin C and merely 0.8% of all incidents involving vitamin products. Only 13% of all vitamin D cases required treatment in a healthcare facility, although adverse signs/symptoms were absent or minimal in almost all patients (92%). Only 5 of the victims had more pronounced signs/symptoms of vitamin D toxicity, but these were not life threatening and there were no serious adverse events reported.

#### Vitamin D-Drug Interactions

There have been relatively few mentions in the literature of vitamin D supplements interacting with other agents or medications, and these are summarized in Table 7. In most cases, the potency of vitamin D is reduced by the other drug and the vitamin dose can be increased to accommodate this. Conversely, very high doses of vitamin D should be avoided due to possible risks of hypercalcemia when taken with digitalis/digoxin or certain diuretics.

Additionally, St. John's wort,<sup>27</sup> excessive alcohol,<sup>153</sup> and tobacco smoking<sup>158</sup> have been reported to potentially reduce the effects of vitamin D. Mineral oil and stimulant laxatives decrease dietary calcium absorption and can influence hypocalcemia.<sup>155</sup> Gastric bypass and other gastric or intestinal resection procedures have been associated with vitamin D insufficiency.<sup>60,106</sup>

It should be noted that not all patients would be affected by these interactions or effects, and vitamin D has not been noted to interfere harmfully with the actions of any medications. Therefore, none of the reported interactions or effects has been indicated in the literature as a contraindication for vitamin D supplementation.

#### Conclusions

Extensive clinical evidence and expert commentary supports the opinion that recommending adequate vitamin D intake for helping patients with chronic musculoskeletal pain and fatigue syndromes should be more widely recognized and acted upon.

**TABLE 7. Drugs Potentially Interacting with Vitamin D****Potency of vitamin D is reduced. The vitamin dose can be increased to accommodate this.**

- antacids (aluminum- or magnesium-containing)
- anticonvulsants (eg, carbamazepine)
- antirejection meds (after organ transplant)
- antiretrovirals (HIV/AIDS therapies)
- barbiturates (eg, phenobarbital, phenytoin)
- cholestyramine
- colestipol
- corticosteroids
- glucocorticoids
- hydroxychloroquine
- rifampin

**Risk of hypercalcemia when taken concurrently. Very high doses of vitamin D should be avoided.**

- digitals/digoxin
- thiazide diuretics

References: Bringham et al<sup>17</sup>; Calcitriol<sup>12</sup>; Ergocalciferol<sup>13</sup>; Holick<sup>14</sup>; Hollis et al<sup>15</sup>; Marcus<sup>16</sup>; Mascarenhas and Mobarhan<sup>17</sup>; ODS<sup>18</sup>; Turner et al<sup>19</sup>

In many cases, contributing factors are nonspecific or undetermined. Even in cases where a specific etiology has been diagnosed, the potential for vitamin D deficit as a factor contributing to and/or prolonging the pain condition should not be ruled out.

Further clinical research studies would be helpful. Vitamin D is not proposed as a "cure" for all chronic pain conditions or in all patients. Optimal clinical outcomes of vitamin D therapy might be best attained via multicomponent treatment plans addressing many facets of health and pain relief. Therefore, vitamin D is not suggested as a replacement for any other approaches to pain management.

To start, a conservative total daily supplementation of 2400 IU to 2800 IU of vitamin D<sub>3</sub> is proposed as potentially benefiting patients. Along with that, some patience is advised regarding expectations for improvements; it may require up to 9 months before maximum effects are realized. In some cases, other factors or undetected conditions may be contributing to a chronic pain condition that vitamin D supplementation alone cannot ameliorate.

In sum, for patients with chronic musculoskeletal pain and related symptoms, supplemental vitamin D has a highly favorable benefit to cost ratio, with minimal, if any, risks. In all likelihood, it would do no harm and probably could do much good. □

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