

REPORT 4 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (A-09)
Appropriate Supplementation of Vitamin D
(Resolution 425, A-08)
(Reference Committee D)

EXECUTIVE SUMMARY

Objective: To highlight key information and considerations for physicians regarding vitamin D, including current recommendations for vitamin D intake and its potential for toxicity in the body. The report reviews the biochemistry and metabolism of vitamin D, as well as its association with various disease outcomes, with a focus on adults. Key limitations in the current literature are highlighted, as are areas requiring further research.

Methods: Literature searches for review articles were conducted in the PubMed database and the Cochrane Database of Systematic Reviews using the search term “vitamin D” in the article title and/or abstract. Web sites managed by federal agencies and applicable professional organizations were also reviewed for relevant information. Additional articles were identified by reviewing the reference lists of pertinent publications.

Results: Vitamins D2 (ergocalciferol) and D3 (cholecalciferol) are seco-steroid prohormones that are essential nutrients if sufficient levels of vitamin D3 cannot be produced in the skin. It is unclear how much sun or ultraviolet B radiation exposure, if any, allows for maximal cutaneous synthesis while minimizing the risk of skin cancer. Thus, fatty fish, fortified foods, and dietary supplements are recommended. 1,25-dihydroxyvitamin D is the active metabolite of vitamins D2 and D3, and is an important hormone, transcriptional activator, and immunomodulator. Since circulating levels of 1,25-dihydroxyvitamin D are tightly regulated by the body, serum 25-hydroxyvitamin D (25[OH]D) is the best indicator available of vitamin D status. A rapidly expanding literature has reported inverse associations between 25(OH)D and/or intakes of vitamin D and numerous outcomes related to bone health, several cancers, cognitive function, cardiovascular disease, diabetes, some infections, and several autoimmune diseases. However, clinical trials have yet to prove that vitamin D is causally related to most of these outcomes. It appears, nevertheless, that many people may have subclinically deficient or insufficient levels of vitamin D, prompting many to recommend intakes of 800 to 1,000 international units (IU) per day of vitamin D or even more, in the form of dietary supplements. However, there are significant limitations in the literature due to inadequate control of confounding variables, variability in serum 25(OH)D assays, and a lack of dose-response data on many skeletal and nonskeletal outcomes, including the potential for adverse outcomes. Caution is warranted given the surprising lack of effects, or sometimes even harmful effects, found in large, long-term trials of other previously promising nutrients and hormones, such as antioxidants and hormone replacement therapy. It is likely that greater vitamin D exposure will benefit at least some in the population, but more research is needed.

Conclusions: While the associations between vitamin D and various disease outcomes appear promising, clinical trials have yet to prove that vitamin D is causally related to most of these outcomes. More long-term, well-designed studies, including large intervention trials, are needed across all life stage and racial and ethnic groups to better understand vitamin D's role in disease prevention, to determine the optimal doses and serum 25(OH)D levels, and to fully elucidate the potential for adverse outcomes at various intakes. Nevertheless, physicians should consider measuring the serum concentration of 25(OH)D in patients at risk of vitamin D deficiency and counsel those with deficient or insufficient levels on ways to improve their vitamin D status.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 4-A-09

Subject: Appropriate Supplementation of Vitamin D
(Resolution 425, A-08)

Presented by: Carolyn B. Robinowitz, MD, Chair

Referred to: Reference Committee D
(James L. Milam, MD, Chair)

1 Resolution 425 (A-08) “Appropriate Supplementation of Vitamin D,” introduced by the Pennsylvania
2 Delegation at the 2008 American Medical Association (AMA) Annual Meeting and referred to the
3 Board of Trustees, asks:

4
5 That our AMA urge the Food and Nutrition Board of the Institute of Medicine to re-examine
6 the Daily Reference Intake values for vitamin D in light of new scientific findings; and

7
8 That our AMA study the advisability of recommending that physicians consider adding the
9 measurement of serum 25-hydroxyvitamin D levels to their health maintenance activities, and
10 where appropriate, recommending dietary supplementation of vitamin D at a dosage of 1,000-
11 2,000 international units (IU) per day, with a report back at the 2009 Annual Meeting.

12
13 The first resolve was completed in the fall of 2008. This report addresses the second resolve by
14 reviewing current recommendations for vitamin D and describing its biochemistry, metabolism, and
15 potential toxicity in the body. Vitamin D’s association with various disease outcomes is outlined, as
16 well as the optimal source and dose, with a focus on adults. Key limitations in the current literature
17 are highlighted, as are areas requiring further research. This report is not intended to provide an
18 exhaustive review of the literature on vitamin D, but rather to emphasize information and
19 considerations that may be of particular interest to physicians.

20 21 CURRENT AMA POLICY RELATED TO VITAMIN D

22
23 The AMA currently has limited policy related to vitamin D. AMA Policy D-330.979 (AMA Policy
24 Database) on Medicare reimbursement for vitamin D therapy for dialysis patients directs our AMA to
25 “petition the Centers for Medicare and Medicaid Services and/or lobby Congress to defeat the
26 ‘Vitamin D Analogs Draft Local Medical Review Policy’ and to prevent its implementation in Florida
27 or any other state.”

28 29 METHODS

30
31 Literature searches for review articles published in the last five years through December 2008 were
32 conducted in the PubMed database and the Cochrane Database of Systematic Reviews using the

Action of the AMA House of Delegates 2009 Annual Meeting: Council on Science and Public Health Report 4 Recommendations Adopted as Amended, and Remainder of Report Filed.

1 search term “vitamin D” in the article title and/or abstract. More than 1,500 review articles were
2 identified, with over 300 published in 2008 alone. The most comprehensive and unique reviews were
3 selected and reviewed. Web sites managed by federal agencies and applicable professional
4 organizations were also reviewed for relevant information. Additional articles were identified by
5 reviewing the reference lists of pertinent publications.

6 7 BACKGROUND: WHY IS VITAMIN D GETTING SO MUCH ATTENTION? 8

9 In recent years, the literature on vitamin D has expanded greatly, particularly since the discovery that
10 most tissues and cells in the body have a vitamin D receptor. No longer just associated with bone
11 health, vitamin D has been implicated in various disease outcomes, including type 1 and type 2
12 diabetes, multiple sclerosis, cardiovascular disease, and several cancers. Improved surveillance of the
13 serum vitamin D status of the population, as opposed to just the prevalence of rickets, osteomalacia,
14 and osteoporosis, has revealed that 30% to 100% of American and European subpopulations have
15 serum levels of vitamin D that are considered deficient or insufficient, including some individuals
16 consuming levels of vitamin D that meet or exceed currently recommended intakes.¹

17
18 Thus, many researchers and health professionals are concerned that the current dietary reference
19 intakes (DRI) for vitamin D are too low for most of the population, including the current tolerable
20 upper intake levels (ULs), which some research suggests may provide the optimal amount needed to
21 prevent cancer and other diseases. However, the best means of obtaining vitamin D is less clear.
22 Supplementation has been recommended because of concerns about skin cancer and the inability of
23 some individuals to produce adequate amounts of vitamin D from limited sun exposure. Concerns
24 also remain about the optimal dose of supplemental vitamin D. While most supplementation trials of
25 vitamin D have found doses above the UL to be safe, the majority of these trials were not adequately
26 designed to assess harm, particularly from long-term supplementation in the general population.

