

## Vitamin D in Orthopaedics

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### Abstract

Vitamin D is an important component in musculoskeletal development, maintenance, and function. Adequate levels of vitamin D correlate with greater bone mineral density, lower rates of osteoporotic fractures, and improved neuromuscular function. Debate exists about both adequate levels required and intake requirements needed to prevent deficiency of vitamin D. Epidemiologic data have identified an increasing number of orthopaedic patients at risk for vitamin D deficiency, with potentially widespread consequences for bone healing, risk of fracture, and neuromuscular function.

Hypovitaminosis D is the accepted term for insufficient or deficient levels of vitamin D. The relationship between hypovitaminosis D and rickets was discovered in the early 20th century; nearly 100 years later, vitamin D deficiency has resurfaced as a potential global health concern.<sup>1</sup> In addition to the positive systemic effects of vitamin D, increasing evidence posits the potential benefits of the vitamin to skeletal health and function. For all of these reasons, vitamin D is of particular interest to orthopaedic surgeons and patients.

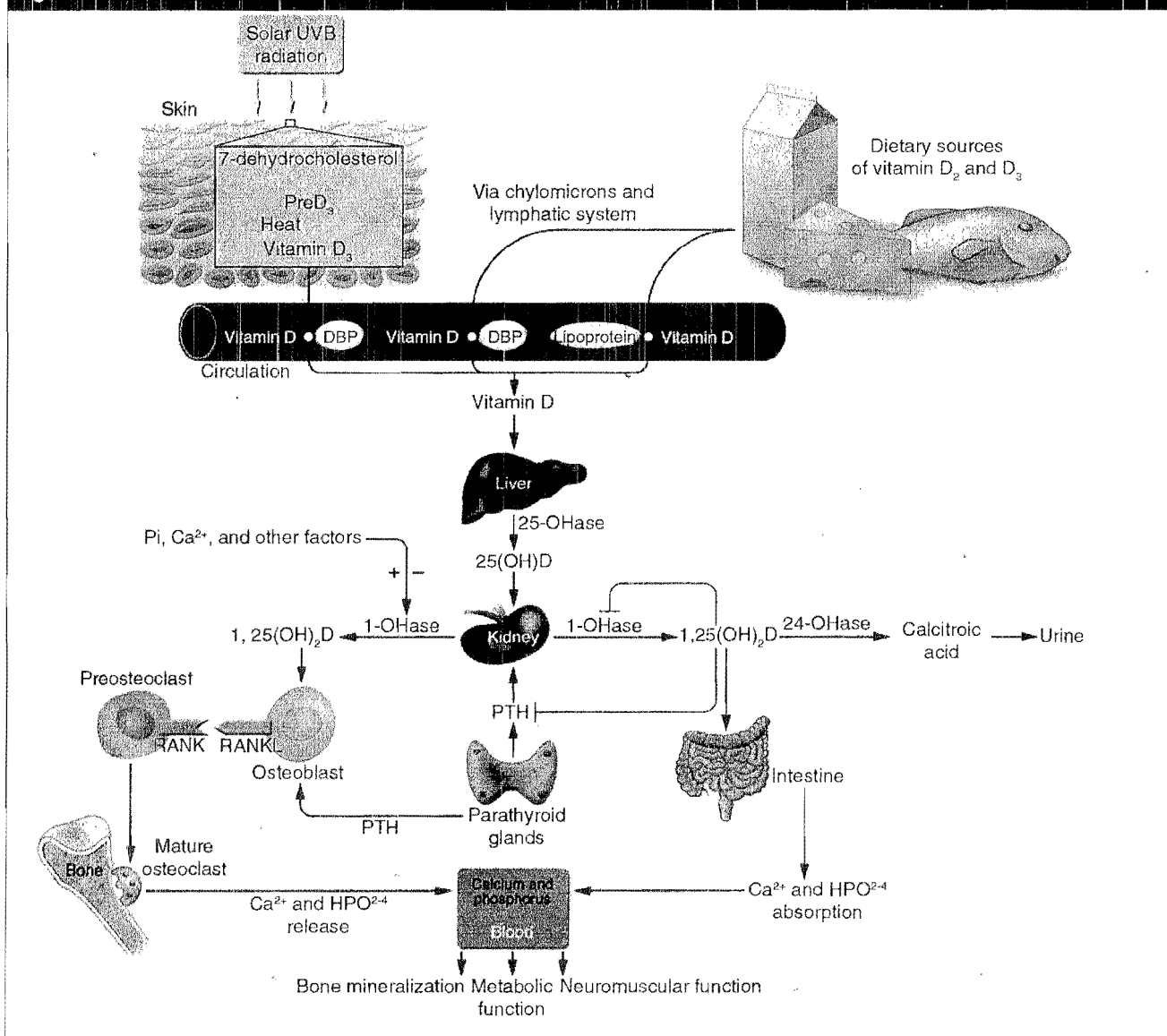
The term vitamin D typically refers to cholecalciferol (ie, vitamin D<sub>3</sub>). Calcifediol (ie, 25-hydroxyvitamin D<sub>3</sub>) and calcitriol (ie, 1,25-dihydroxyvitamin D<sub>3</sub>) are hydroxylated forms of vitamin D<sub>3</sub>. Ergocalciferol (ie, vitamin D<sub>2</sub>) is a less potent, plant-derived form of vitamin D that is frequently found in commercially available oral vitamins. Regrettably, these terms are often used interchangeably in the literature. Additionally, relevant literature and clinical laboratories inconsistently report vitamin D levels as either ng/mL or nmol/L (1 ng/mL = 2.5 nmol/L).<sup>2</sup>

