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Vitamin D – A Neglected 'Analgesic' for Chronic Musculoskeletal Pain

An Evidence-Based Review & Clinical Practice Guidance

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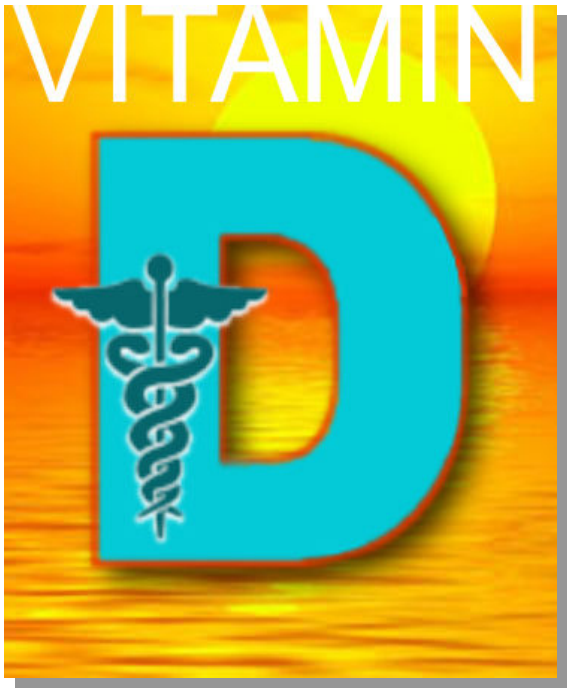


Helping patients to overcome their chronic musculoskeletal aches and pains may be as simple, economical, and well tolerated as a daily supplement of vitamin D.

Yet, this treatment is unknown or overlooked by many health-care providers.

1. Introduction: A 'D-Lightful' Therapeutic Hormone

This report focuses on evidence and commentary from the peer-reviewed medical literature describing the functions of vitamin D, the prevalence and consequences of inadequate vitamin D intake, and the research supporting its benefits for alleviating chronic musculoskeletal pain and fatigue syndromes in outpatients. Guidance for healthcare professionals in recommending vitamin D therapy for these patients is provided. See the ***Side Box*** below for key summary points.

There are extensive reports of pain worldwide and much of it is chronic, lasting 3 or more months, and primarily involves muscles, bones, and joints. In the United States, more than half of all adults participating in surveys have reported long-term persistent or intermittent pain, with the lower and upper back, neck, shoulders, hips, and knees mentioned most frequently [APF 2007; NPF 2008; Watkins et al. 2008]. For lower-back pain alone, an annual incidence of 50% and a lifetime prevalence of up to 80% have been reported [Nachemson et al. 2000]. In more than 8 out of 10 cases, the causes are nonspecific, without evidence of injury, disease, or neurological or anatomical defect [Deyo 2002; Deyo and Weinstein 2001]. More than a quarter (28%) of patients with chronic pain rate the effectiveness of medical treatments as poor, and most (77%) believe that new options are needed to treat their pain [APF 2007; NPF 2008].

At the same time, it appears that soothing the daily musculoskeletal aches and pains plaguing many patients may be as simple, well tolerated, and economical as taking a daily supplement of vitamin D. Experts have recommended that vitamin D inadequacy should be considered in the differential diagnosis of all patients with bone or joint pain, myalgia, fibromyalgia, or chronic fatigue syndrome [Shinchuk and Holick 2007]. However, this seems to be unknown or overlooked by many healthcare providers.

Research on vitamin D is still an emerging field, and there are divergent opinions among experts regarding many aspects of vitamin D pharmacology, function, and adequate intake needed for good health. While further research is needed, the clinical evidence to date recommending vitamin D supplementation for musculoskeletal pain and associated symptoms seems convincing.

In 22 clinical investigations reviewed for this report – which included a total of 3670 patients with musculoskeletal pain – significant vitamin D inadequacies were found in 48% to 100% of the subjects. When supplementation was provided for improving vitamin D status, pain and/or muscle weakness were resolved or at least subsided in most cases, and there were associated improvements in physical functioning.

Vitamin D is known as the "sunshine vitamin" because it is naturally produced by skin exposed to ultraviolet B, or UVB, rays in sunlight [Hollis 2005]. Current thinking is

Vitamin D 'Analgesia' – Summary Points

- Chronic musculoskeletal pain and fatigue syndromes are common and difficult-to-treat clinical challenges.
- Conclusive scientific evidence indicates that adequate levels of vitamin D are essential for musculoskeletal health.
- Vitamin D is a complex nutrient that functions as a hormone to benefit numerous body tissues.
- A majority of all patients, and particularly those with pain, have inadequate intake of vitamin D.
- While further research is needed, current evidence demonstrates that supplemental vitamin D can help to resolve or alleviate chronic pain syndromes in many patients who have been unresponsive to other therapies.
- A 2400 IU to 2800 IU per day supplement of vitamin D_3 is proposed in this report as being helpful for patients with chronic bone and joint pains, and related muscle pain or weakness.
- Vitamin D therapy is easy for patients to self-administer, well tolerated, and very economical. Other therapies need not be discontinued during a trial of vitamin D "analgesia."
- To date, the benefits of vitamin D therapy have been unknown or largely overlooked by the pain treatment field.

that it goes beyond other vitamins in its multitude of beneficial effects throughout the body, and its major active metabolite actually is a hormone or, as one expert on the subject called it, "an underappreciated D-lightful hormone" [Holick 2002b].

Unfortunately, most people in modern society do not have sufficient amounts of vitamin D circulating in their bodies. By all accounts current guidelines for supposedly adequate daily vitamin D intake are outdated, and there is an unfounded fear of "overdoing it" when it comes to vitamin D supplementation that is unsupported by the research data [Vieth et al. 2007]. Supplemental doses of vitamin D that could be appropriate for helping patients with pain are a fraction of what a person can produce endogenously during only 15 minutes of exposure to summertime sunshine.

Benefits of Vitamin D may require time to emerge, and pain relief can range from partial to complete.
It is not a panacea, or a replacement for all other pain treatment modalities.

Vitamin D has been thoroughly investigated, with more than 11,000 citations in MEDLINE® alone naming the agent in their titles; about 55% of those address the effects of vitamin D deficiency, including the relationship to pain syndromes. This is impressive, considering that, as a generic and inexpensive agent without "blockbuster drug" potential, vitamin D would not receive the level of research funding devoted to proprietary pharmaceuticals.

Therefore, it is curious that this treatment has been neglected by the pain management field. Recent and otherwise comprehensive texts and reference books on pain treatment inexplicably omit any mention of vitamin D therapy [*eg,* Berry et al. 2006; McCleane and Smith 2007; Pujol et al. 2007]. Throughout pain management literature, analgesic agents, various adjunctive pharmaceuticals, and interventional therapies are emphasized while nutritional supplements are acknowledged in passing, if at all [ACPA 2007].

It must be emphasized, however, that vitamin D is not a pharmaceutical analgesic in the sense of fostering relatively immediate pain relief, and expectations along those lines would be unrealistic. Because its actions address underlying processes, vitamin D supplementation 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.

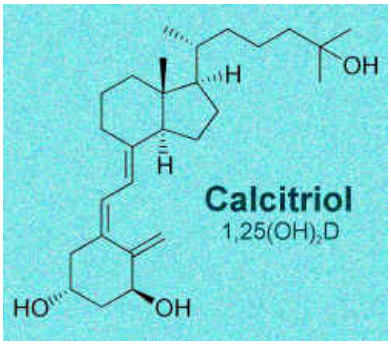
This paper is intended to offer practical clinical guidance regarding vitamin D for physicians, nurses, pharmacists, and other healthcare professionals. All facts and data are from the cited sources and many of the documents can be accessed via the Internet (*see the References section for links*), so interested readers can pursue more detailed information on their own.

The following sections of this report address a number of questions that are essential for an understanding of why, when, how, and in whom to use vitamin D supplementation therapy:

- What is vitamin D and how does it work?
- What is the scientific rationale for vitamin D supplementation in patients with pain?
- What is the evidence for its effectiveness?
- Which patients are candidates for this therapy?
- How much vitamin D supplementation should be recommended?
- What are tolerability and safety considerations?
- What sort of results can be expected? How soon?

The essential conclusion of this report is that a trial of vitamin D supplementation in patients with chronic musculoskeletal pain would be a well tolerated and economical adjunct to any other therapeutic approach. In the final analysis, *it would do no harm and it would most likely do much good at minimal cost.*

2. Vitamin D Pharmacology

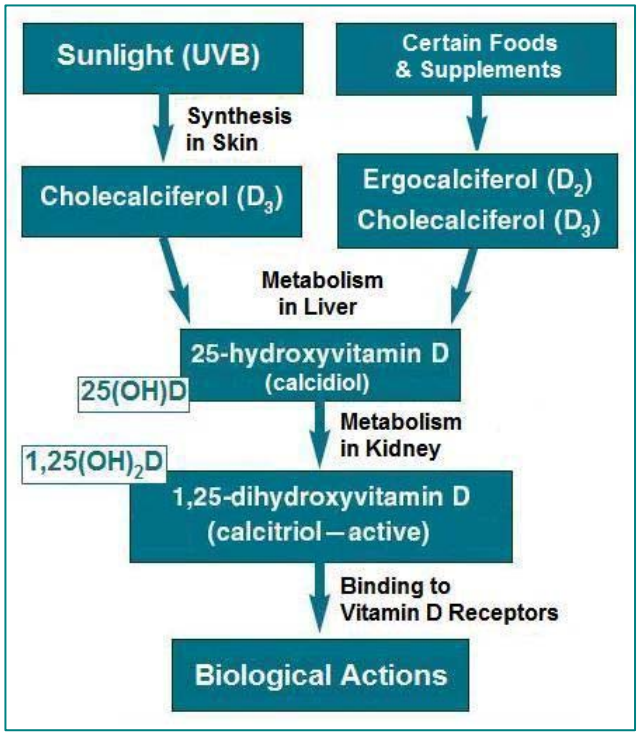


Adequate vitamin D is essential for healthy bones and teeth by maintaining normal calcium and phosphorus levels, and its deficiency is most well known as a cause of rickets in young children. However, the active metabolite of this micronutrient does far more than build bones; in fact, it is active throughout the human body. In adults, numerous clinical investigations have linked deficiencies of "D" to chronic aches and pains, muscle fatigue or weakness, and other disorders [Holick 2003b; ODS 2008; Plotnikoff and Quigley 2003; Reginster 2005; Tavera-Mendoza and White 2007; Vieth 1999]. In this section, a discussion of vitamin D pharmacokinetics – synthesis, metabolism, and disposition – sets the stage for a description of its reported role in helping to alleviate chronic pain syndromes.

2a. Synthesis & Metabolism

Vitamin D comprises a group of fat-soluble micronutrients with 2 major forms: D_2 (*ergocalciferol*) and D_3 (*cholecalciferol*). Vitamin D_3 is synthesized in skin via exposure of endogenous 7-dehydrocholesterol to direct ultraviolet B (*UVB*) radiation in sunlight and it also is obtained to a small extent in the diet. In many countries some foods are fortified with vitamin D_3, and it is the form used in most nutritional supplements [Holick 2007; Johnson 2007]. Vitamin D_2 is found in very few foods and in some dietary supplements [Holick 2007]. Also see s*ection 4* below and ***Appendix 1*** – "Vitamin D_2 & D_3 Sources."

Both D_2 and D_3 are absorbed in the small intestine, and neither has any biological activity in the body. They then go through a 2-stage process of metabolism. See ***Chart*** at right [*Modified from* Holick 2005; Lau and How 2007].



The somewhat similar names for vitamin D metabolites can be confusing. In this report, the abbreviations 25(OH)D and 1,25(OH)$_2$D are used.

1. First, D_2 and D_3 are metabolized via hydroxylation in the liver – which adds 2/3 of a water molecule, or OH – to form 25-hydroxyvitamin D, abbreviated as **25(OH)D** (also called ***calcidiol*** or, rarely, *calcifediol*). It has minimal biological activity but is stored in many tissues, particularly in adipose tissue, and is the major circulating form of vitamin D in the blood [Holick 2005, 2007; Lips 2001; Reginster 2005; Tavera-Mendoza and White 2007].

2. The 25(OH)D metabolite is then converted primarily in the kidneys via further hydroxylation to 1,25-dihydroxyvitamin D, which is abbreviated as **1,25(OH)$_2$D** (also called ***calcitriol***). It is the most important and biologically active vitamin D metabolite. To a lesser extent, many other tissues throughout the body also can transform 25(OH)D to 1,25(OH)$_2$D locally.

The ultimate role of vitamin D, via its active 1,25(OH)$_2$D metabolite, is to facilitate the absorption of calcium from the intestine and to help maintain normal concentrations of this vital agent. Equally important, 1,25(OH)$_2$D sustains a wide range of metabolic and physiologic functions throughout the body [Holick 2002b].

Vitamin D actually was misclassified as a vitamin; today, it is more appropriately considered a prohormone since the active $1,25(OH)_2D$ metabolite has its own receptors found in practically every human tissue. These vitamin D receptors, or VDRs, may affect the function of up to 1000 different genes [Holick and Chen 2008; Marshall 2008; Reginster 2005; Tavera-Mendoza and White 2007; Walters 1992], helping to control cell growth or differentiation. The VDRs themselves can differ in their genetic makeup (*polymorphism*) and activity, which may account for varying individual responses to vitamin D therapy [Kawaguchi et al. 2002; Videman et al. 2001].

Vitamin D actually is a prohormone, and its active $1,25(OH)_2D$ metabolite functions as a hormone throughout the body.

Thus, because the active $1,25(OH)_2D$ metabolite is primarily manufactured in one tissue (kidneys) but circulates throughout the body to physiologically influence many others via its own receptors, it qualifies as a hormone – with vitamin D_2 or D_3 and 25(OH)D being precursor substrates, or prohormones [Marcus 1995; Tavera-Mendoza and White 2007]. One researcher has appropriately referred to this as the "vitamin D endocrine system" [Walters 1992].

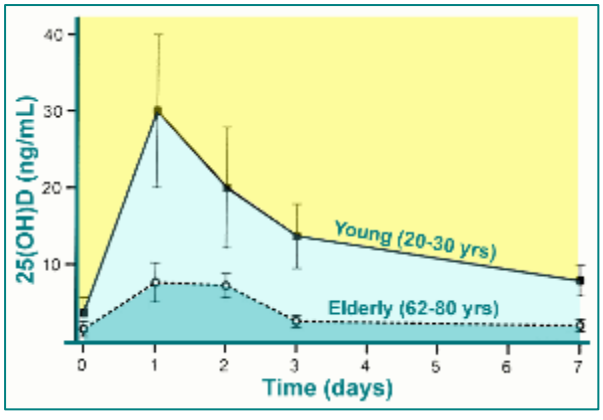
A vital role of vitamin D is maintaining serum calcium in a normal range to optimize bone health and other physiologic functions throughout the body [Holick 2002b]. However, the discovery of vitamin D receptors in many tissues besides intestine and bone – including brain, heart, pancreas, breast, prostate, 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 [Grant 2002; Holick 2003a, 2003c; Johnson 2007; Vasquez et al. 2004]. Research is ongoing in these areas, and a discussion of them is beyond the scope of this report.

2b. Functional Disposition

From a clinical standpoint, there are numerous individual factors that may affect the status of vitamin D and its metabolites in the body. According to the literature, photochemical synthesis of vitamin D_3 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, and no net increase in D_3 production occurs after that [Vieth 2005]. Persons with darker skin require longer sun exposure, but the total yield in D_3 is the same.

In other words, the same UVB light that stimulates vitamin D_3 production can also degrade the vitamin into inert byproducts, so prolonged exposure to sunlight does not generate excessive amounts beyond manageable levels [Hollis 2005]. Formation of vitamin D in the skin also is inhibited if serum 25(OH)D is already at adequate levels [Hathcock 2004].

