Nutritional Supplements in Older Adults

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LEARNING OBJECTIVES

1. Evaluate the impact of regulations and product formulations on clinical decisions and practice approaches regarding nutrient supplements.
2. Evaluate nutritional supplements for safe and beneficial use in older adults, with special focus on omega-3 fatty acids (w-3FAs), vitamin E, and vitamin D.
3. Justify the use of supplementation with w-3FAs, vitamin D, or vitamin E in an older patient.
4. Design a vitamin D replacement regimen, including monitoring, for the patient with documented vitamin D deficiency.
5. Assess the evidence and resources for nutrient supplementation for their clinical relevance to older patients.

ABBREVIATIONS IN THIS CHAPTER

AA	Arachidonic acid
ALA	α-Linolenic acid
AMD	Age-related macular degeneration
CABG	Coronary artery bypass grafting
DHA	Docosahexaenoic acid
DSHEA	Dietary Supplement Health and Education Act of 1994
EPA	Eicosapentaenoic acid
FA	Fatty acid
PUFA	Polyunsaturated fatty acid
RCT	Randomized controlled trial
Total 25 (OH)D	Plasma concentrations of 25(OH)D2 plus 25(OH)D3
VDR	Vitamin D receptor
Vitamin D_2	Ergocalciferol
Vitamin D_3	Cholecalciferol
w-3FA	Omega-3 fatty acid
w-6FA	Omega-6 fatty acid

Table of other common abbreviations.

INTRODUCTION

Nutritional status has an important impact on a person's health. Adequacy of nutrients such as vitamins and w-3 fatty acids (w-3FAs) is essential for optimal health maintenance. Aging is associated with changes in the body's physiologic functions, cognition, and physical changes such as loss of bone mineral density (BMD) and sarcopenia. These changes may result in decreased nutrient intake, impaired nutrient absorption and utilization, and reduced physiological reserve of nutrients. In addition, the presence of chronic diseases such as coronary heart disease, type 2 diabetes, and obesity is associated with systemic inflammation, which can alter nutrient utilization by the body. Optimization of nutrient status is thus a component of the comprehensive management plan for patients, especially older adults.

In individuals with insufficient oral intake or high requirements, nutrient supplementation is widely available without a prescription through the benefit of the Dietary Supplement Health Education Act of 1994 (DSHEA). From a legislative standpoint, DSHEA was intended to promote good health without controversy. However, because nutrients must be formulated into oral dosage forms before marketing, the source of the compound for manufacturing, and whether the manufacturing follows good manufacturing processes can introduce uncertainty and safety concerns. In addition, manufacturers can market products containing mega-doses of micronutrients that are supraphysiological. The widespread availability of these nutrient supplements presents new controversies and challenges for clinicians: Are vitamin and nutrient supplements safe for routine use? Is supplementation associated with improved clinical outcomes? What are the optimal regimens? Are specific products superior to others

in meeting goals? These are important clinical issues that affect not only patients with decreased oral intake or preexisting nutrient deficiencies, but also the general public, who self-supplement certain nutrients according to their perception of their health or the benefits of supplementation.

Nutrient supplements are widely available in pharmacies and grocery stores where pharmacists are highly accessible. Use of some nutrient supplements may alter the response of pharmacotherapy through drug-nutrient interactions. In patients with indications for nutrient supplementation to prevent or treat nutrient deficiencies, pharmacist involvement in optimizing their regimens on the basis of kinetics, dosing frequencies, and other factors such as affordability may improve patients' treatment response and safety.

This chapter will review the science of nutritional supplements and discuss the available evidence to guide treatment decisions. This chapter will focus on w-3FAs, vitamin E, and vitamin D because these are common supplements used in the United States.

Prevalence of Nutritional Supplement Use in the Older Adult Population

Nutritional supplements are commonly used by U.S. adults. In one study, supplements were used by 40% of adults 20–39

years of age and by 74% of adults older than 65 (Kantor 2016). Older adults are using nutritional supplements at increasing rates. In a recent study comparing rates of dietary supplement use among adults 62–85 years of age, dietary supplement use increased from 51.8% to 63.7% in 2005–2011 (Qato 2016). Use of w-3 fish oil supplements and vitamin D had the most significant increase (18.6% prevalence with a 4-fold increase and 15.6% prevalence with a 3.4-fold increase, respectively). Conversely, vitamin E use had the most significant decline during that period (7% prevalence, with a 1.3-fold decrease from 9%). The use pattern also changed significantly with increases in calcium and coenzyme Q10 use and decreases in folic acid, though the degree of change was not as dramatic. This frequency of use has implications for patient safety because supplements can place patients at risk of drug interactions or other adverse outcomes.

Deprescribing is an emerging concept in the care of older adults. Although there is not yet a universally accepted definition, deprescribing is generally thought of as "the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes" (Reeve 2015). Most studies on deprescribing focus on prescription medications, but the principles should also be applied to supplements. The process of deprescribing involves several steps: (1) obtain list of medications and indications, (2) consider the risk of harm caused by the medication, (3) assess each medication for eligibility to be discontinued, (4) prioritize medications for discontinuation, and (5) implement and monitor the medication discontinuation regimen (Scott 2015). When considering the risk of harm caused by supplements, an additional factor must be considered: the lack of FDA regulation.

FACTORS THAT MAY AFFECT THE SAFETY AND EFFICACY OF NUTRITIONAL SUPPLEMENTS

Regulation of Vitamins, Minerals, and Nutritional Supplements

The labeling and safety of dietary supplements are regulated by DSHEA (FDA 2016). Under DSHEA, the manufacturer is responsible for ensuring the safety and efficacy of its product, but no clinical testing of the product is required before its release. Supplements do not need FDA approval before marketing.

Several recent studies suggest that some nutrient supplements tested contain compounds such as mercury and melamine. Even though many of these products were manufactured overseas, DSHEA does not impose additional testing requirements for supplements manufactured outside the United States. The U.S. Pharmacopeial Convention (USP) is known for certifying products and granting supplements a seal or mark on their product labeling. Patients and health care professionals should be aware that the mark or seal does

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BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:
- Recommended daily allowances for vitamins and micronutrients
- General physiological functions of vitamins and minerals
- The impact of vitamin D intake on bone health and osteoporosis prevention
- Regulation of vitamins and supplements in the United States

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:
- NIH. Dietary Supplement Health and Education Act (DSHEA).
- American Heart Association (AHA). Fish and Omega 3 Fatty Acids.
- AHA's Diet and Lifestyle Recommendations.
- National Osteoporosis Foundation. Clinician's Guide to the Prevention and Treatment of Osteoporosis.

not indicate that a product is guaranteed safe and effective. The USP verified mark indicates that the product contains the ingredients listed on the label in the accurate amount, at the potency shown on the label, and without contaminants (USP 2017). Two other organizations, NSF International and ConsumerLab.com, also have a long history of certifying vitamins and dietary supplements. Therefore, pharmacists and other providers who recommend or prescribe supplements should direct patients to products that show the seal of one of these organizations on the label.

Dosage Forms and Regimens

Products intended for oral use only are regulated by DSHEA. With the increase in bariatric surgery procedures in the past decade, vitamin and mineral supplements formulated as transdermal patches are available. Transdermal patches, topical creams/ointment, and intravenous injections are all regulated under the Federal Food, Drug, and Cosmetic Act, but not under DSHEA. The absorption kinetics of most micronutrients through topical administration is poorly understood. Moreover, the efficacy and risks associated with this route are unknown. Although these topical products are attractive options for patients who cannot swallow or tolerate oral supplements, these dosage forms of vitamins and nutrient supplements should not be used in patients unless the products are FDA approved with an established regimen for administration and monitoring. Micronutrient kinetics via intravenous administration is generally better appreciated, although this route of administration is more feasible in the clinic setting or in patients with a permanent indwelling catheter. Intravenous micronutrients are regulated by the Federal Drug Cosmetic Act but not DSHEA.

The salt forms of vitamin and nutrient products may affect their safety and efficacy. Although labeled as a w-3FA on the product, the actual compositions of the w-3FAs and the amount in the oral dosage form have major effects on efficacy. For example, a w-3FA product that contains only flaxseed oil essentially has no anti-inflammatory activity when given at doses tolerable to the GI tract (Arterburn 2006). Vitamin E derived from natural sources contains a significantly larger amount of the active form of vitamin E (*R*-isomer), whereas the synthetic form usually contains the physiologically inactive *S*-isomer. Vitamin E oral liquid formulated with a surfactant, polyethylene glycol 1000 succinate, is associated with higher oral bioavailability, even in the absence of a high-fat meal, because of the increased water solubility. However, this formulation – tocopheryl polyethylene glycol succinate 1000 – is also a potent inhibitor of intestinal P-glycoprotein and can significantly increase the oral absorption of many drugs, which can in turn lead to toxicity if preemptive dose adjustments are not made (Guo 2013). For minerals, the amount of elemental ions provided by the product can differ significantly by changing the salt form, as for calcium and zinc. In addition, the dose-response relationship of many vitamins and nutrients, independent of the dosage and salt forms, is not linear. Therefore, dose changes may lead to unexpected clinical responses.

Overall, the safety and efficacy of nutrient supplements may be specific to the salt form or formulation used. Altering these parameters may lead to unpredictable results and can affect patient safety. When using vitamin or nutrient supplements for a specific purpose (e.g., cardiovascular protection), clinicians should use the dosage form and regimen similar to those in the published evidence.

W-3FA SUPPLEMENTATION IN OLDER ADULTS

For several decades, studies have linked high fatty fish intake with a lower prevalence of cardiovascular diseases. One such historical study involved the Greenland Inuit people (called the "Eskimo diet" in the literature). Although the accuracy and validity of some of these observations have been questioned, the cardioprotective effect was confirmed by the Diet and Reinfarction Trial, a 1980s randomized controlled trial (RCT) involving men with a previous myocardial infarction (Burr 1989). The mean age at study enrollment was 56.5 years. Patients who were randomized to receive a diet high in fatty fish (200–400 g weekly; e.g., mackerel, herring, kipper, pilchard, sardine, salmon, or trout) had a 29% relative reduction in all-cause mortality over 2 years compared with the group not eating fatty fish (RR 0.71; 95% CI, 0.54–0.93; $p<0.05$). A similar benefit was observed later in women from a substudy of the Nurses' Health Study (Hu 2002). An inverse association occurred between fatty fish intake and death related to coronary heart disease among women 34–59 years of age over a 16-year follow-up. Because fatty fish are a rich source of w-3FAs, it was hypothesized that taking supplemental w-3FAs would replicate the positive outcomes associated with high dietary fish intake and perhaps offer health benefits beyond the cardiovascular system on the basis of the physiological functions of w-3FAs.

Overview of the Biology and Kinetics of Polyunsaturated Fatty Acids

Fatty acids are essential compounds in mammalian physiology for the maintenance of cell membrane structure, energy use, and regulation of cellular functions. In particular, polyunsaturated fatty acids (PUFAs) represent a group of long-chain FAs that regulate inflammatory responses, endothelial functions, and lipid metabolism. Two families of PUFAs – w-3 PUFAs derived from α-linolenic acid (ALA) and w-6 PUFAs derived from linoleic acid – are considered essential FAs because the human body cannot synthesize these compounds. These PUFAs must be acquired through diet. The w-3 and w-6 PUFAs are also the essential substrates for the synthesis of prostaglandins and leukotrienes, which regulate inflammation, immune functions, and vascular smooth muscle function (Kalish 2012). Clinical deficiency in w-3 or w-6

PUFAs results in essential FA deficiency syndrome, which may present as alopecia, scaly dermatitis, thrombocytopenia, and immunosuppression. Essential FA deficiency is also associated with impaired cellular and physiologic function.

