Homocysteine and Cardiovascular Disease
Is HDL the Link?

Philip J. Barter, Kerry-Anne Rye

An elevated plasma level of homocysteine has long been known as an independent predictor of cardiovascular disease. However, in the absence of a clear mechanism linking homocysteine to cardiovascular disease, there has been an ongoing debate about whether this relationship is one of cause and effect or whether an elevated level of plasma homocysteine is an epiphenomenon, reflecting the presence of some other proatherogenic factor that is actually responsible for the cardiovascular disease. In the current issue of this journal, Liao et al suggest that the mechanistic link may be a homocysteine-induced reduction in the concentration of high density lipoproteins (HDLs).

Liao et al report that homocysteine reduces the concentration of HDL cholesterol in plasma by inhibiting the hepatic synthesis of apoA-I, the main HDL apolipoprotein. This conclusion supports the findings from another recent study by Mikael et al who also reported that homocysteine inhibits apoA-I synthesis. The results of these 2 studies not only explain the documented inverse correlation between the plasma concentrations of HDL cholesterol and homocysteine but also raise the real possibility that a homocysteine-induced inhibition of apoA-I synthesis is the mechanism linking homocysteine to the development of atherosclerosis.

A low concentration of HDL cholesterol has been shown in numerous human population studies to be highly predictive of premature cardiovascular disease. Furthermore, treatments that increase the level of HDL cholesterol in plasma by inhibiting the hepatic synthesis of apoA-I, the main HDL apolipoprotein. This conclusion supports the findings from another recent study by Mikael et al who also reported that homocysteine inhibits apoA-I synthesis. The results of these 2 studies not only explain the documented inverse correlation between the plasma concentrations of HDL cholesterol and homocysteine but also raise the real possibility that a homocysteine-induced inhibition of apoA-I synthesis is the mechanism linking homocysteine to the development of atherosclerosis.

The mechanism by which homocysteine inhibits the synthesis of apoA-I is not entirely clear. Liao et al concluded that it reduced apoA-I mRNA. However, they also reported that homocysteine reduces the rate of apoA-I synthesis. The results of these 2 studies not only explain the inverse correlation between the plasma concentrations of HDL cholesterol and homocysteine but also raise the real possibility that a homocysteine-induced inhibition of apoA-I synthesis is the mechanism linking homocysteine to the development of atherosclerosis.

HDLs also correct endothelial dysfunction, probably by virtue of antioxidant, antithrombotic, and antiinflammatory properties. The antioxidant properties of HDLs involve activity of compounds such as paraoxonase that cotransport with HDLs, although apoA-I has also been shown to have antioxidant properties. Antiinflammatory effects of HDLs include an ability to inhibit both the cytokine-induced and the CRP-induced expression of adhesion proteins in endothelial cells. HDLs also correct endothelial dysfunction, probably by inducing the synthesis of nitric oxide, and most recently, have been shown to promote endothelial repair. Thus, anything that reduces the synthesis or enhances the catabolism of HDLs and reduces their plasma concentration has the capacity to increase susceptibility to atherosclerosis and its associated clinical cardiovascular disease.

The mechanism by which homocysteine inhibits the synthesis of apoA-I is not entirely clear. Liao et al concluded that it reduced apoA-I protein synthesis in the liver without reducing apoA-I mRNA. In addition, they found that homocysteine reduced the rate of the plasma cholesterol esterification catalyzed by the enzyme lecithin:cholesterol acyltransferase and increased clearance of HDL cholesterol esters from plasma. Mikael et al also found that homocysteine reduces the synthesis of apoA-I, although they concluded that it was the result of a decrease in apoA-I mRNA. But regardless of the mechanism, both studies provide compelling evidence that homocysteine reduces the plasma concentration of apoA-I and HDL cholesterol by reducing the synthesis of apoA-I in the liver. It was also found in both studies that the concentration of HDL cholesterol in human subjects correlates inversely with the level of homocysteine in plasma. The authors of both studies suggest that a low concentration of HDL cholesterol may explain why people with elevated levels of homocysteine are at increased risk of developing cardiovascular disease.

What is the evidence that changing the level of homocysteine in plasma alters the concentration of HDL cholesterol and how does this impact on cardiovascular events? In the recently reported FIELD study, treatment with fenofibrate increased the plasma homocysteine level by 35% from a median of 11.2 μmol/L in the placebo group to 15.1 μmol/L in the treated group. On the basis of the results from epidemiological studies, an increase in homocysteine of this magnitude could translate into a 10% to 20% increase in cardiovascular events. It is noteworthy that the fenofibrate-induced increase in HDL cholesterol in the FIELD study (less than 2% at study end) and the reduction in cardiovascular events (only 11%) were both much less than predicted from the results of trials using other fibrates that have a much smaller effect on levels of homocysteine. The studies by Liao et al and Mikael et al suggest that the disappointing cardiovascular benefits of treatment with fenofibrate in the FIELD study may be the consequence of a sustained increase in the plasma concentration of homocysteine inhibiting the synthesis of apoA-I and thus opposing the expected increase in concentration of HDL cholesterol.

Despite the large body of positive epidemiological evidence and now a potential mechanism, it should be emphasized that a direct causative role of homocysteine in cardio-

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vascular disease is still far from proven. Indeed, the case has been considerably weakened by 3 recent reports of large-scale, well-designed studies that have investigated the effects on cardiovascular outcomes of lowering the concentration of plasma homocysteine by treatment with folate and vitamin B12.18–20 All 3 studies were negative. In each study the plasma level of homocysteine was significantly reduced but in none was there any evidence of a reduction in cardiovascular events. Clearly, these intervention studies do not support the use of folate and vitamin B12 as agents to reduce cardiovascular risk. It has been argued, however, that folate and vitamin B12 do much more than simply reduce plasma homocysteine and that both have other actions with the capacity to promote rather than inhibit atherothrombosis.21 Such actions may override the potential benefits derived from the homocysteine lowering and explain the negative trial results of the trials with folate and vitamin B12. If this is the case, it is possible that a positive cardiovascular outcome could be achieved if homocysteine were to be reduced by other means. Thus, further research into alternate methods for lowering homocysteine should be considered a priority.

In conclusion, observational studies in humans have demonstrated: (1) an inverse relationship between plasma homocysteine levels and the concentration of HDL cholesterol; (2) an inverse relationship between the level of HDL cholesterol and cardiovascular disease; and (3) a positive relationship between the level of plasma homocysteine and cardiovascular disease. The studies by Liao et al19 and Mikael et al20 now provide a link between these observations by showing that homocysteine reduces the concentration of HDL cholesterol by inhibiting the synthesis of the main HDL apolipoprotein. This may explain the results of the FIELD study in which an increase in homocysteine during treatment with fenofibrate was associated with a much less than expected increase in HDL cholesterol and a disappointing reduction in cardiovascular events. Given the internal consistency of these findings, it was most surprising to find that reducing the plasma levels of homocysteine with folate and vitamin B12 had no effect on cardiovascular outcomes. Whereas the possibility exists that these negative results reflect potential proatherogenic actions of folate and vitamin B12 that oppose the benefits resulting from the lowering of homocysteine levels, it must be concluded that the jury is still out and that we still do not know whether an elevated level of homocysteine in plasma is a cause of cardiovascular disease or whether it is an epiphenomenon.

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