Use of Body Fatness Cutoff Points

To the Editor: In the July 2010 editorial of *Mayo Clinic Proceedings*, although correctly making the argument that "BMI [body mass index; calculated as weight in kilograms divided by height in meters squared] does not reflect true body fatness," Lavie et al[1] refer to the "National Institutes of Health [NIH] criterion standards" for percent body fat (BF) as greater than 25% in men and greater than 35% in women. The reference provided for this statement is a pamphlet[2] for the general public, issued by the Weight Information Network (WIN), an NIH initiative to provide "science-based information on weight control, obesity, physical activity, and related nutritional issues." Although I did not find any mention of body fat (BF) cutoff points in that publication, an earlier version[3] did state that "Most health care providers agree that men with more than 25 percent body fat and women with more than 30 percent body fat are considered obese." Note the discrepancy in cutoff for women between the editorial and the pamphlet.

The discrepancy in cutoff for women aside, assuming that the earlier version is the intended citation, it is a bit of a stretch to elevate an unreferenced statement from a WIN pamphlet to an "NIH criterion standard." Moreover, as one of the authors of the editorial recently stated, "Unfortunately, neither the World Health Organization nor any major scientific society involved in the study of obesity has defined a normal value for BF%."[4]

Regarding BMI, the World Health Organization and NIH cutoff point of 25 was chosen because, in most epidemiological studies, mortality in both men and women begins to increase above this value,[5] ie, there is evidence of a threshold effect. By contrast, there is little if any evidence to support that cutoff points of 25% in men and 35% (or 30%) in women are the optimal values for BF-based risk stratification. In the absence of a substantial body of literature characterizing the sex-specific relation between a continuum of BF percent values and morbidity and mortality, as well as potential moderating effects of age and race, the choice of BF percent cutoff points in research or clinical practice remains a highly subjective decision.

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In reply: We appreciate Dr Snitker's interest in our recent editorial[1] and his insightful comments regarding body fat (BF) and obesity. Additionally, we are aware of his clinical and research efforts in the area of obesity in children at the University of Maryland School of Medicine. Dr Snitker is correct that currently there is no definitive cutoff for percent BF in defining overweightness or obesity in men or women. In our efforts to simplify the message for readers, we referenced an easily accessible National Institutes of Health (NIH) publication[2] that we thought was representative. Generally, we have referenced a major source from the World Health Organization (WHO)[3] as opposed to this simple NIH Web site in our research publications from Ochsner Clinic[4] and Mayo Clinic.[5,6] However, we agree with Snitker that, regardless of the reference, there is no criterion standard for defining overweightness or obesity by the BF method.

We previously demonstrated in a cross-sectional design of 13,601 participants (age, 20-80 years; 48% men) from the Third National Health and Nutrition Examination Survey (NHANES III)[6] that the mean ± SD body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) in men was 26.6±4.6 and the mean ± SD percent BF was 24.8%±6.0%. Corresponding values in women were 27.6±6.4 and 36.7%±7.4%, respectively. In 6171 participants in NHANES III who had a BMI in the reference range (18.5-24.9), the highest tertile of BF was greater than 23.1% in men and greater than 33.3% in women (labeled as *normal weight obesity*).[7] In this cohort with normal weight obesity defined by elevated BF, the prevalence of metabolic syndrome was 4 times higher than in those with low BF, and these individuals had a higher prevalence of dyslipidemia (men and women) and of hypertension (men) and a 2.2-fold increased risk of cardiovascular (CV) mortality (women) compared with those with low BF. These data suggest that this level of BF is associated with adverse CV risk and prognosis in primary prevention.

In secondary prevention, having increased BF (>25% in men and >35% in women) appears to be associated with a protective effect in patients with coronary heart disease (CHD).[4] In fact, in patients with CHD[4,8] and in those with heart failure,[9,10] a higher BF was an independent predictor of event-free survival because of the *obesity paradox*, which we discussed in our editorial.[1] Oreopoulos et al[11] in their heart

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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1. Lavie CJ, Milani RV, Ventura HO, Romero-Corral A. Body composition and heart failure prevalence and prognosis: getting to the fat of the matter in the "obesity paradox." *Mayo Clin Proc*. 2010;85(7):605-608.

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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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Dr Grant receives or has received funding from the UV Foundation (McLean, VA), the Sunlight Research Forum (Veldhoven), Bio-Tech-Pharmacal (Fayetteville, AR), the Vitamin D Council (San Luis Obispo, CA), and the Danish Sunbed Federation.

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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.

Indeed, before the new requirements, we observed that only a minority of our international VMSs applied for a Mayo residency position (82/464 [18%]). Dr Bubb states that, after the new requirements were implemented, the percentage of international VMSs who applied for Mayo Clinic residency positions "nominally decreased" (34/205 [17%]). However, this change was not statistically significant (*P*=.80). Dr Bubb further states that we "neglect the fact that before implementation, international students were more likely to be appointed than US students (39% vs 31%)." However, this change also was not statistically significant (*P*=.16).

Because of the new requirements, we expected that the absolute numbers of international VMSs applying for and participating in our VMS program as well as applying for, and being appointed to, our residency programs would correspondingly decrease. We agree that our new requirements discourage international medical students who have not taken the USMLE Step 1 and TOEFL from applying to our VMS program. As a result, it is possible that some international medical students who would be competitive for our residency programs will not visit our campus or participate in our VMS program.

Notably, during 2009, 75 international VMSs participated in our VMS program, of which 32 (43%) applied for Mayo residency program positions and 11 (34%) were appointed to Mayo residency program positions. We are encouraged by these statistics that argue against Dr Bubb's concern that the new requirements adversely affect the culture of our VMS program and that international VMSs "concluded that the environment was not optimal for their educational needs."

Nevertheless, the effects of the USMLE Step 1 and TOEFL requirements deserve ongoing monitoring. Overall, we remain steadfast in our desire to attract the best and brightest international VMSs to participate in the Mayo VMS Program and recruit these students to our residency programs.

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1. Mueller PS, McConahey LL, Orvidas LJ, Jenkins SM, Kasten MJ. The Visiting Medical Student Clerkship Program at Mayo Clinic. *Mayo Clin Proc* 2010;85(8):723-727.

2. Mueller PS, McConahey LL, Orvidas LJ, et al. Visiting medical student elective and clerkship programs: a survey of US and Puerto Rico allopathic medical schools. *BMC Med Educ.* 2010 Jun 7;10:41.

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CORRECTIONS

Incorrect axis labeling in figure in the print (but not the electronic) version: In the print version of the Brief Report entitled "The Utility of Cardiopulmonary Exercise Testing to Detect and Track Early-Stage Ischemic Heart Disease," which was published in the October 2010 issue of *Mayo Clinic Proceedings* (*Mayo Clin Proc*. 2010;85(10):928-932), the y axis in the middle panel of the figure is incorrect. It should have read: **Oxygen pulse (mL/beat)**. The version on our Web site is correct and complete.

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Typographical error in figure: In the article entitled "Hemophilia: A Practical Approach to Genetic Testing," published in the November 2005 issue of *Mayo Clinic Proceedings* (*Mayo Clin Proc*. 2005;80(11):1485-1499), Figure 5, on page 1491, contains a typographical error. On the right side of Figure 5, under the heading "Mother is the carrier," the first female character is labeled "XY." It should have been labeled "**XX**."

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