### Sources and Metabolism

Vitamin D is obtained through dietary sources, oral supplements, and exposure to sunlight. A small number of foods contain naturally occurring vitamin D, but fortified foods such as milk and breakfast cereals are the major dietary source of the vitamin in the United States and Canada. In vivo conversion of 7-dehydrocholesterol to vitamin D<sub>3</sub> by ultraviolet B radiation in the skin is the primary source of vitamin D in most persons.

Vitamin D<sub>3</sub> synthesized in the skin or obtained from dietary sources is inactive and must be converted through hydroxylation in the liver into 25-hydroxyvitamin D. 25-Hydroxyvitamin D is then converted in the kidney into 1,25-dihydroxyvitamin D, the active form of vitamin D (Figure 1). The hydroxylase enzyme found in the kidney is also found in other end organs, including the colon, prostate, and mammary gland, as well as in macrophages and antigen-presenting cells. Activated vitamin D is thought to act through a single, common vitamin D receptor (VDR) that binds to specific DNA

Figure 1



The vitamin D metabolic and endocrine pathway. Cutaneous production occurs in the skin with conversion of 7-dehydrocholesterol to vitamin D<sub>3</sub> by ultraviolet B (UVB) radiation. Dietary-derived and synthesized forms of vitamin D are then hydroxylated in the liver to form 25-hydroxyvitamin D (calcifediol). Further hydroxylation in the kidney produces the active form of vitamin D, 1,25-dihydroxyvitamin D (calcitriol), which maintains calcium and phosphate homeostasis through intestinal absorption and osteoclastic mobilization of calcium and phosphate from bone. DBP = vitamin D-binding protein, OHase = hydroxylase, Pi = inorganic phosphate, PTH = parathyroid hormone, RANK = receptor activator of nuclear factor  $\kappa$ , RANKL = receptor activator of nuclear factor- $\kappa$ B ligand. (Reproduced with permission from Holick MF: Resurrection of vitamin D deficiency and rickets. *J Clin Invest* 2006;116[8]:2062-2072.)

sequences known as vitamin D response elements, currently found on more than 200 genes in a wide distribution of tissues.<sup>2,3</sup>

The production of 1,25-dihydroxyvitamin D is tightly regulated by a homeostatic interaction between

parathyroid hormone (PTH), calcium, and phosphate in the kidneys. Increased PTH, in response to low serum calcium levels, stimulates production of 1,25-dihydroxyvitamin D. Low serum phosphate also stimulates production of 1,25-dihydroxy-

vitamin D. This process is inhibited by fibroblast growth factor 23, which is produced by osteocytes. In addition, high levels of 1,25-dihydroxyvitamin D stimulate the enzymatic production of 24,25-dihydroxyvitamin D, the inactive

form of vitamin D, thereby self-regulating the action of 1,25-dihydroxyvitamin D.