The biotransformation pathways of different PUFAs are summarized in Figure 1-1. Normal physiologic functions and health depends on the balanced actions between w-3– and w-6–derived PUFAs. The most biologically active product from the w-6 PUFA pathway is arachidonic acid (AA), which is the precursor of the 4-series of leukotrienes (e.g., LTB4, LTC4) and the 2-series of prostaglandins (e.g., PGE2). These cytokines have potent proinflammatory effects and increase the permeability of the vascular tissues. On the other hand, the downstream products of the w-3 PUFA pathway are primarily the 5-series of leukotrienes and the 3-series of prostaglandins, which have anti-inflammatory and vascular-stabilizing effects (Kalish 2012). Clinically, the

anti-inflammatory potency is substantially higher for eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) than for ALA. Both DHA and EPA reduce plasma AA concentrations in a dose-dependent fashion. Supplementation of ALA alone does not translate to clinically appreciable benefits in down-regulating the inflammatory cascade. Ingestion of a large amount of ALA is associated with GI intolerance. More importantly, less than 10% of the ingested dose of ALA is converted to EPA or DHA (Arterburn 2006). Therefore, the relative potency of different w-3FA–containing products should be compared on the basis of the amount of EPA and DHA. A daily dose of DHA at 2 g results in a near-maximal anti-inflammatory response on the basis of plasma AA concentrations.

The concurrent intake of w-6FAs or saturated FAs does not appear to impair the oral bioavailability of w-3FAs, which are absorbed slower than w-6FAs. Limited kinetic data also suggest that a sex-based difference in FA disposition
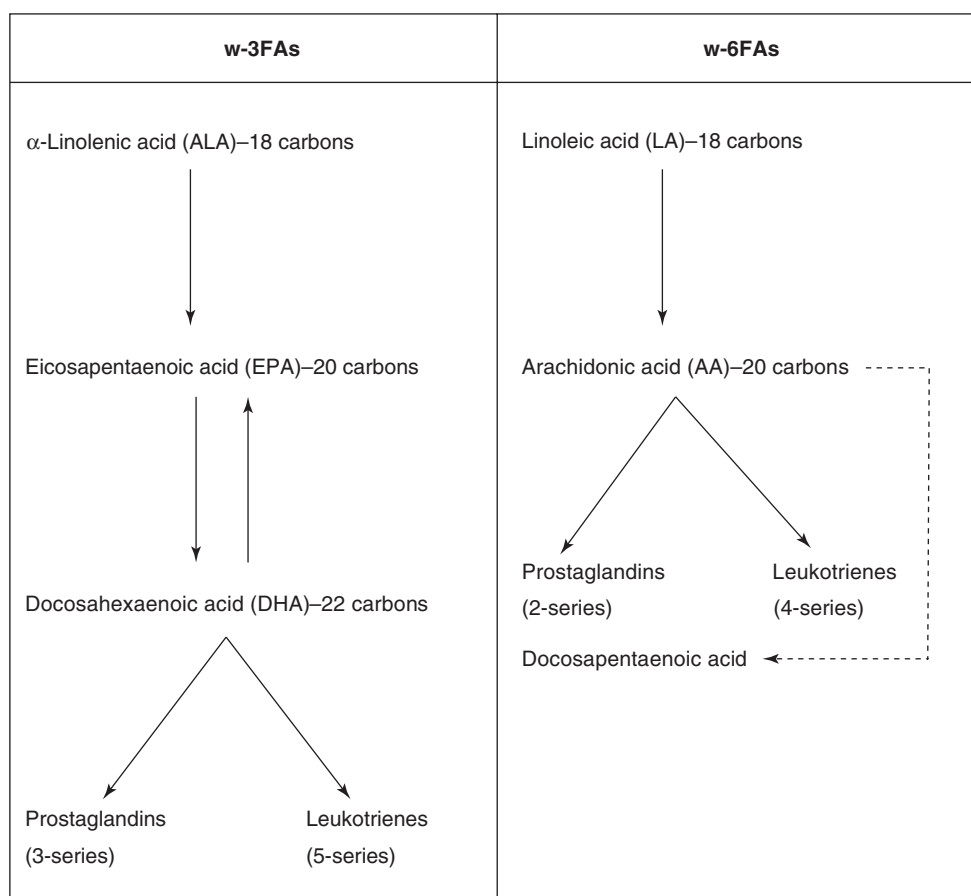

Figure 1-1. Summary of the major metabolic pathways of omega-3 fatty acids and omega-6 fatty acids from their respective 18-carbon fatty acids to different series of prostaglandins and leukotrienes. Enzymes involved in the formation from the 18-carbon FAs to the 22-carbon FAs include several desaturases and elongases. In addition, cyclooxygenase catalyzes the formation of prostaglandins, whereas lipoxygenase and leukotriene synthases catalyze the final steps in leukotriene formation.

w-3FA = omega-3 fatty acid; w-6FA = omega-6 fatty acid.

exists; women tend to have faster rates of w-3FA absorption and clearance (Dias 2015). Increased intake of EPA and DHA is associated with a dose-dependent increase in concentrations of plasma, erythrocytes, and CSF, as well as a reduction in serum triglycerides. A diet with a higher relative w-3 PUFA/w-6 PUFA ratio suppresses inflammatory responses and is associated with better health outcomes.

w-3 Fatty Acids

The primary dietary sources of ALA, EPA, and DHA are summarized in Table 1-1 and Table 1-2. Fish and shellfish contain the highest content of EPA and DHA per serving. For vegetarians, dietary intake of EPA and DHA is very limited; however, their w-6FA intake is also lower because animal meat has the highest AA content. Food and supplements rich in ALA alone (e.g., flaxseed oil) are not an efficient source of EPA and DHA because of the very low downstream conversion rate to DHA. Most dietary supplement versions of w-3FA are labeled as fish oil, but the amount of EPA and DHA varies significantly and is usually much lower than in prescription products. It is important to carefully review the ingredients in these supplements, as some products claim to contain 2 g of w-3FAs, but the label reveals that the primary ingredient is ALA with only a small amount of EPA and DHA. Very limited data suggest that EPA and DHA from krill oil have higher bioavailability than

EPA and DHA from fish oil (Ulven 2015). However, high-quality research is needed before any conclusion can be made.

Table 1-3 summarizes the w-3FA products currently FDA approved as prescription drugs. These products are indicated only for the treatment of hypertriglyceridemia. One of the products contains only EPA, whereas the rest are EPA/DHA combination products. They are formulated as either ethyl ester or free carboxylic acid of the FAs. The bioavailability of the free carboxylic acids is less dependent on concurrent high-fat meals. When administered with a low-fat breakfast, the relative oral bioavailability of the free carboxylic acid formulation is 5 times higher than that of the ethyl ester formulation. Because EPA is absorbed more quickly than DHA, patients with intestinal resection or having significant GI symptoms may tolerate EPA-only formulations better. The re-esterified triglyceride formulation is associated with the highest bioavailability, though it is currently unavailable as a prescription product in the United States (Dyerberg 2010).

Clinical Outcomes of w-3FA Use in Diseases of Interest in Older Adults

The benefits of w-3FA have been evaluated in a variety of diseases and health conditions. The diseases of interest are often driven by the evidence of chronic inflammation or the organs with high w-3FA content, which include the

Table 1-1. Food and Dietary Sources with the Highest Content of EPA and DHA

Food Source	Weight (g)	Serving Size	EPA (g)/ Serving	DHA (g)/ Serving
Fish oil, salmon or sardine	13.6	1.0 tbsp	1.771	1.5−2.5
Atlantic mackerel, raw	112	1.0 fillet	1.006	1.569
Sockeye salmon fillets with skin, smoked	108	1.0 filet	0.977	1.642
Rainbow trout, wild, cooked, dry heat	143	1.0 fillet	0.669	0.744
Atlantic salmon, farmed, cooked, dry heat	85	3.0 oz	0.586	1.238
Whitefish (mixed species), cooked, dry heat	85	3.0 oz	0.345	1.025
Fish oil, cod liver	4.5	1.0 tsp	0.31	0.494
Fresh bluefin tuna, cooked, dry heat	85	3.0 oz	0.309	0.97
Striped bass, cooked, dry heat	124	1.0 fillet	0.269	0.93
Carp, cooked, dry heat	85	3.0 oz	0.259	0.124
Catfish, farmed, cooked, dry heat	143	1.0 fillet	0.029	0.099
Cheese, mozzarella	132	1.0 cup	0.007	0
Nuts, mixed nuts, oil roasted, with peanuts, lightly salted	28.35	1.0 oz	0.001	0
Egg, whole, cooked, fried	46	1.0 large	0	0.029

DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid.
Information from: U.S. Department of Agriculture. USDA Food Composition Databases.

Table 1-2. Food and Dietary Sources Rich in ALA

Description	Weight (g)	Serving Size	ALA (g)/Serving
Flaxseed oil, cold pressed	13.6	1 tbsp	7.258
Canola oil	14	1 tbsp	1.279
Cheese, swiss	132	1.0 cup	0.165
Cream, fluid, heavy whipping	120	1.0 cup	0.146
Pasteurized process cheese food	113	1.0 cup	0.137
Seeds, sunflower seed kernels, oil roasted	135	1.0 cup	0.103
Cheese, parmesan, grated	100	1.0 cup	0.102
Egg, yolk, raw, frozen, sugared, pasteurized	28.35	1.0 oz	0.024
Nuts, mixed nuts, oil roasted, with peanuts, lightly salted	28.35	1.0 oz	0.023
Noodles, egg, dry, unenriched	38	1.0 cup	0.022
Potatoes, mashed, dehydrated, flakes without milk, dry form	60	1.0 cup	0.014

ALA = α-linolenic acid.

Information from: U.S. Department of Agriculture. USDA Food Composition Databases.

retina, brain, and heart. Research with higher-quality data and results in disease states that affect older adults include age-related macular degeneration (AMD), cardiovascular diseases, atrial fibrillation, and Alzheimer disease.

Age-Related Macular Degeneration

Age-related macular degeneration is a primary cause of irreversible vision loss in older adults that has no effective treatment. Because DHA is a major structural component of the retina, epidemiological and animal studies suggest that a higher intake of w-3FAs is associated with a lower risk of developing advanced AMD. According to these data, many interventional clinical trials have been conducted. The results are best represented by two well-designed RCTs: the Age-Related Eye Disease Study 2 (AREDS2) and the Nutritional AMD Treatment 2 Study (NAT2) (Chew 2013; Souied 2013). In brief, AREDS2 was developed according to the findings from AREDS, a prospective cohort study showing that individuals with a higher w-3FA intake according to dietary surveys had a lower risk of AMD development and progression over 12 years (Sangiovanni 2009). In AREDS2, participants 50–85 years of age with a high risk of progressing to advanced AMD were

Table 1-3. Comparison of the Currently FDA-Approved w-3FA Prescription Products[a]

	Ethyl Esters of EPA and DHA	Ethyl Ester of EPA	EPA and DHA Carboxylic Acids
Brand names	Lovaza, Omacor, Omtryg, others	Vascepa	Epanova
Formulation	Oral capsules	Oral capsules	Oral capsules
Ingredients	Each 1 g capsule contains at least 900 mg of the ethyl ester of EPA (about 465 mg) + DHA (about 375 mg)	Every 1 g of icosapent ethyl, which is ethyl ester of EPA	Every 1 g contains 850 mg of EPA + DHA as free FAs with 550 mg of EPA, 200 mg of DHA
EPA/DHA ratio	1.24:1	All EPA	2.75:1
Median Tmax	6 hr (range 5–9) based on 4 g/day	5 hr (range 3–8) based on 2 g BID	6 hr (range 5–12) based on 4 g/day

[a]All the products are approved as an adjunct to diet to reduce serum triglyceride concentrations in adult patients with severe hypertriglyceridemia (≥ 500 mg/dL). The daily dose is 4 g, except for Epanova, whose dose is 2 g or 4 g daily.