27 28 BIOCHEMISTRY AND METABOLISM 29

30 Vitamin D, also known as calciferol, refers to a class of essential fat-soluble seco-sterols.² The two
31 most physiologically relevant forms of vitamin D are the prohormones vitamin D₂ (ergocalciferol)
32 and vitamin D₃ (cholecalciferol).² Sometimes the term “vitamin D” also is used to refer to the
33 metabolites of these prohormones, including the major transport form, 25-hydroxyvitamin D
34 (calcidiol), and the biologically active hormone 1,25-dihydroxyvitamin D (calcitriol).

35
36 Vitamin D₃ is synthesized endogenously in the skin: ultraviolet B (UVB) radiation converts 7-
37 dehydrocholesterol in keratinocytes to previtamin D₃. At skin temperature, previtamin D₃ is quickly
38 converted to vitamin D₃.^{1,2} Vitamin D₃ is carried to the liver by the vitamin D binding protein, which
39 binds and transports most forms of vitamin D and its metabolites in plasma.^{1,3} Extended sunlight
40 exposure does not cause vitamin D toxicity because the continued solar radiation destroys any excess
41 previtamin D₃ and vitamin D₃ produced in the skin.¹

42
43 Vitamin D can also be obtained from foods, fortified foods, and supplements as either vitamin D₂ or
44 vitamin D₃. Specific dietary sources are described in more detail below and in the Appendix. Both
45 dietary vitamin D₂ and D₃ are fat soluble and are thus absorbed through the lymphatic system carried
46 by chylomicrons, which are then metabolized to remnant particles that carry dietary vitamin D to the
47 liver.³

48
49 Both vitamin D₂ and D₃ can be stored in fat cells, and both can be hydroxylated in the liver to form
50 25-hydroxyvitamin D (25[OH]D), the main circulating form of vitamin D and the best functional

1 indicator of vitamin D nutritional status.^{1,3} However, 25(OH)D is not biologically active; it must be
 2 further hydroxylated in the kidneys to 1,25-dihydroxyvitamin D (1,25[OH]₂D).^{1,4} Production of
 3 1,25(OH)₂D in the kidneys is tightly regulated by parathyroid hormone levels generated in response
 4 to serum levels of calcium and phosphorous,² as well as by fibroblast growth factor 23 and other
 5 factors.¹ 1,25(OH)₂D increases the efficiency of renal calcium and intestinal calcium and phosphorus
 6 absorption.¹ 1,25(OH)₂D regulates itself through a negative feedback loop, in which it decreases the
 7 production of parathyroid hormone and increases the synthesis of 25-hydroxyvitamin-D-24-
 8 hydroxylase, which in turn metabolizes 1,25(OH)₂D into calcitroic acid, a water-soluble, biologically
 9 inactive metabolite that is excreted in the bile.¹

10
 11 While the liver and kidneys are responsible for the metabolism of most of the vitamin D in the body,
 12 vitamins D2 and D3 can also be metabolized to 25(OH)D in the skin.⁵ The enzyme 25-
 13 hydroxyvitamin D-1 α -hydroxylase, which metabolizes 25(OH)D to 1,25(OH)₂D, is present in the
 14 kidneys as well as many other tissues, including skin, osteoclasts, macrophages, placenta, colon,
 15 brain, prostate, endothelium, and parathyroid glands.³ However, most 1,25(OH)₂D circulating in the
 16 blood is produced by the kidneys.⁵

17
 18 1,25(OH)₂D is a transcriptional activator⁶ that binds to vitamin D receptors (VDR) throughout the
 19 body, including those in bone, brain, breast, adipose, intestinal, immune, kidney, liver, nerve, ovarian,
 20 pancreas, parathyroid gland, pituitary gland, prostate, and skin cells.^{3,5} The VDR can then form a
 21 complex with the retinoid-x receptor (RXR); this VDR-RXR complex then binds to the vitamin D
 22 response elements in DNA and activates transcription of nearby genes and, in turn, proteins.⁵ Either
 23 directly or indirectly, 1,25(OH)₂D is estimated to control at least 200 different genes, including those
 24 that regulate cell proliferation, differentiation, apoptosis, and angiogenesis.¹

25
 26 **IS VITAMIN D A VITAMIN OR IS IT A HORMONE?**

27
 28 Vitamin D can be considered both a vitamin and a hormone, depending on its form and whether or
 29 not an individual's sun exposure is sufficient to produce enough vitamin D3 endogenously. If an
 30 individual has regular access to sufficient UVB radiation for skin production of vitamin D3, then
 31 vitamin D does not need to be consumed in the diet; in this case, vitamin D is technically not an
 32 essential nutrient. However, as described below, many factors can reduce the skin's exposure to
 33 sufficient UVB. Thus for many people in the modern world, vitamin D is an essential nutrient that
 34 must be obtained via the diet or supplements. Regardless of the source, both vitamins D2 and D3 are
 35 seco-steroid prohormones that can be metabolized to the biologically active form, 1,25(OH)₂D, which
 36 is a hormone, as it is made in one part of the body and circulates to other tissues where it influences
 37 the activities of other cells.⁴

38
 39 **SOURCES OF VITAMIN D**

40
 41 *Sun*

42
 43 The human body is designed to manufacture vitamin D3 from sunlight. Throughout history, and to
 44 this day, sunlight remains the primary source of vitamin D for most people around the world.
 45 Maximum vitamin D3 synthesis is achieved relatively quickly upon UVB exposure, with less than
 46 one minimal erythemal dose required.³ This translates to about five to 30 minutes of sun exposure to
 47 the arms and legs between 10 AM and 3 PM twice a week for most people.¹ However, time of day,
 48 season, latitude, surrounding surface (sand, snow, water, etc.), amount of cloud cover, thickness of
 49 the ozone layer, level of air pollution, time spent outdoors, skin pigmentation (darker skin reduces
 50 vitamin D3 synthesis), body composition, age, clothing, and sunscreen use can affect the amount of

1 vitamin D the skin can produce.^{7,8} For example, it is estimated that above about 42 degrees north
2 latitude (Chicago, Boston), vitamin D₃ cannot be synthesized by the skin from November to February
3 because no UVB radiation reaches the ground.⁸ Cutaneous synthesis of vitamin D is generally
4 possible year round at latitudes below 34 degrees north (a line between Los Angeles and Columbia,
5 South Carolina).⁹