Classically, the primary function of vitamin D is to maintain serum calcium homeostasis. Vitamin D stimulates active intestinal absorption of calcium and phosphate. In the kidney, vitamin D (with PTH) increases distal renal tubule reabsorption of calcium. Vitamin D also stimulates mobilization of calcium from bone via receptor activator of nuclear factor- $\kappa$ B ligand-induced osteoclastogenesis. In the absence of vitamin D, calcium and phosphate intestinal absorption is reduced by as much as 50%, and PTH is maximally produced to maintain the normal calcium-to-phosphate ratio essential for collagen matrix mineralization.<sup>4</sup> This can result in secondary hyperparathyroidism and increased osteoclastic bone resorption. Prolonged disruption of normal bone mineralization can lead to rickets in children and to osteomalacia in adults.

### Vitamin D Deficiency and Insufficiency

Vitamin D has received considerable attention in recent years, in part because of studies demonstrating inadequate levels in otherwise healthy populations.<sup>5,6</sup> Although these low levels are a matter of concern, many argue that these data are difficult to interpret because of a lack of consensus regarding normal and abnormal levels, as well as because of inconsistent diagnostic methodology.<sup>7</sup> Many authors consider 30 ng/mL to be the low end of the normal range, based on responses of PTH and optimal calcium reabsorption to vitamin D levels.<sup>3,8</sup> In 2010, the International Osteoporosis Foundation and Osteoporosis Canada independently recommended an optimum vitamin D level of 30 ng/mL.<sup>9,10</sup> However, in a

2010 review of published literature since their previous report in 1997, the Institute of Medicine found inconsistencies in much of the published literature regarding vitamin D; the institute ultimately defined adequate levels of vitamin D as 20 ng/mL, deficiency as <12 ng/mL, and insufficiency as being between 12 and 20 ng/mL.<sup>11</sup>

Globally, vitamin D deficiency is prevalent in all regions but is most severe in South Asia and the Middle East.<sup>5</sup> In the United States, data from the National Health and Nutrition Examination Survey (NHANES) reveal an overall prevalence of vitamin D <20 ng/mL of 30%.<sup>6</sup> Using the higher cutoff value of 30 ng/mL, the overall prevalence approaches 70%. Regardless of cutoff value, levels were relatively lower in females compared with males and lower in Hispanics and African Americans compared with Caucasians.

Hypovitaminosis D has been widely identified within the orthopaedic patient population. In an Australian series of 761 patients with hip fracture (average age, 82 years), approximately 80% were vitamin D insufficient (ie, <20 ng/mL), and >30% had secondary hyperparathyroidism.<sup>12</sup> In a group of 723 patients who underwent elective orthopaedic surgery at a single institution, Bogunovic et al<sup>13</sup> reported that 15% had vitamin D levels below the normal Institute of Medicine cutoff of 20 ng/mL. A study of 62 British patients undergoing total hip arthroplasty revealed that 24% had vitamin D insufficiency.<sup>14</sup>

There are multiple risk factors and causes of hypovitaminosis D<sup>3,15</sup> (Table 1). The synthesis of vitamin D in the skin is decreased with increasing latitudes, the use of sunscreen, darker skin pigments, and increasing age. Obesity, malabsorption disorders, cholesterol-lowering agents, liver failure, and kidney disease can

