
Low Incidence of Diabetes Mellitus in Coronary Microvascular Dysfunction
An Intriguing Association

We immensely enjoyed reading the recently published article by Sara et al. (1) in JACC: Cardiovascular Interventions. Their endeavors to elucidate the spectrum of coronary microvascular abnormalities in patients with chest pain and nonobstructive coronary artery disease are commendable (1). In summary, they found that microvascular dysfunction occurred in two-thirds of these patients, interestingly these were poorly associated with the conventional risk factors. This study echoes the results found by previous studies demonstrating the role of microvascular dysfunction in this patient population.

In their findings, we paid special attention to the low incidence of diabetes mellitus reported among all the study groups (7% to 12%). We would like to switch gears and bring the readers' attention to a curious similarity between the population in this study and patients with Takotsubo cardiomyopathy (TC). A recent meta-analysis showed that the prevalence of diabetes mellitus in patients with TC was indeed low (2). This fact has been reproduced in subsequent smaller studies. It has been suggested that the blunted catecholamine secretions (autonomic neuropathy) may perhaps be protective against the development of TC (3,4). The success of sympathetic blockade for TC in animal model studies has further supported this hypothesis. It has long been accepted that diabetes mellitus is one of the strong risk factors for coronary microcirculatory disease (5), and the low incidence of diabetes in this study group was peculiar. It almost leads us to wonder whether there might be an overlap of some of these patients with TC, especially with atypical or chronic recurrent forms of TC. That potentially would explain the low incidence of diabetes, and the presence of microcirculatory dysfunction is consistent with the described pathophysiology of TC. Also, this thought-provoking correlation is compelling to suggest that female patients with microvascular dysfunction perhaps may have a unique nontraditional etiological background, for example, they seem less likely to be affected by diabetes mellitus (because both the current study population and previous TC studies demonstrated a female predominance (1,2).

Although the authors were meticulous in their efforts, another aspect that caught our attention was the analysis of cardiac studies, specifically echocardiography and stress testing. The study duration was 20 years, and it is apparent that imaging parameters may vary considerably over time depending on the disease progression or risk-factor modification. It is not clear from their article at what point imaging was performed, and this might have some impact on the analysis of outcomes. The addition of that information could allow a more robust interpretation of these data. Future prospective studies are needed for a better understanding of the role of autonomic influences and clinical markers regarding their association with microvascular dysfunction.

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We recently showed that coronary microvascular dysfunction (CMD) in patients with nonobstructive coronary artery disease (CAD) correlates poorly with so-called traditional cardiovascular risk factors (1). Other studies have similarly shown that traditional risk factors are poor predictors of CMD. In their letter, Dr. Chhabra and colleagues highlight the potential overlap between patients with CMD and those with Takotsubo cardiomyopathy, which is underscored by our observation that coronary endothelial dysfunction is prevalent in patients with Takotsubo, and that it is predictive of recurrent events (2). Atypical risk profiles are implicated in both CMD and Takotsubo cardiomyopathy, there may be an opportunity to learn more about one pathological entity from the other and vice versa. We recently showed that hypothyroidism is independently associated with microvascular endothelial dysfunction in women with nonobstructive CAD (3), and so it could potentially be a common novel risk factor for Takotsubo. Similarly, if sympathetic blockade has been shown to be protective against Takotsubo, this may be mediated through its effects on coronary microvascular function.

The finding of a low prevalence of diabetes mellitus (DM) among patients with CMD was a particularly noteworthy finding in our study. The association between microvascular disease and DM is well established in the nervous system, eyes, and kidneys; however, this relationship has been demonstrated less consistently in the myocardium. Although some reports have shown that chronic hyperglycemia is associated with impaired endothelial-dependent and -independent microvascular function, others have shown that hyperinsulinemia or insulin resistance is not associated with CMD once confounders are accounted for (4). Further studies have suggested that improving insulin sensitivity improves endothelial function and decreases myocardial ischemia in patients with nonobstructive CAD, yet we recently demonstrated that good glycemic control among diabetic patients is not associated with better coronary microvascular function (5). The use of variable, albeit established, indexes to define DM and good/poor glycemic control could account for some of the discrepant findings across studies. Nevertheless, one would expect a more compelling correlation between DM and CMD not only because of the long-established relationships between microvascular disease and DM in other organs, but also because endothelial dysfunction is a systemic disorder affecting multiple vascular beds and can be regarded as an integrated index of overall cardiovascular risk burden. Given that optimal glycemic control does not always mitigate cardiovascular events, it may be that alternative indexes of diabetic control that better reflect cardiovascular risk need to be developed. CMD occurs early in the development of atherosclerotic CAD and is independently linked to cardiovascular events, and so these alternative indexes of diabetic control could be developed in parallel to testing strategies for CMD. In this way, CMD could provide an alternative functional perspective to the management of DM by paving the way for novel therapeutic targets that are more useful for the prevention of cardiovascular events in diabetic patients.

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