failure study used a Gallager classification of BF based on age, sex, and race and classified patients as underweight, normal, overweight, and obese.[12] In preliminary data from our CHD population (n=581) using this Gallager classification, we have found the highest mortality in the underweight and lowest mortality in the overweight, who also had significantly lower mortality than the "normal BF" group during a 3-year follow-up (A.D.S, C.J.L, and R.V.M., unpublished observations, May 1, 2010). The obese group had intermediate mortality, which was significantly lower than the underweight and trended lower than the normal BF group but did not reach statistical significance.

Therefore, current research suggests that the obesity cutoff points of BF are in the 23%-25% range in men and 33%-35% range in women (or 30% in women from the NIH,[2] as Dr Snitker stated in his letter), which are associated with increased CV risk in primary prevention and reduced risk in patients with established CV disease (obesity paradox). However, we agree that additional research is needed to clearly define optimal BF in patients of both sexes and of various ages, races, and ethnic groups, as well as disease states. Clearly, major organizations such as the WHO, NIH, and major obesity societies should attempt to establish such cutoff points for BF, as was done years ago with BMI.

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Does Vitamin D Have a Role in Reducing the Risk of Peripheral Artery Disease?

To the Editor: In their otherwise excellent review, Olin and Sealove[1] did not consider the role of vitamin D status in the development of peripheral artery disease (PAD).

Vitamin D deficiency is highly prevalent in the United States and worldwide. In particular, a recent study reported that vitamin D levels were independently associated with PAD among 4839 participants of the National Health and Nutrition Examination Survey 2001 to 2004.[2] For each decrease of 10 ng/mL in the 25-hydroxyvitamin D level, the multivariable-adjusted prevalence ratio of PAD was 1.35 (95% confidence interval, 1.15-1.59).[2] Furthermore, racial differences in vitamin D concentrations could explain nearly one-third of the excess risk of PAD in black adults, above and beyond differences in established and novel risk factors for cardiovascular disease.[3]

Several mechanisms may explain the association of vitamin D deficiency with PAD. Low vitamin D status is associated with obesity, diabetes, and hypertension, all of which increase the risk of PAD. However, the inverse relationship between vitamin D status and PAD remained after adjustment for these risk factors, suggesting additional explanatory mechanisms.[3]

Vitamin D receptors have a broad distribution that includes vascular smooth cells, macrophages, and lymphocytes. Directly or indirectly, 1,25-dihydroxyvitamin D (the active form of vitamin D) regulates the expression of a number of proteins relevant to the arterial wall, such as vascular endothelial growth factor, matrix metalloproteinase type 9, myosin, elastin, and type I collagen.[4]

PAD manifestations, including claudication, rest pain, and tissue loss, are not related to arterial hemodynamics alone. Indeed, increasing evidence suggests that a myopathy is present, contributes to, and (to a certain extent) determines the pathogenesis of PAD. A state of repetitive cycles of exercise-induced ischemia followed by reperfusion at rest in patients with PAD may mediate a large number of structural and metabolic changes in the muscle, resulting in reduced strength and function. In this setting, vitamin D may exert a fundamental role. Vitamin D status is significantly associated with muscle strength, and a lack of vitamin D can cause myopathy, which tends to be more marked in the proximal muscles. Vitamin D is reported to mediate protein synthesis and cellular adenosine triphosphate accumulation, increase troponin C, and increase actin and sarcoplasmic protein expression in striated muscles.[5]

Thus, vitamin D may have a fundamental role in reducing the risk of PAD, and studies of vitamin D supplementation for patients with PAD are urgently needed. In the meantime, adequate outdoor activity and sun exposure, along with vitamin D supplementation (to reach serum 25-hydroxyvitamin D levels of at least 30 ng/mL), should be considered for both the prevention and the treatment of PAD.

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In reply: Drs Mascitelli, Goldstein, and Grant highlight several important points regarding the potential role of vitamin D in the pathogenesis and treatment of peripheral artery disease (PAD).

Large observational studies have thus far linked low levels of vitamin D to various cardiovascular diseases.[1-3] A case-control study of 18,225 men showed that those with low levels of plasma 25-hydroxyvitamin D were at increased risk of myocardial infarction compared with those with normal levels. This risk of myocardial infarction increased as the level of vitamin D decreased, even after adjusting for traditional cardiovascular risk factors.[1] Pilz et al[4] followed up 3299 patients for 7.7 years and found that vitamin D deficiency was associated with heart failure and sudden cardiac death. Furthermore, vitamin D deficiency has been linked to hypertension,[5] stroke,[6] PAD,[7] and other cardiometabolic factors.[8] Low 25-hydroxyvitamin D levels have been associated with an increased all-cause and cardiovascular mortality in older community-dwelling adults.[9]

Melamed et al[7] analyzed data from a national survey (National Health and Nutrition Examination Survey 2001 to 2004) that obtained vitamin D levels in 4839 adults and showed that those with vitamin D levels in the highest quartile had a significantly lower prevalence of PAD than those with vitamin D levels in the lowest quartile (3.7% vs 8.1%). After adjustment for confounding variables, this remained statistically significant.

Does vitamin D have an important pathogenetic role in cardiovascular diseases, or is the level of vitamin D merely a consequence of the disease? For example, individuals with heart failure, stroke, or PAD have a poor quality of life and markedly reduced functionality, often limiting outdoor activities that may result in low vitamin D levels. Furthermore, there is an inverse relationship between low vitamin D levels and activation of the renin-angiotensin-aldosterone cascade, thus elevating blood pressure and potentially increasing cardiovascular events.[3] Is vitamin D the cause of these perturbations in cardiovascular health, or are these associations noncausal and confounded by other factors?

The letter from Mascitelli et al highlights the potential role of novel risk factors for PAD and should provoke more insightful research in the future. Although the information provided by recent observational studies clearly shows that low vitamin D levels are associated with adverse cardiovascular outcomes, the small number of randomized trials published to date does not confirm these observations.[10,11] In a study of 2686 men and women aged 65 to 85 years, participants were randomized to receive 100,000 IU oral vitamin D_3 (cholecalciferol) supplementation or matching placebo every 4 months for 5 years.[10] Even though fractures were reduced in men and women, there was no difference in all-cause mortality between the group that received vitamin D and the group that received placebo. In the Women's Health Initiative, 36,282 postmenopausal women aged 50 to