Vitamin D_3 produced from a single sun exposure is metabolized and results in peak concentrations of 25(OH)D within 24 hours; it then declines during the next several days [Lips 2001]. However, research has demonstrated that in young adults the peak concentration achieved from sunshine is 4 times higher and the decline more gradual than in elderly persons receiving the same amount of sun exposure. See ***Graph*** [*adapted from* Lips 2001 and Holick 2002b; *original in* Holick et al. 1989]. Essentially, as persons age, it is more difficult for them to acquire adequate vitamin D from UVB radiation.



Generally, less than 25% of a dose of vitamin D_2 or D_3 entering the body – from synthesis in the skin, dietary intake in-

cluding from fortified foods, and nutritional supplements – is actually utilized [Vieth 1999, 2005]. In the case of food or supplement sources, bile is essential for adequate intestinal absorption of vitamin D, and this process is impaired in persons with hepatic or biliary dysfunction [Marcus 1995]. Unused vitamin D is excreted into the bile or otherwise removed within several days [Vieth 2005].

Of the relatively small portion that is put to use, some of it contributes to stores of vitamin D – maintained in adipose tissue, skeletal muscle, and many organs [Vieth 2005] – and the rest is immediately metabolized to 25(OH)D. It is cleared slowly from the body, with an elimination half-life reported as approximately 14 to 21 days [AHRQ 2007; Lips 2001; Marcus 1995]. Therefore, serum concentrations of 25(OH)D accumulate gradually and appear to plateau at steady-state levels by about 40 days [Holick et al. 2008; Vieth 1999, 2005] to 90 days [Hollis 2005; Vieth et al. 2001].

When there is a continuous supply of exogenous vitamin D, an equilibrium is reached that maintains a balance between storage, removal from tissue stores, metabolism, and clearance [Vieth 2005]. If vitamin D intake is diminished or stopped, reabsorption of vitamin D from the tissue-storage reservoirs can be used to sustain conversion to 25(OH)D during several months. However, an abundant supply of vitamin D during certain times, such as summer sun exposure, does not deter its complete depletion during periods of lean intake, such as during winter months [Vieth 2005].

Some studies have shown diminished increases of 25(OH)D following vitamin D administration in obese persons or those with a higher body mass index (BMI), presumably due to vitamin D sequestration in adipose tissue [Brouwer et al. 1998; Holick 2005, 2007; Lips 2001; Reginster 2005; Tavera-Mendoza and White 2007; Turner et al. 2008]. Conversely, others have proposed that this effect is usually minimal and there is relatively little effect of body weight on serum 25(OH)D [Hathcock et al. 2007; Vieth 2005].

Still, in one clinical trial, to achieve comparable success in relieving back pain, female patients weighing >50 kg (110 lb) required twice the dose of vitamin D_3 as those weighing <50 kg [Al Faraj and Al Mutairi 2003]. Also, it has been reported that men overall tend to have higher circulating 25(OH)D concentrations than do women, probably due to a greater storage of vitamin D in the body tissues of females [Hathcock et al. 2007].

Furthermore, clinical research experiments have demonstrated that vitamin D supplementation produces less of an increase in 25(OH)D if the body already has adequate amounts of circulating 25(OH)D [Armas et al. 2004, Holick et al. 2008; Trang et al. 1998]. In fact, there appears to be an inverse relationship whereby the higher the baseline 25(OH)D concentration the less of an increase is produced per IU of vitamin D supplementation [Armas et al. 2004]. This is discussed further in *section 4c*.

For purposes of bone metabolism, calcium homeostasis, and other vital functions served by vitamin D, the 25(OH)D metabolite must be converted to $1,25(OH)_2D$ [Holick 2003b]. This $1,25(OH)_2D$ metabolite has a short circulating half-life of only 4 to 6 hours [Shinchuk and Holick 2007] but it can remain active for 3 to 5 days [Johnson 2007; Marcus 1995]. Its circulating concentrations are typically 500 to 1000 times *less* than 25(OH)D [Hollis et al. 2005; Shinchuk and Holick 2007].

2c. Implications for Pain Syndromes

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 biochemical reactions negatively affecting bone metabolism and health. Even mild hypocalcemia results in an elevation of parathyroid hormone that

can diminish bone density (*osteopenia*) and/or more severely affect bone architecture (*osteoporosis*) [Holick 2003a, 2003c]. These are not normally painful conditions unless there are fractures.

The effect relating more closely to musculoskeletal aches and pains is that increased parathyroid hormone 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 [Holick 2003b; Shinchuk and Holick 2007; Yew and DeMieri 2002].

This dysfunction of bone metabolism (*osteomalacia*) is discussed further in *section 3* below. Overall, 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 weakness [Johnson 2007]. 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 [Shinchuk and Holick 2007].

In many cases involving pain, defects of bone metabolism and osteomalacia may not be clinically detectable but are nonetheless present, or "subclinical." Such disorders are considered to be nonspecific or idiopathic in that an explanatory injury, bone pathology, or anatomical or neurological defect have been ruled out. Some researchers have found this to occur in up to 85% of chronic musculoskeletal pain cases, especially those involving the lower back [Deyo and Weinstein 2001].

This subclinical effect was recently verified by Breuer and colleagues [2008] who employed sophisticated bone scanning techniques and radiolabeled tracers in patients with chronic lower-back pain for which no cause could be clinically determined. They found that the intensity of pain was directly and significantly correlated with otherwise undetectable abnormalities of bone-formation metabolism. (Also see, *section 6c*.)

Beyond the well-established role of vitamin D in bone health, vitamin D receptors have been identified in skeletal muscle. Myopathy presenting as a gradual but continuous decrease in muscle strength, usually in lower limbs, or merely as fatigue, is also part of the osteomalacic symptom complex and may appear before any pain [Glerup et al. 2000b].

Accordingly, the results of investigations some time ago indicated that vitamin D deficiency could produce muscle weakness [Boland 1986; Haddad et al. 1976; Schott and Wills 1976; Simpson et al. 1985; Walters 1992]. More recently, vitamin D inadequacy has correlated with increased body sway [Pfeifer et al. 2001] and an increased risk of falls that often result in painful fractures [Bischoff et al. 2003; Bischoff-Ferrari et al. 2005, 2006; Dukas et al. 2004; Sambrook et al. 2004]. Various investigations have demonstrated benefits of vitamin D supplementation for reversing myopathy and increasing physical endurance [Bischoff-Ferrari et al. 2006; Boxer et al. 2008].

The possible role of vitamin D might be expanded from calcium homeostasis affecting musculoskeletal health to that of a complex hormonal system benefiting diverse pain-associated conditions.

Clinical research investigations relating directly to vitamin D and chronic musculoskeletal pain are discussed in *section 7* of this report and summarized in *Appendix 3*. It also must be noted, however, that clinical researchers have 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 [Walters 1992]. Accordingly, results of some studies in the literature suggest benefits of vitamin D supplementation in addition to helping musculoskeletal pain.

Here is a brief summary of available evidence regarding non-musculoskeletal effects:

- **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, with symptoms improving from "distressing" to "mild" on average [Lee and Chen 2008]. There had been an earlier case report of a patient with type 1 diabetes whose severe neuropathy had confined her to a wheelchair. This patient's aches and pains were resolved by high-dose vitamin D supplementation, and she reportedly was able to walk unassisted within 4 weeks [Prabhala et al. 2000].

- **Inflammation** – Antiinflammatory properties of vitamin D were demonstrated in animal experiments, and recent clinical research indicates that vitamin D supplementation modulates or decreases proinflammatory cytokines (*eg,* C-reactive protein, interleukin 6 and 12, and tumor necrosis factor-alpha) while increasing antiinflammatory cytokines (*eg,* interleukin-10) [Boxer et al. 2008; D'Ambrosio et al. 1998; Schleithoff et al. 2006; Van den Berghe et al. 2003].

  Clinical 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 and Crohn's disease [Tavera-Mendoza and White 2007]. This also might have implications for vitamin D ameliorating musculoskeletal pain evoked by or associated with inflammation processes, but further exploration is needed.

- **Migraine Headaches** – There have been case reports of vitamin D combined with calcium supplementation to alleviate migraine headaches in postmenopausal [Thys-Jacobs 1994a] and premenopausal women [Thys-Jacobs 1994b]. Reductions in both frequency and intensity of migraines were achieved within 2 months; however, more extensive research in this area does not seem to have been pursued.

- **Affective (Mood) Disturbances** – Limited research in animal models found that the $1,25(OH)_2D$ metabolite of vitamin D affected production of the neurotransmitters dopamine, GABA, and norepinephrine [Walters 1992]. This suggests that vitamin D may address the well-known links between chronic pain and mood disturbances.

  One investigation in patients with fibromyalgia syndrome found that pain symptoms, depression, and anxiety were strongly associated with insufficient vitamin D [Armstrong et al. 2007]. Recent large studies examining older persons (aged ≥65 years) found significant associations between 25(OH)D concentration deficiencies, elevated parathyroid hormone levels, and major or minor depressive disorders [Hicks et al. 2008; Hoogendijk et al. 2008]. In one of the studies, inadequate 25(OH)D and depression also were highly correlated with chronic lower-back pain specifically in female patients [Hicks et al. 2008].

  Depression and anxiety also are components of "seasonal affective disorder" (SAD) and there is some evidence that SAD is influenced by diminished stores of vitamin D, which would be expected to occur during winter months. To examine this, subjects with SAD were randomized to receive either supplemental vitamin D or broad-spectrum light therapy (*phototherapy*), which is often recommend in patients with SAD [Gloth et al. 1999]. Vitamin D status improved in both groups, although the increase was twice as much in the supplement group as in those receiving phototherapy. Along with that result, vitamin D supplementation produced significant improvements in all outcome measures of depression, whereas the phototherapy group showed no changes at all.

In an earlier study, patients with clinical depression were randomized to receive vitamin D_3 supplementation or placebo [Lansdowne and Provost 1998]. On self-reported measures, those patients administered vitamin D had significantly enhanced mood and a reduction in negative-affect symptoms. The authors speculated that vitamin D might have had positive effects on brain serotonin levels, similar to how many antidepressant or mood-stabilizing medications affect this neurotransmitter.

Improvements of mood in patients with chronic pain syndromes would be important for overall quality of life, even if the pain itself is only modestly relieved by vitamin D therapy. Research in this regard found that more adequate vitamin D concentrations were significantly associated (p=.0001) with better physical, social, and mental functioning as measured by quality-of-life assessment instruments [Basaran et al. 2007]. Similarly, in a controlled trial, Vieth et al. [2004] found that vitamin D_3 supplementation improved scores on an assessment of well-being that was based on conventional depression-screening tools.

In sum, while further research is needed, the potential of vitamin D might be expanded from its role in calcium homeostasis affecting bone and muscle health to that of a complex hormonal system benefiting other conditions that often accompany chronic pain [Walters 1992]. However, a fundamental principle is that any benefits of vitamin D are realized only when circulating concentrations of its primary metabolite 25(OH)D are at optimal levels, and in most patient populations this is not the case [Tavera-Mendoza and White 2007], as is discussed in *section 3d*.

3. Assessing Vitamin D Status

Clinical research studies involving patients with musculoskeletal pain and fatigue syndromes have examined levels of the 25(OH)D metabolite and other biochemical markers as objective measures of vitamin D deficiency and its negative effects. Whether or not this approach – with its attendant time, expense, and patient inconvenience – also would be necessary in everyday clinical practice merits careful consideration.

3a. Osteomalacic Processes

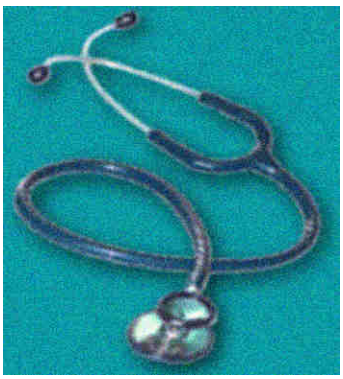
As noted above, chronic musculoskeletal pain and weakness have been largely attributed to effects of osteomalacia. A lack of circulating calcium (*hypocalcemia*) resulting from inadequate vitamin D sets in motion a specific series of biochemical mechanisms negatively affecting bone metabolism and skeletal integrity [AHRQ 2007; Holick 2002b, 2003a,b,c; Johnson 2007; Marcus 1995; Mayo Clinic 2007; Yew and DeMieri 2002]. These can be summarized:

- Absorption of calcium from the gastrointestinal tract is decreased when vitamin D and its 25(OH)D metabolite fall below adequate levels.
- Low serum calcium stimulates the parathyroid glands to produce and secrete parathyroid hormone (PTH). This agent helps conserve the available calcium in circulation by increasing its resorption by the kidneys.
- Increased PTH also causes the kidneys to metabolize available 25(OH)D to produce more $1,25(OH)_2D$ in an attempt to boost absorption of calcium from the intestine.
- However, if circulating 25(OH)D becomes deficient, enough $1,25(OH)_2D$ cannot be produced to maintain absorption of dietary calcium from the intestine.

- When this happens, PTH continues to rise (*secondary hyperparathyroidism*) and it causes the skeleton itself to serve as a substitute source of calcium. This can lead to diminished bone density (*osteopenia*) and, eventually, osteoporosis.
- Another consequence of secondary hyperparathyroidism is that elevated PTH causes excess excretion of phosphorus in the urine leading to a deficiency of this element (*hypophosphatemia*). The combination of both calcium and phosphorus – calcium phosphate – is required for the proper mineralization of bone. In fact, serum calcium levels may remain normal due to calcium being taken from the skeleton, but bone mineralization is still impaired due to a lack of the calcium phosphate compound.
- When calcium phosphate is diminished, bone-forming cells (*osteoblasts*) continue to deposit collagen matrix on both inner bone surfaces (*endosteum*) and under membranes covering the skeleton (*periosteum*). Rather than providing structural support, the resulting rubbery matrix can absorb fluid, become spongy, and may expand under the periosteal coverings. As noted above, this osteomalacic condition may cause outward pressure on the periosteal tissues and, subsequently, aches or pains, since these tissues are highly innervated with pain-sensing (*nociceptive*) fibers.

These biochemical processes leading to osteomalacia, with its attendant pain and negative effects on muscle, form a classic negative feedback loop in endocrine regulation that is reversed by the intake of more adequate vitamin D [Walters 1992]. The clinical challenge, however, is being able to identify when these factors are at work and in which patients presenting with musculoskeletal complaints.

3b. Clinical Indicators



From a clinical perspective, a number of factors may suggest that chronic musculoskeletal pain and related problems could 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, along with the recognition of signs/symptoms that could indicate defects in bone metabolism [Smith et al. 2005].

This clinical examination would occur prior to laboratory assessments of serum 25(OH)D or measurements of other biochemical markers (discussed in *section 3c*). Vitamin D involvement might be clinically suspected if any of the following are present [Johnson 2007, Nellen et al. 1996]:

1. Chronic (>3 months) or recurrent musculoskeletal (muscle, bone, and/or joint) aches or pains at any age, which are largely unexplained by specific injury, disease, neuropathology, or anatomic defect.
2. Persistent muscle weakness, fatigue, and possibly difficulty walking.
3. A history of minimal sunlight exposure and/or inadequate dietary or supplemental vitamin D intake (also see *section 4a*).
4. Clinical signs/symptoms of hypocalcemia (see *section 3c*).
5. Signs/symptoms of clinical osteomalacia (most typically appearing late in the course of the disease (see the ***Box***, below).

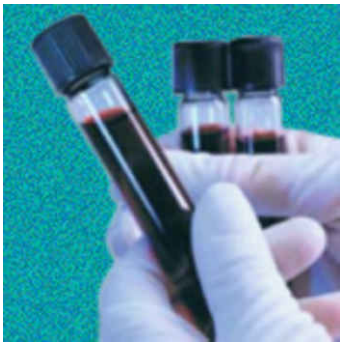
Practice Pointers:

Holick [2003b, 2007] and others [Glerup 2000b; Mascarenhas and Mobarhan 2004] suggest that osteomalacia due to vitamin D deficiency is often misdiagnosed as chronic fatigue syndrome, arthritis or rheumatic disease, depression, or fibromyalgia. One helpful diagnostic sign in cases of clinically detectable osteomalacia is pain or discomfort elicited by the application of pressure with thumb or forefinger on bone close to the surface – eg, sternum, anterior tibia, or radius and ulna. This sign is quite different from the various trigger point sensitivities that are often characteristic of fibromyalgia syndrome.

