Serum Homocysteine and Endothelial Dysfunction in Circulatory Disorders in Women

To the Editor:

We read with interest the recent article by Zylberstein and colleagues dealing with the relationship between serum total homocysteine (tHcy) level and morbidity and mortality from coronary heart disease in women. The results of their study with the Cox regression analyses demonstrated that for the fifth tHcy quintile (mean value 16.75 μmol/L), relative risk was 1.86 for acute myocardial infarction (AMI) and 5.14 for death due to AMI. In addition, the authors indicated that age-standardized Kaplan-Meier plots for the fifth tHcy quintile versus others showed significant differences both for AMI and for death attributable to AMI. The authors proposed that homocysteine in middle-aged women is an independent risk factor for AMI, and in particular mortality due to AMI.

There is evidence that homocysteine might disturb the bioavailability of nitric oxide (NO), which would, at least in part, contribute to the pathophysiology of circulatory disorders in subjects with hyperhomocysteinemia. Stühlinger et al examined the relationship among homocysteine, NO, and endothelial function in patients with peripheral arterial disease and demonstrated that experimentally induced hyperhomocysteinemia increased plasma asymmetric dimethylarginine (ADMA; an endogenous NO synthase inhibitor), an effect that was temporally related to a decline in endothelial vasodilator function. This might be an important mechanism for the endothelial dysfunction that occurs in subjects with hyperhomocysteinemia. In a study presented earlier, we demonstrated that estrogen-induced improvement of membrane fluidity (a reciprocal value of membrane microviscosity) of erythrocytes was counteracted by ADMA, suggesting that ADMA might actively participate in the regulation of rheologic behavior of cell membranes and microcirculation in postmenopausal women. In this context, we speculate that the decreased bioavailability of NO due to ADMA might partially explain the increased risk for coronary heart disease in women with hyperhomocysteinemia. Because the authors described that tHcy and other biochemical parameters were analyzed from frozen serum samples of the subjects, we would like to know whether plasma NO metabolite and ADMA levels might be linked to tHcy in the present study of Dr Zylberstein and colleagues. It would be important to assess more precisely the relationships between homocysteine and endothelial function and their contribution to the pathophysiology of circulatory disorders in women.

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To the Editor:

With great interest we read the article by Zylberstein and coworkers, in which the authors conclude that homocysteine is an independent risk factor for myocardial infarction, in particular fatal myocardial infarction in middle-aged women. Follow-up investigations, especially long-term follow-up studies, are certainly better suited to assess the role of homocysteine in the pathogenesis of disease. However, the question of whether homocysteine itself is responsible for disease progression in vascular diseases is not yet answered; a causality between moderate hyperhomocysteinemia and atherogenesis remains to be demonstrated. This point is also discussed by the authors, whereas the point that homocysteine is an independent risk factor for myocardial infarction and vascular disease requires some comment.

In studies focusing on patients with coronary heart disease, neurodegenerative diseases, and autoimmune disease, we found that moderate hyperhomocysteinemia closely correlates with increased cellular immune activation. Moreover, in vitro production of homocysteine was found in peripheral blood mononuclear cells on stimulation with mitogens. These results point to a role of immune activation in the development of moderate hyperhomocysteinemia. Inflammation and cellular immune activation are crucially involved in atherosclerosis. A link between the pathogenesis of moderate hyperhomocysteinemia and the immunopathogenesis of atherosclerosis is very likely and would take together both concepts. Both events could relate to the overwhelming production of reactive oxygen species by activated macrophages within cellular immune activation. Antioxidants are depleted and oxidative stress develops. Decreased concentrations of antioxidants and vitamins are often encountered in patients suffering from chronic disease, and B-vitamins, folic acid, and vitamin B12 are known to be prone to oxidation. Thus, hyperhomocysteinemia may develop secondary to immune activation.

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Response

We would like to thank Drs Tsuda and Nishio as well as Dr Schroecksnadel et al for their interest in the recently published results from the Population Study of Women in Göteborg. We agree fully with Schroecksnadel and co-workers that even a
statistically independent association between homocysteine and cardiovascular endpoints in an observational study is not proof of a direct causal association. Given the complex metabolic mechanisms involving homocysteine, it is more likely that this metabolite represents an intermediary factor in the causal web eventually resulting in overt disease. For this reason, we are also studying potential mechanisms including a possible mediating role of asymmetric dimethylarginine (ADMA), as suggested by Drs Tsuda and Nishio in their letter. Specifically, blood samples collected at the baseline of our population study are currently being analyzed with respect to ADMA levels, and we hope that these data will provide some insight into the excess myocardial infarction incidence and mortality among women with elevated homocysteine. In this context, plasma homocysteine levels have been observed to be a statistical predictor of other end points, including dementia. Moreover, elevated homocysteine has been observed to be associated with high ADMA and low levels of nitric oxide in patients with Alzheimer’s dementia. Epidemiological studies such as ours represent one level of evidence in disentangling causal relationships. The observed associations have to be complemented by other types of research aiming at exposure variables and genetic polymorphisms affecting the homocysteine levels and potential molecular biological mechanisms.


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