

Menopause Management introduces a new column on cardiovascular issues of particular interest to clinicians treating women in midlife and beyond. The column is co-edited by JoAnn E. Manson, MD, DrPH, and Howard N. Hodis, MD, and will appear four times each year.

## Cardiovascular CORNER

### Vitamin D and Cardiovascular Disease

JoAnn E. Manson, MD, DrPH  
Shari S. Bassuk, ScD

Of all the health benefits of vitamin D, perhaps the best known is that it helps to maintain bone strength by promoting the intestinal absorption of calcium and phosphorous, providing protection against osteoporosis and fracture.<sup>1</sup> The main sources of vitamin D are food, supplements and conversion of 7-dehydrocholesterol in the skin by ultraviolet B (UV-B) radiation from sunlight. Although current US dietary guidelines call for intakes of 400 international units (IU) up to age 70, and 600 IU after age 70,<sup>2</sup> many experts are now recommending intakes of at least 800 to 1,000 IU per day.<sup>3</sup> Evidence is mounting that, at higher doses and independently from calcium, vitamin D may play a critical role in preventing certain cancers (such as those of the colon,<sup>4</sup> breast,<sup>5</sup> and prostate),<sup>6,7</sup> and autoimmune disorders (such as multiple sclerosis<sup>8</sup> and rheumatoid arthritis),<sup>9</sup> as well as preventing declines in cognitive<sup>10</sup> and physical function,<sup>11</sup> type 1 and type 2 diabetes,<sup>12,13</sup> and—the focus of this article—cardiovascular disease (CVD).

At least half of American women age 40 and older and one-third of similarly aged men had suboptimal vitamin D status in 1988–1994, the most recent years for which national data are

available (reference ranges for serum concentrations are presented in the Table on page 30).<sup>14</sup> At particular risk are individuals with limited UV-B exposure, blacks (darker pigmented skin converts UV-B rays to vitamin D less efficiently than lighter skin), obese persons (due to decreased bioavailability of this fat-soluble vitamin), and those with liver or kidney disease, or disorders that affect fat absorption (such as Crohn's or celiac disease). Given the aging population and soaring obesity prevalence of recent years,<sup>15,16</sup> vitamin D insufficiency is becoming an increasingly important public health issue.

#### Vitamin D and Cardiovascular Protection: The Evidence

Rapidly accumulating data from epidemiologic studies that track large numbers of participants over long time periods suggest a strong inverse association between vitamin D status and clinical cardiovascular events. Recent analyses from the Framingham Offspring Study, which followed 1,739 participants (mean age, 59) for 5 years, found a significant relationship between low serum 25-hydroxyvitamin D (25[OH]D, the major circulating vitamin D metabolite), and incident CVD (<37.5 v. ≥37.5 nmol/L: relative risk [RR]=1.62; 95% confidence interval [CI] 1.11–2.36).<sup>17</sup> Among 18,225 American men in the Health Professionals Follow-up Study, there was also a strong association between low serum 25(OH)D and incident coronary heart disease (CHD; RR=2.09; 95% CI 1.24–3.54).<sup>18</sup> In the Third National Health and Nutrition Examination Survey, individuals in the lowest quartile of 25(OH)D experienced a significant 26% increase in total mortality, compared to those in the highest quartile.<sup>19</sup> In a 7.7-year follow-up of ~3,300 coronary angiography patients in Germany, those in the bottom two quartiles of 25(OH)D had significantly higher total mortality and cardiovascular mortality than their counterparts in the top quartile.<sup>20</sup> In this cohort, persons with 25(OH)D <25 nmol/L were also

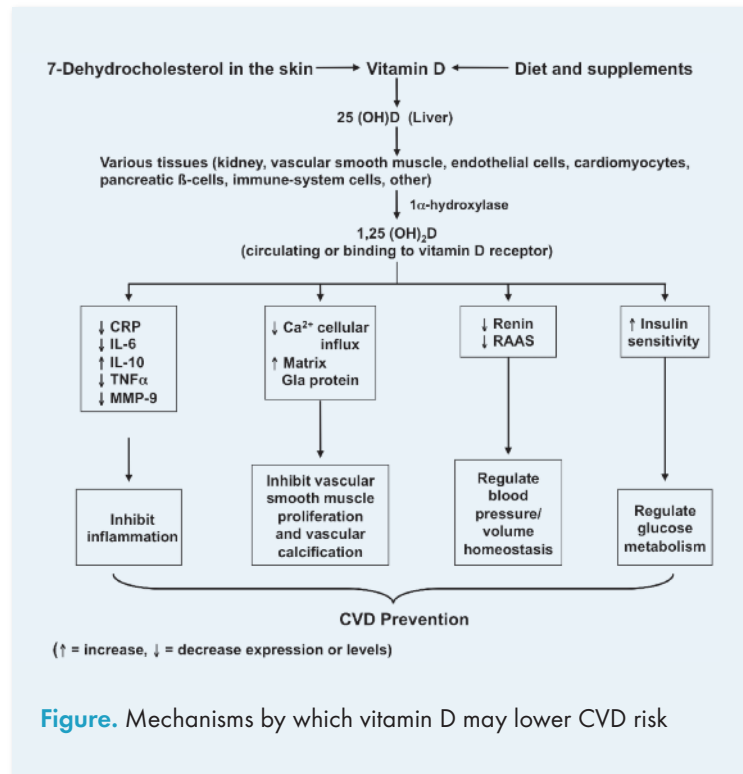
more than twice as likely to die from heart failure and five times as likely to experience sudden cardiac death as those with 25(OH)D  $\geq 75$  nmol/L.<sup>21</sup>