Radiological changes potentially associated with osteomalacia are seen only in advanced stages and include: x-rays visualizing bone demineralization, fibrous lamellae, and/or incomplete ribbonlike areas of demineralization (or pseudofractures) appearing in the cortical outer layer [Johnson 2007; Peach et al. 1982].

Based on positive findings for any of the above clinical observations a trial of vitamin D supplementation might be recommended for the patient, without further assessment. This takes into account that a) vitamin D is well tolerated, with a minimal likelihood of adverse effects, b) over-the-counter supplements are very economical, and c) laboratory assessments of biochemical markers may provide little additional information of value (discussed next).

3c. Biochemical Markers



Relying on clinical observations alone, it can be difficult or impossible to make a *definitive* diagnosis of pain-generating osteomalacia until relatively late in the course of the disease [Peach et al. 1982]. Since osteomalacia is histologically an accumulation of organic matrix (*osteoid*) due to defective bone mineralization, an earlier diagnosis would require invasive and costly bone biopsy [Peach et al. 1982; Yew and DeMieri 2002]. Therefore, surrogate biochemical markers, or biomarkers, of this disorder are more commonly employed.

Laboratory assessments have been important in research studies and may be used in some medical practices for confirmation of the clinical diagnosis and/or validation of a treatment plan. In the case of chronic musculoskeletal pain and its association with vitamin D inadequacies, assessments usually pertain to the measurement of biomarkers that could denote osteomalacic processes, including the following (see ***Table*** [Peacey 2004]):

- 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. These issues are discussed next.

Biochemical Markers of Clinical Osteomalacia

- ⬇ Serum 25(OH)D
- ⬇ Total Serum Calcium (Ca)
- ⬇ Phophate
- ⬆ Parathyroid Hormone (PTH)
- ⬆ Total Alkaline Phosphatase (ALP)

Alkaline Phosphatase (ALP)

At one time, elevations in total ALP – a surrogate marker for bone turnover – were considered as the best biochemical indicator of osteomalacia [Johnson 2007; Peach et al. 1982]. However, such elevations may not be evident in all cases [Glerup et al. 2000a, 2000b; Helliwell et al. 2006; Marcus 1995] and *total* ALP also may be elevated in patients with obesity or type 2 diabetes [Peacey 2004], since all ALP enzymes do not exclusively originate from bone. Increased plasma ALP also is less specific for osteomalacia in the elderly, in whom it may be normally elevated. A

more specific marker might be an increase specifically in *bone* alkaline phosphatase activity, which also has been associated with risk of fractures [Glerup et al. 2000a].

Phosphate (PO)

Phosphate usually decreases when vitamin D is inadequate, due to elevated PTH levels that stimulate increased urinary excretion of phosphorus [Carroll and Schade 2003; Hicks et al. 2008; Johnson 2007]. However, in persons with only mild to moderate vitamin D deficiencies, PO levels may not be abnormal [Helliwell et al. 2006; Lotfi et al. 2007]. Therefore, some researchers have suggested that routine measurement of PO or phosphorus is of negligible clinical value as a marker for osteomalacia [Peacey 2004].

Parathyroid Hormone (PTH)

It is generally believed that elevations of PTH may be the best biochemical marker 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 should 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 [Peacey 2004].

Calcium (Ca)

In some patients with chronic pain syndromes and insufficient vitamin D, serum calcium may *not* be subnormal because elevated PTH can mobilize calcium from bone to maintain homeostasis [Fitzpatrick 2002; Johnson 2007; Lotfi et al. 2007]. Therefore, normal calcium findings (after correction for albumin concentration [Cooper and Gittoes 2008]) can be misleading, since pain-generating osteomalacic processes may still be present.

In unambiguous cases of calcium deficiency (*hypocalcemia*), hallmark symptoms often reflect 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 achy, progressing to cramps or spasms [Cooper and Gittoes 2008; Fitzpatrick 2002; Lyman 2005; Skugor and Milas 2004; Urbano 2000]. See ***Side Box*** note. Lethargy, poor appetite, mental confusion, and life-threatening cardiac arrhythmia may be part of the syndrome [Cooper and Gittoes 2008; ODS 2005].

Recommended adequate calcium intake for adults >18 years of age is 1000 to 1200 mg/day, although elderly women may require more, and the nontoxic upper limit is 2500 mg/day [ODS 2005]. But, according to surveys from the 1990s, 55% of men and 78% of women adults were *not* meeting the recommended daily intake for calcium [ODS 2005]. Calcium is available in some foods (see ***Appendix 4***), but it must be considered that persons with chronic pain may not be able to prepare, or have an appetite for, daily diets providing adequate amounts of essential nutrients, including calcium. See ***Side Box***.

> ***Practice Pointers:***
>
> *It is important to note that some symptoms of hypocalcemia may mimic those of other pain-related conditions, such as neuropathies or skeletal defects.*
>
> *If calcium supplementation is appropriate, its absorption is more efficient in single doses <500 mg. The most commonly used form is calcium carbonate, which is better absorbed if taken with a meal [ODS 2005; Shinchuk and Holick 2007].*

Serum 25(OH)D

The measurement of serum 25(OH)D concentrations was once strictly a research tool, but various assays have relatively recently become available from commercial laboratories [Heaney 2004; Zerwekh 2008]. Deficiencies of 25(OH)D are sometimes proposed as the best indicator of potential osteomalacia [Glerup et al. 2000b; Lotfi et al. 2007].

Circulating 25(OH)D reflects both D_2 plus D_3 intake, but not $1,25(OH)_2D$ concentrations. Measuring $1,25(OH)_2D$ is not recommended because it can be a poor or misleading indicator of vitamin D status [Holick 2002b].

As noted above, when vitamin D is inadequate PTH secretion in increased, and this stimulates renal conversion of available 25(OH)D to $1,25(OH)_2D$. So $1,25(OH)_2D$ might appear either normal or elevated at some points in time even when there actually are vitamin D deficits [Holick 2007]. Serum $1,25(OH)_2D$ usually becomes abnormally low or undetectable only when severe vitamin D deficiency occurs [Holick 2002b; Johnson 2007]. Also, assays of $1,25(OH)_2D$ can be distorted by kidney dysfunction and other disorders, such as primary hyperparathyroidism [Skugor and Milas 2004].

Some clinicians have suggested that patients at risk for vitamin D deficiency should have their 25(OH)D levels tested yearly, preferably at the end of the fall season to ensure that they do not experience problems during winter [Plotnikoff and Quigley 2003]. However, there are a number of important limitations of this test (discussed next, below) and practitioners need to consider what they hope to achieve with such assessments.

Concerns About Biomarkers

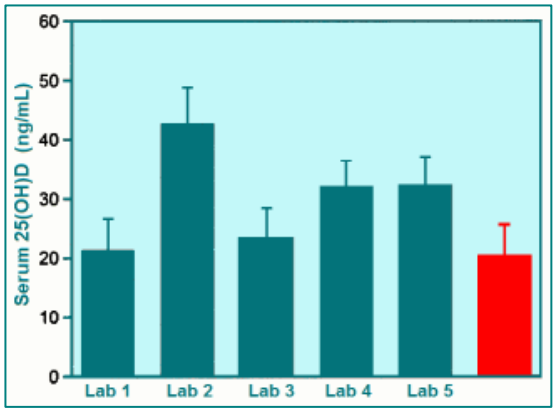
Biomarkers alone, including 25(OH)D, may not be reliable indicators of underlying osteomalacic processes.

Some researchers have stressed that, although abnormal laboratory parameters may be helpful in distinguishing cases of advanced clinical osteomalacia, routine measurements of Ca, PO, and ALP are not reliable predictors of inadequate 25(OH)D concentrations or underlying osteomalacic processes [Holick 2002b; Smith et al. 2005]. Up to 20% of patients with 25(OH)D deficiency and elevated PTH may have normal Ca, PO, and ALP levels [Al Faraj and Al Mutairi 2003; Peacey 2004].

Therefore, without testing for 25(OH)D and PTH a substantial number of patients at high risk for osteomalacia could be missed [Peacey 2004]. Although, there are some concerns about the validity and utility of 25(OH)D assays, including:

- Costs of the 25(OH)D (*calcidiol*) assay at commercial laboratories vary widely but may range up to US$ 200 or more. Some researchers have noted that incurring this expense may be unnecessary in populations that typically have a high prevalence of vitamin D inadequacy to begin with [Peacey 2004], and this population could include most patients with chronic pain (as discussed in *section 6a* below).
- Serum 25(OH)D may exhibit seasonal and situational fluctuations [Glerup et al. 2000a]. Time of year and lifestyle factors (*eg,* sporadic outdoor activities) affect 25(OH)D levels, at least temporarily, so laboratory findings at a single point in time may not always be helpful and natural variations in 25(OH)D need to be taken into account.
- Concerns have been expressed recently about the reliability and precision of some 25(OH)D assays [AHRQ 2007; Singh 2008]. 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 [Lips 2001; Heaney 2004]. In one investigation, assay results

ranged between 41 and 96 ng/mL in samples actually containing 31 ng/mL of 25(OH)D [Singh 2008]. In another analysis, DeLuca [2004] compared results of 25(OH)D assays using kits from 5 different commercial laboratories and found that 3 of the 5 produced results erring significantly higher than the accurately assayed control samples. See ***Graph*** [from DeLuca 2004, *control-sample value is in red, at far right side of graph*].



These concerns should not completely deter testing for biomarkers of osteomalacia 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.

Research results have demonstrated that particular serum 25(OH)D concentrations *alone* are not prognostic of pain or its degree and duration (see *section 6* for a discussion of the research evidence). Some persons may have severe aches and pains with only mild 25(OH)D insufficiencies, which nonetheless improve dramatically with vitamin D supplementation. Therefore, it could be erroneous to assume that vitamin D is not involved in a pain syndrome because it measures on assays at some presumed level of adequacy. Except when very severe 25(OH)D deficiency is suspected, which might suggest benefits of more aggressive high-dose vitamin D supplementation (discussed in *section 7a*), the 25(OH)D test and/or other bioassays might be unnecessary before starting a moderate program of vitamin D supplementation on empirical grounds.

3d. Defining Adequate 25(OH)D Concentration

Despite limitations of the 25(OH)D assay, this is still the measure of vitamin D adequacy most frequently referred to in the scientific literature and some clinicians do find it helpful. Abnormally low vitamin D sometimes is called "hypovitaminosis D" but the phrase "vitamin D deficiency" is preferred [Holick 2004a]. Yet, neither of these phrases is specific and might include various stages of inadequacy as well as true deficits of vitamin D, depending on how they are defined.

While a universal consensus is lacking, most researchers have agreed that a minimum 25(OH)D serum level of about 30 ng/mL or more is necessary for favorable calcium absorption and good health [Heaney 2000; Heaney et al. 2003b; Heaney 2004; Holick 2007; Reginster et al. 1998]. Optimal 25(OH)D concentrations are considered to range from 30 ng/mL to 50 ng/mL; whether levels somewhat above this also may be beneficial remains uncertain [Heaney et al. 2003a; Holick 2002a, 2003a,b,c ; Johnson 2007]. See ***Table***.

25(OH)D Concentrations

[Major Metabolite of Vitamin D from D_2 or D_3]

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

References: Heaney 2004; Heaney et al. 2003a; Holick 2007; Reginster et al. 1998; Tavera-Mendoza and White 2007; Vieth 1999

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.

Most definitions of *deficiency* stress that circulating 25(OH)D concentrations of <20 ng/mL may be associated with increased PTH and greater bone turnover potentially engendering symptoms of subclinical osteomalacia [Heaney 2004; Hickey and Gordon 2004; Marcus 1995]. Concentrations ≤8 ng/mL have been considered as highly predictive of fully-developed, or clinical, osteomalacia [AHRQ 2007; Heaney 2004; Heath and Elovic 2006; Marcus 1995; Plotnikoff and Quigley 2003; Reginster 2005].

Furthermore, levels of circulating 25(OH)D concentrations below an optimal range but above true deficiency status also might have a negative impact. This range – spanning 20 to 29 ng/mL of 25(OH)D – would constitute *insufficiency* [Shinchuk and Holick 2007; [Tavera-Mendoza and White 2007].

Reference ranges depicting "normal" values for serum 25(OH)D are provided by assay manufacturers or laboratories; however, these can be misleading since they are usually based on studies in specific populations [Harinarayan 2004]. The accuracy of such values is limited by climate, sun exposure, lifestyle habits, and other factors *within those populations studied*, and the "normal" ranges may not be typical of patients in particular clinical practices.

Therefore, it is believed that the threshold denoting vitamin D deficiency should be set much higher than the 10 ng/mL to 15 ng/mL 25(OH)D considered as deficient by many physicians, assay manufacturers, and clinical chemistry laboratories [Holick 2004b; Hollis 2005; Hollis et al. 2005]. Large-scale investigations found elevated PTH and increased bone turnover with 25(OH)D of ≤20 ng/mL [Lips et al. 2001], and at this level intestinal calcium absorption was 35% lower than at 25(OH)D levels >30 ng/mL [Heaney et al. 2003b]. Some researchers have suggested that anything less than 40 ng/mL of 25(OH)D is insufficient or dysfunctional, since amounts greater than this can be necessary to maintain physiologic suppression of PTH; in this scenario, an optimal range would be 40 ng/mL to 65 ng/mL [Alonso et al. 2003; Lotfi et al. 2007; Vasquez et al. 2004].

3e. General Prevalence of 'D-ficiency'

In clinical practice, it may be generally assumed that at least 1 of every 2 patients, or more, will be lacking in vitamin D to some extent.

In the general population, there is a growing consensus that vitamin D inadequacies – or what Holick [2004a] has broadly labeled "D-ficiency." – are much more common and severe than might be imagined [Heaney et al. 2003b]. This has been extensively studied and, according to the research evidence, it may be assumed in almost any clinical practice that at least 1 of every 2 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 will have more serious deficiencies of <20 ng/mL 25(OH)D.

There can be physiologic causes of secondary vitamin D deficiency, accounting for a relatively small percentage of the problem worldwide. Certain disease states substantially reduce circulating 25(OH)D, including chronic liver disease, fat-malabsorption syndromes, inflammatory bowel disease, celiac disease, Crohn's disease, pancreatic insufficiency, and cystic fibrosis [Hollis et al. 2005; Johnson 2007; Mascarenhas and Mobarhan 2004].

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 [Gostine and Davis 2006; Johnson 2007; Mascarenhas and Mobarhan 2004]. Numerous factors in modern society also may contribute to the problem, including the popularity of non-dairy beverage consumption, diets devoid of the relatively few foods rich in vitamin D, lifestyles of work or leisure spent predominantly indoors, and concerns about sun exposure with the attendant use of lotions that completely block UVB radiation [Gostine and Davis 2006].