6
7 Nevertheless, even in older adults, in whom production of vitamin D by the skin can be greatly
8 diminished due to thinner skin and lower concentrations of 7-dehydrocholesterol,^{3,8} regular exposure
9 to sunlight or other sources of UVB radiation can correct deficiencies and reduce fracture risks.¹
10 Additionally, although sunscreens with a sun protection factor (SPF) of 15 reduce vitamin D₃
11 synthesis by 99%,¹ in practice, vitamin D₃ synthesis is not completely blocked, since most people do
12 not apply or reapply sunscreen as directed. However, there is no established threshold for a level of
13 UVB exposure that does not increase skin cancer risk.³

14 15 *Diet and Supplements*

16
17 Fatty fish is the richest natural food source of vitamin D (Appendix), although milk and ready-to-eat
18 breakfast cereals are the primary food sources of vitamin D in the United States.^{2,10} Nearly all milk in
19 the United States is fortified with 100 IU of vitamin D (usually D₃) per cup (8 oz),^{9,10} as are most
20 ready-to-eat breakfast cereals.¹⁰ Contrary to public perception, milk products such as yogurt, butter,
21 ice cream, sour cream, cream, cottage cheese, and most varieties of hard and soft cheeses are not
22 regularly fortified with vitamin D.¹⁰ In fact, unlike Canada and Finland, no foods are required to be
23 fortified with vitamin D in this country, although many categories of food are eligible for controlled
24 levels of vitamin D fortification, including milk, milk products, and cereal flours and related
25 products.¹⁰ Even milk is not required to be fortified unless it is labeled as such.¹⁰ The Food and Drug
26 Administration regulates the amount of vitamin D that can be added to foods to prevent over-
27 fortification.¹⁰

28
29 Vitamin D₂ used in foods and supplements is manufactured via the ultraviolet irradiation of
30 ergosterol in yeast and plants.¹ Vitamin D₃ added to foods and supplements is made via the
31 ultraviolet irradiation of 7-dehydrocholesterol from lanolin.¹ Lanolin is an animal product, generally
32 obtained from sheep, and thus, this source of vitamin D may not be suitable for some vegetarians.

33
34 Dietary supplements containing vitamin D₂ or D₃ are widely available over-the-counter as single
35 supplements and as part of standard multivitamins and other multiple vitamin supplements (Table).
36 High doses of vitamin D₂ are available by prescription. Also available by prescription are vitamin
37 D₂ and D₃ analogs and their metabolites, including 1,25(OH)₂D and its synthetic analogs (Table).
38 Calcitriol (1,25[OH]₂D) and its active analogs are used to treat psoriasis (generally topically),
39 secondary hyperparathyroidism, hypocalcemia, and metabolic bone disease in patients with severe
40 chronic renal or liver disease and hypoparathyroidism.¹¹⁻¹³

41 42 *What Source(s) Are Best?*

43
44 If skin cancer risk were not an issue, the sun would likely be considered the best source of vitamin D,
45 as the human body is designed to synthesize vitamin D₃ from sunlight. In addition, other factors
46 described above, such as seasonality, time spent outdoors, clothing, etc., can limit the skin's ability to
47 make vitamin D. Therefore, dietary sources are widely recommended to supplement minimal sun
48 exposure. Since relatively few Americans frequently consume fatty fish, and the natural vitamin D
49 content of other foods is generally low or nonexistent per serving, fortified foods and/or supplements
50 are the best source of vitamin D for many people.¹⁰

1 As to the best form of dietary vitamin D, vitamin D2 has been reported to be only one third as
 2 effective as vitamin D3 at increasing and sustaining serum 25(OH)D levels,^{4,14,15} although recent
 3 research suggests that both forms may be equally effective in raising and maintaining serum
 4 25(OH)D levels.¹⁶ Other factors, such as availability and affordability of supplements, and food
 5 preferences, such as fish intake and vegetarianism, may ultimately determine the “best” source for
 6 many people.

7
 8 *Can Individuals Get Enough Vitamin D from Food or Should They Take Supplements?*
 9

10 It is possible to get sufficient amounts of vitamin D from food alone, although most people would
 11 need to include foods fortified with vitamin D, like milk, orange juice, and breakfast cereal. Whether
 12 or not people need to take a supplement depends on the foods they regularly consume and the
 13 recommended intake for their life stage group and health status (assuming no endogenous synthesis
 14 from UVB radiation). As described below, research continues on the optimal intakes needed to
 15 achieve optimal serum levels of 25(OH)D, the current biomarker of vitamin D status.

16
 17 **INTERACTIONS BETWEEN VITAMIN D AND OTHER SUPPLEMENTS OR MEDICATIONS**
 18

19 A few supplements and dietary components may interfere with the absorption or action of vitamin D
 20 in the body. High doses of vitamin A may inhibit absorption of vitamin D in the intestine, and
 21 vitamin A and retinols may interfere with vitamin D’s action on bone.⁸ The non-absorbable, non-
 22 caloric fat substitute olestra may also prevent the absorption of vitamin D if consumed at the same
 23 time.⁸

24
 25 Several medications may affect vitamin D absorption or metabolism. Medications that reduce fat
 26 absorption, such as bile acid sequestrants (e.g., cholestyramine, colestipol), orlistat, and mineral oil,
 27 may also limit the absorption of vitamin D if consumed at the same time.^{1,8} Anti-convulsants (e.g.,
 28 phenytoin, phenobarbital), glucocorticoids, highly active antiretroviral therapy (HAART), anti-
 29 rejection medications, or other drugs that activate the steroid and xenobiotic receptors may increase
 30 catabolism of vitamin D.¹ In hypoparathyroid patients, vitamin D may also interact with thiazide
 31 diuretics to cause hypercalcemia.¹² In contrast, use of oral contraceptive pills is associated with
 32 higher serum 25(OH)D levels.¹⁷ Other medications also may affect vitamin D metabolism; as with
 33 any drug or dietary supplement, physicians should evaluate the full list of possible interactions and
 34 side effects in the context of each individual patient.

35
 36 **CURRENT RECOMMENDATIONS**
 37

38 The Food and Nutrition Board of the Institute of Medicine (IOM) established the current dietary
 39 reference intakes (DRIs) for adults in 1997.² The recommendations are based on the amount of
 40 vitamin D needed to maintain adequate calcium metabolism and bone health. The Food and Nutrition
 41 Board felt that the state of knowledge at the time was insufficient to establish an Estimated Average
 42 Requirement (EAR) and in turn a Recommended Dietary Allowance (RDA); both cover the nutrient
 43 needs of a specific percentage of individuals. Therefore, it established Adequate Intake (AI) levels
 44 for vitamin D, which nevertheless are estimated to cover the nutrient needs of all individuals in the
 45 life stage group.² The AIs for vitamin D assume that no vitamin D is available from exposure to
 46 sunlight or other sources of UVB radiation.² The AIs for adults are listed below.