**Table 1**

### Risk Factors for Hypovitaminosis D<sup>3,16</sup>

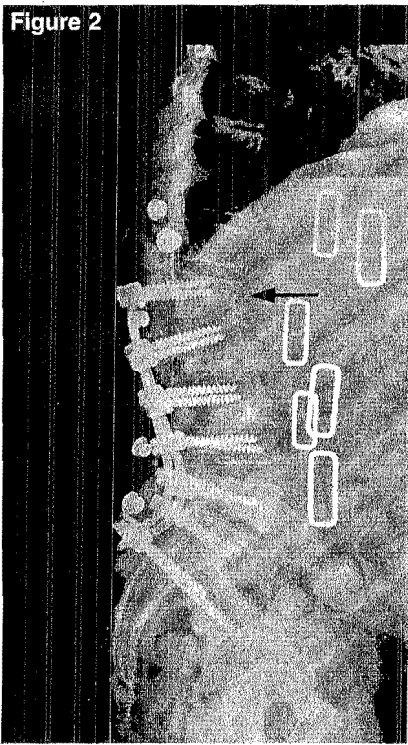
Decreased skin production
Increasing latitudes
Darker skin pigments
Use of sunscreen
Increasing age (institutionalized patients)
Decreased bioavailability and production
Liver or kidney dysfunction
Obesity
Malabsorption disorders
Exclusive breast feeding
Medications
Cholesterol-lowering agents
Glucocorticoids
Anti-seizure medications
Genetic disorders
Pseudovitamin D-deficiency rickets
Vitamin D-resistant rickets
Autosomal dominant hypophosphatemic rickets
X-linked hypophosphatemic rickets
Acquired disorders
Primary hyperparathyroidism
Hyperthyroidism

decrease available, bioactive vitamin D. Glucocorticoids and anti-seizure medications increase vitamin D catabolism. Acquired disorders include primary hyperparathyroidism and hyperthyroidism; genetic disorders include pseudovitamin D-deficiency rickets, vitamin D-resistant rickets, autosomal dominant hypophosphatemic rickets, and X-linked hypophosphatemic rickets.

### Musculoskeletal Impact of Vitamin D

Classically, vitamin D deficiency can lead to poor bone mineralization, resulting in rickets in children and osteomalacia in adults. The incidence of rickets has decreased dramatically since food fortification programs be-

Figure 2



Fracture (arrow) and junctional kyphosis in an adult patient with osteopenia. Further treatment in an orthosis was required.

gan in the 1930s, and children now have among the highest vitamin D intake levels compared with other age groups.<sup>6</sup> In adults, osteomalacia can present as isolated or symmetric bone pain, often with proximal muscle group weakness. It has been proposed that the loss of bone mineralization leads to subsequent hydration of the preserved collagen matrix, increased hydrostatic pressure against the overlying periosteum, and resultant pain symptoms.<sup>17</sup> Radiographically, osteomalacia can appear as thinned cortices, indistinct trabeculae, or a radiolucent Looser line on the concave portion of long bones.

Based on the well-defined role of vitamin D in bone mineralization, several studies have looked at its potential use in fracture prevention. In a meta-analysis of randomized controlled trials that compared oral vita-

min D supplementation, with or without calcium, with calcium or placebo in patients aged  $\geq 60$  years, daily vitamin D doses between 700 and 800 IU reduced the relative risk of hip fracture by 26%.<sup>18</sup> In another meta-analysis of patients  $\geq 50$  years of age, daily doses of at least 800 IU of vitamin D and 1,200 mg of calcium showed a pooled reduction in all fractures of 12% (risk ratio [RR], 0.88; 95% confidence interval [CI], 0.83 to 0.95;  $P = 0.0004$ ).<sup>19</sup> By comparison, a randomized study by the Women's Health Initiative of 400 IU of vitamin D and calcium suggests a possible dose-related effect. Although this lower dose slightly increased bone mineral density, it had no effect on reducing hip fractures in postmenopausal women.<sup>20</sup>

The relationship between vitamin D and fracture prevention is difficult to interpret because of the confounding effects of calcium supplementation. A Cochrane review further concluded that vitamin D supplementation alone was ineffective in preventing fractures but that vitamin D and calcium reduced the risk of hip fractures in elderly patients receiving institutional care (RR, 0.84; 95% CI, 0.73 to 0.96).<sup>16</sup>