Here are some typical prevalences reported in the research:

- An assessment of apparently healthy volunteers at an urban European health center found that about a third had serum 25(OH)D concentrations <15 ng/mL [MacFarlane et al. 2004]. The mean concentration of the total group was only about 19 ng/mL.
- Since greater amounts of protective melanin in darker skin block UVB penetration, black persons generally have 25(OH)D levels that are about half those of whites [Tavera-Mendoza and White 2007]. One national survey in the United States found that 42% of African-American women 15 to 49 years of age were seriously deficient, with serum concentrations less than 15 ng/mL [Nesby-O'Dell et al. 2002].
- In a recently reported clinical trial investigators recruited healthy adults (18-84 years of age) from a northern US city in February [Holick et al. 2008]. Overall, 87% of these persons 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 more than one glass of fortified milk each day.
- Elderly persons are at special risk for vitamin D inadequacies. In one study, 71% of postmenopausal women had 25(OH)D concentrations <20 ng/mL [Bhattoa et al. 2004]. In another investigation, up to 80% of community-dwelling elderly women ranging in age from 70 to 90+ years had severe deficiencies of <12 ng/mL [Reginster et al. 1998]. A large study in the Netherlands, including 1282 persons ≥65 years of age, found that 39% of men and 57% of women had 25(OH)D levels <20 ng/mL; *none* of the subjects had optimal concentrations of 30 ng/mL or more [Hoogendijk et al. 2008].
- Other age groups also have been found at risk, depending on geographic locale and time of year. In a study of otherwise healthy adolescent girls in northern Europe and Scandinavia, 92% had deficient 25(OH)D levels <20 ng/mL, and 37% had severe deficiencies <10 ng/mL [MacFarlane et al. 2004]. Sullivan et al. [2003] found that 48% of a group of girls in Maine, aged 9 to 11 years, were deficient in vitamin D at the end of winter. Tangpricha et al. [2002] reported that nearly one third of the young men and women aged 18 to 29 years examined at the end of winter were vitamin D deficient.
- It might be expected that there would be less prevalence of vitamin D inadequacies in sunnier parts of the world. However, between 44% and 95% of persons have been found to be vitamin D deficient in Saudi Arabia, Egypt, India, Jordan, Lebanon, and Tunisia [*summarized in* Holick 2007; Lotfi et al. 2007], with up to half of the persons studied having 25(OH)D levels less than 20 ng/mL. 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 – 1 of every 2 subjects had concentrations <30 ng/mL and more than a quarter (27%) had levels <20 ng/mL [Jacobs et al. 2008].

Many factors have been found to influence susceptibility to vitamin D inadequacy, and the high prevalence of this disorder in diverse populations and geographies is of concern. The scope and severity of vitamin D inadequacies could vary from one particular clinical practice to another, and achieving adequate levels of vitamin D in most patients without appropriate supplementation could pose difficulties, as is discussed in the next section.

Achieving adequate levels of vitamin D in most patients without appropriate supplementation could be difficult or impossible.

4. Vitamin D Sources

Human skin makes vitamin D when it is exposed to the sun; however, sunshine can be an unreliable and, for many persons, elusive source of adequate vitamin D on a regular basis. Furthermore, the daily vitamin D intake available from foods is practically negligible for most persons. Therefore, the most practical approach in most cases is the use of supplements.

Vitamin D supplements are included in a class increasingly known as "nutraceuticals." These are nutritional agents having pharmaceutical effects on physiological function [ANA 2008], and they are widely available from many outlets and economical in cost.

4a. Natural & Fortified Sources of Vitamin D

Unlike many other essential nutrients, vitamin D is not found in fruits, vegetables, or most other foods. Hollis [2005] has noted that, with the exception of oily fish and fish-liver oil, "for all practical purposes, vitamin D does not naturally occur in foodstuffs that humans eat." A list of natural and fortified sources is in ***Appendix 1***.

During the 1930s through the 1950s a great many foods and beverages were strongly fortified with vitamin D. This practice was discontinued in most European countries and in the United States relatively few items are fortified [Holick 2003b].

Consequently, it is almost impossible to get adequate amounts of dietary vitamin D. For example, it would require either 5 cans of tuna, roughly 10 eggs, 10 or more glasses of fortified milk, or up to 17 cups of fortified cereal to acquire 1000 IU of the vitamin, which is the recommended daily dose for adults (discussed below in *section 4c*). Furthermore, it is difficult to know from labeling how much vitamin D fortification is contained in food products (see ***Side Box***).

> ⚠ ***Caution:***
>
> *Food fortification labeling can be misleading. Most product labels list vitamin D content as a percentage of the recommended daily allowance (RDA) value, but they do not indicate what RDA values are being used. Therefore, the total vitamin D content in terms of standard international units (IU) is unknown, and lower, outdated RDA values may be used by manufacturers to begin with. Also, whether D_3 or D_2 is used in the product is not always specified.*

Since dietary intake is almost always inadequate, nearly all (≥90%) of required vitamin D would need to come from exposure to sunlight [Holick 2003a]. However, there are problems with this.

The UVB radiation responsible for vitamin D production in the skin is also the "burning rays" causing sunburn [Singh 2004a]. Dermatologists advise against extensive direct exposure to the sun and recommend always using protective clothing or lotions when outdoors; although, some experts argue that the sun exposure required for producing adequate vitamin D would *not* substantially increase skin cancer risks [Holick 2003b].

Still, getting adequate sun exposure for purposes of vitamin D production depends on a complex balance of time of day, season, latitude, skin pigmentation, age, and the amount of skin surface without sun protection. Heavily pigmented skin requires 3 to 6 times more sun exposure than light skin to produce a comparable amount of vitamin D [Lotfi et al. 2007]. Elderly persons may require 4 times more exposure than younger ones [Holick 2002b; Lips 2001].

In general, a fair-skinned sunbather in midsummer wearing only a bathing suit would acquire in about 15 minutes a 1.0 minimal erythemal dose (causing slight pinkness to the skin), which would produce an amount of vitamin D_3 equivalent to ingesting 10,000 IU to 20,000 IU [Holick 2003a, 2003c; Hollis 2005; Tavera-Mendoza and White 2007]. This is a self-limiting process; that is, prolonged sun exposure does not generate excessive amounts of vitamin D because UVB light also can degrade the vitamin D_3 into inert byproducts, thus preventing toxic build-up [Hollis 2005]. Formation of vitamin D in the skin also is inhibited if serum 25(OH)D and tissue reserves are

already at adequate levels [Hathcock 2004]; therefore, repeated daily sun exposure does not lead to an accumulation of toxic amounts.

Less extensive sun exposure also can be of benefit. In a fair- to medium-skinned person, exposure of only face, hands, and arms for up to 15 minutes during midday in summer would provide a 0.25 to 0.50 minimal erythemal dose producing the equivalent of 3000 IU of D_3 [Holick 2007]. Some have advised that such exposure would be necessary as little as 3 times a week to maintain adequate vitamin D levels [Johnson 2007, Lips 2001]; however, age, skin color, and time of year must be taken into account.

For most persons, achieving a regular regimen of adequate and non-harmful exposure to sunlight could be unrealistic. For one thing, during at least 6 months of the year in temperate regions of the world UVB light is too weak to induce any significant vitamin D synthesis in the skin [Tavera-Mendoza and White 2007; Webb et al. 1988].

Furthermore, anything interfering with the penetration of solar ultraviolet radiation into the skin – eg, increased melanin pigmentation in darker skin or protective clothing – will diminish vitamin D production. Application of lotion with a sun protection factor (SPF) of only 8 reduces synthesis of vitamin D in the skin by 95% [Holick 2003a; Hollis 2005].

Artificial sunlight sources are available but generally unacceptable. Devices like tanning beds and sunlamps provide high levels of UVA "tanning rays" but relatively little UVB radiation [Singh 2004b]. Special vitamin D lamps marketed as providing narrow-band UVB are available [*eg*, http://sperti.com] and might be of interest to some patients. However, such lamps are expensive and would require regularly scheduled use and great caution to avoid skin and eye damage.

4b. Vitamin D Supplements: D_2 vs D_3

Of the two forms of vitamin D, natural vitamin D_2 (*ergocalciferol*) is rare and found primarily in certain mushrooms. Whereas, D_3 (*cholecalciferol*) comes from animal sources (eg, certain oily fish, cod liver oil) and it is the form produced naturally in humans from sunlight. Also see ***Appendix 1***.

Manufactured vitamin D_2 is produced by exposing a fat extract of yeast to UVB radiation [Vieth 2005]. Certain high-dosage formulations are FDA-approved in the US, since their use predated the Food and Drug Administration (FDA) and they were "grandfathered" as pharmaceutical drugs [Holick et al. 2008; Heaney 2004].

Vitamin D_3 was commercially developed in the 1950s, and manufacturers did not apply for pharmaceutical drug status. It can be made by irradiating 7-dehydrocholesterol obtained from the lanolin in sheep's wool with UVB light [Holick et al. 2008]. Vitamin D_3 is the form most widely used for food fortification and in vitamin D-supplement products.

All once-daily multivitamin products contain vitamin D, ranging from 400 to 800 IU, but this amount would be inadequate for most persons. Taking multiple doses of these to achieve adequate intake of vitamin D would be unwise, as it could result is excessive and harmful amounts of other ingredients.

Vitamin D-specific supplements are available in both prescription pharmaceutical formulations, usually high-dose D_2, and as over-the-counter (OTC) products of various dosages and either as D_2 or D_3. Commercially available OTC vitamin D_3 products are the simplest and least expensive approach to supplementation for most patients with pain.

Results of clinical research studies have demonstrated that D_3 is from 2 to 4 times more potent than D_2 [Armas et al. 2004; Romagnoli et al. 2008; Trang et al. 1998; Vieth 2005]. The exact mechanism behind this is unknown but may involve increased clearance or differential metabolism of D_2 [Cranney et al. 2007; AHRQ 2007].

Vitamin D supplementation for nutritional and clinical purposes should specify cholecalciferol, vitamin D_3.

However, in a recently reported well-controlled trial, Holick and colleagues [2008] assessed effects of 1000 IU/day of oral D_2 vs D_3 administered for 11 weeks to healthy adults, of whom 60% were deficient in vitamin D (<20 ng/mL 25[OH]D) at baseline. Both formulations were found to be equivalent in raising total 25(OH)D serum concentrations.

Meanwhile, vitamin D_3 is readily available, at no greater cost than D_2, and it is the form naturally produced by the skin, so there appears to be no advantage to recommending D_2. Vieth [2005] has strongly urged that "all use of vitamin D for nutritional and clinical purposes should specify cholecalciferol, vitamin D_3."

Vitamin D_3 products are available at pharmacies, heath food stores, other outlets, and from Internet-based sources. In the United States, under the Dietary Supplement Health and Education Act of 1994 (DSHEA), manufacturers of vitamins were responsible only for ensuring that their products were "safe" prior to marketing. Until recently, the vitamin industry has remained largely unregulated [ACPA 2007; FDA 2006].

In 2007, the FDA established regulations requiring current Good Manufacturing Practices (cGMP) for dietary supplements [FDA 2007]. Manufacturers are required to evaluate the identity of ingredients, their strength, and the composition of their products, and to report all product-related serious adverse events to the FDA. This ruling will be phased in during a 3-year period, extending to 2010 for the smallest manufacturers.

At present, very few manufacturers of nutraceuticals have chosen to participate in established testing and monitoring programs, and only a handful of vitamin D supplements – at lower doses or in combination with calcium – are certified. The US Pharmacopeia [http://usp.org] has a program for assessing the strength, purity, and quality of dietary supplements, and awards its "USP Verified" label to those that are accepted. Similarly, NSF International [http://nsf.com], a worldwide nonprofit, non-government organization, awards its "Certification Mark" to products that comply with its rigorous standards of quality.

OTC vitamin D supplements are typically available as 400 IU, 1000 IU, or 2000 IU tablets or capsules, usually D_3. Some Internet-based nutritional supplement distributors also make available larger doses of D_3 – 2400 IU, 5000 IU, and 50,000 IU – *without* prescription. The easy availability of the latter is of particular concern, since taking 50,000 IU too frequently could soon result in harmful toxicity. Patients should be warned against purchasing large-dose products unless specifically directed to do so.

Vitamin D supplements are quite economical and affordable by all patients. Prices *per daily dose* range from approximately US$ 0.04 or less for 400 IU to US$ 0.07 for 1000 IU, and products are often steeply discounted further; 2000 IU per day of vitamin D_3 may cost as little as US$ 0.10. Adding calcium in a combination vitamin D-plus-calcium tablet roughly doubles the cost, and, due to the small proportion that is vitamin D, a separate vitamin D supplement still would be required.

It must be noted that the low cost of OTC vitamin D supplements may create its own problems in terms of perceived effectiveness. In a recently reported study, 82 persons were told that they were either being given an analgesic pill costing US$ 2.50 at regular price or a discount-priced analgesic costing only US$ 0.10 [Waber et al. 2008]. After taking the pill, which actually was a *placebo in both cases*, and undergoing a pain-inducing electric-shock procedure,

40% more persons in the "regular-price pill" group reported pain reduction than in the "cheap pill" group (85% vs 61%).

Besides endorsing the benefits of placebo effects – since both groups experienced pain relief to a significant extent – this study has implications for both practitioner and patient expectations. Each might harbor a belief, possibly subconsciously, that potent and effective medicine for pain is also expensive. Presented to patients in the wrong way – such as with little enthusiasm – inexpensive vitamin D might be unjustly perceived as being of questionable analgesic benefit and even precondition a set of negative expectations, a so-called "nocebo" effect.

The low cost of vitamin D supplements could be a detriment unless presented to patients in an appropriate way.

4c. Vitamin D Intake – Healthy Patients

According to available evidence, at least 1000 IU/day of vitamin D_3 is necessary to maintain adequate serum 25(OH)D levels at or above 30 ng/mL in *healthy persons* (without chronic pain). However, the optimal daily intake of vitamin D for health is still being debated, and there are differences of opinion based on available evidence (see the ***Table***):

'Adequate' Vitamin D Intake

1997 – Institute of Medicine

200 IU/d – children & adults to age 50 years
400 IU/d – men & women aged 50 - 70 years
600 IU/d – those older than 70 years.

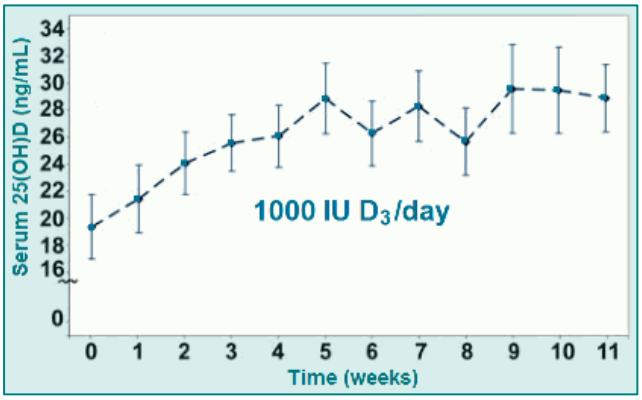
2005 – Dietary Guidelines for Americans

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.

1. More than a decade ago, in 1997, the US Institute of Medicine determined that there was insufficient data to specify a Recommended Daily Allowance (RDA). 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 as people age they would need extra vitamin D supplementation [IOM 1997; ODS 2008].
2. The most recent *2005 Dietary Guidelines for Americans* from the US government [DHHS 2005], and recommendations from researchers at the Harvard School of Public Health [*in* Tavera-Mendoza and White 2007] and others [Heaney et al. 2003a; Holick 2007; Tangripricha et al. 2003; Vieth 1999] conclude that healthy children and adults of any age should consume *no less than 1000 IU/day* of vitamin D_3 to reach and maintain minimum serum 25(OH)D levels of at least 30 to 32 ng/mL. To achieve this, the *Dietary Guidelines* specify that a combination of dietary and supplemental vitamin D would be necessary for any persons without adequate sun exposure – which includes almost all persons for at least some portions of the year.

There are some concerns about this guidance. The US Agency for Healthcare Research and Quality [AHRQ 2007] concluded: "Given the limitations in the measurement of 25(OH)D concentrations and the lack of standardization and calibration, it is difficult to suggest precise recommendations for adequate intakes, especially since optimal levels of serum 25(OH)D have not been defined."



