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Toxic Effects of Hyperhomocysteinemia in Chronic Renal Failure and in Uremia: Cardiovascular and Metabolic Consequences

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Hyperhomocysteinemia, highly prevalent in well-nourished patients with chronic renal failure and in uremia, causes toxic effects that can be envisioned in terms of cardiovascular risk increase. However, its effects on cellular metabolism and on gene expression, not to mention receptor regulation, only recently are being evaluated. For example, it has been shown that hypomethylation induced by hyperhomocysteinemia can alter erythrocyte membrane protein repair and gene expression. In addition, increased plasma protein L-isoaspartyl content, related to hyperhomocysteinemia and uremic toxicity, determines specific effects on protein function, with a reduced binding of homocysteine to albumin. We propose that uremia is a state in which proteins present a widespread derangement of structure-function relationships.
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Homocysteine levels are high in chronic renal failure and in uremia; normal levels are approximately 10 μmol/L; diabetic patients, for reasons related to the hormonal pattern, have lower plasma levels. Mild increases in homocysteine levels have been linked to cardiovascular risk. In chronic renal failure and end-stage renal disease homocysteine levels are between 30 and 40 μmol/L on average if patients are not taking any folate supplements. However, it is possible to encounter much higher levels in uremic patients, even more than 100 μmol/L, which are similar to those present in homocystinuria (Fig 1). High homocysteine levels and premature cardiovascular mortality characterize this genetic disease.

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Cardiovascular Disease and Hyperhomocysteinemia

Consequences of hyperhomocysteinemia in chronic renal failure and in uremia usually are seen essentially in terms of cardiovascular disease, and, ultimately, patient mortality. At present, a controversy exists between those advocating that, as in the general population, high homocysteine levels correlate with patient mortality and therefore are harmful, and those who find a positive correlation between low homocysteine levels and mortality, so-called *reverse epidemiology*.

Looking at the mortality issue, a study by Mallamaci et al[1] found a significant correlation between higher homocysteine levels and mortality. Patients were followed-up prospectively for 2.5 years and those with higher levels showed a decreased survival rate. In this report, homocysteine levels were adjusted for albumin.

Kalantar-Zadeh et al[2] proposed that when homocysteine levels are low there is a higher mortality rate. Unfortunately, they did not adjust their data for albumin levels. If homocysteine levels and albumin levels both are low then this is not a coincidence of events. Homocysteine and albumin levels are

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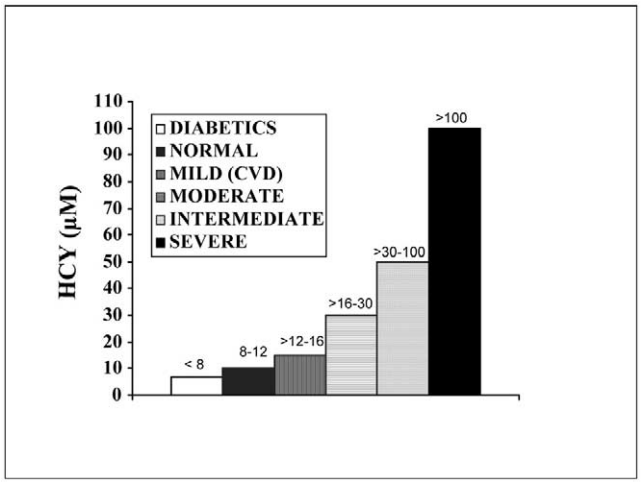

Figure 1 Homocysteine concentrations in health and in disease. □, Diabetic; ■ , normal; ■ , mild (cardiovascular disease); ■ , moderate; □ , intermediate; ■, severe.

correlated tightly. Homocysteine is itself an amino acid and a derivative of methionine, which is an essential amino acid. Therefore, if albumin and homocysteine levels are both low, it simply could mean that the low homocysteine levels are caused by malnutrition, which will influence mortality powerfully. In this study more than half of the patients were diabetic, and in the deceased group 75% were diabetic. This is also important in the evaluation of these data because diabetic patients have lower homocysteine levels, even if they are uremic.

