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

79 years were randomized to receive calcium (1000 mg/d) and vitamin D_3 (400 IU/d) or placebo.[11] During 7 years of follow-up, there was no difference in the rate of myocardial infarction, coronary heart disease, death, or stroke in the calcium/vitamin D_3 group compared with the group receiving placebo.

Therefore, we do not support the use of vitamin D supplementation for either the prevention or the treatment of PAD or other cardiovascular diseases until large-scale randomized, controlled studies demonstrate efficacy.

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Changes in the Visiting Medical Student Clerkship Program at Mayo Clinic

To the Editor: Implementation of a policy described by Mueller et al[1] for the Mayo Clinic Visiting Medical Student Clerkship Program appears to have had unanticipated consequences. New requirements that international visiting medical students pass licensing and language examinations were expected to increase the fraction of visiting students who apply to Mayo residency positions, on the basis of the rationale that students who passed would likely pursue US residencies. As predicted, the policy change precipitated a decline in the international applicant pool to the visiting student program that was accompanied by a similar decrease (from 82 to 34 during the 3-year observation period) in the number of international participants who applied for Mayo residency positions. However, the fraction of participating students applying for Mayo residency did not increase as expected but nominally decreased (82/464 [18%] before to 34/205 [17%] after implementation). The authors correctly note that, among participants in the visiting clerkship, international students who apply for Mayo residency program positions are just as likely as US students to be appointed to Mayo residency program positions, but they neglect the fact that before implementation, international students were more likely to be appointed than US students (39% vs 31%). Overall, these data suggest that this policy substantially decreased the international applicant pool without increasing the fraction of seriously interested students or the quality of applicants, as reflected by their lower frequency of appointment to residency. To the extent that such changes are causally related to the policy change, it is interesting to speculate why the consequences were opposite of those predicted. Could it be that a policy that discouraged applications and decreased participant number affected the culture of the program to the extent that these students concluded that the environment was not optimal for their educational needs?

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In reply: We appreciate Dr Bubb's feedback. It is true that we expected an increase in the percentage of our international visiting medical students (VMSs) who apply for residency positions at our institution as a result of our VMS program's new requirements that international medical students successfully complete the US Medical Licensing Examination (USMLE) Step 1 and Test of English as a Foreign Language (TOEFL) before being considered for our VMS program. Also, as we stated in the article, a corollary reason for the new requirements was our desire to reduce "the number of elective and clerkship slots taken by VMSs who did not intend to apply for [Mayo] residency program positions" in order to make these slots available to VMSs who did.[1] Like other VMS programs,[2] residency recruitment is a major objective of ours.