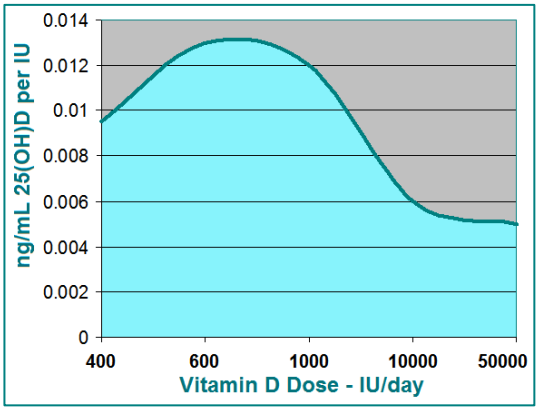
Many experts stress that 1000 IU/day of vitamin D may be inadequate for maintaining health. For example, as part of a recently reported larger study, Holick et al. [2008] administered 1000 IU/day of oral vitamin D_3 to healthy adults for 3 months, and concentrations of 25(OH)D were assessed weekly. See ***Graph*** [adapted from Holick et al. 2008; data points are mean ± SEM]. Serum 25(OH)D plateaued by about 6 weeks, and there was an average increase in 25(OH)D of about 9 ng/mL; however, relatively few of the subjects

(most of whom had typically inadequate 25[OH]D concentrations at the outset) achieved an optimal concentration of 30 ng/mL or more.

Similarly, Vieth and colleagues [2001] had found that 1000 IU/day of vitamin D_3 was ineffective for achieving optimal 25(OH)D concentrations. Whereas, 4000 IU/day D_3 in their study assured more adequate levels >30 ng/mL.

It should be further understood that supplemental vitamin D results in only a modest dose-response increase above baseline levels of circulating 25(OH)D, unless extremely large quantities are used. According to various data, there can be a variable increase in 25(OH)D *per each IU of vitamin D intake*, ranging from 0.002 to >0.01 ng/mL, with the greatest increases per IU at lower daily doses [AHRQ 2007; Barger-Lux et al. 1998; Cranney et al. 2007; Heaney 2004; Hollis 2005; Trang et al. 1998; Vieth 2005; Vieth et al. 2004].

Furthermore, the data indicate that the trend of 25(OH)D production in response to vitamin D_3 dose is curvilinear. That is, as the dose is increased, 25(OH)D concentrations per IU do not increase in direct proportion. See ***Graph*** [hypothetical approximation using integration of data from Barger-Lux et al. 1998 and Vieth 2005].



Greater increases appear at lower dose ranges, and the increments by which much larger amounts of vitamin D increase 25(OH)D levels are significantly smaller [Vieth et al. 2004]. Additionally, the effect of any increase in vitamin D also depends on the existing, or baseline, concentrations of 25(OH)D; if there are higher baseline levels of 25(OH)D to begin with, increases in vitamin D appear to have less profound effects [Heaney 2004; Lips 2001; Vieth 2005].

For example, in one experiment, a single dose of 50,000 IU of vitamin D_3 produced only a 7 ng/mL increase of 25(OH)D in young, healthy patients who already had optimal mean 25(OH)D concentrations of 32 ng/mL at baseline [Armas et al. 2004]. Whereas, when healthy subjects with mean baseline 25(OH)D concentrations of about 17 ng/mL were administered 4000 IU/day of vitamin D_3 for 2 weeks there was an average 25(OH)D increase of 9 ng/mL [Trang et al. 1998]. It is of interest to note that in the study by Holick and colleagues [2008] described above – in which 1000 IU/day of D_3 was administered – the same 9 ng/mL increase was observed but it took 6 weeks on average. In sum, however, increases of 25(OH)D at all 3 doses were modest.

There are several implications of these data for daily clinical practice:

Supplemental vitamin D produces only modest increases in circulating 25(OH)D, unless very large quantities of the vitamin are used on a daily basis.

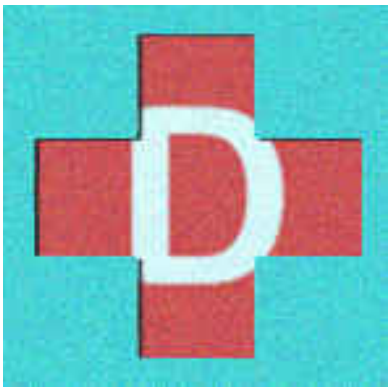
- Relatively smaller supplements of vitamin D_3 may be able to achieve meaningful increases of 25(OH)D, but they may take longer than larger doses. For example, given ample time, 1000 or 4000 IU/day of D_3 may have equivalent effects in raising 25(OH)D levels.
- Concentrations of 25(OH)D do not increase proportionately to the amount of supplementation increase. For example, tripling the D_3 dose – such as going from 600 IU/day to 1800 IU/day – does not increase the concentration of 25(OH)D by 3 fold.
- The increase in 25(OH)D also is dependent on the concentration of this metabolite at the start of treatment. At equivalent vitamin D doses, patients with more severe inadequacies will have larger, more rapid increases in 25(OH)D.
- What might be considered large doses of vitamin D_3 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, as noted above, a single 50,000 IU dose

of D_3 may produce a significantly smaller increase in 25(OH)D than 1000 IU given daily over time, and the increases from either of these could be modest.

- However, it must be noted that continuous megadoses of vitamin D could produce robust, possibly toxic, increases in the 25(OH)D metabolite. In one experiment that administered 50,000 IU of vitamin D_3 *per day for 8 weeks*, 25(OH)D was increased by 257 ng/mL [Barger-Lux et al. 1998], which could induce vitamin D toxicity [Hathcock et al. 2007].

In daily practice, exceptionally large amounts of daily vitamin D dosing would rarely be necessary. 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 daily supplementation of only about 1300 IU [Heaney 2004] to 1700 IU [Vieth et al. 2007] of vitamin D_3. Within the context of this report, 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 (see *section 7a*).

5. Vitamin D Safety Profile



The other side of adequate intake is the question: How much vitamin D is too much? Safety is always an important consideration when recommending nutritional supplements, and there have been concerns among some healthcare providers about "overdoing" vitamin D.

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 rare.

5a. Tolerance & Toxicity

Excessive intake and accumulation of vitamin D sometimes is called "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*** [Barrueto et al. 2005; Blank et al. 1995; Calcitriol 2007; Carroll and Schade 2003; Ergocalciferol 2007; Johnson 2007; Klontz and Acheson 2007; Koutkia et al. 2001; Mayo Clinic 2007; Todd et al. 1987; Vieth et al. 2002].

Signs/Symptoms – D Toxicity

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

The rather diverse signs/symptoms in patients with pain may be difficult to attribute to hypercalcemia due to vitamin D intoxication, since they might mimic those of neuropathy, opioid side effects, or other ailments. Paradoxically, some symptoms match those of *hypo*calcemia (see *section 3c*), and patients with serum 25(OH)D at toxic levels also can be clinically asymptomatic [Blank et al. 1995]. Total serum calcium values denoting hypercalcemia may range from mild (10.5-12 mg/dL) to moderate (>12-14 mg/dL) to severe (>14 mg/dL) [Carroll and Schade 2003].

Hypercalcemia also may be associated with certain cancers (*eg,* lymphoma), granulomatous disease (*eg*, tuberculosis or sarcoidosis), rare genetic disorders, and certain medications

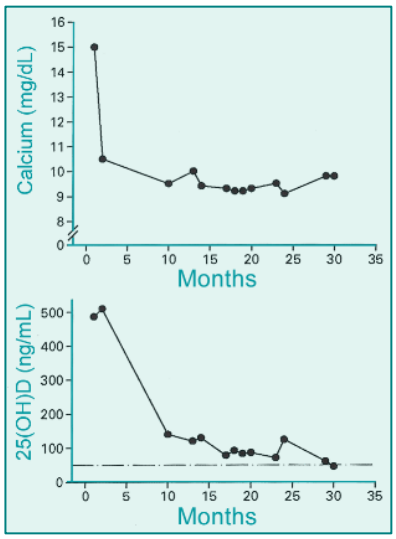
(*eg*, lithium, thiazide diuretics) [Carroll and Schade 2003; Mayo Clinic 2007]. In these patients, toxicity may occur at levels of vitamin D intake that normally would be well tolerated [Hathcock 2004].

A history of excessive vitamin D intake may be the only clinical clue differentiating vitamin D toxicity from other causes of hypercalcemia.

Typically, persons older than 50 are more sensitive to abnormal elevations in calcium [Mayo Clinic 2007]. Hypersensitivity to vitamin D also can occur in persons with primary hyperparathyroidism, which may stimulate overproduction of $1,25(OH)_2D$ from 25(OH)D and foster hypercalcemia [Vieth 1999].

A history of excessive vitamin D intake may be the only clinical clue differentiating vitamin D toxicity from other causes of hypercalcemia. Serum 25(OH)D levels are usually elevated to >150 ng/mL in such cases, while concentrations of $1,25(OH)_2D$ may be normal and its measurement is not needed to confirm the diagnosis [Johnson 2007].

Besides hypercalcemia, a case definition of "vitamin D poisoning" might also include hypercalciuria, hyperphosphatemia, nephrocalcinosis, and nephrolithiasis [Koutkia et al. 2001; Sterkel 1998]. Besides in the kidneys, calcifications also may occur in muscle, cartilage, or heart tissue [Blank et al 1995; Hathcock 2004].



In cases of verified vitamin D intoxication resulting in hypercalcemia, the agent is immediately discontinued and treatment usually requires hospitalization. Several therapies may be combined, including intravenous fluids, loop diuretics, bisphosphonates, calcitonin, glucocorticoids, and hemodialysis [Barrueto et al. 2005; Carroll and Schade 2003; Calcitriol 2007, Ergocalciferol 2007; Johnson 2007; Mayo Clinic 2007]. Calcium levels can be fairly rapidly brought under control with treatment; conversely, 25(OH)D can take many months to approach more normal concentrations due to the release of stores accumulated in body tissues, and this accumulation would depend on how long the person had been taking excessive doses of vitamin D. See ***Graph*** [adapted from Koutkia et al. 2001].

There have not been any reports in the literature of a single, one-time excessive dose of vitamin D (D_2 or D_3) being toxic or fatal in humans. And, it appears that daily dosing of very large amounts over time is required to produce toxic concentrations of circulating 25(OH)D and hypercalcemic effects.

Since full exposure to sunlight can provide the vitamin D_3 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 exposure to sunlight [Hollis 2005]. Concentrations of 25(OH)D observed in persons with extensive daily sun exposure – *eg*, lifeguards, farmers – range up to 94 ng/mL, and this has not been demonstrated as causing hypercalcemia or being otherwise toxic [Vieth 2005].

Still, supplementation via commercially produced vitamin D supplements would circumvent natural mechanisms in human skin that prevent excess D_3 production and accumulation resulting from sun exposure, as described in *section 2b*. A Tolerable Upper Intake Level, or UL, for oral vitamin D_3 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 [ODS 2008].

However, many experts assert that the 2000 IU/day UL is far too low [Heaney 2004; Heaney et al. 2003a; Holick 2003a, 2003c; Vasquez et al. 2004; Vieth 2005]. In fact, recent results of a clinical trial in adolescents found that 2000 IU/day of D_3 (given as 14,000 IU once per week) was not only safe but *minimally* necessary for achieving adequate 25(OH)D levels [Maalouf et al. 2008].

The Washington, DC-based Council for Responsible Nutrition has proposed that the UL for supplementation should be 2400 IU/day at a minimum [Hathcock 2004]. And, an extensive review

by Hathcock et al. [2007], applying risk-assessment techniques, concluded that the UL for vitamin D consumption by adults actually could be 10,000 IU/day of D_3, without risks of hypercalcemia or renal stone formation.

The *duration* of high vitamin D intake may be the more critical factor. Taking 10,000 IU of D_3 daily for 6 months has been implicated as toxic [Jacobus et al. 1992; Reginster 2005], whereas Holick [2007] noted that this daily amount in adults can be well tolerated for 5 months. And, this 10,000 IU dose was used successfully and safely during 3 months in one study for relieving back pain [Al Faraj and Al Mutairi 2003].

Vieth et al. [2004] demonstrated that 4000 IU of D_3 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.

A common feature of vitamin D overdose incidents is that the victims were not knowingly or intentionally taking excessive amounts, and no one was taking vitamin D under practitioner supervision.

Looking at much larger doses, some researchers have proposed that long-term, daily consumption of 40,000 IU of vitamin D would be needed to cause hypercalcemia [Tavera-Mendoza and White 2007; Vieth 2005]. The US Office of Dietary Supplements [ODS 2005] notes that hypercalcemia can result from 50,000 IU/day or more taken for an extended period of time.

Used on an *infrequent* basis, extremely large doses of vitamin D have not produced adverse effects. This included 100,000 IU of D_3 administered every 4 months [Trivedi et al. 2003] and once-yearly doses of 300,000 IU of D_2 [Smith et al. 2007]. (See *section 7a* for a further discussion.)

However, a number of case reports of vitamin D toxicity involving very high doses, and including 6 fatalities, have appeared in the literature. See ***Appendix 2*** for a summary of incident reports.

A common feature of the incidents is that victims were not knowingly or intentionally taking excessive amounts of vitamin D, and no one was taking vitamin D under practitioner supervision. Most cases appear to have hinged on either the purchase of tainted vitamin D supplements, inattention to the appropriate use of supplements as indicated in directions, or accidental use of supplements not intended for human consumption. One report involved milk fortified with harmfully excessive amounts of vitamin D.

In the incident reports, 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. Considering the extremely large amounts consumed, it is noteworthy that there were few deaths, and it appears from the reports that the fatalities resulted from secondary causes during treatment for hypercalcemia. In almost all cases, toxic overdoses could have been avoided with better quality control in product manufacture and/or proper education of patients in their use. See ***Box***.

> ⚠ ***Caution:***
>
> *Patients should be instructed in how to take vitamin D supplements and advised to purchase them from sources they know and trust. In most cases, patients should consult their pharmacist for a recommended brand of product.*
>
> *Patients also should be warned against purchasing large-dose products (eg, >2000 IU) unless specifically directed to do so.*
>
> *Finally, vitamin D tablets cannot be split into smaller dose sizes with any surety of strength in each portion.*

As another measure of safety, consolidated data were examined from 2006 (the most recently reported) from 61 poison control centers serving 300 million persons in the United States [Bronstein et al. 2007]. 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. About 1 in 5 vitamin D cases involved children under age 6, only 13% of all cases required treatment in a healthcare facility, and in almost all patients (92%) adverse signs or symptoms were absent or minimal in nature. Only 5 (8%) 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.

5b. Vitamin D-Drug Interactions

There have been relatively few mentions in the literature of vitamin D supplements interacting with other agents or medications. These are summarized in the ***Table*** [Bringhurst et al. 2005; Calcitriol 2007; Ergocalciferol 2007; Holick 2007; Hollis et al. 2005; Marcus 1995; Mascarenhas and Mobarhan 2004; ODS 2005; Turner et al. 2008]. In most cases, the potency of vitamin D is reduced and the dose can be increased to accommodate this (◆). Conversely, very high doses of vitamin D can be avoided if there is a risk of hypercalcemia (o).

Potentially Interacting Drugs

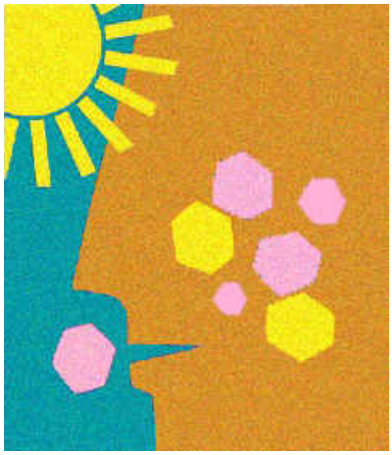
- ◆ antacids (aluminum- or magnesium-containing)
- ◆ anticonvulsants (eg, carbamazepine)
- ◆ antirejection meds (after organ transplant)
- ◆ antiretrovirals (HIV/AIDS therapies)
- ◆ barbiturates (eg, phenobarbital, phenytoin)
- ◆ cholestyramine
- ◆ colestipol
- ◆ corticosteroids
- ◆ glucocorticoids
-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

- ◆ Aluminum- or magnesium-containing antacids can negatively affect calcium and phosphate absorption and excretion, making vitamin D supplementation less effective.
- ◆ Anticonvulsants (eg, carbamazepine), antiretrovirals (AIDS therapies), and antirejection medications (after organ transplant) may activate more rapid destruction of vitamin D metabolites, requiring higher vitamin D dosing.
- ◆ Barbiturates (eg, phenobarbital, phenytoin) may decrease circulating levels of 25(OH)D or cause resistance to effects of the 1,25(OH)2D metabolite. Higher doses of vitamin D supplements may be required.
- ◆ Cholestyramine and colestipol (anticholesterol agents) may decrease vitamin D effects.
- ◆ Corticosteroids and glucocorticoids may inhibit intestinal calcium absorption or cause more rapid calcium depletion, thereby decreasing therapeutic benefits of vitamin D.
- ◆ Hydroxychloroquine (Plaquenil®) is an antirheumatic agent that has been noted to possibly inhibit conversion of 25(OH)D to the active 1,25(OH)2D [Huisman et al. 2001].
- ◆ Rifampin may increase vitamin D metabolism or accelerate its clearance, requiring higher vitamin D dosing.
- o Digitalis/digoxin may interact with elevated calcium levels facilitated by vitamin D supplements to increase risks of hypercalcemia. High-dose vitamin D should be avoided.
- o Thiazide and similar diuretics in conjunction with vitamin D supplementation may decrease calcium excretion by the kidneys and increase risks of hypercalcemia. High doses of vitamin D supplementation should probably be avoided.