Metabolic and endocrine abnormalities have long been linked with decreased fracture healing. In a recent series of 683 orthopaedic trauma patients diagnosed with fracture nonunion, 37 were referred to an endocrinologist for evaluation of an endocrine or metabolic abnormality.<sup>21</sup> Of these, 84% (31 of 37 patients) had a newly diagnosed endocrine abnormality, and 68% (25 of 37) were found to be vitamin D deficient. In eight of these patients, the nonunion healed following medical treatment alone. In an animal model of osteoporosis, daily administration of 1,25-dihydroxyvitamin D to ovariectomized rats with femoral fractures significantly increased bone

histomorphometric parameters and biomechanical strength.<sup>22</sup>

Trends in spinal surgery indicate that increasingly complex procedures are being performed in an aging patient population. Spinal instrumentation, like that of the appendicular skeleton, relies on the integrity of the bone-implant interface. Biomechanical testing has shown a linear positive correlation between vertebral bone mineral density and screw pull-out strength ( $r = 0.68$ ).<sup>23</sup> In a single-center study of 759 patients aged  $>50$  years who underwent spine surgery, 51% of women and 15% of men had osteoporosis identified by dual-energy X-ray absorptiometry.<sup>24</sup> Low vitamin D and poor bone mineral density may be a significant factor in instrumentation failure, loss of deformity correction, adjacent fractures, pseudarthrosis, and the need for revision surgery (Figure 2). Despite the wide prevalence of poor bone density, only 20% of 114 surveyed spine surgeons indicated that a metabolic workup was routinely used for patients aged  $>50$  years.<sup>25</sup> Increased awareness of the potential role of vitamin D and metabolic bone disease in the care of complex and elderly orthopaedic patients is needed.

Vitamin D may also affect neuromuscular function and patient falls. A meta-analysis of randomized controlled trials that compared varying doses of oral vitamin D to calcium or placebo demonstrated a pooled reduction in falls by 22% as well as improvements in sit-to-stand and walking tests.<sup>26</sup> However, a recent randomized controlled trial demonstrated that elderly community dwellers who received an annual oral dose of 500,000 IU of vitamin D were more likely to fall and to have fractures compared with those who received placebo.<sup>27</sup> In an age-, sex-, and comorbidity-matched cohort study of 62 patients who underwent

total hip arthroplasty, patients with a vitamin D level >16 ng/mL outperformed matched patients with levels <16 ng/mL.<sup>14</sup> The vitamin D-sufficient group had higher preoperative Harris hip scores ( $P = 0.018$ ) and attained a higher percentage of excellent postoperative Harris hip scores >90 ( $P = 0.038$ ). In addition, vitamin D levels had a positive Spearman correlation of +0.332 with postoperative Harris hip scores ( $P = 0.008$ ). This may reflect the association of vitamin D and improved neuromuscular function; alternatively, vitamin D levels may be representative of the patient's overall health status.

More recent studies have investigated the possible role of vitamin D and its receptors in the pathogenesis of various musculoskeletal conditions. The action of vitamin D at the cellular level requires that it bind to the VDR. Polymorphisms in the VDR gene have been linked to various musculoskeletal conditions, including low bone mineral density in adolescent idiopathic scoliosis patients<sup>27</sup> as well as multilevel degenerative disk disease in young adults.<sup>28</sup> In animal studies, VDR gene-knockout mice lose neuromuscular function and undergo rapid phenotypic aging, with a 50% shortened life span.<sup>29</sup>

### Management of Hypovitaminosis D

The diagnosis and management of hypovitaminosis D and other endocrine and metabolic abnormalities is no longer the sole responsibility of the primary care physician. Initiatives such as Own the Bone by the American Orthopaedic Association have attempted to improve patient education and physician communication regarding osteoporosis and treatment, including vitamin D and calcium supplementation.<sup>30</sup> In addition,

**Table 2**

#### Institute of Medicine Updated Dietary Intake Allowances for Vitamin D<sup>11</sup>

Age	Recommended Daily Dietary Allowance (IU) (1997)	Recommended Daily Dietary Allowance (IU) (2010)
0-12 mo	200	400
1-18 yr	200	600
19-50 yr	200	600
51-70 yr	400	600
>70 yr	600	800

tion, counseling on vitamin D and calcium intake for the prevention of osteoporosis in patients aged >50 years is a Centers for Medicare and Medicaid Services quality measure.<sup>31</sup>