Life Stage	Adequate Intake (AI) for vitamin D per day
Aged 19 – 50 years	200 IU (5.0 µg)

Aged 51 – 70 years	400 IU (10 µg)
Aged > 70 years	600 IU (15 µg)
Pregnant, Aged 14 – 50 years	200 IU (5.0 µg)
Lactating, Aged 14 – 50 years	200 IU (5.0 µg)

1 The UL for all adults is currently 2,000 IU (50 µg) per day. This level is based on one study, which
2 observed hypercalcemia (serum calcium level above 2.75 mmol/L) in adults consuming 3,800 IU (95
3 µg) of vitamin D per day for three months. In the same study, no observed adverse effects were
4 reported at intakes of 2,400 IU (60 µg) per day. After factoring in the lack of certainty about the
5 effect of these doses in a larger population of individuals, some of whom might be more sensitive to
6 supplemental vitamin D, as well as the short duration and small sample size of the study, the UL was
7 set at 2,000 IU per day. While not explicitly considered in its analysis, the Food and Nutrition Board
8 noted case reports of severe adverse effects (described under Toxicity, below) from intakes of 10,000
9 to 50,000 IU (250 to 1,250 µg) per day over many years.²

10
11 An ad hoc expert committee for the Food and Nutrition Board is currently reviewing the DRIs for
12 vitamin D and calcium.¹⁸ Its thorough examination of the literature will include studies on vitamin
13 D's relation to risk of cancer and other chronic diseases and conditions. This new DRI report is
14 expected to be released in 2010.

15
16 In the meantime, the American Academy of Pediatrics (AAP), which previously endorsed the AI of
17 200 IU vitamin D for healthy infants, children, and adolescents, recently revised its recommendation
18 to a minimum 400 IU per day beginning soon after birth.⁷ The AAP cited evidence that 200 IU of
19 vitamin D per day fails to maintain serum 25(OH)D concentrations above 20 ng/mL (50 nmol/L) in
20 infants, which is the level some researchers have associated with deficiency in adults. The AAP
21 agrees with the Centers for Disease Control and Prevention, American Cancer Society, and many
22 other organizations that sunlight exposure should be minimized to reduce the risk of skin cancers, and
23 therefore recommends that adequate vitamin D levels be achieved through supplementation.⁷

24
25 The AAP further recommends that health care professionals providing obstetric care consider
26 measuring the serum 25(OH)D concentrations of pregnant women and recommends supplements for
27 those women with 25(OH)D concentrations below 32 ng/mL (80 nmol/L), the level at which the AAP
28 defined vitamin D sufficiency in adults. It noted that prenatal vitamins containing 400 IU of vitamin
29 D3 appear to have minimal impact on maternal serum 25(OH)D levels.⁷ For lactating women,
30 vitamin D doses of 1000 to 2000 IU per day do not significantly increase the 25(OH)D levels in their
31 breastfeeding infants, although studies on the effect of higher doses are limited. Therefore, the AAP
32 advised against universal high-dose supplementation of lactating women and recommended giving
33 vitamin D supplements directly to breast-fed infants.⁷

34
35 Like the AAP, other organizations have recently recommended intakes of vitamin D that exceed the
36 current AIs. The North American Menopause Society recommends that women at risk of vitamin D
37 deficiency due to inadequate sunlight exposure take 700 to 800 IU of vitamin D per day.¹⁹ The
38 National Osteoporosis Foundation recommends that adults under age 50 years consume 400 to 800 IU
39 of vitamin D (either D2 or D3) daily and that adults aged 50 years and older consume 800 to 1,000 IU
40 vitamin D per day for optimal bone health.²⁰ The Canadian Cancer Society advises adults to talk to
41 their physician about taking 1,000 IU of vitamin D per day during the fall and winter, and all year if
42 they are elderly, have dark skin, spend limited time outdoors, or wear clothing that covers most of
43 their skin.²¹ In 2006, the Canadian Cancer Society, along with several other organizations, including
44 the American Cancer Society, American College of Rheumatology, Canadian Dermatology

1 Association, and the World Health Organization Collaborative Centre for the Promotion of Sun
 2 Protection endorsed the message that supplementation and small amounts of sun exposure are the
 3 preferred methods of achieving optimal vitamin D status.²² However, the American Academy of
 4 Dermatology recommends that vitamin D be obtained from foods and/or supplements and not from
 5 unprotected ultraviolet radiation exposure.²³

7 ASSOCIATIONS OF VITAMIN D WITH HEALTH OUTCOMES

9 *Bone Health*

11 Vitamin D is most well known for its impact on bone health. Vitamin D is necessary for proper
 12 growth and skeletal development in utero and during childhood and adolescence,^{1,7} which also may
 13 help prevent osteoporosis and fracture in adulthood.²⁴ In adults, insufficient vitamin D can lead to
 14 osteopenia, osteoporosis, osteomalacia, muscle weakness, and fracture.¹

16 In general, serum 25(OH)D concentrations are directly associated with bone mineral density (BMD).
 17 Some research has found that maximal BMD, and lowest risk of hip and other nonvertebral fracture,
 18 is achieved at serum concentrations of approximately 36 to 40 ng/mL (90 to 100 nmol/L), although
 19 the slope of this association may vary between ethnic and racial groups.²⁵ For example, African
 20 Americans tend to have higher BMD than whites, and lower risk of osteoporotic fractures, despite
 21 lower levels of 25(OH)D.²⁶ Still, low serum 25(OH)D levels result in higher parathyroid hormone
 22 concentrations and lower BMD even among blacks.^{25,27} A recent systematic evidence-based review
 23 found fair evidence that serum 25(OH)D levels were inversely associated with both BMD and falls in
 24 older adults.²⁸ However, this same review found inconsistent evidence that serum 25(OH)D
 25 concentrations are associated with reduced fracture risk in elderly and postmenopausal women.^{3,28}

27 Inconsistent results have also been observed for the effect of vitamin D supplementation on fracture
 28 risk and falls, even though vitamin D-fortified foods and supplements are associated with increases in
 29 serum 25(OH)D concentrations in most,²⁸ but not all populations.²⁶ Uncontrolled confounding
 30 variables (e.g., seasonality, baseline vitamin D and calcium status, body mass index, age, underlying
 31 disease, and compliance) likely contributed, at least in part, to the inconsistency across studies. In
 32 addition, the doses studied may have been insufficient to increase serum levels of 25(OH)D to a high
 33 enough degree. It appears that to reduce fracture risk, mean serum concentrations of 25(OH)D need
 34 to be approximately 40 ng/mL (100 nmol/L). Doses of 400 IU/d of vitamin D3 appear generally
 35 ineffective at achieving this serum concentration and, in turn, reducing fracture risk. Most effective
 36 have been doses of 700 to 800 IU vitamin D3/d, particularly in those with baseline concentrations of
 37 25(OH)D between 17 and 31 ng/mL (44 and 77 nmol/L).²⁵ On the whole, however, the evidence
 38 appears insufficient that supplemental doses of vitamin D alone decrease risk of bone fracture or
 39 increase BMD in pre- and postmenopausal women and elderly men, although supplementation with
 40 calcium and vitamin D combined does.³ Risk of falls, though, remains inconsistent in
 41 postmenopausal women for supplemental vitamin D and calcium combined.³