Other agents/effects have been noted in the literature (but are not on the table):

- ◆ St. John's wort may accelerate the destruction (*catabolism*) of 25(OH)D and 1,25$(OH)_2$D thereby reducing effects of vitamin D [Shinchuk and Holick 2007].
- ◆ Alcohol can work against vitamin D by reducing intestinal absorption of calcium and/or inhibiting conversion of vitamin D in the liver to 25(OH)D [ODS 2005]. The amount of alcohol consumption leading to these deleterious effects is unknown.
- ◆ Mineral oil and stimulant laxatives decrease dietary calcium absorption and can influence hypocalcemia [ODS 2005].
- ◆ Gastric bypass and other gastric or intestinal resection procedures have been associated with vitamin D insufficiency [Lyman 2005; Turner et al. 2008].
- ◆ Tobacco smoking is associated with significantly reduced levels of both 25(OH)D and 1,25(OH)2D, as compared with nonsmokers [Brot et al. 1999]; therefore, smokers may need higher amounts of vitamin D supplementation.

It should be noted that not all patients would be affected by the interactions or effects, and vitamin D has not been noted to interfere with the actions of any medications. The active 1,25(OH)2D metabolite may weakly induce the enzyme CYP3A4 in the liver, but no effects on the many drugs metabolized by this enzyme have been reported [Calcitriol 2007]. Therefore, *none of the interactions listed above has been indicated in the literature as a contraindication for vitamin D supplementation*.



6. Clinical Research – Vitamin D in Chronic Pain

Aches, pains, and other symptoms associated with vitamin D inadequacies have been documented for more than a century in the scientific literature [Holick 2004a]. *Sections 2c and 3* of this report discussed the scientific rationale for these effects, largely relating to osteomalacic processes. The clinical research evidence extends beyond theoretical possibilities and demonstrates implications for daily medical practice in patients with chronic musculoskeletal pain.

6a. Evidence Summary

Appendix 3 summarizes 22 clinical investigations of vitamin D in patients with chronic musculoskeletal-related pain, which were discovered during the literature search for this report. These studies were conducted in various countries and included approximately 3670 patients representing diverse populations and age groups.

The percentages of patients having pain in association with inadequate vitamin D 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.

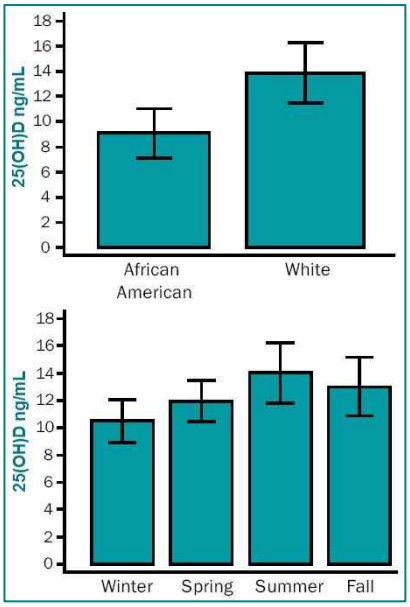
While this percentage is a high rate of deficiency, some of the reported 25(OH)D deficits in patients with pain might be considered as merely reflecting the background prevalence of vitamin D inadequacy in the general population (as noted in *section 3e*). However, the several investigations that included 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 [Bensen et al. 2006; Erkal et al. 2006; Glerup et al. 2000b; Lofti et al. 2007].

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 overall prevalence of vitamin D inadequacy in the various populations, and it also confirms that vitamin D deficits do not *always* result in musculoskeletal pain in all persons.

In one of the larger cross-sectional studies, Plotnikoff and Quigley [2003] included 150 children and adults (ages 10 to 65 years) with chronic (>1 year), *non-specific* musculoskeletal pain that was refractory to standard pharmaceutical therapy and presumably due to osteomalacic processes. Patients with diagnosed fibromyalgia, complex regional pain syndrome, or other disorders that might have accounted for the pain were excluded.

The researchers found that 93% of the patients were vitamin D-deficient: mean 25(OH)D = 12.8 ng/mL (95% confidence interval 11.18-12.99 ng/mL). More than a quarter (28%) had severe deficiencies ≤8 ng/mL. All age groups were equally affected, and there were no differences between males and females.

Of interest, 100% of dark-skinned patients (*eg*, African-American, East-African, Hispanic) had severely deficient levels of vitamin D. In a typical pattern, mean serum 25(OH)D levels in African-Americans were significantly lower than in white patients (p<.007). See ***Graph*** top.



Also as expected, the researchers found seasonal differences in their study conducted in a northern US city (Minneapolis, MN). Overall serum 25(OH)D levels were significantly lower in winter than summer (p=.009, see ***Graph*** bottom), although adequate levels still were not achieved during sunnier months.

This study was important because it showed that the risk of deficient vitamin D affecting pain in the United States is not bound to traditional risk categories, such as the elderly. Indeed, similar deficits were seen across all groups regardless of age, sex, race, or season. The authors also note that, surprisingly, the possibility of vitamin D-related osteomalacia *was not previously suspected as a diagnosis* in any of the patients, despite the fact that most patients had extensive prior contact with healthcare providers regarding their chronic musculoskeletal pain symptoms.

In 4 of the studies, researchers reported results of vitamin D supplementation therapy in response to the symptoms putatively related to the 25(OH)D deficiencies that they detected.

- In a 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 severe 25(OH)D deficiencies [Al Faraj and Al Mutairi 2003]. This study was of interest because, as in the study by Plotnikoff and Quigley [2003] described above, only cases of idiopathic pain most probably associated with osteomalacia were included; patients with diagnosed pain due to anatomical, neuropathic, or injury-related causes were excluded.
- In a small 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 [de la Jara et al. 2006]. 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 5 patients who had been confined to wheelchairs [Prabhala et al. 2000]. Four of the patients reportedly became fully mobile upon normalization of their 25(OH)D concentrations.
- An earlier case report of 5 patients by Gloth and colleagues [1991] noted that vitamin D supplementation produced significant and rapid improvements in hyperesthesias (nonspecific oversensitivity to physical stimuli) that had been unresponsive to analgesic therapy.

While there are certain limitations of the research to date on vitamin D therapy for chronic pain syndromes, there also are many strengths. Both aspects are considered in *section 6d*.

6b. Analgesic-Sparing Effects

The diffuse musculoskeletal pains associated with vitamin D inadequacy are often poorly responsive to opioid and NSAID analgesics [Nellen et al. 1996], sometimes resulting in patients taking large doses of these medications on a daily basis. Several investigations are suggestive of a potential analgesic-sparing effect achieved by more adequate vitamin D concentrations in such patients, and this could have important implications for better pain management.

The concept was first suggested in an animal model. Vitamin D-deficient rats exhibited increased pain sensitivity and developed morphine tolerance more rapidly than non-deficient animals [Bazzani et al. 1984]. Both the pain sensitivity and opioid tolerance were normalized by vitamin D_3 administration.

Possible analgesic-sparing effects of vitamin D therapy could be an important benefit even if the pain itself is only partially resolved.

In humans, studies at the Mayo Clinic found that more than half (140/267) of the enrolled patients with chronic pain were taking opioid analgesics [Hooten et al. 2007; Turner 2008]. However, almost twice the amount of morphine-equivalent opioid was required by patients who had inadequate vitamin D. They also were taking opioids significantly longer, reported poorer physical functioning, and had poorer health perceptions than opioid-taking patients having adequate vitamin D levels.

Another investigation reported analgesic consumption in 33 women with chronic symptoms of osteomalacia and deficient 25(OH)D concentrations. Their use of both opioids and NSAIDs decreased by 75% as a result of vitamin D supplementation therapy [de la Jara et al. 2006].

In a case report, a 94-year-old woman experiencing severe lower leg pain was taking oxycodone/acetaminophen every 4 hours. Within 1 week of daily therapy with 1600 IU D_2, and only a small increase in her very deficient serum 25(OH)D level, she could discontinue the opioid medication, and analgesia consisted mainly of once-daily acetaminophen [Gloth et al. 1991].

The relative roles of vitamin D in achieving analgesic-sparing effects by either reducing pain sensitivity, improving the activity of NSAIDs or opioids, or resolving underlying pain-generating processes (*eg*, osteomalacia, myopathy) need further exploration. Meanwhile, this could be an important benefit of vitamin D supplementation, even if the pain itself is only partially resolved.

6c. Subclinical Phenomena

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 are nevertheless contributing sources of nociception in patients with chronic pain [Turner et al. 2008]. In these cases, 25(OH)D concentrations, if measured, might erroneously not be considered as *inadequate enough* to influence bone, joint, or muscle complaints. Additionally, other traditional biomarkers of dysfunctional bone metabolism and osteomalacia – such as abnormal calcium or phosphorous – may be absent.

This has been proposed as a "subclinical" effect of vitamin D inadequacy [Glerup et al. 2000b; Lotfi et al. 2007; Masood et al. 1989]. In such cases, subjective musculoskeletal pain or weakness develops prior to the emergence of more objective clinical indicators.

Lotfi et al. [2007] 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.

In their study of 60 female patients with chronic lower-back pain [Lofti et al. 2007], very few had overt signs/symptoms of osteomalacia. This study was interesting in that the researchers also used a high threshold of 40 ng/mL to define 25(OH)D "deficiency," and a significant portion of patients with pain were below this level compared with a control group of pain-free patients. Chronic pain was significantly correlated with respectively lower 25(OH)D and higher PTH concentrations ($p<.05$). However, there were no differences in calcium or phosphorus concentrations between groups.

Other clinical studies confirm that musculoskeletal pain and/or myalgia may be present as a result of osteomalacic processes, without exhibiting all of the traditional clinical signs or biomarkers of the disorder. For example, calcium, alkaline phosphatase, and/or phosphorus concentrations may be normal in the presence of 25(OH)D deficiencies and elevated PTH levels [Glerup et al. 2000b; Helliwell et al. 2006]. Although, in other cases, elevated alkaline phosphatase may be the only early warning sign of vitamin D deficiencies capable of causing musculoskeletal pain and fatigue syndromes [Masood et al. 1989].

Musculoskeletal pain can be related to inadequate vitamin D with or without diagnostic biomarkers denoting underlying disturbances of bone metabolism and osteomalacia.

The important principle seems to be that musculoskeletal pain can be related to inadequate vitamin D with or without a set of diagnostic biomarkers denoting underlying disturbances of bone metabolism and osteomalacia. Even 25(OH)D concentrations themselves may not be at a level that many practitioners would consider inadequate [Block 2004], yet supplementation with vitamin D could be of benefit in helping to provide pain relief.

For example, one case report noted a severe chronic pain syndrome in an 86-year-old woman whose 25(OH)D concentration was 41 ng/mL [Gloth et al. 1991]. A single 50,000 IU dose of D_2 improved her pain within 1 week.

As Holick [2004a] 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 deficit in nanograms-per-milliliter may not matter – as long as the shortfall is corrected to the extent necessary.

6d. Research Strengths & Limitations

Taken as a whole, the research evidence summarized in *Appendix 3* and discussed above supports vitamin D supplementation as a potentially important therapy for helping to ameliorate muscle, bone, and joint aches and pains. Several strengths of the evidence should be acknowledged:

1. There is a plausible physiologic mechanism of action, validated by scientific research in humans, explaining the role of vitamin D in maintaining calcium homeostasis and healthy bone metabolism. The potential of vitamin D inadequacy to foster osteomalacic processes that contribute to musculoskeletal pain syndromes is well understood and may imply a possible cause-effect relationship. See *sections 2 and 3* above.

   For example, in one report, a patient whose pain was relieved by vitamin D supplementation stopped the therapy and redeveloped 25(OH)D deficiency, at which point the pain returned [Gloth et al. 1991]. When supplementation was resumed the pain again was resolved, which is suggestive of the pain resulting secondarily from 25(OH)D deficiency.

2. In the research investigations to date, patients found to have inadequate 25(OH)D concentrations had been variously diagnosed with fibromyalgia syndrome, hyperesthesia, rheumatic disorders, osteoarthritis, back pain, bone and joint pain, muscle weakness, and other chronic somatic complaints. All of these chronic conditions had been resistant to other therapies for pain and most could not be traced to known injuries, disease, or anatomic defects.

3. The evidence has demonstrated that the rate of 25(OH)D inadequacy in these patients with variously diagnosed chronic pain syndromes was significantly greater than the normal background prevalence of such deficits in the general population.

4. In afflicted patients, vitamin D supplementation therapy has been clinically observed to significantly resolve or ameliorate symptoms of pain and/or muscle weakness.

Despite research limitations, vitamin D therapy has demonstrated significant effectiveness for various musculoskeletal pain conditions and in diverse patients.

In fair balance, there are several limitations of the research that must be equally acknowledged:

A. Randomized controlled trials (RCTs) have not been conducted to assess vitamin D therapy for chronic, nonspecific musculoskeletal pain and fatigue syndromes. Such investigations would be helpful and could be important for defining which disorders are relieved most by vitamin D therapy and the dosing regimens that are optimal for particular groups of patients.

B. Studies to date have been observational in design, and some included small numbers of patients or were case reports. Also, while it might be expected that followup vitamin D therapy was provided to all patients with pain having inadequate 25(OH)D concentrations, such treatments and their outcomes were reported by relatively few investigators.

C. Since none of the studies that did report treatment outcomes was placebo-controlled, there is the possibility of a placebo effect that influenced reported pain reductions. However, depriving subjects known to have deficient 25(OH)D levels of active therapy could be unethical [Vieth et al. 2004]. Judging from the significant improvements facilitated by vitamin D therapy in patients with previously recalcitrant pain conditions it is unlikely that a placebo effect would be the only or most plausible explanation.

Hopefully, future investigations of vitamin D for chronic musculoskeletal pain will employ more rigorous research designs to further define benefits of this therapy. For example, it is evident that not all persons with inadequate 25(OH)D levels develop musculoskeletal maladies; however, predisposing factors affecting one person but not another are unknown.

Certainly, if clinical osteomalacia and/or hypocalcemia are diagnosed, vitamin D supplementation would be clearly indicated. In more ambiguous cases, possibly subclinical in nature, the underlying pathology may be unknown, and there would be questions about exactly which pain conditions and which patients could benefit most from vitamin D therapy. The research to date does not provide definitive answers to such questions.

Vitamin D therapy has demonstrated significant effectiveness in those trials that have reported its application for various musculoskeletal pain conditions and in diverse patients. However, from the research to date, it would be presumptuous to consider vitamin D supplementation as a remedy for *all* such conditions in *all* patients. And, there is no evidence to suggest that any other treatments for chronic pain should be cast aside in favor solely of vitamin D therapy.

Still, relying on the preponderance of current evidence, along with expert commentary reviewed for this report, it appears that vitamin D therapy could be a reasonable adjunctive approach for treating almost any patient experiencing chronic nonspecific musculoskeletal pain, and associated muscle weakness or fatigue. The next section discusses how interested healthcare providers might incorporate this therapy into daily practice.