BID = twice daily; w-3FA = omega-3 fatty acid.

randomized to one of four arms: daily supplementation of lutein plus zeaxanthin, DHA plus EPA, lutein plus zeaxanthin and DHA plus EPA, or placebo. Lutein and zeaxanthin are two main components of the macular pigments. The total daily doses of DHA and EPA were 350 mg and 650 mg, respectively. All participants were further randomized to take a vitamin formulation that contains vitamins C and E and copper, with two doses of zinc and beta-carotene. The study analyzed 4203 adults with a median age of 73.1 years over 5 years. Although the participants in the w-3FA arm had a 30%−40% and a 90%−120% increase in serum DHA and EPA concentrations, respectively, the development of moderate vision loss and progression to AMD were not different than without DHA and EPA supplementation (HR 0.96 [95% CI, 0.84–1.09; p = 0.50]; and HR 0.98 [95% CI, 0.89–1.08; p = 0.74], respectively) (Chew 2013). The NAT2 study was much smaller, with only 263 patients, and focused on AMD prevention by DHA and EPA. The dose was DHA 840 mg/day and EPA 270 mg/day for 3 years. The overall incidence of the disease-defining presentation, choroidal neovascularization, did not differ between the treatment and placebo arms in 3 years (Souied 2013). Both studies have similar limitations, including suboptimal dosing of DHA and EPA (total daily DHA dose was less than 1 g and w-3FA dose was less than 1.2 g) and insufficient statistical power (each arm in AREDS2 included just over 1000 patients). Adherence was also an issue in NAT2. Overall, no high-quality evidence supports the routine use of EPA and DHA supplements to prevent or slow AMD progression. To determine whether using higher doses of DHA and EPA translates to better clinical outcomes warrants additional research.

Cardiovascular Diseases and Atrial Fibrillation

The effects of w-3FAs on cardiovascular diseases have been extensively investigated because of their anti-inflammatory and antiplatelet characteristics. Overall, current knowledge suggests that w-3FA supplementation reduces vascular death, defined as death related to heart disease or stroke (RR 0.86; 95% CI, 0.75−0.99; p = 0.03, based on 13 studies). However, w-3FAs do not appear to reduce overall death, coronary events, revascularization, stroke, or hospital admission related to heart failure (Kotwal 2012). In animals, w-3FAs have also had antiarrhythmic properties. The results in clinical trials for arrhythmia, however, are more challenging to interpret. The overall effect on all-cause arrhythmia appears neutral, according to five studies. But a large volume of data are available in atrial fibrillation prevention. Two recently published meta-analyses have had conflicting results, likely because of the differences in inclusion criteria (Costanzo 2013; Mariani 2013). But it appears that w-3FAs may have protective effects against the development of atrial fibrillation associated with surgery for coronary artery bypass grafting (CABG). The daily doses of w-3FA vary significantly at 464−1860 mg and 335−1500 mg of EPA and DHA, respectively. The total daily w-3FA dose in the atrial fibrillation trials was about 2 g.

Alzheimer Disease

Because DHA plays a key role in neural development and is abundantly present as part of the phospholipid in the neuron, it has long been a nutrient of interest in Alzheimer disease prevention and treatment. Although several interventional studies have been published in this area, the findings are best represented by the OmegAD study. The OmegAD study is an RCT followed by an open-label extension treatment involving 174 Swedish adults with mild to moderate Alzheimer disease (Freund-Levi 2006). The study aimed to compare the effect of w-3FA on cognition, safety, and inflammation markers. The patients received DHA 1.72 g and EPA 0.6 g daily or placebo for 6 months, followed by 6 months of open-label treatment with the same dose of DHA/EPA combination therapy. The mean age of the study participants was 72 years. w-3FA supplementation for up to 1 year did not delay the rate of cognitive decline, as assessed by the Mini-Mental State Examination scores (Freund-Levi 2006). In the follow-up, cohort-based subanalyses, w-3FA supplementation did not significantly alter the markers of inflammation and oxidative stress in either the plasma or the CSF (Freund-Levi 2009). Many small cross-sectional studies had similar results. One study suggested an inverse relationship between w-3FA intake on the basis of fish consumption and cognitive decline (Vercambre 2009). Some of the limitations for these studies include small sample size, short follow-up, and inconsistent definition of cognitive decline. Overall, current evidence does not support a significant benefit of w-3FA supplementation in preventing disease progression, even at a daily dose of greater than 2 g of DHA and EPA, in patients with Alzheimer disease.

Summary and Recommendations

In summary, quantification of w-3FA intake should be based on EPA and DHA contents of food and products. Current evidence suggests that EPA and DHA supplementation reduces death associated with cardiovascular events or stroke, or risk of atrial fibrillation after CABG, though it is unclear whether specific patient groups benefit more than others. Routine w-3FA supplementation does not appear to alter the course of other cardiovascular diseases, AMD, or Alzheimer disease. A recent systematic review suggests that the adverse events related to w-3FA supplements are fairly benign in older adults, with GI disturbances being the most common adverse effect (Villani 2013).

VITAMIN E SUPPLEMENTATION IN OLDER ADULTS

Overview of the Biology of Vitamin E

Vitamin E is a group of lipid-soluble compounds that generally includes many analogs of tocopherols and tocotrienols. These compounds are acquired exclusively through diet. The primary physiological role of vitamin E is as a chain-breaking antioxidant that prevents the propagation of free radical

reactions such as lipid peroxidation. Free radical attack is a component of the inflammatory response induced by the host's immune system. Uncontrolled and dysregulated free radical reactions lead to tissue damage and necrotic cell death, which may in turn lead to organ dysfunction. Evidence is also strong that vitamin E contributes to cell signaling, especially in relation to protein kinase C, and regulates the expression of genes involved in inflammation, cell adhesion, platelet aggregation, and cell cycle control.

Vitamin E, usually present in all cell membranes, can directly and independently neutralize the effects of free radicals and other reactive oxygen species (e.g., superoxide radical, oxygen). Vitamin E also functions synergistically with other antioxidants. Ascorbic acid and glutathione, which use selenium as a cofactor, further facilitate the recycling of vitamin E and help restore the antioxidant properties of vitamin E. Vitamin E also has pro-oxidant effects by interfering with normal tissue homeostasis in the absence of sufficient free radicals for it to neutralize.

Many health benefits have been suggested with optimal vitamin E intake. The role of vitamin E has been evaluated in the clinical setting to reduce the risk of cardiovascular diseases, control immune-mediated disorders such as asthma and autoimmune diseases, serve as a protective agent against neurological and hepatic injuries, treat nonalcoholic steatohepatitis, and prevent cancer (Galli 2017).

Naturally-occurring tocopherol and tocotrienol have four homologs. α-Tocopherol is biologically the most active form and is commonly used in formulations of vitamin E supplements. Natural forms of vitamin E, which exist only as *RRR* isomers, are often labeled as *RRR*-tocopherol (formerly *d*-tocopherol). Synthetic forms of vitamin E are racemic mixtures of the stereoisomers and are often labeled as all racemic mixtures of α-tocopherol (*all-rac*-α-tocopherol) or dl-α-tocopherol. These racemic mixtures of vitamin E can be found in nutrient supplements. When given at the same dose, natural vitamin E is more active than synthetic forms, which can affect clinical activity. The dose comparison is summarized in Table 1-4.

Vitamin E in the form of α-, β-, γ-, and δ-tocopherol is primarily absorbed in the small intestine, with the highest rate and capacity in the ileum. Some absorption also takes place in the cecum and colon (Goncalves 2015). This absorption pattern may be especially important for patients with extensive ileal resection. Vitamin E absorption is facilitated mainly by a transporter-mediated process that occurs in the small intestine, though passive diffusion cannot be ruled out. The role of two transport proteins, Niemann-Pick C1-like type 1 (NPC1L1) and Scavenger receptor class B type I (SR-BI), has been confirmed to facilitate the intestinal absorption of vitamin E. Efflux transporters are also present, which may serve as a counter-regulatory mechanism to prevent toxicity (Reboul 2011). In the presence of FAs and bile salts, both natural and synthetic forms of vitamin E are well absorbed in the form of chylomicrons. Pancreatic, hepatic, or intestinal dysfunction can impair vitamin E absorption. A high-fat meal

Table 1-4. Unit Conversion and Comparative Potency for Various Forms of Vitamin E

Vitamin E Forms	Conversions USP Units (IU)/mg	Relative Potency (%)
Natural vitamin E		
RRR-α-tocopherol	1 mg = 1.49 IU	100
RRR-α tocotrienol	1 mg = 0.75 IU	50
RRR-β-tocopherol	1 mg = 0.75 IU	50
RRR-γ-tocopherol	1 mg = 0.15 IU	10
Synthetic vitamin E		
RRR-α-tocopheryl acetate	1 mg = 1.36 IU	91
RRR-α-tocopheryl acid succinate	1 mg = 1.21 IU	81
all-rac-α-tocopherol[a]	1 mg = 1.10 IU	74
all-rac-α-tocopheryl acetate	1 mg = 1.00 IU	67
all-rac-α-tocopheryl acid succinate	1 mg = 0.89 IU	60

[a]*all-rac* = all racemic mixtures.

Information from Eitenmiller R, Lee J. Vitamin E: Food Chemistry, Composition, and Analysis. New York: Marcel Dekker, 2004.

can significantly increase vitamin E absorption (Dimitrov 1991). The standard American diet also contains large amounts of -tocopherol because of the extensive use of corn- and soybean-based products. However, after absorption, only α-tocopherol is identified by the α-tocopherol transfer protein in the liver for incorporation into very-low-density lipoproteins, with subsequent distribution to the peripheral tissues. Most of the ingested β-, γ-, and δ-tocopherols are not absorbed or are removed by enterohepatic recirculation. That the plasma α-tocopherol concentration is usually over 10-fold higher than the γ-tocopherol concentration shows this diminished absorption of non−α-tocopherols, despite the high dietary intake of γ-tocopherol (Brigelius-Flohé 2006).

In humans, the absolute oral bioavailability of vitamin E is highly variable because of the variance introduced by factors such as salt forms, diet, formulation, vitamin E status, and dose administered. The bioavailability of α-tocopherol acetate was 10%−33% in healthy subjects, depending on the fat content of the meal taken with vitamin E (Bruno 2006). The dose-response relationship for tocopherol is non-linear. In most cases, the increase in a person's plasma tocopherol concentration is no more than 2- to 3-fold, despite increasing the dosage amount by more than 3 times (Brigelius-Flohé 2002). Increasing the oral doses does not lead to a proportional increase in plasma tocopherol concentration, possibly because of incomplete dissolution, poor solubility in the intestinal lumen with high concentration, saturable absorption, or increased hepatic distribution relative to the plasma. After oral administration for doses up to 1200 international units, the plasma tocopherol concentration peaks in 12−24 hours (Dimitrov 1991). All forms of vitamin E undergo w-hydroxylation by CYP3A4 and CYP4F2, followed by β-oxidation. The final metabolite undergoes glucuronidation or sulfation and is eliminated in the bile or urine (Brigelius-Flohé 2006). An in vitro study also showed that CYP3A4 can be induced by vitamin E. These characteristics suggest that drugs that induce or inhibit CYP3A4 can alter the disposition of vitamin E. However, the clinical significance of this is unclear because of the extensive distribution of vitamin E in all tissues and the close regulation of its availability, depending on the body's status.

Plasma total vitamin E or α-tocopherol concentrations can be used to assess the body's vitamin E status. In practice, decreased circulating vitamin E concentrations are assumed to reflect a lower total vitamin E pool. However, this assumption has limitations because (1) vitamin E is extensively distributed in the liver, skeletal muscle, and adipose tissue; and (2) α-tocopherol concentrations are higher in the mitochondrial fractions and the endoplasmic reticulum than in the circulation. Although laboratory tests that reflect the functional status of vitamin E (e.g., total antioxidant capacity and malondialdehyde concentration) have been used in some clinical studies, these tests reflect the body's antioxidant system response in oxidative stress and are nonspecific for vitamin E. Other than in patients with fat malabsorption syndrome (e.g., chronic pancreatitis, cystic fibrosis), the benefits of routinely assessing vitamin E status using plasma concentrations have not been established.