43 *Other Musculoskeletal Outcomes*

45 VDRs are present in skeletal muscle and deficiency of vitamin D is associated with muscle
 46 weakness.¹ Performance speed and muscle strength have been found to improve as 25(OH)D levels
 47 increase to at least 40 ng/mL (100 nmol/L).¹ However, in the elderly, results for physical performance
 48 have been inconsistent³ and a recent randomized trial of vitamin D plus calcium found no effect on
 49 physical functioning or performance in older women.²⁹

1 There is some evidence that chronic nonspecific musculoskeletal pain, a symptom of hypovitaminosis
2 D, is being misdiagnosed and mistreated. One study observed that 93% of patients aged 10 to 65
3 years admitted to a hospital emergency department complaining of persistent, nonspecific muscle
4 aches and bone pain were deficient in vitamin D.³⁰ Over 90% had been previously evaluated by a
5 health care provider regarding their chronic pain and all had used over-the-counter or prescription
6 analgesics without improvement; none had been tested for vitamin D deficiency. Patients with
7 nondetectable levels of serum 25(OH)D had previously had their symptoms attributed to stress,
8 depression, gestational diabetes, nondegenerative joint disease, and other causes.

9 10 *Cancer Prevention*

11
12 Some, but not all, studies have found that individuals living at higher latitudes (i.e., with presumably
13 less sun exposure) have a higher risk of contracting and dying from several cancers, including
14 Hodgkin's lymphoma, colon, pancreatic, prostate, ovarian, breast, and others,¹ although latitude is not
15 necessary directly associated with serum 25(OH)D levels, particularly in Europe.⁸ Epidemiological
16 evidence has found a 30% to 50% increased risk of cancers of the colon, prostate, and breast in
17 individuals with serum 25(OH)D levels less than 20 ng/mL (50 nmol/L), as well as increased
18 mortality from these cancers.¹

19
20 A recent extensive review of the literature concurred that there is consistent evidence supporting an
21 inverse association between serum 25(OH)D levels and colorectal cancer and sporadic colorectal
22 adenoma; however, only limited evidence supported an actual causal link, as two large randomized
23 trials did not support an effect of vitamin D on colorectal cancer risk.^{8,31,32} This same extensive
24 review found only limited evidence that vitamin D reduced risk of breast cancer; only one
25 randomized trial examined this association and observed no effect of vitamin D plus calcium on
26 breast cancer incidence.³³ The review found no evidence for reduced risk of prostate cancer and
27 insufficient evidence to evaluate other cancers.⁸ Evidence was suggestive that vitamin D supplements
28 (range 300 to 2000 IU/d; mean dose 528 IU) may lower all-cause mortality,⁸ based primarily on a
29 meta-analysis of randomized trials.³⁴

30
31 Many possible explanations account for the lack of efficacy in trials: supplemental doses of vitamin D
32 may have been too low (400 to 830 IU/d), vitamin D may have interacted with hormone replacement
33 therapy, poor compliance, short study durations, lack of baseline serum 25(OH)D data, etc., but the
34 fact remains that good evidence showing a causal effect of vitamin D on any cancer risk is lacking.⁸
35 It is possible that vitamin D exerts more influence on cancer progression and mortality rather than on
36 cancer incidence, and/or that serum 25(OH)D is a risk marker of cancer occurrence rather than a
37 causal risk factor.⁸

38 39 *Cognitive Function*

40
41 Some cross-sectional studies suggest that vitamin D may be associated with cognitive function and
42 Alzheimer's disease.³⁵⁻³⁸ Vitamin D receptors are found in neurons, as well as regions often affected
43 in Alzheimer's disease, such as the hypothalamus, substantia nigra, cortex, and hippocampus.³⁶ In
44 vitro and animal studies also suggest vitamin D may have neuroprotective effects.³⁶ However, no
45 prospective studies or randomized trials have confirmed this association in the general population.

46 47 *Depression and Mood*

48
49 Deficient levels of vitamin D have been associated with higher rates of depression and low
50 mood.^{1,38-40} Few randomized trials have attempted to confirm this association.⁴⁰

1 *Cardiovascular Disease*

2
3 Hypertension and cardiovascular disease risk have been directly associated with latitude.¹
4 Deficiencies in vitamin D have been associated with hypertension,⁴¹ cardiovascular disease,^{42,43} and
5 congestive heart failure, as well as with inflammatory factors such as C-reactive protein and
6 interleukin-10.¹ However, two randomized trials involving vitamin D supplementation failed to find
7 an effect on cardiovascular disease risk.^{31,44} In hypertensive patients (as opposed to the general
8 population), a small trial of UVB radiation three times per week for three months resulted in a
9 reduction of both systolic and diastolic blood pressure by 6 mm Hg to normal levels.⁴⁵ While
10 recognizing the need for more research, a recent review of vitamin D and cardiovascular disease risk
11 recommended monitoring serum 25(OH)D status and outlined specific therapies for correcting
12 vitamin D deficiency.⁴⁶

13
14 *Diabetes*

15
16 Research suggests that supplemental vitamin D in pregnant women, infants, and children reduces the
17 risk of type 1 diabetes.¹ In adults, a recent cross-sectional study found that low levels of 25(OH)D
18 were associated with increased insulin resistance in nondiabetic persons.⁴⁷ A large prospective study
19 observed that supplementation of 800 IU of vitamin D plus 1200 mg of calcium per day decreased the
20 risk of type 2 diabetes.⁴⁸ However, a large randomized controlled trial of 400 IU of vitamin D3 plus
21 1000 mg of calcium per day did not reduce diabetes incidence over seven years of follow-up.⁴⁹

22
23 *Immunity and Autoimmune Disease*

24
25 1,25(OH)₂D is considered a powerful immunomodulator,¹ particularly for its effects in suppressing
26 the immune response.⁵⁰ Vitamin D in various forms has been inversely associated with several
27 autoimmune diseases, including multiple sclerosis,⁵¹ rheumatoid arthritis, osteoarthritis,¹ systemic
28 lupus erythematosus,^{52,53} and inflammatory bowel diseases such as Crohn's disease and ulcerative
29 colitis.⁵⁰ While some of these associations may be in part a consequence of the disease and/or
30 treatment (e.g., malabsorption and corticosteroid treatments), research suggests that vitamin D plays a
31 role in the development, progression, and/or severity of the disease.^{50,52} For example, increasing
32 latitude of residence has been associated with increased risk of multiple sclerosis and Crohn's
33 disease.¹ Likewise, higher intakes of vitamin D have been associated with reduced incidence of
34 multiple sclerosis⁵⁴ and rheumatoid arthritis⁵⁵ and with the slower progression of osteoarthritis.⁵⁶

