Vitamin therapy of hyperhomocysteinaemia in chronic renal failure

M. Hages, K. Pietrzik

Institute für Ernährungswissenschaft, Abt. Pathophysiologie der Ernährung des Menschen, Rheinische Friedrich-Wilhelms-Universität, Bonn, Germany

In patients with chronic renal failure, plasma homocysteine levels are already elevated significantly at an early stage and show a negative correlation with the glomerular filtration rate and serum creatinine concentration, respectively. End-stage renal disease patients on dialysis have homocysteine levels three- or four-fold above normal [1,2].

In several studies moderate hyperhomocysteinemia has been identified as a potential independent risk factor for premature cardiovascular disease, a frequent complication of advanced renal diseases. The mechanism of the atherogenic action of homocysteine is not clearly understood, but it is theorized that homocysteine is cytotoxic to the endothelial wall and promotes the oxidative modification of LDL cholesterol [3]. The elevated homocysteine concentration in patients with renal failure is mainly caused by the decreased catabolism of homocysteine in the proximal tubular cells due to reduced filtration and to tubular dysfunction. Additionally, the extrarenal homocysteine metabolism is decreased due to inhibition by retained metabolites [4].

Homocysteine is an amino acid, which is formed as an intermediate in the metabolism of methionine. Homocysteine can be remethylated to methionine with folic acid as methyl-donor and vitamin B12 as co-factor. Additionally, it can be converted to cystathionine by condensation with serin in an irreversible reaction. This metabolic step requires vitamin B6 as cofactor.

The status of vitamin B6, B12, and folic acid is regarded as an important factor influencing the homocysteine level. However, many renal patients with elevated homocysteine concentrations have normal baseline serum- and red cell folate levels, as well as normal serum B12 and B6 concentrations. Therefore, it is unlikely that manifest vitamin deficiencies contribute to the elevated homocysteine levels in patients with ureaemia and end-stage renal disease. Nevertheless, the folic acid and vitamin B12 status in these patients is negatively correlated with their plasma homocysteine concentration [5,6].

Patients with renal failure, especially dialysis patients, frequently show vascular dysfunction as manifested by an elevated plasma level of von-Willebrand factor (vWF)-antigen, which is reported to be one of the specific markers of endothelial activation and inflammation. The elevated concentration of this indicator of endothelial damage is not only due to the reduced clearance in renal failure because there is no correlation between GFR and the blood level of this factor. Moreover, the level of von-Willebrand factor antigen in dialysis patients is negatively correlated with the duration (years) of hemodialysis [7]. These observations suggest the possibility of endothelial injury.

There is in-vitro evidence that homocysteine promotes the release of von-Willebrand factor antigen [8]. However, in most studies, the fasting homocysteine plasma concentration and von-Willebrand factor don't correlate [9]. But after methionine loading test (0.1 g methionine/kg BW), the post-load homocysteine levels showed a significant relationship to the endothelial function parameter [9]. A methionine loading test stresses the pathway involved in homocysteine metabolism and is a valid diagnostic test for an abnormal homocysteine handling.

Treatment with high doses of folic acid (5 mg/d) significantly lowers [10,11] the elevated homocysteine concentrations, both in non-dialyzed and in hemodialized patients, by the stimulation of the remethylation of homocysteine. This can be observed even in the absence of evident folate deficiency. In patients with mild hyperhomocysteinaemia and peripheral arterial occlusive disease, the vitamin is also able to reduce the elevated levels of von-Willebrand factor and appears to ameliorate the endothelial function [9]. Corresponding studies with renal failure patients are missing. Separate or additive effects of vitamin B6 and/or vitamin B12 on the homocysteine concentration in patients with renal failure have not been observed so far.

Further research is needed to identify the optimal therapeutic dose and/or combination of vitamins in the therapy of hyperhomocysteinaemia due to renal insufficiency.

References