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Therapy of Hyperhomocysteinemia in Chronic Kidney Disease

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Recent published evidence suggests that the correction of the multiple remethylation pathway abnormalities in chronic kidney disease (CKD), beyond folate-related disturbances, enhanced removal of uremic toxins and/or homocysteine (Hcy), and maneuvers aimed to displace Hcy from protein-binding sites, may represent valuable strategies to normalize total Hcy concentrations in CKD patients. The relevance of decreasing Hcy levels for cardiovascular disease in CKD patients should be shown definitively by the results of ongoing randomized trials.
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A moderate increase of plasma total homocysteine (Hcy) concentration is present in the early stage of chronic kidney disease (CKD), increases in parallel with the degree of reduction in renal function, and persists after starting dialysis treatment.[1] In a recent meta-analysis, hyperhomocysteinemia was a modest independent predictor of ischemic heart disease and stroke in healthy populations.[2] Although some studies in CKD patients observed an inverse relationship between hyperhomocysteinemia and cardiovascular disease (CVD),[3] the pooled data from 3 prospective studies in CKD patients led to a relative risk estimate for incident or recurrent CVD conferred by hyperhomocysteinemia of 2.8 (95% confidence interval, 1.6-5.0).[4] In view of these epidemiologic data and the high frequency of CVD in CKD patients,[5] numerous attempts have been made to decrease plasma total Hcy concentrations in CKD patients. In this report, we outline Hcy-decreasing strategies (intervention therapies and/or dialysis modalities) and discuss whether such strategies decrease the excessive incidence of CVD in CKD patients.

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Hcy-Decreasing Strategies in CKD Patients

Folic acid therapy in CKD patients has been shown to reduce, albeit not to normalize, plasma total Hcy concentrations, particularly in dialysis patients.[1] The relative resistance to folate action in CKD patients could explain why the correction of total Hcy concentrations generally remains partial.[6] Indeed, routine minimal folic acid supplementation of less than 1 mg daily, in contrast to what usually is observed in the population at large, does not have any effect on plasma total Hcy concentration in CKD patients, despite the induction of a supernormal plasma folate level.[6] Oral supplementation with high doses of folic acid (≤15 mg/d), which leads to a 20- to 50-fold increase of plasma folate concentrations, only partially is effective in decreasing plasma total Hcy concentrations.[1] The relative resistance to folate action does not appear to be caused by defects in folate absorption or impairment in folic acid conversion in the plasma to the active metabolite 5-methyltetrahydrofolate.[7] Moreover, active reduced forms of folic acid did not lead to a greater decrease in plasma total Hcy levels than those observed with native folic acid supplementation in hemodialysis patients.[8-11] Of note, folic acid supplementation also did not enhance the impaired Hcy clearance in 6 CKD patients, even though it decreased total Hcy levels.[12] One recent interpretation of these findings has been that folic acid enhances Hcy remethylation in tissues and decreases Hcy efflux into the plasma compartment, but this would not be sufficient to override the primary defect in Hcy metabolism (ie, the reduction of Hcy clearance from

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plasma) or to obtain normal steady-state levels in dialysis patients.[13]

Other abnormalities of the remethylation pathway, for instance, relative resistance to vitamin B_{12} action, that are not related to folate have been observed in CKD patients.[14] Theses abnormalities also may participate in the genesis of hyperhomocysteinemia in these patients. However, the correction of these abnormalities in folate-replete patients had either no effect[15] or only a partial additional effect on fasting total Hcy levels in CKD patients.[16] For example, Elian and Hoffer found that administering a pharmacologic dose (1 mg/wk parentally) of hydroxycobalamin to vitamin B_{12}-replete hemodialysis patients who were receiving 5 to 6 mg/d of folic acid and 5 mg/d of pyridoxine increased their mean serum vitamin B_{12} concentration 60-fold and reduced their mean plasma total Hcy concentration to 32% less than the lowest level that previously had been attained by using high-dose folic acid and pyridoxine.[16] However, after 16 weeks of hydroxycobalamin supplementation, a substantial degree of residual hyperhomocysteinemia persisted, as shown by a mean plasma total Hcy concentration of 18.4 μmol/L.[16]

The main reason for the genesis of hyperhomocysteinemia and the reduced efficacy of Hcy-decreasing therapies in dialysis CKD patients is unclear at present. The accumulation of uremic toxins and the decrease in Hcy clearance and metabolism owing to a decreased functioning renal mass are the 2 most probable explanations.[1,2] It is noteworthy that in patients with CKD who are not yet on dialysis, folic acid therapy normalizes total Hcy levels, in contrast to the large majority of dialysis patients.[1] More efficient dialysis procedures could allow an improved removal of uremic toxins and/or Hcy. Standard dialysis procedures using low-flux dialyzers are unable to remove sufficient amounts of Hcy to maintain total Hcy levels within the normal range.[17] High-flux dialysis also did not lead to a better reduction in total Hcy concentrations than low-flux dialysis.[18] In contrast, dialysis in superflux mode significantly decreased total Hcy concentrations compared with a high-flux mode.[19,20] Of note, the Hcy-decreasing effect of extremely efficacious high-flux dialyzers also may be caused partially by albumin removal because the major part of circulating Hcy is protein bound. Recently it was shown that total Hcy levels were significantly lower among patients undergoing daily nocturnal hemodialysis, with its excellent dialytic removal of both small and middle molecules, compared with patients treated by standard hemodialysis procedures (geometric mean, 12.7 versus 20.0 μmol/L, respectively).[21]