35
36 While vitamin D is linked to the suppression of autoimmune disease, it also can stimulate the immune
37 response to at least some microorganisms.⁵⁰ Before the development of antibiotics, sunshine was
38 recognized as a cure for many tuberculosis patients.⁵ Recently, researchers discovered that exposure
39 to *Mycobacterium tuberculosis* causes monocytes and macrophages to up-regulate gene expression of
40 the VDR and the enzyme that converts 25(OH)D to 1,25(OH)₂D (25(OH)D-1- α -hydroxylase), which
41 in turn increases production of the antimicrobial peptide cathelicidin and the destruction of
42 intracellular *M. tuberculosis*.⁵⁷ A recent trial confirmed that supplemental vitamin D augments a
43 marker of antimycobacterial immunity in healthy adults exposed to tuberculosis, possibly through
44 other mechanisms as well.⁵⁸ Low serum 25(OH)D levels have also been associated with increased
45 risk for upper respiratory tract infections such as the common cold.⁵⁹

1 CLINICAL MEASUREMENT OF VITAMIN D STATUS

3 *Which Form of Vitamin D Should be Measured?*

5 As described above, 25(OH)D is the main circulating form of vitamin D and best functional indicator
6 of vitamin D nutritional status.^{1,2} Levels of the biologically active vitamin D metabolite (i.e., the
7 hormone), 1,25(OH)₂D, are tightly regulated and will often be normal or even elevated in those with
8 vitamin D deficiency because of secondary hyperparathyroidism.¹ Serum levels of vitamin D2 and
9 D3 are likewise not good indicators of vitamin D status due to their relative short half-lives, as they
10 are quickly stored in fat or metabolized in the liver.² The half-life of 25(OH)D is estimated at 10 days
11 to three weeks.² Clinicians should note that some laboratories report 25(OH)D2 and 25(OH)D3
12 separately; however, these may be simply added together to obtain the total of both types of
13 25(OH)D.^{1,11}

15 *Identifying Deficiency*

17 Traditionally, vitamin D deficiency has been defined by its overt clinical symptoms related to the
18 inadequate mineralization or demineralization of the skeleton, such as rickets and osteomalacia.²
19 However, subclinical deficiency or insufficiency of vitamin D is believed to be much more common,
20 and is typically identified by measuring serum levels of 25(OH)D;¹¹ values below 20 ng/mL (50
21 nmol/L) are generally considered deficient^{1,11} (although some argue this level may be unnecessarily
22 high⁸). Serum 25(OH)D levels of 21 to 29 ng/mL (52 to 72 nmol/L) are considered insufficient,
23 based on research that parathyroid hormone levels do not level off until serum 25(OH)D levels are in
24 the range of 30 to 40 ng/mL (75 to 100 nmol/L) and that intestinal calcium transport is diminished at
25 25(OH)D levels below 32 ng/mL (80 nmol/L).¹ Using these definitions, an estimated one billion
26 people are vitamin D deficient or insufficient, including an estimated 30% to 100% of American and
27 European subpopulations.¹

29 Deficient levels of vitamin D may be caused by a number of factors, including:

- 30 • Inadequate skin synthesis due to dark skin pigmentation, age, clothing, season, etc.
- 31 • Inadequate intakes of vitamin D from foods or supplements.
- 32 • Decreased bioavailability of vitamin D due to fat malabsorption, which may be caused by
33 various disorders (e.g., cystic fibrosis, celiac disease, Crohn's disease), gastric bypass
34 surgery, medications that reduce cholesterol absorption, or obesity, which is believed to
35 sequester vitamin D in body fat.
- 36 • Increased catabolism of 25(OH)D and/or 1,25(OH)₂D by certain medications, including
37 anticonvulsants, glucocorticoids, HAART, and anti-rejection medications.
- 38 • Reduced production of 25(OH)D due to liver dysfunction.
- 39 • Increased loss of 25(OH)D in the urine due to nephrotic syndrome.
- 40 • Reduced production of 1,25(OH)₂D due to chronic kidney disease.
- 41 • Heritable rickets disorders, including vitamin D-resistant rickets.
- 42 • Acquired disorders, such as tumor-induced osteomalacia, primary hyperparathyroidism,
43 granulomatous disorders, sarcoidosis, tuberculosis, certain lymphomas, and
44 hyperthyroidism.¹

46 *Optimal Serum Levels of Vitamin D*

48 While optimal levels have yet to be established, serum 25(OH)D levels of 30 ng/mL (75nmol/L) or
49 greater are generally recognized as sufficient.^{1,60} Some researchers believe that values of 40 to 60

1 ng/mL (100 to 150 nmol/L) are more appropriate,⁶¹ while others suggest levels as high as 55 to 90
2 ng/mL (137.5 to 225 nmol/L)⁶² are necessary to sufficiently prevent adverse health outcomes. Others
3 are less comfortable using even serum 25(OH)D values as high as 20 or 30 ng/mL (50 to 75 nmol/L)
4 to define sufficiency in the absence of more rigorous randomized trial data.⁸ Notably, in some
5 people, such as those with chronic granulomatous disorders, serum 25(OH)D levels should not exceed
6 30 ng/mL (75 nmol/L) because at higher levels macrophage synthesis of 1,25(OH)₂D leads to
7 hypercalciuria and hypercalcemia.¹

9 *Limitations in Measuring Serum 25(OH)D*

10
11 Circulating levels of the prehormone 25(OH)D is the best biomarker available of dietary and
12 endogenous vitamin D exposure, although it also reflects other processes like absorption and
13 metabolism.⁶³ It is not an ideal biomarker because it has not been specifically and reliably related to
14 any functional outcomes or indicators, in part because it is related to outcomes impacted by many
15 other factors, such as BMD, which also reflect long-term exposures.³ In addition, results of 25(OH)D
16 assays vary by analytic method and even sometimes within the same analytic method and by
17 laboratory, due primarily to the lack of a standard reference material. However, a new standard
18 reference material for 25(OH)D is expected to be available soon.⁶⁴ Because of these limitations,
19 serum 25(OH)D is most clinically useful at identifying toxicity and deficiency, compared with status
20 in the middle range, where it is less predictive of adverse health outcomes in the general population.⁶³

22 *Optimal Dose of Vitamin D*

23
24 It is unknown exactly how much supplemental vitamin D needs to be consumed to increase serum
25 25(OH)D levels, even to minimally sufficient levels, because individual responses vary widely and
26 depend on the nature and extent of the deficiency,^{5,11} as well as other factors related to endogenous
27 synthesis, absorption, storage, metabolism, and some that may be yet unknown.^{3,63} The greatest
28 responses to vitamin D from foods and sun exposure are typically seen when serum 25(OH)D levels
29 are below 20 ng/mL (50 nmol/L).³