Clinical Outcomes of Interest in Older Adults

Relatively few well-conducted studies specifically address the role of vitamin E. One of the primary limitations is that the clinical trials and meta-analyses involved interventions using vitamin E as a component of an antioxidant cocktail that often included compounds such as vitamin C, vitamin A, selenium, or w-3FA. Clinical outcomes could be confounded by the interactions between vitamin E and other antioxidants.

Cardiovascular Diseases

Coronary heart disease prevention with vitamin E is a primary area of interest in clinical research that affects older adults. In several large cohort studies, including the Cambridge Heart Antioxidant Study, Heart Outcomes Prevention Evaluation (HOPE) trial, Primary Prevention Project, and Women's Health Study, vitamin E supplementation alone was associated with conflicting outcomes ranging from reduced coronary events to no benefit. In an extension of the HOPE trial, vitamin E use was linked with a higher risk of heart failure (RR 1.13; 95% CI, 1.01−1.26) and hospitalization for heart failure (RR 1.21; 95% CI, 1.00−1.47) (Lonn 2005). A meta-analysis that included nine RCTs with stroke as the clinical outcome suggested that although vitamin E supplementation was associated with a 10% reduction in ischemic stroke (p=0.02), the risk of hemorrhagic stroke was increased by 22% (p=0.045). The range of vitamin E doses analyzed was 75−800 international units/day (Schürks 2010). However, in a recently published meta-analysis that included 16 RCTs with myocardial infarction as the clinical outcome, vitamin E given alone (33−800 international units/day) was associated with a 0.36% absolute risk reduction (3.0 vs. 3.4%; RR 0.82; 95% CI, 0.70−0.96). Given the small difference in absolute risk reduction, the clinical significance can be questioned. A subgroup meta-analysis with four trials suggested that a daily dose of at least 400 international units of vitamin E was associated with the most significant risk reduction (Loffredo 2015). According to the contradictory findings from the current literature, the benefits of vitamin E supplementation in older adults in preventing cardiovascular events remain unclear; vitamin E supplementation should therefore not be recommended as a routine practice in all patients. If supplementation is considered to reduce the risk of myocardial infarction, it should be limited to patients with an extremely low risk of hemorrhagic stroke (e.g., without other cardiovascular comorbidities such as hypertension).

AMD and Cataracts

The benefits of using vitamin E alone to improve the outcomes of AMD and cataracts have been disproven by the

results from two major RCTs of adults up to 80 years of age (Christen 2008; Taylor 2002). Supplementation with natural sources of vitamin E at 300–500 international units daily does not prevent the development or progression of early or later stages of AMD or cataracts. Furthermore, the benefits of vitamin E in combination with other antioxidants were not shown in the AREDS2 trial (Chew 2013). Although a recent study suggests that a higher vitamin A status, as reflected by higher α-tocopherol serum concentrations and dietary intake, is associated with reducing cataracts, this outcome could be the result of a healthier lifestyle and a more balanced diet in the treatment group, rather than the use of vitamin E (Zhang 2015). Overall, current knowledge does not support the routine use of supplemental vitamin E for AMD and cataracts.

Alzheimer Disease and Dementia

Free radical damage and oxidative stress have been suggested to contribute to the development of dementia and Alzheimer disease. A neuroprotective effect against dementia and cognitive impairment with higher plasma vitamin E concentrations was also suggested by at least one observational trial (Cherubini 2005). However, the benefit of vitamin E supplementation has been evaluated in clinical trials with variable findings. A meta-analysis of published RCTs showed that the benefits of vitamin E in these diseases are unconvincing, even at daily doses of 2000 international units (Farina 2012). In addition, a recent substudy from the Women's Health Study found no difference in the risk of cognitive decline between placebo and α-tocopherol acetate supplementation (600 international units every other day) at up to 9.6 years after initial randomization (Kang 2015). Overall, vitamin E supplementation does not appear to significantly decrease the risk of neurologic decline associated with aging.

Prostate Cancer Prevention

Much of the interest surrounding vitamin E supplementation has been on cancer prevention and survival. Results of these studies should be interpreted with caution because combinations of vitamins and antioxidants were used, and dietary sources of vitamin E and other micronutrients were not controlled. A significant study is the Selenium and Vitamin E Cancer Prevention Trial, one of the largest RCTs designed to assess the benefit of vitamin E on prostate cancer prevention (Lippman 2009). This four-arm RCT involved over 35,000 men with a mean baseline age of 62 years and a median follow-up of 5.5 years. The 5-year incidence of prostate cancer was similar in the placebo and treatment groups with 400 units of *all-rac*-α-tocopheryl acetate daily (range 4.43%–4.93%), suggesting no outcome benefits with vitamin E. However, the 0.5% higher incidence in the vitamin E–alone arm over placebo, though statistically insignificant, raised concern. When the long-term data (7–12 years follow-up) were analyzed, vitamin E supplementation alone was associated with

an absolute increase in prostate cancer risk of 17% compared with placebo (p=0.008). Neither selenium alone nor selenium in combination with vitamin E had a comparable risk (Klein 2011). This significantly contradicts the results from older studies like the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, which showed vitamin E's protective effect on prostate cancer.

These conflicting results may be associated with interactions between vitamin E and other micronutrients, purity of the products, salt forms, natural versus synthetic forms, dose, and other health-related factors. Moreover, the type of vitamin E used may be significant. Although α-tocopherol is widely used in clinical trials, an antitumor effect was more consistent with γ-tocotrienol, which has not been studied in clinical trials for this purpose (Ochi 2015).

In summary, vitamin E's overall role, especially α-tocopherol supplementation, in prostate cancer prevention is underwhelming, and its clinical benefits are inconsistent. Vitamin E's risk associated with prostate cancer raises further safety concerns. Until more high-quality data become available from well-designed RCTs, evidence is insufficient to support the routine use of vitamin E supplementation for cancer prevention.

Summary and Recommendations

Overall, available published research has failed to consistently show the clinical benefits associated with vitamin E supplementation in older adults. Moreover, the association between chronic vitamin E use and higher risk of prostate cancer or hemorrhagic stroke raises a primary safety concern. Routine vitamin E supplementation to prevent cardiovascular diseases, progression of dementia or Alzheimer disease, or degenerative eye diseases is not recommended.

VITAMIN D SUPPLEMENTATION AND MONITORING IN OLDER ADULTS

Overview of the Biology of Vitamin D

Vitamin D is an important endocrine hormone that regulates calcium homeostasis, which is important to autocrine function in regulating innate and adaptive immunity, and modulates cellular differentiation and maturation in the immune and musculoskeletal systems. Recent research has also shown vitamin D's broad epigenomic effect. The function of several hundred genes in humans is believed to be affected by 25(OH)D (calcidiol), but especially by 1,25(OH)D (calcitriol), through the binding to the vitamin D receptor (VDR), a nuclear transcription factor expressed in at least 38 cell types in the human body (Fetahu 2014). As such, recent research has linked a person's vitamin D status with his or her health. What remains unclear is whether vitamin D interventions can alter the course and progression of chronic diseases, such as osteoporosis, neuromuscular disorders, or some autoimmune diseases.

Patient Care Scenario

A 72-year-old woman is establishing care in your clinic. Her husband of 50 years recently died, and she moved across the country to be closer to her son and his family. She is moving into a retirement community and will be living independently and managing her medications with her son's assistance. Her history is significant for AMD, osteoporosis, hypertension, and hypothyroidism. She does not drink alcohol and has never used tobacco products. Her current medications include levothyroxine 50 mcg daily; amlodipine 10 mg daily; PreserVision AREDS2 1 capsule twice daily; Caltrate 600 plus cholecalciferol (vitamin D_3)

1 tablet daily; Nature Made flaxseed oil 1000 mg 1 capsule twice daily; and Nature Made vitamin E 400 units 1 capsule daily. She attributes her relative good health to a healthy lifestyle and use of supplements. She is "terrified" of losing her vision because that would affect her independence. Her laboratory test results and vital signs are within normal limits. Her son is concerned that she "takes too many pills" and wonders whether she should continue all of them. Cost is not a concern for the patient, but her son is worried about the expense of unnecessary medications because her housing cost "is pretty high."

ANSWER

Assessing a patient's regimen that includes supplements presents several unique challenges. The pharmacist should first assess the clinical benefits and risks of supplements, using the published literature as a guide and paying special attention to doses and dosage forms used within studies. The pharmacist should also determine the amount of active ingredient(s) in each product the patient is using because available products can vary significantly in amount and combination of active ingredients, excipients, and formulations.

Next, the pharmacist should determine the quality and purity of the product the patient is using. The USP verified mark on the product label ensures that the product is reliable with respect to active ingredient(s), amount(s), and absence of contaminants. Additional considerations include patient adherence and cost of supplements. In older adults, particularly, knowing the patient's functional status and understanding the goals, preferences, and expectations of both patients and their families are important when making treatment decisions.

The following plan should be discussed with the patient and her son:

- Continue amlodipine and levothyroxine at the current doses.
- Continue calcium plus D. Its benefit for bone health is well established and outweighs any risk; the current product contains calcium carbonate 600 mg plus vitamin D_3 800 units in each tablet. Because she has osteoporosis, she would benefit from vitamin D monitoring. The vitamin D dose can be adjusted to target 25-hydroxyvitamin D (25(OH)D) concentrations greater than 20 ng/mL. She can use either ergocalciferol (vitamin D_2) or vitamin D_3; ensure that she is using a product with the USP verified mark.
- Continue PreserVision AREDS2. This may help the patient's AMD; doses in the product are not harmful, and the patient has a strong preference for continuing.
- Discontinue flaxseed oil, vitamin E – evidence of cardiovascular benefit is weak from flaxseed oil because the product contains mainly ALA; harm from vitamin E is absent because the patient does not have a prostate; cost and pill burden are considerations of the patient's son.

1. Holmes HM, Todd A. The role of patient preferences in deprescribing. Clin Geriatr Med 2017;33:165-75.
2. Scott IA, Hilmer SN, Reeve, et al. Reducing inappropriate polypharmacy the process of deprescribing. JAMA Intern Med 2015;175:827-34.

Endogenous vitamin D is derived from the 7-dehydrocholesterol (or provitamin D_3) present in skin tissues and converted to previtamin D_3, a secosterol, by UVB waves (wavelength 290–315 nm). Previtamin D_3 then undergoes thermal-induced isomerization to vitamin D_3 and is released into the systemic circulation. The efficiency of UVB-mediated previtamin D_3 synthesis is affected by skin melanin content, adiposity, time and length of day, seasonal variation, cloud cover, latitude, altitude, air pollution (e.g., ozone, smog), and sunscreen use. The solar zenith angle during winter and early morning and late afternoon also reduces the UVB entering the atmosphere, especially above and below about 33° latitude. Therefore, the most active period for the cutaneous synthesis of vitamin D_3 associated with sun exposure is limited to 10 a.m.–3 p.m. in most places (Hossein-Nezhad 2013).

