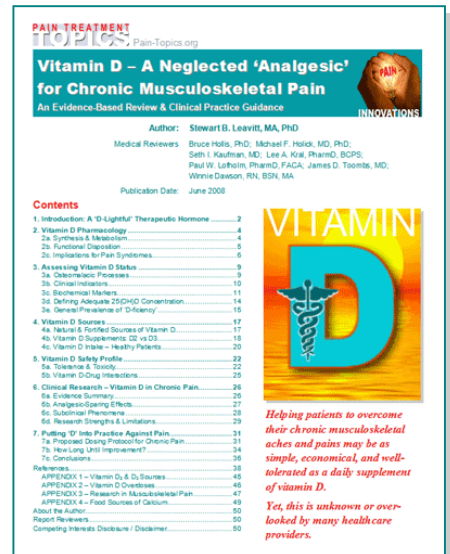


Vitamin D – A Neglected ‘Analgesic’ for Chronic Musculoskeletal Pain

This Practitioner Briefing summarizes a 50-page report on this topic that should be consulted for more complete information, including references. The report is available for download at: <http://Pain-Topics.org/VitaminD>



Summary Points

- Chronic musculoskeletal pain and fatigue syndromes are common and difficult-to-treat clinical challenges.
- Vitamin D is a complex nutrient that functions as a hormone to benefit numerous body tissues, especially bones, joints, and muscles.
- A majority of all patients, and particularly those with pain, may 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 and fatigue syndromes in many patients who have been unresponsive to other therapies.
- A 2400 IU to 2800 IU per day supplement of vitamin D₃ is proposed as being helpful for patients with chronic nonspecific 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.”

Pain is the most common complaint leading patients to seek medical care and much of it is chronic, involving muscles, bones, and joints. According to peer-reviewed clinical research examining adult patients of all ages, inadequacies of vitamin D have been linked to chronic musculoskeletal pain of various types, muscle weakness or fatigue, fibromyalgia syndrome, rheumatic disorders, osteoarthritis, hyperesthesia, migraine headaches, and other chronic somatic complaints. It also has been implicated in the mood disturbances of chronic fatigue syndrome and seasonal affective disorder. For many patients, helping to ameliorate these problems may be as simple, well tolerated, and economical as an extra daily supplement of vitamin D.

The Vitamin D Endocrine System

Adequate vitamin D intake is essential for healthy bones by helping to maintain calcium and phosphorus homeostasis. However, vitamin D does far more than build strong bones; in fact, its major biologically active metabolite works throughout the human body at special receptors.

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 is unknown or overlooked by many healthcare providers.

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

Vitamin D has 2 major forms (see [Chart](#)): D₂ (*ergocalciferol*) and D₃ (*cholecalciferol*). Vitamin D₃ is synthesized in skin via exposure to ultraviolet B (UVB) radiation from sunlight. It also is obtained to a small extent in the diet, primarily from fatty fish, while vitamin D₂ is found in only a few plant-based foods. Additionally, certain foods, such as milk or cereals, may be fortified with vitamin D – usually D₃.

Both D₂ and D₃ are absorbed in the small intestine, and neither has any biological activity. They then go through a two-stage process of metabolism, first in the liver to form 25-hydroxyvitamin D, abbreviated as 25(OH)D (also called *calcidiol*). This has minimal biological activity but is stored in many tissues, particularly adipose tissue, and it is the major circulating form of vitamin D in the blood.

The 25(OH)D metabolite is then converted primarily in the kidneys to 1,25-dihydroxyvitamin D – abbreviated as 1,25(OH)₂D and also called *calcitriol* – which is the most important and biologically active vitamin D metabolite. The ultimate role of vitamin D, via the 1,25(OH)₂D metabolite, is to facilitate the absorption of dietary calcium from the intestine. Equally important, 1,25(OH)₂D functions as a hormone, with its own receptors in a variety of tissues to help sustain a wide range of metabolic and physiologic functions throughout the body. This has been referred to as the “vitamin D endocrine system.”