7. Putting 'D' Into Practice Against Pain

From the research, it appears that individual responses to vitamin D therapy can vary. Other factors – sun exposure, diet, season of year, age, physical health, and other medications or supplements – also can play roles. Therefore, optimal vitamin D dosing requirements for individual patients having various types of chronic musculoskeletal pain and related symptoms are not fully defined. In most cases, it appears that any amount of supplementation achieving a significant rise in 25(OH)D levels can have at least some beneficial effects.

Various vitamin D dosing protocols to overcome inadequacies of the 25(OH)D metabolite have been reported in the literature. Some are quite aggressive, using high doses of vitamin D. This report recommends a reasonably conservative approach as a start, plus some patience regarding expectations for improvement.

7a. Proposed Dosing Protocol for Chronic Pain

In both healthy persons and in patients with pain, researchers have examined daily vitamin D supplementation ranging from 600 IU to 50,000 IU [Barger-Lux et al. 1998; Shinchuk and Holick 2007; Vieth 2005], as well as much larger amounts. However, there do not appear to be any standardized guidelines recommending particular dosing protocols for all situations.

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 extremely large oral or intramuscular megadoses on an infrequent basis. For example, single doses of 300,000 IU D_2 have been used in the expectation that they would suffice for many months or even a whole year [Smith et al. 2007].

An objective of such aggressively high dosing is to fill vitamin D reservoirs in adipose and other tissue, and also to provide ample amounts for conversion to the 25(OH)D and 1,25(OH)2D metabolites [Shinchuk and Holick 2007]. This is often called "stoss therapy" (German for *to bump*) and it has been more commonly used outside the US [Vieth 1999].

Some researchers have proposed less extreme but still relatively high dosing. Hathcock et al. [2007] and others [Trivedi et al. 2003] noted that amounts of vitamin D up to 100,000 IU would not be toxic if restricted to 1 administration every 4 months, or daily for a single period of 4 days. In one study, patients with chronic musculoskeletal pain and severe 25(OH)D deficiencies were treated with 100,000 IU of D_2 via intramuscular injection weekly for 1 month, followed by 1 injection per month for 5 months. Additionally, patients received a daily oral supplementation of up to 600 IU D_2, plus 800 to 1200 mg of calcium carbonate. They experienced a 5-fold increase in serum 25(OH)D and significant improvements in pain symptoms, without reported toxicity or adverse effects [Glerup et al. 2000b].

Other experts have suggested that remediation of vitamin D deficiency can be achieved by 50,000 IU of D_2 on a monthly basis [Heath and Elovic 2006], or once per week [Holick 2003b, Malabanan et al. 1998; Prabhala et al. 2000; Shinchuk and Holick 2007], or daily for up to 60 days [Russell 1994; Ziambaras and Dagogo-Jack 1997]. Holick [2007] recommended that in patients with clinically verified 25(OH)D deficiency a cost-effective approach for its correction and to maintain adequate levels is administering a 50,000 IU pharmaceutical vitamin D_2 capsule once weekly for 8 weeks, followed by 50,000 IU of D_2 every 2 to 4 weeks thereafter.

In one study of patients with chronic back pain, subjects were treated for 3 months with 5000 IU/day to 10,000 IU/day of vitamin D_3 (heavier patients >50 kg received the larger dose)

[Al Faraj and Al Mutairi 2003]. There were no episodes of hypercalcemia reported, and pain symptoms were relieved in 95% of the patients.

In most cases, extremely large doses of vitamin D would be unnecessary to achieve pain relief; assuming pathways of vitamin D metabolism are intact.

Despite the reported successes of larger-dose vitamin D supplementation, many healthcare providers may be uncomfortable in 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.

To maintain normal physiological needs in otherwise healthy patients, some experts have recommended a daily vitamin D intake of 1000 to 2000 IU [Holick 2007; Johnson 2007; Maalouf et al. 2008]. Others have proposed 3000 IU to 4000 IU as necessary [Holick 2007; Vasquez et al. 2004; Vieth et al. 2004]. Higher-range doses can be especially important during winter months [Heaney et al. 2003a] and in those older adults who have malabsorption problems [Gostine and Davis 2006].

However, in patients with chronic pain, Gloth and colleagues [1991] observed that symptom relief often can be achieved with relatively modest increases in 25(OH)D and $1,25(OH)_2D$ 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 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 quantity (upregulated) and, thereby, physiologically requiring extra amounts of the $1,25(OH)_2D$ hormone.

Consequently, in many cases, less frequent large doses of vitamin D may not offer an advantage over consistent daily dosing with more moderate quantities. Gloth et al. [1991] treated patients with chronic pain syndromes with 1600 IU of D_2 per day and noted only modestly increased 25(OH)D levels but effective resolution of pain symptoms. Administration of a single 50,000 IU D_2 dose in similarly afflicted patients produced equivalent, but not better, results.

Another study compared one group of patients administered a daily oral regimen of 800 IU of D_3 plus 1000 mg calcium with a second group receiving the same oral regimen *plus* 2 intramuscular injections of 300,000 IU D_3 one month apart [de la Jara et al. 2006]. Both regimens produced equivalently effective pain relief, so the booster injections provided no added benefit.

It also should be noted that very large doses of vitamin D – whether oral or intramuscular – would be most safely administered by a healthcare provider during an office visit, incurring added cost and patient inconvenience. Smaller, daily doses can be easily taken by patients or administered by a caregiver at home.

In the study by Lee and Chen [2008], patients experiencing painful neuropathy self-administered approximately 2000 IU per day of D_3 for 3 months. At this moderate dose, the researchers reported a 67% increase in serum 25(OH)D (from 18 ng/mL to 30 ng/mL, on average, or 0.006 ng/mL per IU) and a nearly 50% improvement in pain scores.

Finally, it must be emphasized that there appears to be a minimum threshold for vitamin D supplementation below which benefits are not realized. In one study of elderly persons, daily vitamin D supplementation of less than 800 IU was no better than placebo in terms of improved muscle strength [Broe et al. 2007]. Minimum doses required for alleviating chronic pain conditions have not been determined, but as most of the research evidence suggests they could be significantly higher than doses required by persons without pain for health-maintenance purposes.

Therefore, based on available evidence, the best choice for startup vitamin D supplementation in most patients with chronic musculoskeletal pain might be a compromise between higher, more aggressive dosing and amounts that could be too low for producing meaningful results. As with any other pharmacotherapy, the most prudent path would be to start at a moderate dose of vitamin D expected to be effective, to monitor outcomes for a period of time, and to go higher if necessary as individual patient needs might dictate. A proposed conservative dosing protocol is outlined in the ***Side Box***.

As noted above in this report, patients with chronic, nonspecific pain and fatigue syndromes can be reasonably assumed to have inadequate 25(OH)D concentrations. They all should be advised to take a daily multivitamin providing essential nutrients, including at least a basic amount of calcium and from 400 IU to 800 IU of vitamin D_3.

Patients should further be advised to add a daily supplement of 2000 IU of vitamin D_3 to this regimen, bringing the total daily vitamin D_3 intake to 2400 IU to 2800 IU. This is also a convenient supplement dose, since inexpensive 1000 IU D_3 tablets or capsules are available from most pharmacies or health food departments in many stores, and some are now stocking 2000 IU/dose tablets.

Over time, this total daily vitamin D_3 supplement might be expected to raise serum 25(OH)D concentrations by approximately 17 ng/mL to 28 ng/mL, depending on baseline levels (see *section 4c*). The greatest increases would be in patients having more severe vitamin D deficiencies at the start, so there would be no concerns about 25(OH)D concentrations rising to anywhere near toxic levels as a result of this supplementation protocol. In fact, some patients still might not reach the most optimal levels of 25(OH)D (>30 ng/mL).

Vitamin D therapy would be contraindicated in patients with pre-existing excessive levels of calcium, and special caution might be advised in those prone to forming kidney stones. Some medications and physical conditions may limit therapeutic response to vitamin D, requiring higher dosing (see ***Side Box*** cautions and *section 5b*).

Although many patients with pain may not have adequate daily calcium intake, its supplementation beyond the added amount provided by diet (see ***Appendix 4***) and the multivitamin may be unnecessary. The vitamin D_3 supplementation will allow available calcium to be used more efficiently. However, if a calcium deficiency is suspected, and/or there are concerns about osteoporosis

Vitamin D Supplementation for Chronic Pain
Proposed Conservative Dosing Protocol

1. 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.
2. 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.
3. Recommend a daily 2000 IU vitamin D_3 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 (eg, in postmenopausal women or the elderly).*
4. Monitor patient compliance and results for up to 3 months. *Other therapies for pain already in progress do not necessarily need to be discontinued.*
5. 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_3 with or without added calcium as appropriate, followed by ongoing supplementation as maintenance.

⚠ Caution:

Vitamin D supplementation would be contraindicated in patients with hypercalcemia or hypercalcuria [Ergocalciferol 2007].

It should be cautiously used in patients prone to renal stone formation [Hathcock et al. 2007].

Certain conditions may limit response to vitamin D therapy, such as chronic renal or liver disease, or intestinal malabsorption due to age, inflammatory bowel disease, Crohn's disease, or celiac disease [Hollis et al. 2006; Johnson 2007; Mascarenhas and Mobarhan 2004]. Higher dosing of vitamin D may be required to achieve therapeutic effects.

(*eg*, in postmenopausal women or the elderly), calcium supplementation can be recommended [Johnson 2007; Lips 2001].

To the extent practical, patient compliance with the regimen should be monitored; some patients may not adhere to the daily routine or take the recommended amount of vitamin D_3. This problem would probably relate more to forgetfulness, rather than product cost or a difficult dosing regimen serving as deterrents.

Some results of vitamin D_3 therapy may be experienced within a week but more likely it could take months, as is discussed in the next section. Current therapies for chronic pain, started prior to initiating vitamin D_3 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_3 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_3 dosing protocol, there are several possibilities and potential courses of action to consider:

More time, rather than increased doses, may be necessary for vitamin D_3 therapy to effectively raise concentrations of 25(OH)D, lower PTH levels, and saturate vitamin D receptors.

- In most cases, more time rather than increased doses may be necessary for vitamin D_3 therapy to effectively raise 25(OH)D concentrations, lower PTH levels, and/or saturate vitamin D receptors with the $1,25(OH)_2D$ metabolite. However, obese persons, alcohol abusers, or tobacco smokers may need somewhat higher dosing.
- The severity of vitamin D deficiency or PTH elevation fostering osteomalacic processes could have been greater than suspected, and laboratory assessments might be helpful at this point. If indicated, the patient might benefit from a course of high-dose vitamin D_3 supplementation described above in this section: *eg*, 5000 or 10,000 IU/day for 3 months, 50,000 IU/day for several weeks, etc. This would be followed by more conservative doses for ongoing maintenance. Healthcare professionals unfamiliar with high-dose regimens may want to consult with or refer patients to a specialist with more expertise in this application of vitamin D therapy.
- The particular chronic pain condition might be such that it cannot be alleviated by vitamin D_3 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.

Assuming that at least some pain relief and/or other benefits of vitamin D therapy can be achieved, a next question is: *How long should supplementation be continued*? At conservative doses recommended in this report, 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 [Marshall 2008].

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. Also, as patients improve they may become more active outdoors and can be instructed to acquire substantive vitamin D from sun exposure, thereby, at least during summer months, less daily vitamin D from supplementation might be required.

7b. How Long Until Improvement?

From the clinical research it appears that improvement resulting from vitamin D therapy may require up to several months or longer. However, it is important to first consider what is meant by "improvement" – that is, how will patients with chronic musculoskeletal pain and their healthcare providers know if vitamin D therapy is helping?

Rapid and complete pain relief would be easy for patients to detect, but in most cases this could be an unrealistic expectation. Even long-term treatment with strong opioids in some patients may fail to produce measurable improvements in chronic pain [Toombs 2007]. And, according to a meta-analysis examining pharmacologic interventions for osteoarthritis, oral opioids or NSAIDS produce only a temporary 10% improvement in pain scores [Bjordal et al. 2007]. Therefore, it might be unreasonable to hold vitamin D therapy to an extremely high standard of performance as an analgesic.

The evidence for pain-relieving and other benefits of vitamin D therapy – discussed in *sections 2c and 6* – is suggestive of a potential range of improvements, some more obvious than others. For example, besides complete pain relief, patients may experience partial pain relief, reduced intensity or frequency of pain, less soreness or stiffness in muscles, increased stamina or strength, reductions in NSAID or opioid use, and improvements in mood or overall quality of life. These results are less spectacular than complete pain relief, but are still important and worthwhile outcomes.

Unfortunately, patients may have difficulty in noticing or verbalizing their perceptions of these positive effects. Elderly persons in particular, who may have become resigned to their daily aches and pains, may not be sensitive to functional improvements that gradually develop. Therefore, healthcare professionals may face challenges in eliciting meaningful feedback from patients that helps to assess benefits of vitamin D supplementation. The general topics in the ***Side Box*** may be of assistance for exploration during followup interviews with patients or their caregivers.

Practice Pointers – Improvement?

To gauge results of vitamin D therapy, a number of general topics should be explored with patients:

- Has the pain completely vanished?
- Is there less pain overall, or less in specific areas?
- Is the pain less frequent? Or, less intense?
- Is there less muscle stiffness or soreness?
- Is there less fatigue during all or part of the day?
- Do muscles feel stronger, especially in the legs?
- Are fewer analgesic doses – opioids or non-opioids – being taken each day?
- Has mood improved (*eg*, less depression or anxiety)?
- Is there more energy for work, socializing, hobbies, or other daily activities?
- Overall, is there a greater sense of well-being?

A further complication is that individual responses to vitamin D therapy can differ. In addition to the nature of the chronic pain condition itself, there would be differences in the extent of 25(OH)D inadequacy at baseline, as well as the extent of PTH and calcium involvement in osteomalacic processes. As noted in *section 2a*, there can even be genetic differences and functionality in vitamin D receptors.

With adequate vitamin D supplementation, serum 25(OH)D and $1,25(OH)_2D$ concentrations begin to increase within 1 or 2 days [Armas et al. 2004; Johnson 2007]. In general, if hypocalcemia and/or hypophosphatemia are present, serum calcium and phosphorus may increase within about 10 days. If bone-formation defects are present, there may be sufficient visible evidence on x-rays of improved mineralization by the third week [Johnson 2007].

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 [Gloth et al. 1991]. In other cases, pain and muscle weakness reportedly resolved "within weeks" of beginning supplementation [van der Heyden et al. 2004].

In cases of such rapid response, a placebo effect might be suspected. However, Vasquez et al. [2004] advise that, since vitamin D administration can affect intracellular mechanisms quite quickly, the appearance of short-term benefits should not be dismissed as merely due to placebo effects or other causes.

In terms of vitamin D pharmacokinetics (discussed in *section 2b*), steady-state 25(OH)D concentrations could be achieved as early as 40 days following the start of daily supplementation. Although, in some cases it could take up to 90 days or more for concentrations to reach plateau levels. This was observed in the study by Lee and Chen [2008] in which significant pain relief from neuralgia was achieved at 3 months after beginning vitamin D supplementation.

In another clinical investigation, female patients with osteomalacia who responded to vitamin D supplementation first noticed symptom resolution at about 40 days after the start of therapy, and pain relief was nearly complete by roughly 90 days [de la Jara et al. 2006]. However, one of the patients required 7 months of supplementation to become pain-free.

Similarly, other researchers have suggested that bone-related pain may require approximately 3 months of adequate vitamin D supplementation for its relief [de la Jara et al. 2006; Heath and Elovic 2006]. However, muscle pain may need 6 months and muscle weakness or fatigue may require up to 12 months to resolve [de la Jara et al. 2006; Glerup et al 2000b; Heath and Elovic 2006], but some improvements in muscle discomfort could be felt within 4 to 6 weeks.

Overall, Vasquez and colleagues [2004] 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. [2004] suggested that the greatest physiologic responses may occur after 6 months of supplementation.