30
31 The current guidelines of the IOM's Food and Nutrition Board and other organizations were outlined
32 above. Recommended intake values range from 200 to 1,000 IU per day. The upper range of these
33 recommendations is consistent with the daily doses of 800 to 1,000 IU of vitamin D3 currently
34 recommended by many researchers to achieve minimally sufficient serum 25(OH)D values of 30
35 ng/mL or greater^{1,5,11}; some recommend daily doses as high as 2000 IU.⁶¹ Sensible sun exposure or
36 use of tanning beds or other UVB radiation lamps is also recommended by some,¹ although others
37 adamantly recommend avoiding all exposure to sunlight and other sources of UVB radiation.²³
38 Higher doses of supplemental vitamin D2 or D3 may be warranted in those whose deficiencies are
39 secondary to comorbid conditions or medication use, as previously reviewed by Holick.¹

40
41 Others remain cautious about increasing current recommendations for vitamin D intakes due to the
42 lack of solid randomized trial evidence.⁸ Concerns also exist about potentially increasing serum
43 25(OH)D levels above what some people might naturally produce from sun exposure alone.^{3,65} Such
44 caution is warranted given the surprising lack of effects, or sometimes even harmful effects, noted in
45 trials of other previously promising nutrients and hormones (e.g., antioxidants, hormone replacement
46 therapy).⁸

1 Toxicity

2
3 Serum 25(OH)D levels above 150 ng/mL (375 nmol/L) are indicative of vitamin D intoxication,¹
4 which leads to hypercalcemia and hyperphosphatemia.^{1,2} Prolonged intakes of vitamin D have been
5 associated with reduced renal function, and calcification of soft tissues in the kidney, blood vessels,
6 heart, and lungs, as well as with severe depression, anorexia, nausea, and vomiting.² Toxic serum
7 levels of 25(OH)D are observed after ingestion of 40,000 to 50,000 IU per day or more for several
8 week or years.^{1,5} Researchers believe that 25(OH)D is the form of vitamin D that is most likely
9 responsible for toxic effects in the body, rather than vitamin D2 or D3 itself, but this has not been
10 established.⁶³

11
12 While some argue that it is highly unlikely that doses up to 10,000 IU per day (250 ug) are harmful,⁶⁶
13 others believe much remains unknown about the mechanisms of vitamin D action and potentially
14 toxic forms of vitamin D.³ For example, the α -tocopherol, β -carotene Cancer Prevention Trial
15 (ATBC) in Finnish smokers reported a three times greater risk of pancreatic cancer in men with the
16 highest 25(OH)D concentrations (>65.5 nmol/L vs. < 32.0 nmol/L; or >26.2 ng/mL vs. <12.8
17 ng/mL).⁶⁷ Furthermore, although several trials reported no kidney stones in those taking vitamin D
18 supplements,³ at least one found an absolute increase in the number of women reporting kidney
19 stones who consumed 400 IU of vitamin D3 and 1000 mg of calcium per day.⁶⁸

20
21 Several other concerns remain about the potential adverse effects of vitamin D supplementation,
22 including the lack of long-term studies; studies in all life stage and racial and ethnic groups; and
23 studies on the potential nonskeletal effects, such as aortic and other soft-tissue calcification.³ There
24 are no established toxic endpoints for vitamin D and few studies were designed to assess its potential
25 toxicity. Most studies were inadequately powered to detect adverse effects, nor did they test
26 relatively high doses or include individuals with potentially greater susceptibility to adverse
27 outcomes, such as those with liver or kidney disease. This may have biased the literature against the
28 finding of adverse effects.³

29 30 AREAS REQUIRING FURTHER RESEARCH OR ATTENTION

31
32 Despite significant gains in knowledge about vitamin D in the last decade, recent reviews and expert
33 discussions³ have identified substantial limitations in the literature:

- 34 • Many studies failed to control for important potential confounders, such as baseline 25(OH)D
35 concentrations, skin pigmentation, seasonality, body mass index, compliance, disease status,
36 and physical activity.
- 37 • Variability in serum 25(OH)D assays, including the lack of a standard reference material.
- 38 • Limited data on vitamin D's effects independent of calcium, magnesium, and phosphate.
- 39 • Lack of dose-response studies for both skeletal and nonskeletal outcomes.
- 40 • Lack of studies on the relation of extrarenal hydroxylation to functional outcomes.
- 41 • Inadequate data on the vitamin D content of foods.

42
43 In addition, concerns remain about the potential significance of differences in the metabolic
44 partitioning of endogenously produced vitamin D and that from dietary sources – in other words, does
45 the initial transport and metabolism of dietary vitamin D on chylomicrons have significant
46 consequences compared to cutaneously produced vitamin D3 that enters circulation on vitamin D
47 binding proteins?^{3,63} Likewise, little is understood about the extent of vitamin D storage in the body
48 and the potential hazards of high stores in adipose tissue, including any effects of saturating the
49 storage pools.⁶³ This is particularly important because serum 25(OH)D concentrations do not specify

1 whether vitamin D is entering and leaving the tissues, which could be relevant to the potential for
2 excess exposure in some people.⁶³

3
4 Furthermore, daily intakes of 800 IU vitamin D or greater are difficult to obtain from food alone, even
5 including fortified food sources. Not everyone wants to consume, or has access to, fortified foods or
6 supplements. For these people, is there a minimal sunlight exposure that could raise serum 25(OH)D
7 levels to sufficient levels, without increasing risk of skin cancer? What is the risk of skin cancer in
8 such individuals relative to increased risk of other cancers due to a lack of vitamin D? How does this
9 vary across populations?

10
11 Clearly, much more research is needed to answer these and other questions, particularly in the form
12 of:

- 13 • Long-term, well-designed dose-response trials on bone health and other functional outcomes
14 (e.g., immune function and chronic disease prevention) that also address adverse outcomes
15 and potential confounders across all life stage groups.
- 16 • Studies to determine serum 25(OH)D threshold values to relevant functional outcomes across
17 life stage and racial and ethnic groups.
- 18 • Studies on the bioavailability, storage, mobilization, and turn-over of vitamin D metabolites
19 across a range of intakes to assess how these might be affected by age, changes in body
20 weight and composition, or other factors.⁶³
- 21 • Long-term studies to establish the doses at which vitamin D toxicity begins to occur, and if
22 this dose varies by population subgroups.³

23 24 SUMMARY AND CONCLUSION

25
26 The vitamins D2 and D3 are seco-sterol prohormones whose active metabolite, 1,25(OH)₂D, is an
27 important hormone, transcriptional activator, and immunomodulator. Serum 25(OH)D is the best
28 functional indicator available of vitamin D status, and a rapidly expanding literature has reported
29 inverse associations between serum 25(OH)D and/or intakes of vitamin D and numerous outcomes
30 related to bone health, several cancers, cognitive function, cardiovascular disease, diabetes, and
31 several autoimmune diseases. However, clinical trials have yet to prove that vitamin D is causally
32 related to most of these outcomes. Nevertheless, improved surveillance of the 25(OH)D status of the
33 population indicates many people may have subclinically deficient or insufficient levels of vitamin D,
34 prompting many researchers and health organizations to recommend intakes of 800 to 1,000 IU per
35 day of vitamin D; some researchers recommend even 2,000 IU per day, which is currently the UL set
36 by the Food and Nutrition Board. It is difficult for most Americans to consume that much vitamin D
37 from food alone, even including fortified food. Since it is unclear how much sun or UVB exposure, if
38 any, allows for maximal cutaneous synthesis of vitamin D while minimizing risk of skin cancer, this
39 means most Americans would have to take a dietary supplement to achieve these levels of vitamin D
40 in their diet.