Other evidence also suggests a protective role for vitamin D in relation to CVD. Laboratory studies indicate that many cell types, including vascular smooth muscle cells and endothelial cells, produce 1 $\alpha$ -hydroxylase—which converts 25(OH)D to 1,25-dihydroxyvitamin D (1,25 [OH]<sub>2</sub>D), the natural ligand of the vitamin D receptor (VDR).<sup>13,22-24</sup> Numerous vasculo-protective effects are exerted by 1,25(OH)<sub>2</sub>D (Figure), including inhibition of vascular smooth muscle cell proliferation<sup>25</sup> and vascular calcification.<sup>26</sup> Vitamin D also regulates the renin-angiotensin-aldosterone system,<sup>27,28</sup> controlling volume homeostasis and blood pressure.<sup>29</sup> Vitamin D also may inhibit atherogenesis via anti-inflammatory pathways. Experimental data suggest that vitamin D inhibits pro-inflammatory cytokines, such as interleukin-6 and tumor necrosis factor- $\alpha$ , decreases C-reactive protein and regulates expression of matrix metalloproteinase-9.<sup>30,31</sup> In rodents, administration of vitamin D improves insulin sensitivity and insulin secretion,<sup>32-34</sup> and prevents type 1 diabetes.<sup>35-37</sup> Animal studies also have demonstrated that a lack of vitamin D action leads to hypertension<sup>27</sup> and increased thrombogenicity.<sup>38</sup>

Ecologic studies show higher cardiovascular mortality during the winter and in regions with less average exposure to UV-B radiation from sunlight.<sup>39</sup> Clinically, low levels of circulating 25(OH)D have been found in patients with vascular calcification,<sup>40</sup> myocardial infarction,<sup>41</sup> stroke,<sup>42</sup> heart failure,<sup>43</sup> peripheral arterial disease,<sup>44</sup> greater carotid intima-media thickness,<sup>45</sup> and manifest CVD.<sup>23,46</sup> Overall, available research suggests favorable effects of vitamin D—measured by intake or blood

concentrations—on vascular risk factors (particularly hypertension),<sup>47-50</sup> impaired glucose tolerance or type 2 diabetes,<sup>13,51-53</sup> type 1 diabetes,<sup>12,57</sup> inflammation<sup>31,54-56</sup> and mortality related to kidney disease.<sup>58-60</sup>

A 2007 meta-analysis of data from 18 randomized clinical trials of vitamin D supplementation in 57,311 individuals showed that vitamin D lowered total mortality by 7%, a statistically significant reduction.<sup>61</sup> Participants were followed for an average of 6 years, and daily doses ranged from 300 to 2,000 IU (mean, 528 IU). Most of these trials, however, tested relatively low doses of vitamin D (such as the 400 IU/day assessed in the Women's Health Initiative [WHI]<sup>62</sup>) or were of short duration. In a British trial in which 2,686 adults, ages 65–85, were randomized to receive 100,000 IU of oral vitamin D<sub>3</sub> or placebo (one capsule every 4 months),<sup>63</sup> treatment-associated relative risks for CVD incidence and CVD mortality were 0.90 (95% CI 0.77-1.06) and 0.84 (95% CI 0.65-1.10), respectively—suggestive findings for a small trial. In the much larger WHI, which tested only 400 IU/day, the intervention did not reduce CHD or stroke incidence.<sup>62</sup> In a review



