Is a Simple Biomarker for Peripheral Arterial Disease on the Horizon?

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Atherosclerosis is the leading cause of morbidity and mortality in the Western world, and one of the major clinical complications of atherosclerosis is the impairment of blood flow to the lower extremity, which is commonly referred to as peripheral arterial disease (PAD). Although long underrecognized and underdiagnosed in the medical community, the prevalence of PAD in the United States alone is estimated to be 8 to 12 million, and PAD is also quite common in Europe and Asia.\(^1\)\(^-\)\(^4\) In fact, the prevalence of atherosclerosis primarily, or solely, affecting the lower extremity, cerebral vascular system, renal arteries, and visceral organs is now equal to or greater than the number of individuals afflicted with ischemic heart disease.\(^5\)\(^,\)\(^6\) The reasons that PAD of the lower extremity has been underdiagnosed are likely multifactorial. Even today, these explanations include but are certainly not limited to (1) an overlap of symptoms of what is perceived to be “normal” aging, (2) a sense that treatment options are limited and that the disease is very stable over time, (3) the attributing of the symptoms of true pain when present to other disease processes such as neuropathy, and (4) the need for busy physicians and healthcare providers to perform additional measures as part of a physical examination in an environment of decreasing time available to each patient. The facts are very clear that PAD imparts an increase in the risk of cardiovascular death and stroke,\(^8\) that treatment options for PAD are expanding,\(^7\)\(^,\)\(^8\) and that even in minimally symptomatic patients over time, evidence points to a decrease in functional capacity.\(^9\) Therefore, a pressing need exists for a simple, readily assessable, reliable biomarker to test for PAD.

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To that end, the article in this issue of Circulation by Wilson et al\(^{10}\) from the laboratory of Dr John Cooke at Stanford University, along with colleagues at Mount Sinai Medical Center and industry, take a major step toward the development of the first true biomarker for PAD. This study used a novel, high-throughput proteonomic technology and combined it with a series of logical, targeted, human investigation. The results suggest that \(\beta2\)-microglobulin may ultimately serve as this desperately needed test. The concept of the study was based on the knowledge that patients with PAD would have recurrent bouts of lower-extremity ischemia and reperfusion injury. The authors hypothesize that a protein could be released from the ischemic muscle and would be a “unique” protein present in the plasma in this patient population. They performed 3 sequential studies. First, they performed a discovery study in which they examined patients with known PAD and compared blood samples to a group known to be free of PAD. Using a novel approach, they identified one of several targets and proceeded to investigate one of these proteins in detail. They then did a second study (ie, an initial validation). In this study, subjects with and without PAD were matched by age and gender. Finally, they did a third study (ie, a second validation) of 237 patients undergoing coronary angiography in which they sought to confirm that \(\beta2\)-microglobulin levels would be different across subjects with no coronary artery disease or PAD, coronary artery disease alone, or coronary artery disease plus PAD. Additional data were provided to suggest that higher levels of \(\beta2\)-microglobulin were associated with a lower ankle-brachial pressure index (ABI) and lower walking times. In the Discussion, the authors appropriately concluded that their finding “provides encouragement to pursue studies to determine the utility of \(\beta2\)m [\(\beta2\)-microglobulin] as a biomarker for PAD.”

The study by Wilson et al\(^{10}\) has limitations, and many additional questions will eventually need to be addressed. First and foremost, it is far different to detect a statistically significant difference in mean values between patient groups than it is to use a single data point on an individual to make an assessment of the presence or absence of PAD. Even in the second of the study groups, the difference in plasma measures of \(\beta2\)-microglobulin between subjects with PAD and without PAD was 2.17±0.63 versus 1.72±0.43, respectively. The relative differences when measured in serum were similar to but not better than those in plasma. Although the difference in the mean values between groups was statistically significant, it is quite clear that a great deal of the values obtained would place a person in either the PAD or the no-PAD group. It would be interesting to know the kinetics of the release of \(\beta2\)-microglobulin and how it might be incorporated to eventually improve the ability of the blood test to answer the all-important question of whether PAD is present. Second, no data were provided on the day-to-day variability of the blood measure within a given patient. Third, although the ABI is the “standard” used to diagnose the presence or absence of PAD, it is quite clear that a nontrivial fraction of subjects with
symptoms of advanced claudication (leg pain on walking that is relieved with rest) will have a normal resting ABI that decreases with exercise by \( > 20\% \). In the study by Wilson et al., such subjects, if present, could well have been classified as not having PAD. Fourth, although the results show an association/correlation of higher \( \beta_2 \)-microglobulin with lower ABI, much of this difference is driven by the group differences between PAD and no PAD, not by differences across the PAD group. It is not clear whether the status of critical limb ischemia, the other major manifestation of lower-extremity PAD, was assessed. Although we would assume that patients with critical limb ischemia would have high \( \beta_2 \)-microglobulin, this assumption needs to be tested. Finally, a real value of a simple blood test for PAD will ultimately lie in its ability to differentiate the functional impairment of arthritis from that of PAD, distinguish pain caused by diabetic neuropathy from ischémic rest leg pain in patients with diabetes mellitus, and perhaps even differentiate ischemic from nonischemic ulcers, refinements that were beyond the scope of the report by Wilson et al. Thus, like many important studies, the finding from this study may be just the beginning.

Following data obtained by Hirsch et al. in the seminal PAD Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) study, a number of groups and societies have been strong advocates for an increase in PAD awareness. These include but are not limited to the Society for Vascular Medicine and Biology, the Society for Vascular Surgery, the Vascular Disease Foundation, the National Institutes of Health (an emerging supporter of PAD research), the American College of Cardiology, and the American Heart Association, to name a few. The American Diabetes Association, in particular, is to be commended for its recommendation years ago that the ABI be performed in all diabetic patients \( > 50 \) years of age because of the high prevalence of PAD in that patient population. The results of the study by Wilson et al. when advanced to a simple and commercially available test are likely to provide a valuable aide to improving the identification and diagnosis of PAD.

Could there be any real negatives if a simple biomarker for PAD is found? The unfortunate reality is that a readily accessible laboratory blood test is likely to be used by many as a replacement for, not an accessory to, the physical examination. PAD awareness must extend beyond the lower extremity, and the importance of the physical examination for PAD in other beds needs to be on the minds of all cardiologists, internists, and family and general practitioners, as well as extenders involved in treating patients at risk for PAD. If and when this simple blood test becomes readily available, what will be the consequences of a false-negative test in subjects at risk for PAD, many who may truly warrant aggressive risk-factor modification? Despite these potential concerns, clear examples are available of biomarkers (eg, troponin and brain natriuretic peptide) that can be an invaluable adjuvant to the physical examination and can provide added value for diagnosis and/or risk stratification.

It is quite clear that in modern high-technology studies, in this case a proteomic study, the true value lies in the appropriately targeted clinical question and the clinical study design. The hope has been that these types of studies would help to identify novel mechanisms involved in the pathogenesis of, or that result from, PAD. Although \( \beta_2 \)-microglobulin has been implicated in inflammation and thus could be implicated in the pathogenesis of PAD, this protein certainly would not have been chosen as a candidate, or target, before the results of this study. This raises the possibility that the same approach can be used to identify markers for other forms of vascular disease. Whatever the final outcome, the article by Wilson et al. offers a major step forward for the field of PAD.

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References


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