41
42 Despite significant gains in knowledge in this rapidly evolving area of research, substantial
43 limitations remain due to inadequate control for confounding variables, variability in serum 25(OH)D
44 assays, the inability to discern vitamin D's effects independent of other factors such as calcium
45 intake, the lack of dose-response data on both skeletal and nonskeletal outcomes, inadequate data on
46 the vitamin D content of foods, and a lack of understanding of the metabolic partitioning of different
47 sources of vitamin D as well as the extent of vitamin D storage capacity in the body. These are
48 significant issues to consider when recommending supplementation for the population at large,
49 particularly given the surprising lack of effects, or sometimes even harmful effects, found in large,

1 long-term randomized trials of other previously promising nutrients and hormones, such as
2 antioxidants and hormone replacement therapy. More long-term, well-designed studies are needed
3 across all life stage and racial and ethnic groups, to address these and other issues, including the
4 potential for adverse outcomes at various doses, to determine serum 25(OH)D threshold values
5 relevant to functional outcomes, and to better understand the bioavailability and turnover of vitamin
6 D metabolites.

7
8 The Food and Nutrition Board is currently reviewing the literature on vitamin D and is expected to
9 release new guidelines in 2010. In the meantime, clinicians may wish to assess the serum 25(OH)D
10 levels of their patients who may be at risk of vitamin D deficiency, and counsel those with deficient
11 or insufficient levels on how they might improve their vitamin D status.

12 RECOMMENDATIONS

13
14
15 The Council on Science and Public Health recommends that the following statements be adopted in
16 lieu of Resolution 425 (A-08) and the remainder of this report be filed:

- 17
18 1. That our American Medical Association (AMA) support continued research on vitamin D
19 and its metabolites, particularly long-term studies that address the benefits, adverse
20 outcomes and potential confounders across all life stage groups. (Directive to Take
21 Action)
- 22
23 2. That our AMA educate physicians about the evolving science of vitamin D and its impact
24 on health and develop resources about vitamin D for patients. (Directive to Take Action)
- 25
26 3. That our AMA encourage physicians to consider measuring the serum concentration of
27 25-hydroxyvitamin D in patients at risk of vitamin D deficiency and counsel those with
28 deficient or insufficient levels on ways to improve their vitamin D status. (New HOD
29 Policy)
- 30
31 4. That our AMA monitor the development of new dietary references intakes for vitamin D
32 in 2010 and respond as appropriate. (Directive to Take Action)

Fiscal Note: \$ 3,500

TABLE. SOURCES OF VITAMIN D AND SELECTED METABOLITES^{1, 9, 12, 13, 69}

Source	Estimated dose (IU) ^a	Form of vitamin D
Natural		
Sunlight or UVB radiation, minimum 0.5 erythemal dose ^b	3000	D3
Salmon		
Fresh, wild salmon, 3.5 oz	600 – 1000	D3
Fresh, farmed salmon, 3.5 oz	100 – 250	D3 or D2
Canned salmon, 3.5 oz	300 – 600	D3
Sardines, canned in oil, drained, 1.75 oz	250	D3
Mackerel, jack, canned, drained, 3.5 oz	250	D3
Tuna, light, canned in oil, drained, 3.5 oz	230	D3
Cod liver oil (1 tsp)	400-450	D3
Shiitake mushrooms		
Fresh, 3.5 oz	100	D2
Sun-dried, 3.5 oz	1600	D2
Egg yolk	20	D3 or D2
Liver, beef, cooked, 3.5 oz	15	D3
Fortified Foods^c		
Milk, 8 oz	100	Usually D3
Vitamin D-fortified soy milk, 8 oz	100	Usually D2
Vitamin D-fortified orange juice, 8 oz	100	D3
Fortified breakfast cereals, 1 serving	40 - 100	Usually D3
Supplements^d		
Over the counter		
Multivitamin	400	D3 or D2
Vitamin D3	400, 800, 1000, or 2000	D3
Prescription		
Alendronate sodium plus cholecalciferol (Brand name: <i>Fosamax plus DTM</i>) Tablet	2800 or 5600	D3
Ergocalciferol ^e (Brand name: <i>Drisdol</i> ®) Gelatin capsule Drisdol liquid supplements (per mL)	50,000 8000	D2
Prescription Vitamin D Metabolites		
Doxercalciferol (Brand name: <i>Hectorol</i> ®) Gelatin capsule Intravenous solution (per 1 mL)	0.5 µg or 2.5 µg 2 µg	1α-hydroxyvitamin D2
Calcitriol (Brand name: <i>Rocaltrol</i> ®, <i>Calcijex</i> ®) Gelatin capsule ^e Oral solution (per mL) ^e Intravenous solution (per 1 mL ampul) ^e	0.25 µg or 0.5 µg 1 µg 1 µg	1,25-dihydroxyvitamin D3
Paricalcitol (calcitriol analog) (Brand name: <i>Zemplar</i> ®) Gelatin capsule Intravenous solution (per 1 mL)	1 µg, 2 µg, or 4 µg 2 µg or 5 µg	19- <i>nor</i> -1-α- dihydroxyvitamin D2

<p>Calcipotriene (vitamin D3 analog) (Brand name: <i>Dovonex</i>®, <i>Taclonex</i>®) Ointment, cream, or solution^e</p>	<p>0.005%</p>	<p>Vitamin D3 derivative</p>
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^aAll doses given in international units (IU), where 1 IU = 25 ng, unless otherwise noted.

^bAn estimated 0.5 minimal erythematol dose of ultraviolet B radiation would be absorbed after an average of 5 to 10 minutes of exposure of the arms and legs to direct sunlight (the exact amount depends on the time of day, season, latitude, and skin sensitivity).

^cNote that vitamin D3 is manufactured from lanolin, an animal product, and thus may not be suitable for some vegetarians.

^dProducts labeled “vitamin D,” “calciferol,” or “ergocalciferol” usually contain vitamin D2, while products labeled “vitamin D3” or “cholecalciferol” contain vitamin D3.

^eGeneric equivalent available.

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