The amount of endogenously produced vitamin D_3 alone is generally insufficient in most of the population. Dietary sources are thus needed to maintain normal health. Dietary supplements of vitamin D can contain either vitamin D_2 or vitamin D_3, depending on the source. Sources of food-based vitamin D are relatively limited. Animal-based food such as fatty fish, cheese, and egg yolks provide vitamin D_3, and 25(OH)D is also present in some animal-based food. Exposure of ergosterol to UVB leads to the formation of vitamin D_2, which is the most common source of dietary vitamin D from vegetables. Plant-based vitamin D_3 has been identified in several species (e.g., garden tomatoes, several varieties of squash, and peppers) but is present only in the leaves, not the fruit (Jäpelt 2013).
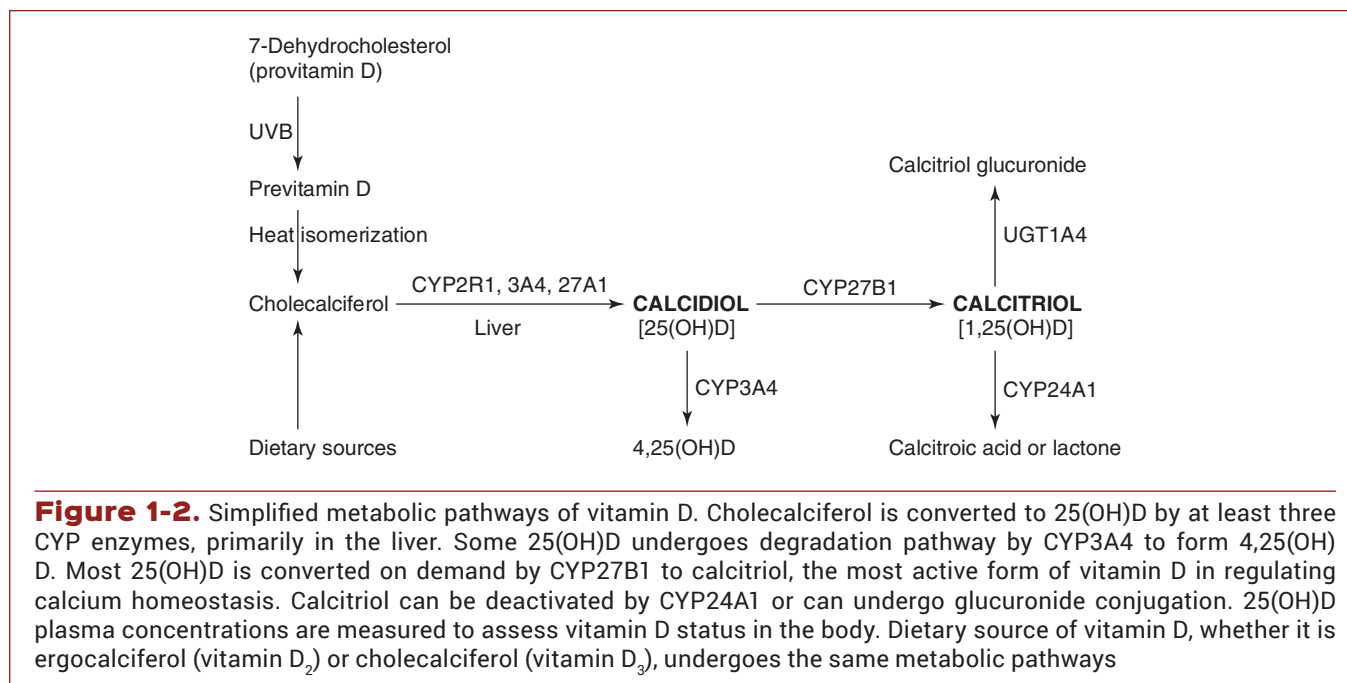
After oral ingestion, vitamin D (vitamin D_3 or vitamin D_2) is absorbed slowly in the small intestine. In most adults, peak

plasma concentration occurs 4–10 hours after ingestion. The highest absorption efficiency is in the distal jejunum and ileum (Goncalves 2015). Thus, patients with extensive ileal resection will likely have significant malabsorption of vitamin D and may require very large doses of supplementation to prevent deficiency. Vitamin D absorption is mediated by both passive diffusion and transporter-mediated processes present in the small intestine. Currently, three transport proteins – CD36, NPC1L1, and SR-BI – have been identified as the intestinal vitamin D transporters in humans (Reboul 2011). Dietary fat promotes the release of bile salts, facilitating vitamin D absorption through incorporation within chylomicrons. The oral bioavailability of vitamin D_3 varies in humans under normal physiology, at 55%–99% (Borel 2013). According to a single-dose study of 30 healthy men, the bioavailability of oral vitamin D_2 is 3-fold lower than of vitamin D_3, as measured by their respective plasma 25(OH)D metabolites (Armas 2004).

The metabolic pathways of vitamin D_3 are summarized in Figure 1-2. Both vitamins D_2 and D_3 undergo the same CYP-mediated biotransformation in the liver to 25(OH)D. In the plasma, 25(OH)D is highly protein bound – with over 80% to vitamin D–binding protein and 10%–15% to albumin – and is transported to target tissues for further bioactivation. Although CYP27B1 in renal cells takes the primary role in converting 25(OH)D to 1,25(OH)D, this pathway is not exclusive to the kidneys. Many cells (e.g., mammary epithelial cells, osteoblasts, keratinocytes, macrophages, and mast cells) also express CYP27B1 and can synthesize calcitriol locally. Tissue-derived calcitriol is thought to play a more important role in autocrine function than in calcium regulation.

CYP3A4 is a catabolic enzyme for 25(OH)D; thus, CYP3A4 inducers such as rifampin, phenytoin, and carbamazepine can contribute to hypovitaminosis D (Wang 2012). Currently, specific inducers of CYP24A1, the primary catabolic enzyme for calcitriol, have not been identified. Although calcitriol is the most active compound in regulating calcium homeostasis, 25(OH)D also has mild physiological activities and is believed to play an important role in regulating the action of 1,25(OH)D by competing with its binding site, VDR, as well as its metabolism.

The physiologic effects of vitamin D vary depending on the tissues involved. From the endocrine perspective, the binding of VDR by calcitriol in the small intestine increases the efficiency of transporter-mediated transcellular intestinal calcium absorption from around 10%–15% to 30%–40% and that of intestinal phosphorus absorption from around 60%–80% to over 90%. In the kidneys, calcitriol enhances calcium reabsorption from the glomerular filtrate (Holick 2007). In other tissues, calcitriol serves an autocrine function by binding to the nuclear VDR, which then interacts with DNA and regulates the transcription of specific genes after coupling with the retinoic acid X receptor (Hossein-Nezhad 2013). The downstream effects are cell-specific, which may include increased chemotaxis, tissue proliferation, or apoptosis. Finally, the disposition and physiological actions of vitamin D can be altered by genetic polymorphisms (Box 1-1). For example, polymorphisms of vitamin D–binding protein and *CYP2R1* are associated with altered serum 25(OH)D concentrations in whites (Nissen 2014). African Americans may have a higher frequency of carrying a specific vitamin D–binding protein genotype than whites, resulting in lower

Figure 1-2. Simplified metabolic pathways of vitamin D. Cholecalciferol is converted to 25(OH)D by at least three CYP enzymes, primarily in the liver. Some 25(OH)D undergoes degradation pathway by CYP3A4 to form 4,25(OH)D. Most 25(OH)D is converted on demand by CYP27B1 to calcitriol, the most active form of vitamin D in regulating calcium homeostasis. Calcitriol can be deactivated by CYP24A1 or can undergo glucuronide conjugation. 25(OH)D plasma concentrations are measured to assess vitamin D status in the body. Dietary source of vitamin D, whether it is ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3), undergoes the same metabolic pathways

plasma concentrations of 25(OH)D and vitamin D–binding protein (Powe 2013).

Role of Vitamin D in Health and Diseases

The best-understood functions of vitamin D in humans are calcium homeostasis and bone health. Although uncommon, up to 4% of vitamin D toxicity cases may present with hypercalcemia (Pérez-Barrios 2016). Overt hypocalcemia is uncommon in vitamin D deficiency because the body tries to maintain a normocalcemic state by mobilizing calcium from bone. Chronic vitamin D deficiency is an independent risk factor for osteoporosis and bone fracture. Altered vitamin D status occurs in other diseases, including cognitive decline, depression, cardiovascular diseases, hypertension, diabetes mellitus, asthma, tuberculosis, and cancer. However, existing data suggest only an association, rather than causality. Finally, limited observational studies suggest that a patient's vitamin D status affects the clinical response of biologic therapy in the treatment of non-Hodgkin lymphoma and inflammatory bowel disease. Many of these studies are retrospective in design with very small sample sizes. Well-designed RCTs are needed to confirm these findings.

Risks Factors that May Precipitate Vitamin D Deficiency

The adequacy of vitamin D status is maintained by both endogenous production and optimal dietary intake. A diet low in vitamin D content, malabsorptive disorders, extensive small bowel resection, and a diet low in fat may all lead to vitamin D deficiency. Compared with meat eaters, vegetarians and vegans consistently have lower plasma total 25(OH)D concentrations (Crowe 2011). Although contemporary bariatric surgical procedures such as Roux-en-Y gastric bypass or laparoscopic sleeve gastrectomy do not impair the function or length of the functional ileum, these procedures are associated with a significantly reduced total caloric intake, which is associated with vitamin D deficiency. Obesity is an independent risk factor for vitamin D deficiency as vitamin D is sequestered into adipose tissue (Beckman 2013). Cutaneous synthesis of vitamin D is also lower in individuals with obesity than in individuals with normal weight (Wortsman 2000). Other factors that may increase the risk of vitamin D deficiency include aging, reduced time spent outdoors, renal dysfunction, and drug-drug or drug-nutrient interactions (e.g., use of CYP3A4 inducers) (Meehan 2014).

Assessment and Interpretation of Vitamin D Status

Although 1,25(OH)D is the most active form of vitamin D, it is not the preferred clinical marker to assess vitamin D status because of its short serum half-life of 4–6 hours. In addition, serum 1,25(OH)D concentrations may not correlate with overall body status because certain tissues activate 25(OH)D to 1,25(OH)D locally. Plasma 1,25(OH)D concentrations are often normal or even increased in patients with vitamin D deficiency as a result of secondary hyperparathyroidism (Hossein-Nezhad 2013). Therefore, routine measurement of plasma 1,25(OH)D concentrations to diagnose hypovitaminosis D should be discouraged because this can lead to an erroneous interpretation of vitamin D status.

However, 25(OH)D has a serum half-life of around 15 days and is the primary circulating form of vitamin D. Moreover, the 25(OH)D concentration is regarded as a measure of the effective body pool of vitamin D. Therefore, according to current knowledge, plasma 25(OH)D concentration is the preferred laboratory test to assess vitamin D status. Although some laboratories can quantify vitamins D_2 and D_3, total plasma 25(OH)D concentrations should be used as the initial assessment and are adequate for diagnosing hyper- or hypovitaminosis D. In selected patients whose clinical response to standard vitamin D replacement regimens has been inadequate, quantification of vitamins D_2 and D_3 may be considered to refine clinical strategies or rule out other causes of undertreatment such as insufficient dosing, malabsorption, or nonadherence. In patients with chronic renal failure, 1,25(OH)D concentrations may be measured to complement 25(OH)D concentrations to optimize vitamin D regimens because the renal activation of 25(OH)D to 1,25(OH)D is impaired, even if patients have a normal 25(OH)D concentration.

The accuracy of assessing vitamin D status, especially for plasma 25(OH)D concentrations, is also limited by the analytic method. Although liquid chromatography-tandem mass spectrometry is the gold standard for measuring calcidiol, institutions and commercial laboratories continue to use a variety of assays (e.g., chemiluminescence immunoassays, radioimmunoassay, and high-performance liquid chromatography) because of limitations from institutional resources, personnel expertise, and costs. The variance between these assays can be over 20%, which can translate to different clinical decisions and health care consequences that are biased by the analytic techniques used (Enko 2014). Standardization of the quantification method of vitamin D from tissue samples is urgently needed to optimize clinical decisions and outcomes.

