

Issue 105

In a nutshell

Patients with end-stage renal disease have elevated homocysteine levels and these levels can be reduced by giving supplements of folate, vitamin B12 and vitamin B6.

Whether such supplementation has long term effects on homocysteine levels and whether this will in turn produce significant clinical benefits are things yet to be established.

Homocysteine and renal disease

Arbor Clinical Nutrition Updates 2001 (October);105:1-2
ISSN 1446-5450

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NUTRITION RESEARCH REVIEW

Study one: Endothelial function not corrected

Folic acid supplementation partially corrects hyperhomocysteinaemia in patients with chronic renal failure, according to research from England. However, it does not improve endothelial function.

Subjects: 100 patients (mean age 62 years) with chronic renal failure predialysis.

Method: Randomised, controlled trial of 12 weeks of folic acid (5 mg/day) or placebo.

Results: Homocysteine levels were reduced in the active compared with placebo groups (15.1 versus 20.1 $\mu\text{mol/L}$, $p < 0.001$). However, there were no significant differences in endothelial function (measured by endothelium-dependent dilation of the brachial artery, combined serum nitrite/nitrate concentrations and plasma von Willebrand factor assay).

Reference: Thambyrajah J et al. Does folic acid decrease plasma homocysteine and improve endothelial function in patients with predialysis renal failure? *Circulation* 2000;102: 871-5

Study two: Does elevated homocysteine cause renal disease?

Elevated Hcy is associated with the development of microalbuminuria. Thus it may be a cause rather than just an effect of renal disease. These conclusions are based on the results of a recently published Dutch study.

Subjects: 316 subjects without any sign of microalbuminuria. Of these, 66 had non-insulin-dependent diabetes mellitus (NIDDM).

Method: Prospective case-control study in which the subjects were followed up for a mean of 6.1 years. Hcy levels in subjects who developed microalbuminuria were compared with levels in those who did not. Analysis was controlled for a range of other variables, in both the diabetic and non-diabetic subjects.

Results: After adjusting for glucose tolerance status and other demographic variables, regression analyses showed a significant correlation between high baseline Hcy levels and development of microalbuminuria (odds ratio in Hcy $>19.0 \mu\text{mol/L}$ vs $<9.1 \mu\text{mol/L}$ = 5.1, 95% CI: 1.1 to 23.0, $p < 0.05$). A similar result was found when only the non-diabetic patients were included in the analysis.

Reference: Jager A. Serum homocysteine levels are associated with the development of (micro)albuminuria: the Hoorn study. *Arterioscler Thromb Vasc Biol* 2001;21:74-81

Comments

Patients with end-stage renal disease have elevated homocysteine levels. They also have a much higher risk of cardiovascular (CV) disease. This is true both of patients being treated with dialysis and those who have had renal transplantation. It seems to be even more so in patients who have diabetes together with renal disease.

There are various theories about why renal patients have elevated Hcy levels, and why they are so much more likely to suffer cardiovascular disease. So far they remain just theories. The obvious question is: are the elevated Hcy a cause of the high rate of CV disease? If so, would lowering the Hcy levels reduce the high likelihood of patients with end-stage renal failure getting CV complications?

A large amount of research has been published in the last few years on Hcy in renal disease. As a result of all this work, several things have become clear. Firstly, that giving supplements of folate, vitamin B12 and vitamin B6 will reduce Hcy levels in renal patients.

Secondly, that it is harder to reduce Hcy to a normal range in renal patients than it is in people who do not have renal disease. This is probably because of the complex metabolic disturbances associated with renal failure. Therefore supplementation to reduce Hcy in renal patients may need to be at relatively high doses for lengthy periods.

It also seems that vitamin B6 is more likely to be needed to successfully reduce Hcy in renal patients than it is in other clinical situations. This is because abnormalities in vitamin B6 status are more likely in renal disease.

Other things are not so clear. What is the best combination, dosage and form of these 'Hcy-reducing' vitamins? For example, is intravenous folinic acid more effective than oral folate? Is it helpful to give intramuscular vitamin B12 injections?

But the crucial question remains: will giving supplements to reduce Hcy levels make any difference to the clinical

outcome? There are very few clinical studies that address this question.

The first study summarised above is important because it considers the impact of reducing Hcy in renal patients on a physiological measure which is related to atherosclerotic CV disease, even if it is not a clinical end-point. Endothelial function is currently thought to be the most likely mechanism by which elevated Hcy could contribute to CV disease.

This study failed to show a benefit on endothelial function. This is consistent with another trial from Holland published last year which failed to show any benefit on carotid artery stiffness from giving folate to end-stage renal failure patients, despite producing a reduction in their Hcy levels¹.

On the other hand, this study was focused just on folate supplementation (i.e. it did not include vitamins B12 or B6). The supplementation was moderate in dose compared with some other studies, and after being given for just 12 weeks did not produce consistently normal Hcy levels. Future studies that manage to produce more dramatic drops in Hcy levels over a longer time period in a larger group of patients may yet demonstrate that there is clinical benefit from doing so.

The second study raises the possibility that it may not just be renal disease causing elevated Hcy, but could be the other way around as well. On the other hand, the association demonstrated in this study may be due to some other third variable not included in the analysis. Even so, it is known that Hcy can be a toxin. Whether it can cause significant renal damage is yet to be confirmed.

If it were confirmed, it would be one good reason to take aggressive steps to lower Hcy levels in patients with renal disease, whether or not this in turn reduced the risk of CV complications.

Reference:

1. van Guldener C et al. Carotid artery stiffness in patients with end-stage renal disease: no effect of long-term homocysteine-lowering therapy. *Clin Nephrol* 2000;53:33-41

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