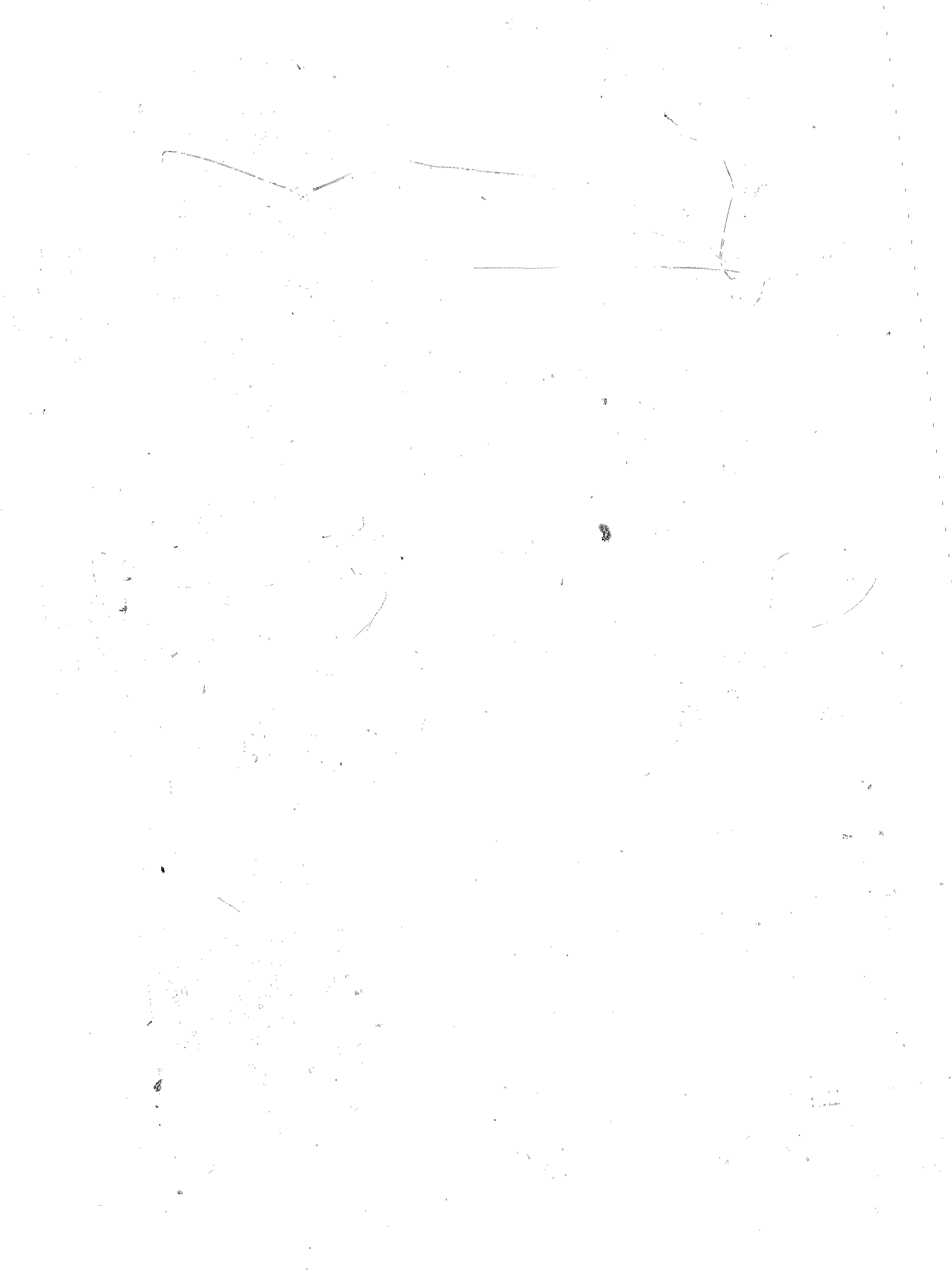
Orthopaedic trauma, spine, and arthroplasty patients aged >50 years, patients with a fragility fracture and/or those being treated for osteoporosis, and patients with a non-union should be screened for vitamin D insufficiency or deficiency, as should patients with known risk factors. Laboratory evaluation should, at minimum, include 25-hydroxyvitamin D and serum calcium levels as well as a PTH level to evaluate for secondary hyperparathyroidism. 25-Hydroxyvitamin D has a 2- to 3-week half-life and is the preferred clinical measure of vitamin D status. If appropriate, a referral to a metabolic bone specialist may be helpful in identifying other underlying metabolic abnormalities.