Controversies in the Definition of Vitamin D Deficiency and Threshold for Treatment

The precise definition of vitamin D deficiency continues to be a point of debate. Using a population model aimed at preventing vitamin D deficiency in 97.5% of the general population, the Institute of Medicine defined the optimal daily vitamin D intake as 600 international units for all adults up to 70 years of age and 800 international units for those older than 70. In addition, a plasma 25(OH)D concentration of 20 ng/mL or above is considered as clinically adequate, 12–19 ng/mL as insufficient, and less than 12 ng/mL as deficient (IOM 2011). In the past few years, some clinicians and professional organizations have advocated a higher daily intake of vitamin D (e.g., 1000–2000 international units) and routine monitoring of vitamin D status using 30 ng/mL as the threshold for vitamin D sufficiency. The intent is to provide vitamin D supplementation to maintain plasma 25(OH)D at 30 ng/mL or higher. The rationale of this approach is based on the assumption that a positive correlation exists between vitamin D status and general health, especially bone health, and that vitamin D has a wide margin of safety. Despite the limited merits of this approach, supported mainly by small-scale, uncontrolled observational studies, it has not been validated by high-quality controlled clinical trials. Using randomized trials and case-control studies nested within the Women's Health Initiative, a recent analysis by the U.S. Preventive Services Task Force (USPSTF) failed to identify high-quality studies aimed to evaluate whether screening for vitamin D deficiency is associated with clinical benefit or harm. The USPSTF analysis also showed that the treatment of vitamin D deficiency in asymptomatic individuals, regardless of whether the plasma 25(OH)D concentration cutoff for treatment was 20 ng/mL or 30 ng/mL, may reduce the mortality risk in institutionalized older adults and the risk of falls, but not fractures. The USPSTF study found no significant increase in harm between the groups treated with vitamin D compared with placebo, though none of the studies included was designed specifically to assess harm (LeBlanc 2015). These findings suggest that the target plasma calcidiol concentrations in most adults should be at least 20 ng/mL, whereas the benefit of targeting calcidiol concentrations to greater than 30 ng/mL requires confirmation by high-quality research.

Plasma 25(OH)D concentrations are affected by seasonal changes. Epidemiological data analyses have shown that the incidence of vitamin D deficiency is 1.5–4 times higher in winter than in summer months among Europeans when the same cutoff value is used. Seasonal variation occurs in people living in all regions, though it appears to be more dramatic for those living farther from the equator. For example, U.S. studies showed that the average seasonal variation is around 5 ng/mL in residents living in the southern states (North Carolina and Mississippi), about 7 ng/mL in the Pacific Northwest, and 11 ng/mL in Southern Alaska (Cashman 2016; Fohner 2016; Chan 2015; Michos 2014). Currently, however, no consensus has been established with respect to the best season to assess vitamin D status. Also unknown is whether minimizing seasonal variations by supplementing vitamin D in the winter months is associated with improved health outcomes.

Using the same diagnostic threshold, the incidence of vitamin D insufficiency and deficiency is consistently associated with interracial/interethnic differences, especially in North America. Epidemiological and surveillance studies show that whites generally have higher average 25(OH)D concentrations than Latinos. African Americans tend to have the lowest 25(OH)D concentrations among most ethnic groups and are often described as having the highest incidence of vitamin D deficiency in the United States. Despite these differences, the incidence of both bone fracture and osteoporosis among African Americans is similar to the incidence of these conditions in other ethnic groups. One study showed that about 50% of African immigrants in the United States had 25(OH)D concentrations less than 20 ng/mL, but less than 10% had evidence of deficiency on the basis of clinical signs or secondary hyperparathyroidism (Thoreson 2015). Currently, evidence is insufficient to suggest using different diagnostic cutoffs and intervention targets on the basis of race or ethnicity.

Approaches Toward Supplementation

The benefits of continuous vitamin D supplementation are highly questionable in healthy individuals without risk factors for deficiency. A single episode of vitamin D deficiency should be responsive to one of the established treatment regimens and usually does not warrant maintenance supplementation. Supplementation should be considered in patients with chronically reduced intake, history of small intestinal resection, fat malabsorption syndrome, and bariatric surgery and those taking chronic CYP3A4 inducers. Otherwise, the need for vitamin D supplementation should be based on an individual's risk factors and guided by plasma 25(OH)D concentrations. We also recommend vitamin D supplementation as maintenance therapy in patients with at least two episodes of vitamin D deficiency, as documented by plasma 25(OH)D concentrations less than 20 ng/mL despite adequately completing previous treatment courses. Patients with chronic kidney disease will likely require supplementation of calcitriol, instead of 25(OH)D, unless there are other reasons leading to a deficiency in dietary vitamin D intake or absorption.

Treatment for Clinical Deficiency

The dose-response relationship of vitamin D supplementation has been evaluated in healthy men living in the midwestern United States in winter when cutaneous vitamin D_3 synthesis is minimal. These men, living in Omaha, Nebraska (latitude 41.2°N), with a mean age of 38.7 years and a BMI of 26.2 kg/m², were randomized to receive a daily vitamin D_3 supplement in oral tablet form at various doses of 1000–10,000

international units. Their average baseline 25(OH)D concentration was 28 ng/mL. Results showed a linear dose-response relationship: for every 100 international units/day of vitamin D_3, plasma 25(OH)D increased by around 0.7 ng/mL at steady state. Mean residency time for the supplemented vitamin D_3 was about 40 days (Heaney 2003). According to these results, in an adult with a plasma 25(OH)D concentration of 15 ng/mL, supplementing vitamin D_3 800 international units daily would result in a target 25(OH)D concentration of about 20 ng/mL after 6–8 weeks. Limited data suggest that the change in plasma 25(OH)D is more substantial in patients who are vitamin D deficient (Hossein-Nezhad 2013). The change in 25(OH)D concentrations in individuals with a lower BMI would likely be higher. Whether the same dose-response relationship is maintained in older adults is unclear.

A group from the Netherlands developed the following weight-based equation to estimate the total vitamin D dose needed to treat deficiency:

Total vitamin D dose = 40 × (75 − (current 25(OH)D concentration (ng/mL) × 2.5)) × wt (kg)

This equation was derived from 208 middle-aged subjects (mean age 55.2 years; 68% women; mean BMI 28.1 kg/m^2) with a target 25(OH)D concentration of 30 ng/mL (van Groningen 2010). The total deficiency would be replaced by a weekly dose of no more than 25,000 international units. For example, the estimated total vitamin D deficiency for a man weighing 75 kg with a baseline 25(OH)D concentration of 15 ng/mL would be 112,500 international units. A weekly oral supplementation of 12,000 international units for nine doses would bring the 25(OH)D concentration to just under 30 ng/mL.

Although several simplified vitamin D replacement regimens have been published, the most widely accepted approach is to supplement 50,000 international units weekly for 8 weeks and recheck vitamin D status (Holick 2007). This regimen, equivalent to 7100 international units daily for 8 weeks, is expected to increase the plasma 25(OH)D concentration by 15–30 ng/mL by the end of treatment and should the restore 25(OH)D concentration to above the desired threshold in most patients (Heaney 2011). Given its long serum half-life, vitamin D supplementation given once weekly is a good alternative approach to increase adherence. Moreover, vitamin D_2 capsules containing 50,000 units each are a prescription product covered by most health plans. Therefore, this weekly regimen also offers cost savings to patients who might purchase OTC vitamin D formulations, which would not be covered by most insurance plans.

Vitamin D_2 vs. Vitamin D_3

An ongoing debate in vitamin D supplementation involves whether vitamin D_3–based products are preferable to vitamin D_2 products. From the kinetic perspective, vitamin D_3 appears to be slightly better absorbed with a longer residence time than vitamin D_2. In a single-dose, placebo-controlled, non-crossover study, 30 healthy men living in Nebraska received a single 50,000-international unit dose of vitamin D_3, vitamin D_2, or placebo during the summer months. Serial serum concentrations of vitamin D_3 or vitamin D_2 and their respective 25(OH)D concentrations were measured over 28 days. Product potencies were confirmed before the study. Product potencies were confirmed before the study. Vitamin D_3 administration was associated with a 3.4-fold higher 25(OH)D AUC (i.e., D_2 plus D_3) on days 0-28 than vitamin D_2 [204.7 ± 32.4 ng/day/mL vs. 60.2 ± 23.4 ng/day/mL; p<0.002]). Although the plasma total 25(OH)D concentration profiles were similar in both arms during the first 3 days, total 25(OH)D remained increased on day 28 in the vitamin D_3 arm, whereas it returned to baseline by day 15 in the vitamin D_2 arm (Armas 2004). In a follow-up, randomized, parallel-group study with 50,000 international units of each supplement given weekly for 12 weeks in 33 healthy white adults (30 women, 3 men), the respective total 25(OH)D AUC at days 0–84 was 1.5 times higher in the vitamin D_3 arm (p=0.005). In subjects whose vitamin D_3 content was evaluated in adipocytes, the increase in total vitamin D content was 2 times higher in the vitamin D_3–treated group. The total 25(OH)D serum half-life was also longer with vitamin D_3 treatment (27 vs. 16 days, p=0.003). Peak total 25(OH)D concentrations, observed on day 84 in both arms, were twice as high (Heaney 2011). These data suggest that at treatment doses (50,000 international units), vitamin D_3 is more effective than vitamin D_2 in increasing total plasma 25(OH)D concentrations.

For maintenance therapy, the data are not as clear. In a randomized, double-blind, placebo-controlled trial conducted during the winter in Dunedin, New Zealand (latitude 46°S), 95 healthy subjects received a daily tablet of placebo, vitamin D_3, or vitamin D_2 (each of 1000 international units) for 24 weeks. Placebo treatment was associated with a 54% reduction in plasma total 25(OH)D concentrations. After 24 weeks, vitamin D_2–supplemented subjects had a mean increase in 25(OH)D_2 concentration of 12.8 ng/mL, but their mean 25(OH)D3 decreased by 21.2 ng/mL, resulting in an overall reduction in mean total 25(OH)D concentrations from baseline (from 29.6 ng/mL to 22.4 ng/mL; p<0.001). Serum parathyroid hormone concentrations were also decreased by 8%, though the difference was not statistically significant. In comparison, the subjects in the vitamin D_3 arm had no measurable change in plasma concentrations of 25(OH)D_3, total 25(OH)D, and parathyroid hormone (Logan 2013). A similar study was also conducted in Bergen, Norway (latitude 60°N), in which 107 subjects received placebo, vitamin D_2, or vitamin D_3 2000 international units daily for 8 weeks. The potency of both supplements was confirmed before the study. As expected, the placebo group had a significant decrease in 25(OH)D2, 25(OH)D3, and total 25(OH)D concentrations. Vitamin D_2 supplementation was associated with a 47% reduction in 25(OH)D3 concentrations, but this reduction was offset by a net increase in 25(OH)D2 concentrations by

over 17 ng/mL. Subsequently, both vitamin D_2– and vitamin D_3–supplemented subjects had a significant increase in total 25(OH)D concentrations from baseline (80% vs. 104%, respectively), though the average total 25(OH)D concentration was 8.5 ng/mL higher in the vitamin D_3–supplemented group. Parathyroid hormone concentrations were unchanged in all groups (Lehmann 2013). Collectively, these studies suggest that daily supplementation of either calciferol (vitamin D_2 or vitamin D_3) is effective in preventing vitamin D deficiency and increasing plasma total 25(OH)D concentrations, though vitamin D_3 is more effective than vitamin D_2.