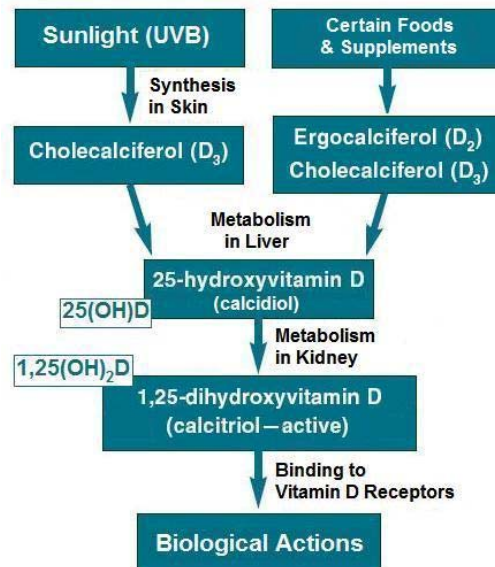
Relationship of Vitamin D to Pain Syndromes

The process that links vitamin D to musculoskeletal pain is presumed to begin with a lack of circulating calcium (hypocalcemia) due to inadequate vitamin D. This calcium deficiency stimulates increased parathyroid hormone secretion and sets in motion a cascade of biochemical reactions negatively affecting bone metabolism. Even mild hypocalcemia results in an elevation of parathyroid hormone that can diminish bone density (*osteopenia*) and/or more severely affect bone architecture (*osteoporosis*).

The effect relating most closely to musculoskeletal aches and pains is that the increase in parathyroid hormone levels can lead to a softening of bone surfaces – or *osteomalacia* – which generates pain in periosteal tissues covering the skeleton. Osteomalacia has been proposed as an explanation of why many patients with vitamin D inadequacies may complain of dull, persistent, generalized musculoskeletal aches and pains. Myopathy also is part of the osteomalacic complex, so fatigue or decreases in muscle strength, usually in lower limbs, may appear prior to any pain.

In many cases involving pain and myopathy, 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 is not evident. This may occur in a significant number of chronic musculoskeletal pain cases that have been resistant to treatment, and, according to the research, many of the problems can be attributed to inadequate vitamin D.

Clinical researchers also 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 found in various brain structures, the spinal cord, and sensory ganglia. Accordingly, results of some studies suggest benefits of vitamin D supplementation in helping to ameliorate neuropathies, as well as relieving mood disturbances such as depression or anxiety often associated with pain syndromes or seasonal affective disorder (SAD).



The 1,25(OH)₂D metabolite functions as a hormone, with its own receptors in a variety of tissues to help sustain a wide range of metabolic & physiologic functions throughout the body.

Defining Serum 25(OH)D Adequacy

While a universal consensus is lacking, most researchers agree that a minimum 25(OH)D serum level of about 30 ng/mL or more is necessary for favorable calcium absorption, suppression of parathyroid hormone (PTH), and good health. Optimal 25(OH)D concentrations generally range up to 50 ng/mL or somewhat higher, although those greater than 150 ng/mL can be toxic (see [Table](#)).

Deficiency has been defined as circulating 25(OH)D concentrations <20 ng/mL, which may be associated with elevated PTH and greater bone turnover, potentially fostering subclinical osteomalacia. Concentrations \leq 8 ng/mL have been considered as highly predictive of fully-developed, or clinical, osteomalacia. Furthermore, levels of circulating 25(OH)D concentrations below an optimal range but above true deficiency status – ie, 20 to 29 ng/mL – could have a negative impact on health and constitute *insufficiency*.

There is a growing awareness that vitamin D inadequacies in the general population are common and, in many cases, severe. According to the research evidence, in most clinical practices up to 50% of patients, possibly more, will have 25(OH)D concentrations <30 ng/mL. A significant proportion will have serious deficiencies of <20 ng/mL. Such deficits have been found equally among males and females in all age groups.

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. Other factors also contribute to the problem, including diets devoid of the relatively few foods rich in or fortified with vitamin D, lifestyles focused on indoor activities, and concerns about sun exposure with the attendant use of lotions completely blocking UVB radiation.