There is no agreed-on protocol for oral vitamin D supplementation in the setting of hypovitaminosis D. Most observational and randomized studies have used doses of vitamin D ranging from 400 to 1,000 IU per day. Currently, daily supplementation in lower doses is thought to be superior to large, annual doses, and vitamin D<sub>3</sub> has been shown to be more effective than vitamin D<sub>2</sub> in maintaining levels over time.<sup>32</sup> Vitamin D toxicity is rare and limited to a few case reports in the literature. It presents primarily as hypercalcemia,

with varying symptoms of malaise, pain, confusion, fever, and chills. Some studies have shown daily intake upper limits of 10,000 IU without signs of toxicity.<sup>33</sup> In a recent report, the Institute of Medicine increased the Recommended Daily Allowance for vitamin D for nearly all age groups (Table 2) and determined a safe daily upper limit of 4,000 IU.<sup>11</sup>

Given the uncertainty of the optimal therapeutic dose as well as the rarity of vitamin D toxicity, we typically recommend a target 25-hydroxyvitamin D level of between 30 and 40 ng/mL. Although the Institute of Medicine affirmed the role of vitamin D in bone health, conflicting evidence in the literature led to their more conservative recommendation of 20 ng/mL. Our threshold for treatment, however, is based on the PTH response to vitamin D levels <30 ng/mL, similar to recent recommendations from Osteoporosis Canada and the International Osteoporosis Foundation. This threshold also accounts for temporal variations in individual levels of vitamin D.<sup>9,10</sup>

For patients with insufficient vitamin D levels of between 25 and 30 ng/mL, a daily oral dose of 2,000 to 4,000 IU of vitamin D<sub>3</sub> is often effective. For patients with levels <25 ng/mL, 50,000 IU of vitamin D<sub>2</sub> administered weekly for 8 to 12 weeks is preferred. In addition, we recommend 1,000 mg of daily calcium supplementation for adults aged ≤50



years and 1,200 mg of daily calcium for adults aged >50 years. In all patients, vitamin D levels are rechecked at 3-month intervals after initiation of treatment.

For causes of vitamin D deficiency other than decreased nutritional intake or cutaneous synthesis, patients may not respond to typical supplementation. For example, disease states resulting in hepatic or renal dysfunction can disrupt the vitamin D metabolic pathway and may require treatment with vitamin D<sub>3</sub> or 1,25-dihydroxyvitamin D<sub>3</sub>, respectively. In the setting of vitamin D resistance, such as in X-linked hypophosphatemic rickets, treatment with 1,25-dihydroxyvitamin D<sub>3</sub> and careful monitoring of PTH and phosphorous levels should be directed by an endocrinologist with experience in metabolic bone disorders.

## Summary

A growing body of literature identifies the potential musculoskeletal benefits of vitamin D as well as the negative implications of deficiency. We therefore recommend active involvement by the orthopaedic surgeon in the diagnosis and treatment of patients with potential vitamin D deficiency. Regrettably, however, current evidence is of insufficient quality to define optimum vitamin D levels among patients and to establish evidence-based treatment guidelines. Nonetheless, active evaluation and management of vitamin D among the orthopaedic patient population is safe and simple and may be effective in improving patient care.

## References

**Evidence-based Medicine:** References 18, 20, and 32 are level I studies. References 16, 19, 22, and 26 are

level II studies. References 7-9, 12-14, and 27-29 are level III studies. References 2-6, 10, 15, 17, 21, 23-25, 30, 31, and 33 are level IV studies.

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