Practically speaking, however, the benefits of vitamin D_3– over vitamin D_2–based supplements are limited by two issues. First, the efficacy of any product may be limited by lack of purity and inconsistency. In the United States, oral vitamin D products are regulated under DSHEA, which does not require the manufacturer to submit proof of product purity and potency. A product on the market claiming to provide vitamin D_3 may contain some or all vitamin D_2, or other impurities. Similarly, intra- and inter-batch consistency may not be guaranteed because of the lack of testing. Therefore, a product labeled as vitamin D_3 may be no better than a pure vitamin D_2 product. Second, vitamin D_3–based products are associated with a high cost. The prescription vitamin D 50,000-international unit formulations covered by insurance plans, commonly used for vitamin D deficiency, are vitamin D_2–based products. Vitamin D_3–based supplements are OTC vitamins that are generally not covered by health plans. Therefore, the overall cost to the patient for an 8-week course of daily vitamin D_3 can be substantially higher than for a course of weekly vitamin D_2 50,000 international units for eight doses. The cost will be even more substantial for chronic maintenance therapy. In patients with financial hardships, medication cost is a common cause for nonadherence and treatment failure. For these reasons, affordability and ease of access to the product should be part of the decision process in designing the vitamin D supplementation regimen. Depending on the circumstance and other patient factors, both vitamin D_2 and vitamin D_3 are reasonable options. The vitamin D_2 doses may need to be increased to attain the target results. In a patient whose clinical response to vitamin D_2 is insufficient, as assessed by an inadequate increase in plasma calcidiol concentration, vitamin D_3 may be considered. In choosing a vitamin D_3 product, clinicians should recommend a reputable brand with product quality certified by USP. Certification of the product should be current.

Maintenance Therapy to Prevent Deficiency
Daily vitamin D intake of 600–800 international units through diet should be adequate to prevent vitamin D deficiency in most adults. The benefit of routine vitamin D monitoring or supplementation in otherwise healthy individuals has not been shown (LeBlanc 2015). In at-risk patients, plasma 25(OH)D concentration can be monitored to determine the need for supplementation to prevent deficiency. Older adults are at an increased risk of developing vitamin D deficiency because of aging-related decreases in cutaneous previtamin D_3 synthesis (MacLaughlin 1985). Increased dietary intake of oily fish can prevent vitamin D deficiency as well as provide other vital nutrients such as w-3FA and zinc. Maintenance doses of vitamin D can be given daily, weekly, monthly, or quarterly. However, monthly vitamin D_3 doses of 60,000 international units increase the incidence of falls in older adults, and annual vitamin D_3 doses of 500,000 international units are associated with a higher risk of fracture (Bischoff-Ferrari 2016; Sanders 2010). Therefore, doses greater than 50,000 international units per month for preventive purposes should be used with extreme caution.

Clinical Outcomes of Interest in Older Adults
Bone Health
A recent review of existing RCTs or quasi-RCTs that included 53 trials showed that supplemental vitamin D alone at doses of 400 international units daily to 500,000 international units single dose had no protective effect against fractures in postmenopausal women and older men. Treatment duration was 6–46 months. However, a protective effect occurred when vitamin D was used together with calcium supplements (Avenell 2014). In an RCT of 409 home-dwelling women from Finland 70–80 years of age, the incidence of falls (discussed later in the text in the Falls and Functional Decline section) and changes in BMD were compared over 2 years among individuals receiving vitamin D, exercise, and vitamin D plus exercise versus placebo. Vitamin D was administered as vitamin D_3 800 international units daily. Exercise consisted of supervised, progressive group training classes twice weekly in the first year and reduced to once weekly in the second year. Vitamin D supplementation resulted in an increase in plasma 25(OH)D concentrations from 25.1 ng/mL to 37 ng/mL. Femoral BMD decreased in all groups with no difference between groups, whereas lumbar spine BMD did not change significantly (Uusi-Rasi 2015). Another study of postmenopausal women was aimed at determining whether maintaining plasma 25(OH)D concentrations greater than 30 ng/mL with high-dose vitamin D for 1 year would increase total fractional calcium absorption and BMD compared with low-dose vitamin D_3 or placebo. In the high-dose arm, participants received a loading dose of 50,000 international units of vitamin D_3 daily for 15 days to increase baseline 25(OH)D concentrations, followed by 50,000 international units every 15 days (equivalent to 3333 international units/day). Participants in the low-dose arm received vitamin D_3 800 international units daily. The mean age and BMI of these 230 participants were 61 years and 30.8 kg/m², respectively. Their baseline plasma 25(OH)D concentrations were 14–27 ng/mL. The post-loading dose 25(OH)D concentrations were significantly different

between the two dosing groups throughout the study, with the high-dose group average consistently over 30 ng/mL and the low-dose group average under 30 ng/mL. Total fractional calcium absorption from the intestine in the high-dose group was about 3% higher than in the low-dose group. Despite the differences in 25(OH)D concentrations and calcium absorption, no difference was detected in BMD, trabecular bone score, muscle mass, or functional status as measured by a health assessment questionnaire (Hansen 2015). These results suggest that in older adults who are not vitamin D deficient (baseline plasma 25(OH)D concentration greater than 12 ng/mL), neither taking high doses of vitamin D supplementation nor maintaining plasma 25(OH)D concentrations greater than 30 ng/mL is associated with a significant effect in preserving BMD or preventing fracture.

Falls and Functional Decline

In a simulation study of fall-related outcomes, three national databases that included accidents and ED visits in the United Kingdom were examined. The investigators suggested that empiric daily supplementation of 800 international units of vitamin D_3 in adults 60 and older would be associated with substantial reductions in mortality and cost-savings over 5 years. The potential benefits might include prevention of over 430,000 minor falls, 1579 acute deaths, 84,000 person-years of long-term care, and 8300 deaths associated with increased mortality in long-term care (Poole 2015). However, the results from this simulation model are contradicted by at least two recently published, well-designed RCTs. In the Finnish trial of 409 older adults discussed previously, vitamin D supplementation (800 international units daily) alone did not reduce the risk of falls compared with placebo, but exercise alone and exercise plus vitamin D both significantly reduced the risk of falls with injury compared with placebo (HR 0.47 [95% CI, 0.23–0.99] and 0.38 [95% CI, 0.17–0.83], respectively (Uusi-Rasi 2015). This finding is consistent with another recently published study of home-dwelling adults older than 70 (Bischoff-Ferrari 2016). Two hundred adults with a baseline plasma 25(OH)D concentration less than 20 ng/mL were randomized to receive monthly doses of vitamin D_3 24,000 international units (around 800 international units/day), 60,000 international units, or 24,000 international units plus 25(OH)D3 300 mcg for 12 months. The incidence of falls was assessed monthly. In addition, functional decline as measured by physical performance, physical examination, and appendicular muscle mass were monitored longitudinally. Average plasma 25(OH)D concentrations greater than 30 ng/mL were attained in all intervention groups and correlated with the doses administered. Overall, functional status, lower-extremity function, and muscle mass were not different among treatment groups at 12 months. Nevertheless, compared with the low-dose group (24,000 international units/day), both groups receiving higher doses of vitamin D supplementation had an 18% higher incidence of falls (48% vs.

66% for both groups; p=0.048). Together, these clinical trial data suggest that although vitamin D supplementation at 800 international units daily is sufficient to treat vitamin D deficiency in older adults, its empiric use is not associated with reduced fall risks and function decline. In fact, consistent with previous observations, large vitamin D_3 doses (e.g., greater than 50,000 international units/month) are associated with increased fall risk (Sanders 2010). A carefully designed exercise regimen is potentially more cost-effective in fall prevention for older adult patients.

Cardiovascular Diseases

Many recently published trials have evaluated the potential benefits of vitamin D supplementation on cardiovascular diseases, including hypertension, heart failure, and stroke. Compared with placebo, vitamin D_3 2800 international units daily for 8 weeks in older adults with obesity (BMI and age 30.4 ± 5.4 kg/m^2 and 60.0 ± 11.1 years, respectively; n=188) had no effect on systolic and diastolic blood pressure or several cardiovascular risk factors such as plasma concentrations of renin, aldosterone, and B-type natriuretic peptide and 24-hour urinary albumin excretion. Unexpectedly, moreover, a 14% increase (p=0.013) in serum triglycerides was observed, though the clinical significance is unclear. Intervention led to an increase in plasma 25(OH)D concentrations from 22.0 ± 5.5 ng/mL to 36.2 ± 7.3 ng/mL (Pilz 2015). In older adults with heart failure (New York Heart Association classes II–IV), vitamin D_3 50,000 international units weekly for 6 months led to a net increase in plasma calcidiol concentrations by 42.3 ± 16.4 ng/mL from baseline. However, increased vitamin D status was not associated with improved aerobic capacity as measured by peak oxygen uptake, functional performance as measured by 6-minute walk, or muscle strength as measured by isokinetic dynamometer (Boxer 2013).

With respect to stroke, an observational study involving over 7000 patients (3100 of whom were older than 65) showed that vitamin D deficiency, defined as a plasma 25(OH)D less than 12 ng/mL, was significantly associated with an increased risk of cardiovascular disease, coronary heart disease, and stroke after adjusting for age, sex, and season of blood obtained. The hazard ratio for stroke was 1.58 (95% CI, 1.16–2.17). An inverse association was also detected between these risks and 25(OH)D concentrations below 30 ng/mL. Average follow-up time was 6.5 years (Perna 2013). However, baseline plasma 25(OH)D concentrations did not predict the prevalence of subclinical brain infarcts as revealed on serial cerebral MRIs, disease progression, or cognitive impairment over 10 years (Michos 2014). In fact, in the extension trial, which used the data of over 29,000 postmenopausal women from the Women's Health Initiative, the risk of cardiovascular diseases and all-cause mortality at 5 years after the end of interventions was similar between women who received placebo and women who received vitamin D supplementation (up to 1000 international units/day; mean dose 773 international

units/day) (Cauley 2013). Overall, vitamin D deficiency and increased risk of cardiovascular diseases, especially stroke, appear to be associated. However, evidence is insufficient to determine whether using empiric vitamin D supplementation or maintaining plasma 25(OH)D concentrations greater than 20 ng/mL improves clinical outcomes for these diseases.

Other Diseases

The roles of vitamin D status and vitamin D supplementation in other disease states and medical conditions (e.g., prevention of breast cancer and colorectal cancer, cancer survival, chronic obstructive pulmonary disease, and depression) have been evaluated in small studies. Currently, however, in the absence of vitamin D deficiency, evidence is insufficient to support the benefits of empiric vitamin D supplementation in improving the prognosis of these disease states.

Summary and Recommendations

The value of providing vitamin D treatment to achieve targeted plasma 25(OH)D concentrations versus standard oral intake at 800 international units/day should be compared. Studies should be designed to compare outcomes according to different targeted calcidiol concentrations. As the population continues to age, studies that enroll adults older than 80 are needed. The impact of genetic polymorphisms of vitamin D disposition on the dosing regimen and clinical outcomes should be investigated. The reasons behind the increased fall risks with "mega-doses" of vitamin D should be explored further.

MAJOR ONGOING CLINICAL RESEARCH

Many well-designed RCTs are under way or will have results published soon. Findings of these studies will have implications for clinical practice.

- BEST-D (Biochemical Efficacy and Safety Trial of Vitamin D), University of Oxford.

  Study aim: To determine the daily dose of vitamin D needed in older adults to maintain blood concentrations of vitamin D similar to those in healthy younger people at the end of the summer months.

- VDOP (Vitamin D supplementation in older people), University of Cambridge.

  Study aim: To examine the relationship between vitamin D supplementation at a range of doses (12,000, 24,000, or 48,000 international units/month, equivalent to 400, 800, and 1600 international units/day, respectively) and the change in BMD in older people living in private households in the North East of England.

- VITAL (Vitamin D and Omega-3 Trial), Harvard Medical School.

  Study aim: To determine whether taking daily dietary supplements of vitamin D_3 (2000 international units) or w-3FAs (Omacor fish oil, 1 g) reduces the risk of

developing cancer, heart disease, and stroke in people who have no history of these illnesses.

- D-Health: A trial of vitamin D for the prevention of mortality and cancer in older Australian adults, University of Queensland, Australia.