There can be physiologic causes of vitamin D deficiency, accounting for a relatively small extent of the problem. Conditions substantially reducing circulating 25(OH)D include chronic liver disease, fat-malabsorption syndromes, inflammatory bowel disease, celiac disease, Crohn's disease, pancreatic insufficiency, and cystic fibrosis.

Researchers have consistently found that a disproportionately large percentage of persons with chronic pain syndromes have vitamin D inadequacies, as compared with the general population. In such cases, vitamin D supplementation therapy was clinically observed to significantly resolve or ameliorate their symptoms of pain and/or muscle weakness.

Recommended Daily Vitamin D Intake

According to the latest US Dietary Guidelines, at least 1000 IU/day of vitamin D₃ is necessary to maintain adequate serum 25(OH)D levels at or above 30 ng/mL in *healthy persons* (without chronic pain). Prior guidance – from the US Institute of Medicine in 1997 – specified daily vitamin D intake ranging from 200 IU/day in children and younger adults to 600 IU/day in those older than age 70 (see [Table](#)).

Still, many experts believe that even the newly recommended 1000 IU/day may be inadequate for healthy persons, and some have suggested that up to 4000 IU/day of vitamin D₃ could be optimal. For patients with chronic pain syndromes, 2000 IU/day or more may be proposed as a reasonable and conservative approach (see [page 6](#)).

The relationship of vitamin D intake to ultimate 25(OH)D concentrations in serum appears to be a self-regulating process. Although exposure to sun can produce the equivalent of 10,000 to 20,000 IU of vitamin D₃, prolonged

25(OH)D Concentrations

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

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

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

'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

Proposed for Patients with Pain

2000+ IU/d – adults

*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.*

or every day sun exposure does not generate toxic amounts. Similarly, administration of vitamin D₃ supplements does not increase 25(OH)D in a linear fashion and is limited by preexisting serum levels of the metabolite. For example, tripling the dose of vitamin D₃ does not necessarily result in a 3-fold increase in 25(OH)D, and, in fact, the increase may be quite modest in persons with serum 25(OH)D concentrations already at or near adequate levels.

Vitamin D supplements are economical and available over-the-counter from many sources including pharmacies, health food stores, some grocery stores, and via the Internet. They are typically available as 400 IU, 1000 IU, or 2000 IU tablets or capsules; however, some Internet-based sources market much larger doses, even as high as 50,000 IU, without prescription. Patients should be warned against purchasing larger-dose supplements, unless directed to do so, and it is essential that they buy a high-quality product of accurate strength. When in doubt, patients should be instructed to consult their pharmacist for a reliable brand of supplements.

Of the two forms – D₂ or D₃ – vitamin D₃ (*cholecalciferol*) is preferred. D₃ is no more expensive, it is the form naturally produced in the body from sunshine, and most research has demonstrated that it can be more effective than D₂.

Favorable Safety Profile

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. The main signs/symptoms of vitamin D toxicity result from excessive serum calcium, or hypercalcemia (see **Side Box**). Some researchers have proposed that daily consumption of 40,000 IU to 50,000 IU of vitamin D taken for an extended period of time would be needed to cause clinically significant hypercalcemia. As noted above, serum 25(OH)D levels are usually elevated to >150 ng/mL in cases of toxicity.

The Tolerable Upper Intake Level (UL) for oral vitamin D₃ supplementation – which is the long-term dose expected to pose *no risk* of observed adverse effects – has been 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. However, many experts have variously asserted that the UL actually should be from 2400 IU/day to 10,000 IU/day of D₃.

Published incident reports of vitamin D toxicity describe extremely large daily amounts ranging from 160,000 IU/day up to an astounding 2.6 million IU/day taken for periods ranging from days to years. 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. Only 6 fatalities attributed to vitamin D poisoning have been reported in the literature, and those appear to have been due to secondary causes during treatment for hypercalcemia.

