The Homocysteine Paradox

Roman N. Rodionov, Steven R. Lentz

There is little doubt that elevation of plasma total homocysteine is associated with increased cardiovascular risk. Over the past 2 decades, many large prospective studies have established that hyperhomocysteinemia predicts for an increased relative risk of coronary events, stroke, venous thromboembolism, and death.\(^1,2\) Hyperhomocysteinemia also has been shown to produce abnormalities of vascular structure and function in animal models.\(^3\) Paradoxically, however, several intervention trials have failed to demonstrate any clinical benefit from homocysteine-lowering therapy.\(^4\)\(–\)\(^8\)

What is the explanation for this paradox?

See accompanying article on page 1158

One possibility is that hyperhomocysteinemia is a clinically important risk factor only when plasma total homocysteine is elevated to extremely high levels. The hypothesis that homocysteine is a cardiovascular risk factor first arose from clinical and pathological observations in children and young adults with hereditary homocystinuria.\(^9\) If untreated, these individuals develop severe hyperhomocysteinemia, with plasma total homocysteine levels greater than 100 µmol/L, and they have a high risk of developing pathologic vascular lesions and thromboembolic events at a young age.\(^10\) When placed on homocysteine-lowering therapy (high doses of vitamin B6, vitamin B12, folic acid, or betaine, along with dietary methionine restriction), their risk of adverse vascular events decreases markedly.\(^11\) Improvement in vascular outcome occurs despite a moderate level of residual hyperhomocysteinemia.

In contrast to the clear clinical benefit of homocysteine-lowering therapy in severe hyperhomocysteinemia, its potential role in mild hyperhomocysteinemia remains unproven. All of the recent intervention trials of homocysteine-lowering therapy have been performed in subjects with relatively mild hyperhomocysteinemia (plasma total homocysteine levels between 10 and 30 µmol/L). The negative results of these trials may indicate that mild hyperhomocysteinemia is not a causative risk factor or that the statistical power of the trials was insufficient to exclude a small clinical benefit. It is also possible that homocysteine-lowering therapy with combinations of B vitamins produces some adverse vascular effect that masks the benefit of lowered homocysteine.\(^6\)

Larger trials with longer durations of homocysteine-lowering therapy may be necessary to completely settle this issue, although some closure may come from a planned collaborative meta-analysis.\(^12\) Trials of population interventions to lower homocysteine as a primary prevention strategy also have been proposed.\(^13,14\)

As we await more clinical trial data, the possibility must be considered that mild hyperhomocysteinemia is associated with increased vascular risk not because it is directly involved in the pathogenesis of vascular disease but because it is a marker of another deleterious process. An obvious candidate for this other process is chronic kidney disease. Renal dysfunction is a recognized risk factor for increased cardiovascular morbidity and mortality. The relationship between chronic kidney disease and cardiovascular risk extends in a graded fashion from mild renal impairment to end-stage renal disease.\(^15\) The kidney also plays a major role in homocysteine metabolism.\(^16\) Plasma total homocysteine increases as renal function declines; it is elevated in the vast majority of patients with end-stage renal disease. The glomerular filtration rate (GFR) is a strong determinant of plasma homocysteine concentration, even in individuals with very mild renal dysfunction.\(^17\) The strong correlation between homocysteine and GFR led Andrew Bostom to suggest almost 10 years ago that elevated homocysteine may be an epiphenomenon of renal dysfunction, or “expensive creatinine.”\(^18\)

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, a new article by Potter et al provides a nice confirmation of the relationship between homocysteine and renal function. The authors performed a posthoc analysis of data from 173 participants in one of the large international homocysteine-lowering trials, the Vitamins to Prevent Stroke (VITATOPS) trial. VITATOPS was designed to determine the safety and efficacy of daily supplementation with B vitamins (2 mg folic acid, 25 mg vitamin B6, and 0.5 mg vitamin B12) to prevent secondary vascular events in patients with a recent stroke or transient ischemic attack.\(^19\) The cross-sectional analysis by Potter et al included an assessment of cystatin C (a sensitive marker of GFR), total homocysteine, and 2 surrogate markers of vascular risk, carotid artery intima media thickness (IMT) and brachial artery flow-mediated dilation (FMD), in subjects who had been treated with B vitamins or placebo for at least 2 years. As expected, a strong linear relationship between total homocysteine and cystatin C was observed in both the vitamin and placebo groups. Both total homocysteine and cystatin C were found to correlate significantly with the vascular end points (carotid IMT and brachial FMD). Only cystatin C, however, was an independent predictor of FMD. Importantly, adjustment for renal function eliminated the relationship between total homocysteine and both IMT and FMD.
The data shown in Figure 2 of the article by Potter et al provide a particularly compelling illustration of the effects of vitamin supplementation on the relationship between homocysteine and renal function. In a subgroup of 132 subjects for which both baseline and posttreatment serum samples were assayed for homocysteine and cystatin C, a significant separation of the regression lines was observed in the posttreatment samples. This figure clearly shows that treatment with vitamins lowered total homocysteine without influencing the strong relationship between homocysteine and GFR. Coupled with the observation that there was no significant difference in FMD between the vitamin and placebo groups, these data imply that renal dysfunction is a stronger determinant of vascular function than is homocysteine. By extension, these findings suggest that impaired renal function may account for a large component of the epidemiological association between mild hyperhomocysteinemia and increased cardiovascular risk.

On first glance, the idea that elevated homocysteine may be a marker of renal dysfunction rather than a mediator of vascular disease appears to contradict a considerable amount of evidence from animal models of hyperhomocysteinemia. In mice and other animals, hyperhomocysteinemia leads to endothelial dysfunction, vascular hypertrophy, accelerated thrombosis, and predisposition to atherosclerosis. Similar vascular phenotypes are observed when hyperhomocysteinemia is induced by a variety of different genetic or dietary approaches. These findings in animal models suggest, but do not prove, that elevated homocysteine itself is a causative factor in vascular dysfunction. Renal function was not measured in most of these animal studies, and it is conceivable that the methods used to induce hyperhomocysteinemia may have caused alterations in GFR. The possibility cannot be excluded, therefore, that renal dysfunction might account for some of the adverse vascular phenotypes seen in hyperhomocysteinemic animals.

Several mechanisms have been proposed to cause vascular pathophysiology in chronic kidney disease. These include endothelial dysfunction, activation of the renin-angiotensin system, hypertension, dyslipidemia, and altered calcium homeostasis. One potential mechanism for endothelial dysfunction in renal disease is the accumulation of asymmetrical dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase. Like plasma total homocysteine, plasma ADMA is inversely related to GFR and is predictive of increased mortality in patients with chronic kidney disease. Some of the potential mechanistic relationships between renal dysfunction, ADMA, homocysteine, and vascular disease are summarized in the Figure.

Although it suggests a potential explanation for the homocysteine paradox, the article by Potter et al represents a relatively small posthoc analysis that has several limitations. Unfortunately, carotid IMT and brachial FMD were not assessed at baseline, before initiating treatment with vitamins or placebo. The VITATOPS trial is still ongoing, and we do not yet have access to data on hard clinical end points such as recurrent stroke, coronary events, or venous thromboembolism. It will be necessary to confirm the relationships between homocysteine, renal function, and vascular outcomes in larger data sets from VITATOPS and other trials before concluding that mild hyperhomocysteinemia is simply a marker of decreased renal function rather than an independent vascular risk factor.

Disclosures

None.

References


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doi: 10.1161/ATVBAHA.108.164830
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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