A displacement of homocysteine from protein-binding sites, allowing increased free homocysteine availability for plasma clearance by dialysis procedures, could be an alternative strategy to reduce total Hcy concentrations further. Thus, the acute intravenous administration of N-acetylcysteine (5 g in 5% glucose for 4 hours) during a hemodialysis session, which presumably can displace homocysteine from protein-binding sites, was able to normalize completely the total Hcy concentrations at the end of the session, with residual efficacy for 2 days.[22] Although promising, the long-term efficacy and safety of intravenous administration of N-acetylcysteine needs, however, to be evaluated before drawing a definite conclusion. On the other hand, long-term oral N-acetylcysteine administration (1.2 g twice a day) did not reduce total Hcy levels significantly in hemodialysis patients.[23]

Taken together, these data suggest that intensified dialysis procedures and/or maneuvers aimed to displace homocysteine from protein-binding sites may represent valuable strategies to normalize total Hcy levels in dialysis patients.

Hcy-Decreasing Strategies and CVD

The impact of Hcy-decreasing strategies on the risk for CVD in CKD patients has not yet been evaluated extensively. An acute decrease of total Hcy concentrations by N-acetylcysteine supplementation during the dialysis session has been shown to improve pulse pressure and endothelial function in hemodialysis patients.[22] However, N-acetylcysteine may exert other effects (eg, via its antioxidant capacity), which could explain the endothelial actions independently of decreasing the total Hcy concentration. Moreover, several studies failed to show a significant improvement in endothelial dysfunction after folate supplementation despite a significant reduction in total Hcy concentrations in patients with different stages of CKD.[24-26] In contrast to these negative results in CKD patients, oral folic acid supplementation has been shown to decrease plasma total Hcy concentrations and to restore impaired endothelium-dependent vasodilatation in healthy patients[27] and in patients with familial hypercholesterolemia.[28]

In a recent clinical trial of folic acid in dialysis patients, Wrone et al[29] reported that composite rates of cardiovascular events and mortality did not decrease with increasing levels of folic acid therapy. This negative result is disappointing because the patients had increased baseline plasma total Hcy concentrations, and vitamin supplementation achieved a mean reduction in plasma total Hcy concentrations of 3.7 μmol/L or more in the 3 arms of the study. These latter reasons were given to explain the negative results observed in the Vitamin In Stroke Prevention study, in which vitamin supplementation failed to reduce the risk for CVD and death in 3,680 stroke survivors.[30] However, a short follow-up period, the lack of a placebo arm, and particularly a lack of power to evaluate the effect of vitamin supplementation on CVD alone (not included in a composite end point with mortality) may explain these negative findings. It is important to distinguish between CVD and all-cause mortality in clinical trials in CKD patients because all-cause mortality in these patients include deaths related to malnutrition and/or inflammation, and as discussed elsewhere in this issue (Suliman ME, et al, pages 14-19) these 2 prevalent factors could decrease the levels of plasma total Hcy levels and might outweigh the increased risk for CVD associated with high total Hcy levels in CKD patients.[3]

It currently is unknown if these negative results in CKD patients are caused by the particularly aggressive complex nature of the vascular disease in CKD stages 3 to 5, by the

inability to normalize total Hcy concentrations, or by the relative resistance to folate action. Early intervention at CKD stages 1 or 2 may lead to a beneficial effect in vascular disease, as observed in a recent preliminary study in renal transplant recipients.[31] It is also of interest that in an open noncontrolled study the intravenous administration of 5-methyltetrahydrofolate was associated not only with reduced plasma total Hcy concentrations, but also with an improvement of endothelial function in patients undergoing convective hemodialysis.[32]

It is important to keep in mind that in the human cardiovascular system Hcy metabolism is limited to the remethylation pathway.[33] Because an alteration of the remethylation pathway, but not of the transsulfuration pathway, has been shown in hemodialysis patients,[34] the correction of the multiple remethylation pathway abnormalities may be the key in CKD patients not only to decrease Hcy concentrations but also to ameliorate Hcy metabolic capacity in the cardiovascular system.

Therefore, the impact of Hcy-decreasing strategies on CVD in CKD patients can be assessed reliably only by large-scale randomized trials that aim to evaluate the effects of correcting the multiple remethylation pathway abnormalities by vitamin B supplementation on pooled CVD outcomes at an early stage of CKD and over a long follow-up period. Such a trial is underway in 4,000 stable renal transplant patients (ie, the Folic Acid for Vascular Outcome Reduction In Transplantation Study), with an estimated completion date of May 2007.[35]

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