There have been relatively few references in the literature to vitamin D supplements interacting with other agents or medications. In some cases, the potency of vitamin D is reduced, so increased vitamin D might be needed in patients taking anticonvulsants, antiretrovirals, barbiturates, corticosteroids/glucocorticoids, hydroxychloroquine, or rifampin. Conversely, very high doses of vitamin D should be avoided with digitalis/digoxin or thiazide diuretics.

Most important, vitamin D has not been noted to *harmfully* interfere with or alter the actions of any medications. Therefore, none of the potential interactions with the drugs noted above has been suggested as an absolute contraindication for vitamin D supplementation.



Vitamin D₃ supplements are widely available as 400, 1000, or 2000 IU tablets or capsules.

Patients should be warned against buying larger-dose supplements unless directed to do so.

Hypercalcemia Signs/Symptoms

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

Note: Some signs/symptoms mimic those of neuropathies, opioid side effects, and other conditions.

Assessing Vitamin D Status

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 is a review of patient history, lifestyle, and dietary habits that might pose risks for deficiency.

Indicators of defects in bone metabolism may include chronic muscle, bone, or joint pains, as well as persistent muscle weakness, fatigue, and possibly difficulty walking. Signs/symptoms of hypocalcemia (see [Side Box](#)) and/or clinical osteomalacia most typically relate to severe vitamin D deficiency and are more likely to appear late in the course of the disease.

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

Elevations of parathyroid hormone (PTH) may be the best biochemical marker of osteomalacia since, at the least, secondary hyperparathyroidism negatively affects bone metabolism. A diagnosis of inadequate vitamin D with osteomalacic involvement to some extent could be presumed if PTH is elevated in association with low calcium levels, which also would serve to exclude patients with *primary* hyperparathyroidism due to other causes

Serum 25(OH)D assays are available from commercial laboratories and reflect both D₂ plus D₃ 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.

There have been some concerns expressed about the expense and inaccuracies associated with some of the 25(OH)D assays. Furthermore, research results have demonstrated that particular serum 25(OH)D concentrations *alone* are not prognostic of pain or its degree and duration. Therefore, it could be erroneous to assume that vitamin D is not involved in a pain syndrome because 25(OH)D measures on a test at some presumed level of adequacy.

Vitamin D Therapy for Pain

From the clinical research to date, it appears that individual responses to vitamin D therapy can vary. Other factors – sun exposure, season of year, diet, age, physical health, and medications – also can play roles. Therefore, optimal vitamin D dosing requirements for individual patients having different types of chronic musculoskeletal pain and related symptoms are not fully defined.

Various vitamin D dosing protocols to rectify inadequacies of the 25(OH)D metabolite in patients with pain syndromes have been reported in the literature. Some are quite aggressive, using higher doses of vitamin D ranging from 5,000 IU/day to 50,000 IU/day, or greater, for limited periods of time. More conservatively, a recently reported trial of 2000 IU/day in patients with neuropathic pain produced a 67% increase in 25(OH)D levels and a 50% improvement in pain scores during 3 months of treatment.

Some researchers have observed that pain and other 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 are also becoming depleted in storage depots; therefore, they cannot accumulate in needed quantities and any added amount is beneficial. These researchers also suggested that pain

Hypocalcemia Signs/Symptoms

- paresthesias (*numbness, tingling, prickling, or burning*) in lips, tongue, fingertips, and/or toes
- fatigue
- anxiety
- muscles painful, achy, progressing to cramps or spasms
- lethargy
- poor appetite
- mental confusion
- cardiac arrhythmia

Note: Some signs/symptoms mimic those of neuropathies, fibromyalgia, skeletal defects, etc.



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.

Based on available evidence, a proposed conservative dosing protocol for startup vitamin D supplementation in most patients with chronic musculoskeletal pain is outlined in the **Side Box**. The recommended time-frame for monitoring results – up to 3 months – should be considered a minimum period of watchful waiting. If there are no improvements, more time rather than increased doses may be necessary for vitamin D₃ therapy to effectively raise 25(OH)D concentrations, lower PTH levels, and/or saturate vitamin D receptors with the 1,25(OH)₂D metabolite.

