Renal Disease, Homocysteine, and Cardiovascular Complications

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Cardiovascular morbidity and mortality remain major problems in the end stage renal disease population. Patients with mild or moderate degrees of renal insufficiency are also at increased risk of a similar fate.

The causes of this poor cardiovascular prognosis in patients with renal disease are complex although many abnormalities occur in patients with renal dysfunction which predispose to such complications. Prime among these must be hypertension and diabetes, but other abnormalities also occur, including disorders of lipid metabolism. In the Hoorn study of mild renal insufficiency, other significant risk factors for cardiovascular mortality included age, body mass index, a rising pulse pressure, and a prior history of cardiovascular disease. Increasing levels of C-reactive protein, von Willibrand factor, soluble vascular cell adhesion molecule 1, and serum creatinine, as well as the presence of microalbuminuria, were also significant. In addition, increases of asymmetric dimethylarginine have been noted in patients with early chronic renal disease. It is unclear if some of these abnormalities are a cause or a result of the underlying metabolic derangement produced by renal dysfunction.

See p 369

Attention has also focused on homocysteine as a risk factor for vascular disease in patients with chronic renal insufficiency and end stage renal disease. It has been known for many years that the metabolism of homocysteine and other sulfur-containing amino acids becomes deranged in these patients; in 1980, Wilcken et al found an accumulation of cysteine and homocysteine in patients on maintenance hemodialysis. In end-stage renal disease populations on hemodialysis, median levels of homocysteine are markedly elevated, often in the range of 25 to 30 μmol/L (compared with a normal range of 12 to 15 μmol/L). Evidence has now accumulated showing that an elevated plasma homocysteine concentration is a risk factor for vascular disease in both normal patients and those with renal disease. In one prospective study of dialysis patients, the risk of vascular disease rose 1% for each 1 μmol/L increase in total homocysteine concentrations. How homocysteine may produce its ill effects is unclear, but elevated concentrations may induce endothelial dysfunction or abnormalities of coagulation factors and platelets.

In normal subjects, homocysteine concentrations may be lowered easily by using folic acid. This B vitamin is converted into 5-methyltetrahydrofolate, which donates a methyl group to homocysteine and reconstitutes the methionine from which homocysteine has been derived. In most normal subjects or in patients with cardiovascular disease, a dose of 400 to 600 μg produces a prompt fall of 20% to 30% in total plasma concentrations. In contrast, patients with end stage renal disease are characteristically resistant to this homocysteine-lowering action of folic acid and even the use of pharmacological doses of folic acid or reduced folates does not normalize circulating homocysteine concentrations. Alternatively have been explored. In one study, vitamin B12 lowered homocysteine concentrations by 17% when given orally and, in another, by over 30% when administered subcutaneously, but levels were not normalized. Likewise, neither betaine, which transfers a methyl group to homocysteine in an alternative remethylation pathway, nor vitamin B6, an essential cofactor for the transsulfuration of homocysteine, normalize fasting plasma concentrations. The use of different dialysis techniques has also been explored to lower homocysteine concentrations. Although only modest success has been reported for high-flux and super-flux dialyzers, some excellent results have recently been reported using nocturnal dialysis. This also had beneficial effects on other biochemical parameters, including circulating vitamin and albumin concentrations.

In the current issue of Circulation, Scholze et al report the effects of intravenous administration of acetylcysteine, a sulfhydryl-containing substance, on plasma homocysteine concentrations during hemodialysis. Acetylcysteine has powerful antioxidant properties. It also has beneficial effects on glutathione stores and adhesion molecules and improves peripheral and coronary arterial function. Acetylcysteine is used to treat acetaminophen toxicity and more recently has been indicated in the prevention of radio-contrast–induced nephropathy. Despite nausea and vomiting in some patients, it is generally well tolerated when administered systemically. Acetylcysteine also reduces the plasma concentration of homocysteine, but in one study of hemodialysis patients, it failed to reduce levels to a statistically significant degree when administered orally. Scholze et al used a 5 g dose via an intravenous route at the time of dialysis. The plasma homocysteine concentration fell dramatically from a mean of 20 μmol/L before hemodialysis to 2.2 μmol/L after. Under control conditions, in the absence of acetylcysteine, the homocysteine concentration fell from a similar baseline value to a mean of 12 μmol/L. The effect of acetylcysteine persisted until the next dose of dialysis. The authors also noted a decrease in pulse pressure, and analysis of plethys-
mographic waveforms suggested that these alterations were related to improved endothelial function.

A reduction in concentration of homocysteine—a weak but independent risk factor for vascular disease—may make intuitive sense, but does it translate into improved clinical outcomes? In patients with coronary artery disease, Schnyder et al.\textsuperscript{15} administered a combination of folic acid, vitamin B\textsubscript{12}, and pyridoxine (vitamin B\textsubscript{6}). The treatment reduced homocysteine levels by about 35\%, decreasing the rate of restenosis.\textsuperscript{15} In a later extension of this work using the same treatment, a composite end point of death, nonfatal myocardial infarction, and need for repeat revascularization was evaluated at 6 months and 1 year. This too was lower in the treated patients, but was principally the result of a reduced rate of target lesion revascularization.\textsuperscript{16} In a larger, open-label study, patients with stable coronary artery disease were given folic acid and followed for a mean of 2 years. Plasma homocysteine levels fell by 18\%, but all-cause mortality and a composite end point of vascular events were not significantly reduced.\textsuperscript{17} Other studies in similar patients are in progress.

In patients with renal disease, investigations are also underway to test the usefulness of high dose folic acid. In the Homocysteinemia in Kidney and End Stage Renal Disease Study (HOST), currently ongoing in the Veterans' Administration system, folic acid is being administered to patients with end stage renal disease and advanced chronic renal failure. Despite the failure to normalize homocysteine concentrations in previous studies of patients with end stage renal disease, the outcome of this study is awaited with interest as the concentration of homocysteine may still be reduced.

In addition, folic acid may improve vascular function by mechanisms unrelated to homocysteine lowering.\textsuperscript{18} High dose folic acid treatment will also be investigated in renal transplant patients in the Folic Acid for Vascular Outcome Reduction In Transplantation (FAVORIT) study.\textsuperscript{19} Until these results are available, the findings of Scholze et al.\textsuperscript{10} demonstrate that the potential for normalizing plasma homocysteine concentration in these patients may not be as bleak as previously thought and may be associated with improved vascular function. It is tempting to think these 2 outcomes are directly linked. Like folic acid, however, acetylcysteine may have independent effects—lowering the concentration of homocysteine on the one hand, and improving vascular function by a different mechanism on the other.\textsuperscript{18} Additional studies are needed to clarify the mechanism(s) of acetylcysteine in lowering circulating homocysteine concentrations and improving vascular function and outcomes. An improvement in a composite cardiovascular end point in patients with end-stage renal disease after administration of acetylcysteine suggests that this may be a promising area for further work.\textsuperscript{20} Reducing homocysteine in this manner, either alone or combined with novel modes of dialysis, offers a new and potentially important therapeutic opportunity in patients with end stage renal disease.

References

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