**Figure.** Mechanisms by which vitamin D may lower CVD risk

of studies examining serum 25(OH)D levels in relation to several health outcomes, Bischoff-Ferrari et al<sup>1</sup> found that advantageous 25(OH)D levels began at 75 nmol/L, and optimal levels were between 90 and 100 nmol/L. In most individuals, these levels are not achievable with currently recommended daily vitamin D intakes; for example, in the WHI, 400 IU per day of vitamin D<sub>3</sub> raised median plasma 25(OH)D from 42.3 nmol/L to only 54.1 nmol/L.<sup>64,65</sup> Thus, increasing the recommended intake of vitamin D to at least 1,000 IU—the value needed to bring 25(OH)D concentrations up to 75 nmol/L in at least 50% of American adults—may be warranted.<sup>1</sup>

### Need for a Large Randomized Trial

The purported health benefits of vitamin D are receiving increasing attention in both the medical literature and the popular press. The Canadian Cancer Society recently raised its recommended dose to 1,000 IU per day, and many researchers are urging a similar move in the US.<sup>3</sup> Indeed, sales of individual vitamin D supplements nearly doubled between 2006 and 2007. The growing enthusiasm for vitamin D underscores the urgent need for a timely initiation of a large randomized trial to rigorously test an adequate dose of this vitamin before supplementation and food fortification become so prevalent as to render participant recruitment and hypothesis testing impossible. More defin-

itive data are urgently needed on both benefits and risks of high doses.<sup>66-68</sup> Accordingly, our research group has proposed a large-scale trial of high-dose vitamin D supplementation for the primary prevention of CVD, cancer and other chronic diseases in American adults.

### Clinical Recommendations

Until trial results are available, what should clinicians do when treating midlife women? Given the high prevalence of suboptimal vitamin D in this population, consider testing for low 25(OH)D levels (Table) in all patients, particularly the elderly or those with additional risk factors, such as limited UV-B exposure, obesity or nonwhite race. Advise patients that the sun's UV-B rays trigger vitamin D synthesis in the skin, so sun exposure is an important source of vitamin D. Being in the sun without sunscreen for 10 to 15 minutes twice per week usually provides an adequate dose, except in northern states during winter months.

Many patients may, however, wish to obtain vitamin D from food or supplements rather than sunlight, aiming for 800 to 1,000 IU per day. Natural food sources of vitamin D are limited, and include fatty fish (one serving, 250-360 IU), cod liver oil (1 tablespoon, 1,360 IU) and eggs (1 yolk, 20 IU).<sup>69</sup> Vitamin D is added to milk (1 cup, 100 IU) and some cereals, and is also available in multivitamins, some calcium tablets and osteoporosis medications, and as a stand-alone

**Table.** Serum 25(OH)D Concentrations and Health

Serum 25(OH)D*		Clinical Effects
nmol/L	ng/mL	
<25-62	<10-25	Generally considered inadequate for bone and overall health in healthy individuals
≥75	≥30	Proposed by some as desirable for overall health and disease prevention, although clinical trials of vitamin D supplementation are needed
>500	>200	Considered potentially toxic, leading to hypercalcemia and hyperphosphatemia

\*Serum concentrations of 25(OH)D are given in both nmol/L and ng/mL (2.5 nmol/L = 1 ng/mL)

Adapted from Office of Dietary Supplements. Dietary supplement fact sheet: vitamin D. Available at: <http://ods.od.nih.gov/factsheets/vitamind.asp>. (Accessed September 12, 2008)

supplement. Although the optimal supplement formulation remains controversial,<sup>70</sup> many experts favor supplements containing vitamin D<sub>3</sub> (cholecalciferol) rather than vitamin D<sub>2</sub> (ergocalciferol). Although the current upper “safety limit” for vitamin D intake is 2,000 IU per day,<sup>2</sup> this is a conservative recommendation, and some experts believe there is little risk of toxicity with doses up to 10,000 IU per day.<sup>71</sup> Indeed, for patients with clear vitamin D deficiency (ie, 25[OH]D <25 nmol/L), administration of 50,000 IU once per week for 8 weeks and every 2 weeks thereafter until 25(OH)D levels no longer indicate deficiency is a reasonable strategy. Subsequent maintenance doses of 800–1,000 IU/day should help most patients achieve the recommended levels of 25(OH)D. ■

**JoAnn E. Manson, MD, DrPH, is Chief of Preventive Medicine, Brigham and Women’s Hospital; Professor of Medicine and the Elizabeth Fay Brigham Professor of Women’s Health, Harvard Medical School.**

**Shari S. Bassuk, ScD, is an Epidemiologist, Division of Preventive Medicine, Brigham and Women’s Hospital, Boston, MA.**

*Dr. Manson and Dr. Bassuk report no potential conflicts related to the content of this article.*

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The complete list of references for this column can be accessed at [www.menopausegmt.com/issues/18-01/references.pdf](http://www.menopausegmt.com/issues/18-01/references.pdf)

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(continued from page 19)

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