Therefore, the timeframe recommended in this report – monitoring results for up to 3 months – should be a *minimum* period of watchful waiting. Some patients may start to notice improvements within weeks, if they are alert to subtle changes, while others may become discouraged unless they are advised at the start that vitamin D supplementation could take a number of months, even up to 9 months, to reach its full potential in helping to relieve musculoskeletal aches, pains, and/or related symptoms.

7c. Conclusions

The importance of adequate vitamin D intake for helping patients with chronic musculoskeletal pain should be more widely recognized and acted upon.

Based on an extensive review of clinical evidence and expert commentary in the scientific literature, this report endorses the general opinion that the importance of recommending adequate vitamin D intake for helping patients with chronic musculoskeletal pain and fatigue syndromes should be more widely recognized and acted upon [*eg*, Koes 2005; Lewis 2005]. In a great many cases, contributing factors are nonspecific or undetermined, and there is considerable evidence implying that vitamin D inadequacies can be strongly associated with these pain syndromes in both adults and children of any age [Holick 2003b; Lewis 2005]. Even in cases where a specific etiology has been diagnosed, the potential for vitamin D deficit as a factor contributing to the pain condition should not be ruled out.

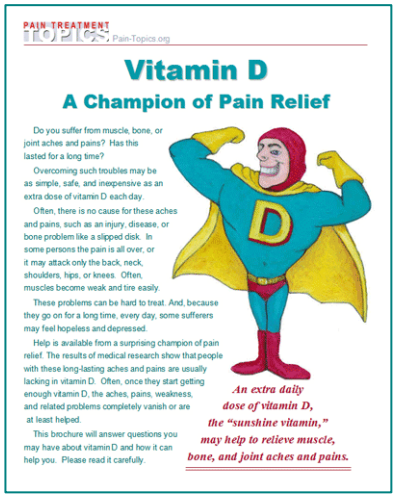
Therefore, many experts have recommended that vitamin D inadequacy should be considered in the differential diagnosis and treatment plans for all patients with bone or joint pain, muscle pain or weakness, fibromyalgia, or chronic fatigue syndrome [Shinchuk and Holick 2007], and it also has been found to play a role in neuropathic pain [Lee and Chen 2008]. In clinical investigations, supplementation with adequate vitamin D has been demonstrated to help relieve the

various pain symptoms either completely or partially, as well as providing other benefits such as increased stamina or strength, reductions in NSAID or opioid use, and improvements in mood and quality of life.

However, further clinical research studies would be helpful, and 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 [Vasquez et al. 2004]. Therefore, vitamin D is not recommended as a replacement for all other approaches to pain management.

This report proposes a conservative total daily supplementation of 2400 IU to 2800 IU of vitamin D_3, to start, as potentially benefitting patients with chronic musculoskeletal pain and fatigue syndromes. Along with that, some patience is advised in 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.

It also must be noted that patient education is always a critical aspect of any therapy. Patients should be instructed to buy vitamin D supplement products of good quality from reliable sources. If in doubt, they should consult their pharmacist. Purchases of very high-dose formulations or from questionable sources, via the Internet or elsewhere, should be discouraged. They also must follow the recommended dosing regimen daily and self-monitor for improvements in their condition over time.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Vitamin D

A Champion of Pain Relief

Do you suffer from muscle, bone, or joint aches and pains? Has this lasted for a long time?

Overcoming such troubles may be as simple, safe, and inexpensive as an extra dose of vitamin D each day.

Often, there is no cause for these aches and pains, such as an injury, disease, or bone problem like a slipped disk. In some persons the pain is all over, or it may attack only the back, neck, shoulders, hips, or knees. Often, muscles become weak and tire easily.

These problems can be hard to treat. And, because they go on for a long time, every day, some sufferers may feel hopeless and depressed.

Help is available from a surprising champion of pain relief. The results of medical research show that people with these long-lasting aches and pains are usually lacking in vitamin D. Often, once they start getting enough vitamin D, the aches, pains, weakness, and related problems completely vanish or are at least helped.

This brochure will answer questions you may have about vitamin D and how it can help you. Please read it carefully.

An extra daily dose of vitamin D, the "sunshine vitamin," may help to relieve muscle, bone, and joint aches and pains.

For patients and/or their caregivers, *Pain Treatment Topics* has created a brief, easy-to-understand brochure titled ***Vitamin D: A Champion of Pain Relief***. This explains in question and answer format what vitamin D is and its natural sources, how it works in the body, how much is needed for health, and the possible role inadequate intake plays in muscle, bone, or joint pain. It discusses the possible benefits of vitamin D supplementation for pain relief and how long this may take. Finally, the brochure advises patients to consult their healthcare providers when starting a vitamin D supplementation program.

This brochure is available for free access and download at the Pain-Topics.org website. Healthcare providers can refer patients to the website or copy and distribute the document to patients themselves.

See: http://Pain-Topics.org/VitaminD

In sum, as the introduction to this report also concluded, 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.*

In the final analysis, vitamin D would do no harm, and it could help relieve chronic musculoskeletal pain at minimal cost.

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APPENDIX 1 – Vitamin D_2 & D_3 Sources

Source	Vitamin D Content
Higher-Yield Natural Sources	
Exposure to sunlight, ultraviolet B radiation (0.5 minimal erythemal dose)†	3000–10,000 IU D_3
Salmon fresh, wild (3.5 oz*)	600–1000 IU D_3
Salmon fresh, farmed (3.5 oz)	100–250 IU D_3
Salmon canned (3.5 oz)	300–600 IU D_3
Herring, pickled (3.5 oz_	680 IU D_3
Catfish, poached (3.5 oz)	500 IU D_3
Sardines, canned (3.5 oz)	200–360 IU D_3
Mackerel, canned (3.5 oz)	200–450 IU D_3
Tuna, canned (3.6 oz)	200–360 IU D_3
Cod liver oil (1 tsp / 0.17 oz)	400–1400 IU D_3
Eastern oysters, steamed (3.5 oz)	642 IU D_3
Shiitake mushrooms fresh (3.5 oz)	100 IU D_2
Shiitake mushrooms sun-dried (3.5 oz)	1600 IU D_2
Egg yolk, fresh	20–148 IU D_3
Fortified Foods	
Fortified milk	60–100 IU/8 oz, usually D_3
Fortified orange juice	60–100 IU/8 oz usually D_3
Infant formulas	60–100 IU/8 oz usually D_3
Fortified yogurts	100 IU/8 oz, usually D_3
Fortified butter	50 IU/3.5 oz, usually D_3
Fortified margarine	430 IU/3.5 oz, usually D_3
Fortified cheeses	100 IU/3 oz, usually D_3
Fortified breakfast cereals	60–100 IU/serving, usually D_3
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).	
Supplements	
Over The Counter / Internet	
Multivitamin (including vitamin D)	400–800 IU vitamin D_2 or D_3‡
Vitamin D (tablets, capsules)	Various doses 400–50,000 IU (primarily D_3)
Prescription / Pharmaceutical	
Vitamin D_2 (ergocalciferol)	50,000 IU/capsule
Drisdol®, Calciferol®, others (vitamin D_2) liquid supplements	8000 IU/mL
Rocaltrol®, Calcigex®, others ($1,25[OH]_2D$) available outside US	0.25-0.5 mcg capsules 1 mcg/mL solution

Sources: Calcitriol 2007; Ergocalciferol 2007; Holick 2007; Marcus 1995; ODS 2008; Singh 2004a; Tavera-Mendoza and White 2007; Vieth 2005.

* 1 oz = 28.3 grams = 29.6 mL; 1 IU = 40 mcg (microgram)

† A 0.5 minimal erythemal 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.

‡ Calciferol on product label signifies D_2; cholecalciferol signifies D_3.

APPENDIX 2 – Reported Vitamin D Overdoses	
Source	**Incident**
Klontz and Acheson 2007	A 58-year-old woman was hospitalized after taking a dietary supplement for 2 months that had been erroneously formulated with 188,640 IU/day of vitamin D_3 rather than the intended 400 IU/day. Upon admission 25(OH)D concentration was 468 ng/mL and both calcium and PTH were elevated.
Barrueto et al. 2005	Mistaken administration of 2,400,000 IU vitamin D during a 4-day period to a 2-year-old boy produced resistant hypercalcemia (14.4 mg/dL) and hypertension; 25(OH)D peaked at 470 ng/mL 3 days after hospital admission. The boy's mother had purchased a mail-order supplement containing 600,000 IU per ampule of vitamin D and did not understand the instruction that 1 or 2 drops (2,500 – 5,000 IU) should be given each day, rather than the entire ampule as she did.
Vieth et al. 2002	An isolated incident of either accidental or intentional mixing of crystalline vitamin D_3 into the table sugar of a father and his adult son resulted in vitamin D_3 intakes as high as 1,680,000 IU/day for several months. The toxic signs of the resulting hypercalcemia included pain, conjunctivitis, anorexia, fever, chills, thirst, vomiting, and weight loss. Upon hospitalization, serum 25(OH)D concentration in the father was 622 ng/mL, and 1480 ng/mL in the son. Both patients had severe nephrocalcinosis. Following treatment, 25(OH)D in the son was 100 ng/mL at 17 months followup; 72 ng/mL in the father at 21 months followup. Of interest, both father and son denied taking any dietary supplements, making these cases a diagnostic challenge and the source of adulterated sugar was never determined.
Koutkia et al. 2001	A 42-year-old man was hospitalized with hypercalcemia after 2 years of taking a powder supplement containing 156,000 to 2,604,000 IU of vitamin D_3 per day. The powder had been adulterated during manufacture and each gram had up to 430 times the amount of D_3 listed on the label (2000 IU per recommended dose). On admission to the hospital serum 25(OH)D was 487 ng/mL; $1,25(OH)_2D$ and PTH were normal. Of interest, after treatment, discontinuation of vitamin D supplementation, and avoidance of sun exposure it took 30 months for 25(OH)D concentration to return to a more normal level (47 ng/mL), although calcium declined rapidly during hospital therapy to more normal limits.
Adams and Lee, 1997	Four patients with osteoporosis used several nonprescription dietary supplements, including some containing unadvertised high levels of vitamin D, for at least 6 months and developed hypercalciuria. Two women taking animal-extract preparations, not advertised as containing vitamin D but found to contain D_2, had the highest 25(OH)D levels of 80 and 89 ng/mL. None of the patients had hypercalcemia or elevated total $1,25(OH)_2D$.
Blank et al. 1995	A dairy in Boston serving 33,000 customers had faulty equipment measuring vitamin D concentration in its milk. During 1985-1991 milk was erroneously fortified with vitamin D doses ranging from 35,000 IU to 300,000 IU per quart, instead of the allowable 400 IU. Toxicity was identified in 56 persons, with customers receiving the dairy's milk for the entire time period being at greatest risk. Mean 25(OH)D concentration was 224 ng/mL; calcium levels averaged 13.1 mg/dL. Two deaths occurred in susceptible elderly persons: an 86-year-old man died from fatal cardiac dysrhythmia; a 72-year-old woman died from an opportunistic infection secondary to immunosuppressants used for hypercalcemia.
Pettifor et al. 1995	After using a veterinary vitamin D concentrate as a cooking oil (2,000,000 IU D_3 per gram), 11 patients (8-69 years of age) were hospitalized for toxicity. All patients had hypercalcemia, serum 25(OH)D ranged from 339-661 ng/mL; total $1,25(OH)_2D$ was elevated in only 3 patients, but most had elevated free-$1,25(OH)_2D$ concentrations. Four patients died from unspecified complications during treatment for hypercalcemia.
Todd et al. 1987	A 72-year-old man with a 10-day history of nausea, vomiting, and weight loss subsequent to a month of thirst, polyuria, and poor mental concentration was found to have consumed 600,000 IU vitamin D_2/day for several weeks.

APPENDIX 3 – Vitamin D Research in Musculoskeletal Pain

Researchers/Population	Subjects	Vitamin D Status	Comments
Turner et al. 2008 – 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. 2007]	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. 2008 – 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 *(25[OH]D was significantly lower in older patients)*	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. 2007 – 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 *(This is a much higher threshold for defining deficiency than used in other studies)*	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 68% of the variance between groups, even in this sunny climate.
Armstrong et al. 2007 – 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 2007 – 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. 2006 – 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.
Gostine and Davis 2006 – 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. 2006 – 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. 2006 – 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. 2006 – 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 generalize 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. 2005 – 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.

APPENDIX 3 – Research Continued			
Researchers/Population	**Subjects**	**Vitamin D Status**	**Comments**
Baker et al. 2004 – 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. 2004 – 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 musculoskeletals pains, and polymyalgia rheumatica.
van der Heyden et al. 2004 – 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 2004 – 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 2003 – 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 2003 – 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. 2001 – 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. 2000b – 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. 2000 – 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. 1996 – USA – 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.
Gloth et al. 1991 – 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.

APPENDIX 4 – Food Sources of Calcium

Non-Dairy, Standard Amount	Calcium (mg)	Dairy Products, Standard Amount	Calcium (mg)
Fortified ready-to-eat cereals (various), 1 oz	236-1043	Plain yogurt, non-fat (13 g protein/8 oz), 8-oz container	452
Soy beverage, calcium fortified, 1 cup	368	Romano cheese, 1.5 oz	452
Sardines, Atlantic, in oil, drained, 3 oz	325	Pasteurized process Swiss cheese, 2 oz	438
Tofu, firm, prepared with nigari, ½ cup	253	Plain yogurt, low-fat (12 g protein/8 oz), 8-oz container	415
Pink salmon, canned, with bone, 3 oz	181	Fruit yogurt, low-fat (10 g protein/8 oz), 8-oz container	345
Collards, cooked from frozen, ½ cup	178	Swiss cheese, 1.5 oz	336
Molasses, blackstrap, 1 Tbsp	172	Ricotta cheese, part skim, ½ cup	335
Spinach, cooked from frozen, ½ cup	146	Pasteurized process American cheese food, 2 oz	323
Soybeans, green, cooked, ½ cup	130	Provolone cheese, 1.5 oz	321
Turnip greens, cooked from frozen, ½ cup	124	Mozzarella cheese, part-skim, 1.5 oz	311
Ocean perch, Atlantic, cooked, 3 oz	116	Cheddar cheese, 1.5 oz	307
Oatmeal, plain and flavored, instant, fortified, 1 packet prepared	99-110	Fat-free (skim) milk, 1 cup	306
Cow peas, cooked, ½ cup	106	Muenster cheese, 1.5 oz	305
White beans, canned, ½ cup	96	1% low-fat milk, 1 cup	290
Kale, cooked from frozen, ½ cup	90	Low-fat chocolate milk (1%), 1 cup	288
Okra, cooked from frozen, ½ cup	88	2% reduced fat milk, 1 cup	285
Soybeans, mature, cooked, ½ cup	88	Reduced fat chocolate milk (2%), 1 cup	285
Blue crab, canned, 3 oz	86	Buttermilk, low-fat, 1 cup	284
Beet greens, cooked from fresh, ½ cup	82	Chocolate milk, 1 cup	280
Pak-choi, Chinese cabbage, fresh cooked, ½ cup	79	Whole milk, 1 cup	276
Clams, canned, 3 oz	78	Yogurt, plain, whole milk (8 g protein/8 oz), 8-oz	275
Dandelion greens, cooked from fresh, ½ cup	74	Ricotta cheese, whole milk, ½ cup	255
Rainbow trout, farmed, cooked, 3 oz	73	Blue cheese, 1.5 oz	225
		Mozzarella cheese, whole milk, 1.5 oz	215
		Feta cheese, 1.5 oz	210

Source: DHHS 2005. Adequate Intake (AI) of calcium for adult men is 1000–1200 mg/day or up to 2000 mg/day in older women. Both calcium content and bioavailability should be considered when selecting dietary sources of calcium. Some plant foods have calcium that is well absorbed, but the large quantity of plant foods that would be needed to provide as much calcium as in a glass of milk may be unachievable for many. Many other calcium-fortified foods are available, but the percentage of calcium that can be absorbed is unknown for many of them.

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