  Study aim: To determine whether increasing the mean plasma calcidiol concentrations in the general population

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Practice Points

Nutritional supplements are commonly used by U.S. adults, and rates of use among older adults have been increasing. Clinical pharmacists can play an important role in optimizing their patients' health by recommending safe and efficacious supplement regimens.

Supplements in General

- Oral supplements are not regulated by the FDA and thus are not held to the same standard as prescription drugs.
- Choose supplement products with verified mark to ensure quality, consistency, and potency.
- Pharmacists can take an active role in helping patients and prescribers choose supplements wisely, according to safety and efficacy data gleaned from literature review, along with specialized knowledge of biologic processes and the unique properties of different dosage forms.

w-3FAs

- Choose products and foods consisting of primarily DHA and EPA for maximal anti-inflammatory effect.
- Products and foods containing primarily ALA (e.g., flaxseed oil) have negligible anti-inflammatory properties.
- The evidence for w-3FAs supports its use for reducing death associated with cardiovascular events or stroke, or reducing atrial fibrillation after CABG.

Vitamin E

- Routine use of vitamin E for to prevent cancer, cardiovascular disease, dementia, or degenerative eye disease is unsupported by evidence. In some cases, such as risk of prostate cancer or cerebral hemorrhage, the risk may be increased.
- Use of vitamin E for other medical conditions requires further study.

Vitamin D

- Routine plasma 25(OH)D concentration monitoring for all patients is not cost-effective.
- Patients with risk factors for deficiency would benefit from monitoring of plasma calcidiol concentrations.
- The definition of deficiency varies and is affected by several factors, including race/ethnicity.
- The target concentration of plasma 25(OH)D for most patients is greater than 20 ng/mL.
- There is no significant clinical difference between using vitamin D_2 and vitamin D_3 to supplement.
- High doses of vitamin D (doses higher than 50,000 units/ week) in patients with normal diet or ability to absorb nutrient are harmful in older adults.

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through widespread supplementation results in improved health outcomes.

- FIND (Finnish Vitamin D trial), University of Eastern Finland.

  Study aim: To determine the benefits and risks of vitamin D_3 (1600 international units/day, 3200 international units/day, or placebo) in the primary prevention of cardiovascular and cancer among 18,000 men 60 years and older and women 65 years and older.

- VIDAL (Vitamin D and Longevity trial), London School of Hygiene & Tropical Medicine.

  Study aim: To determine whether taking vitamin D (100,000 international units/month or placebo) can reduce mortality and morbidity among older adults in the general population 64–85 years of age.

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Self-Assessment Questions

1. A 72-year-old man has a medical history of cirrhosis, chronic pancreatitis, and fat malabsorption syndrome. His plasma vitamin E concentration is low, and he has developed symptoms suggestive of vitamin E deficiency, including truncal and limb ataxia, diffuse muscle weakness, and hyporeflexia. Chronic vitamin E supplementation would most likely increase this patient's risk of which one of the following complications?

   A. Hemorrhagic stroke
   B. Ischemic stroke
   C. Bladder cancer
   D. Invasive breast cancer

2. A 71-year-old woman with a medical history of osteoarthritis, lower back pain, and hypertension comes to the clinic. She has heard that fish oil may help with inflammation, and she asks for your recommendation. A product with which one of the following content profiles is best to recommend for this patient?

   A. 500 mg each of α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA)
   B. 1500 mg of ALA alone
   C. 1000 mg of DHA and 500 mg of EPA
   D. 1000 mg of EPA and 500 mg of ALA

3. A 71-year-old woman has a medical history of hypertension, osteoporosis, and anxiety. Her home drugs include hydrochlorothiazide 25 mg daily, alendronate 70 mg every Monday, and calcium 600 mg with vitamin D 400 international units twice daily. Her diet is strictly vegetarian, but she has difficulty finding vegetarian options to increase her w-3FA intake. Which one of the following diet plans would be best to recommend to increase this patient's w-3FA intake?

   A. Increase daily intake of green leafy vegetables and carrots.
   B. Increase consumption of soy-based products such as soymilk and tofu.
   C. Add extra cheese and nuts to salad; use a dressing that contains nut oil.
   D. Add flaxseed to salad or cooked vegetables; increase intake of potatoes instead of bread.

4. A 70-year-old man has a medical history of atrial fibrillation, seizures, benign prostatic hyperplasia, and Parkinson disease. Three months ago, his primary care provider (PCP) initiated vitamin D 2000 international units by mouth daily. Today, new laboratory tests show the patient's vitamin D concentration is unchanged.

Which one of his home drugs is most likely affecting this patient's vitamin D concentration?

   A. Amiodarone
   B. Carbamazepine
   C. Selegiline
   D. Tamsulosin

5. A 62-year-old woman has a medical history of hypothyroidism, rheumatoid arthritis, and lower back pain. She comes for her annual physical examination, and her vitamin D concentration has never been measured. Which one of the following laboratory tests is best to recommend for this patient?

   A. Plasma concentrations of 25(OH)D2 plus 25(OH)D3 (total 25(OH)D)
   B. Plasma 1,25(OH)D
   C. Whole blood total 25(OH)D
   D. Whole blood 1,25(OH)D

6. A 58-year-old woman presents to a Seattle clinic to establish care. Her medical history includes rheumatoid arthritis, microcytic anemia, celiac disease, and hypertension. She reports that she is not currently taking any medications. The patient has no known drug allergies but has lactose intolerance. Which one of the following patient factors most supports an annual check of vitamin D concentrations in this patient?

   A. Age
   B. Residence
   C. Microcytic anemia
   D. Celiac disease

Questions 7–9 pertain to the following case.

F.G., a 68-year-old man (weight 82 kg), has just visited his PCP for his annual checkup. His PCP told him that his vitamin D concentration is low and that he should take vitamin D supplements. He was referred to you for product and dose selection. F.G.'s other medical history includes hypertension, type 2 diabetes, and hypothyroidism. He has taken atorvastatin 20 mg daily for 8 years and metformin 1000 mg daily for 4 years. F.G.'s plasma 25(OH)D concentration from 1 week ago is 12 ng/mL.

7. Using the method developed by van Groningen and colleagues, which one of the following best describes F.G.'s total vitamin D deficit?

   A. 4000 international units
   B. 40,000 international units
   C. 114,000 international units
   D. 140,000 international units

8. Which one of the following is best to recommend to increase F.G.'s 25(OH)D concentration to 20–25 ng/mL within 3 months?

   A. Increase daily vitamin D intake by 400 international units.
   B. Increase daily vitamin D intake by 1200 international units.
   C. Give a weekly supplemental vitamin D dose of 2000 international units.
   D. Give a daily supplemental vitamin D dose of 50,000 international units.

9. Which one of the following best describes the interaction between vitamin D and F.G.'s current medications?

   A. Atorvastatin is a CYP3A4 inducer and may increase his vitamin D requirement.
   B. Metformin decreases vitamin D absorption from the GI tract; high vitamin D doses may be needed to reach his treatment goal.
   C. Vitamin D inhibits the metabolism of atorvastatin and may increase his risk of rhabdomyolysis.
   D. There is no established interaction between vitamin D and his current medications.

Questions 10 and 11 pertain to the following case.

H.T., a 67-year-old man with hypertension, heart failure, hyperlipidemia, and coronary artery disease, presents to the clinic for a post-hospital follow-up after CABG. His current drugs include atorvastatin 80 mg daily; lisinopril 20 mg daily; metoprolol tartrate 25 mg twice daily; aspirin 81 mg daily; a prescription brand of omega-3-acid ethyl esters, 2 g twice daily; vitamin E 400 international units by mouth daily; and an OTC fish oil supplement (360 mg of EPA/240 mg of DHA) daily.

10. Which one of the following is best to recommend to optimize H.F.'s drug regimen?

    A. Discontinue vitamin E and fish oil supplement.
    B. Discontinue prescription w-3FA and vitamin E.
    C. Initiate vitamin D 800 international units daily; discontinue vitamin E and fish oil supplement.
    D. Discontinue fish oil supplement and prescription w-3FA.

11. A few months later, H.T. returns to the clinic with a new diagnosis of atrial fibrillation. According to current data, which one of the following total daily w-3FA dosages would be best to recommend to maximize H.T.'s potential antiarrhythmic benefits?

    A. 1200 mg
    B. 1500 mg
    C. 1800 mg
    D. 2000 mg

12. A 69-year-old man has moderate-severity Alzheimer disease (Mini-Mental State Examination score 17), hypertension, gout, age-related macular degeneration (AMD), and diabetes. The patient presents for a medication review. His home drugs include memantine hydrochloride (Namenda) extended release 28 mg once daily, metformin 1000 mg twice daily, lisinopril 10 mg once daily, allopurinol 200 mg once daily, and PreserVision AREDS2 eye vitamins and minerals 1 capsule twice daily. The patient's caregiver asks you about adding fish oil (w-3FA); she has heard that it will help with his memory loss and slow the damage caused by macular degeneration. Which one of the following is the best response to this caregiver's question about fish oil?

    A. It significantly reduces Alzheimer-related memory loss and slows AMD progression.
    B. It significantly reduces Alzheimer-related memory loss, with no effect on AMD.
    C. It does not reduce Alzheimer-related memory loss or slow AMD progression.
    D. It slows AMD progression but has no effect on Alzheimer-related memory loss.

13. A 60-year-old postmenopausal woman was recently hospitalized after a fall. Her medical history is significant for hypertension, hyperlipidemia, anemia, and bipolar disorder. The patient's home drugs include amlodipine 10 mg daily, atorvastatin 20 mg at night, ferrous sulfate 325 mg twice daily, and divalproex sodium (extended release tablets) 1 g once daily at bedtime. A review of her medical record from the last 8 years shows no vitamin D concentration on file. The PCP asks if vitamin supplementation would reduce this patient's fall risk. Which of the following is the best response to give the PCP regarding this patient?

    A. Assess her nutritional and daily vitamin D intake. No need for vitamin D supplementation if daily dietary vitamin D intake is at least 600 international units and she has no other factors predisposing vitamin D deficiency.
    B. Empirically supplement vitamin D_3 800 international units daily for 1 year.
    C. Empirically supplement vitamin D_3 2000 international units weekly for 12 weeks and then check $25(OH)D_3$ concentration. Repeat the same vitamin D regimen as needed until $25(OH)D_3$ concentration is over 50 ng/mL.
    D. Empirically supplement vitamin D_3 50,000 international units monthly for 1 year.

14. A 78-year-old man has a medical history of atrial fibrillation, hypertension, and benign prostatic hyperplasia. His family history includes prostate cancer (father) and Alzheimer disease (mother). His partner has suggested

the patient take vitamin E supplementation for its purported health benefits. His current home drugs include metoprolol 25 mg twice daily, lisinopril 20 mg daily, warfarin 5 mg at bedtime, and tamsulosin 0.4 mg at bedtime. Which one of the following is best to recommend for this patient?

A. Give vitamin E 400 international units daily for cardiovascular benefit.
B. Give vitamin E 800 international units daily to prevent Alzheimer disease.
C. Give vitamin E 300 international units daily to prevent AMD.
D. Risk of vitamin E supplementation outweigh benefits for this patient.

15. A 71-year-old woman living in San Diego was prescribed vitamin D_3 2000 international units daily 1 year ago for low vitamin D. In addition to taking vitamin D_3, the patient started walking outdoors 3 days/week for 30 minutes about 3 months ago. Her plasma 25(OH)D concentrations over the past year are as follows: 12 months ago, 14 ng/mL; 6 months ago, 18 ng/mL; and today, 25 ng/mL. In addition to encouraging her lifestyle changes, which one of the following is best to recommend to reduce this patient's risk of falls and fractures?

A. Continue vitamin D_3 2000 international units daily.
B. Increase vitamin D_3 to 3000 international units daily.
C. Decrease vitamin D_3 to 800 international units daily.
D. Discontinue vitamin D_3.