Other studies recently have put forward the theory of reverse epidemiology. For example, Wrone et al[3] compared 3 groups of patients taking folic acid supplements of different dosages (1, 5, and 15 mg/d) and found no difference with respect to cardiovascular events after 2 years. In this trial, no placebo was used and patients already were taking folates (no washout), therefore it is difficult to draw inferences about reverse epidemiology or about effects on cardiovascular events (because treatment by itself, regardless of dosage, could affect event rates). Moreover, when adjustment for albumin levels was performed, the reverse epidemiology disappeared (only age, albumin, and race/ethnicity remained significant predictors). Diabetic patients accounted for more than 40% of the total patients in all 3 groups. At present, we believe that we should wait for other carefully designed prospective studies and intervention trials that take potent confounders such as nutritional status into account before we decide to keep homocysteine levels in the high range to increase patient survival chances.

Metabolic Consequences of Hyperhomocysteinemia

Homocysteine metabolism is shown in Fig 2. Recently, some unforeseen consequences of hyperhomocysteinemia, coming from other laboratories and ours, have been explored that can affect mortality. These include the dynamics between folate receptors and therapy and the complex interplay between homocysteine levels, gene expression, and protein binding and its effects.

A key role for homocysteine has been shown by Antony et al[4] in the regulation of folate-receptor biosynthesis. Folate receptors and reduced folate carriers mediate cellular acquisition of folates. Folate receptors are up-regulated in folate deficiency and down-regulated after folate repletion, but the basis of this regulation was unknown until now. Antony et al[4] proposed the following mechanism: folate depletion inactivates methionine synthase, which will cause an increase in homocysteine levels. Homocysteine in turn determines the synthesis of folate receptors by increasing the interaction between messenger RNA and a nuclear protein. Folate repletion reactivates methionine synthase, and homocysteine levels will decrease. Methionine has no effects on the interaction between RNA and the nuclear protein. In this way, folate-receptor synthesis shuts down. In addition, they showed that during high-dose folate repletion, folates have an indepen-

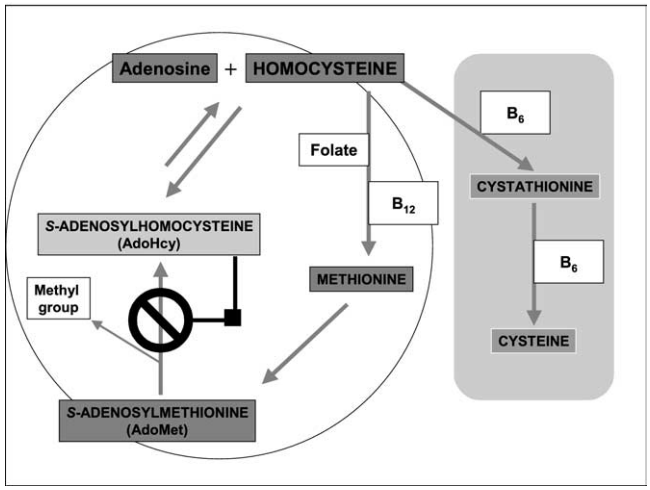

Figure 2 Homocysteine (Hcy) metabolism. Methionine is activated by reacting with adenosine triphosphate, resulting in the formation of AdoMet (enzyme: AdoMet synthetase). AdoMet is the methyl donor for approximately 40 methyltransferases, the methyl-accepting substrate being small molecules (amino acids, phospholipids, amines, and so forth) and macromolecules (DNA, RNA, proteins). AdoHcy is the demethylated product of AdoMet and a powerful competitive inhibitor of all AdoMet-dependent enzymes. AdoHcy is hydrolyzed rapidly to Hcy and adenosine (enzyme: AdoHcy-hydrolase) under physiologic conditions. This is the only source of Hcy in human beings. However, this reaction is fully reversible, and thermodynamics actually favor biosynthesis over hydrolysis. Hcy is metabolized through almost equally partitioning into transsulfuration to cysteine or remethylation into methionine. Transsulfuration requires pyridoxalphosphate as the active form of vitamin B_6 (rate-limiting step is catalyzed by cystathionine-β-synthase). Remethylation is catalyzed mostly by methionine synthase, which requires methylcobalamin, the active form of vitamin B_{12}, as an essential cofactor. Methyltetrahydrofolate is the active folate derivative, which functions as the methyl donor in the latter reaction. Methyltetrahydrofolate is formed from methylenetetrahydrofolate (enzyme: methylenetetrahydrofolate reductase). An alternative pathway for Hcy remethylation requires betaine as the methyl donor.

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