In some cases, the particular chronic pain condition might be such that it cannot be alleviated by vitamin D₃ 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.

When vitamin D supplementation is effective, some patients may start to notice improvements within weeks, if they are alert to subtle changes. 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.

In most cases rapid and complete pain resolution would be an unrealistic expectation. The evidence for pain-relieving and other benefits of vitamin D therapy is suggestive of a potential range of improvements, some more obvious than others. These are listed in the **Side Box**, and patients should be questioned about these effects to help gauge outcomes.

At conservative doses recommended here – ie, 2400 IU/day to 2800 IU/day – 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 are still under investigation. Therefore, 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.

Vitamin D Supplementation for Chronic Pain Proposed Conservative Dosing Protocol

- In patients with chronic, nonspecific musculoskeletal pain and fatigue syndromes, it often can be expected that vitamin D intake from combined sources is inadequate and concentrations of serum 25(OH)D may be insufficient or deficient.
- All patients should take a multivitamin to assure at least minimal daily values of essential nutrients, including calcium and 400 to 800 IU of vitamin D.
- Recommend a daily 2000 IU vitamin D₃ supplement, bringing total supplement intake to 2400 IU/day to 2800 IU/day (including 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).
- Monitor patient compliance and results for up to 3 months. *Other therapies for pain already in progress are generally not discontinued.*
- If results are still lacking after 3 months, or a persistent 25(OH)D deficiency or osteomalacia is verified, consider a brief course of prescribed high-dose vitamin D₃ with or without added calcium as appropriate, followed by ongoing supplementation as maintenance.

Potential Improvements with Vitamin D Therapy

- pain completely resolved
- less pain overall or less in specific areas
- pain less frequent or less intense
- less muscle weakness or soreness
- less fatigue during all or part of the day
- muscles feel stronger, especially in legs
- fewer analgesic doses taken each day (opioids or non-opioids)
- mood improved – eg, less depression or anxiety
- more energy for work, socializing, hobbies, or other daily activities
- overall, greater sense of well-being

Conclusion

Experts have advised that the potential benefits of recommending adequate vitamin D intake for helping patients with chronic pain and fatigue syndromes should be more widely recognized and acted upon. In a great many cases, factors contributing to these conditions are nonspecific or undetermined, and there is considerable supportive evidence to suggest that vitamin D inadequacies can be strongly associated with these syndromes in both adults and children of any age. Even in cases where a specific etiology has been diagnosed, the potential for vitamin D deficits as a factor contributing to pain or myalgia should be considered.

As noted on page 1, the possibility of inadequate vitamin D intake should be considered in the differential diagnosis of chronic musculoskeletal pain of various types, muscle weakness or fatigue, fibromyalgia syndrome, rheumatic disorders, osteoarthritis, hyperesthesia, migraine headaches, and other chronic somatic complaints. Also, it has been noted as a factor potentially contributing to the mood disturbances of chronic fatigue syndrome and seasonal affective disorder.

Further clinical research studies would be helpful, and vitamin D is not proposed as a "cure" for all chronic pain and fatigue conditions in all patients. Optimal clinical outcomes with vitamin D therapy might be best attained via multicomponent treatment plans addressing many facets of health and pain relief. Therefore, vitamin D is not suggested as a replacement for any or all other approaches to pain management; rather, it should be considered as an adjunct that may eventually allow a decrease or discontinuation of other drugs or therapy regimens.

It also must be remembered that patient education is always a critical aspect of any therapy. For patients and/or their caregivers, *Pain Treatment Topics* has created a brief, easy-to-understand brochure explaining what vitamin D is, how it works, and the possible role of inadequate intake in muscle, bone, or joint pain. 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: Vitamin D: A Champion of Pain Relief

At: <http://Pain-Topics.org/VitaminD>

In summary, for patients with chronic musculoskeletal pain, supplemental vitamin D has a favorable benefit to cost ratio with minimal, if any, risks. It should be considered early in the course of pain management.

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For the 50-page Report, go to:
<http://Pain-Topics.org/VitaminD>

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