Hyperhomocysteinaemia in liver transplant recipients

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Increased circulating total homocysteine has been implicated as an independent risk factor for atherosclerotic vascular disease.^{1,2} Homocysteine (HCY) is a non-essential, sulphur-containing amino acid derived from the metabolism of an essential amino acid. HCY is formed from methionine as a product of numerous S-adenosylmethionine-dependent transmethylation reactions.³ It is removed by either remethylation to methionine or conversion to cysteine via a transsulphonation pathway. In the liver, a substantial proportion of HCY is remethylated by betaine-homocysteine methyltransferase,³ which uses betaine as a methyl donor.

The concentration of homocysteine in plasma increases because of the reduced activity of one of the enzymes, cystathione- β -synthase, methyltransferase or methionine synthase or because of deficiencies of B12, B6, B2 and folate, which function as coenzymes in homocysteine metabolism.³ Dietary intake of folate, vitamin B12 and vitamin B6 are the chief nutritional determinants of blood homocysteine concentrations, with folate being the predominant vitamin.⁴

The underlying mechanisms by which hyperhomocysteinaemia leads to the development of cardiovascular diseases are not fully understood. Experimental evidence suggests atherogenesis associated with hyperhomocysteinaemia may be caused by endothelial dysfunction and injury, potentially induced by foam cell generation, lipid peroxides and oxidized LDL formed via production of reactive oxygen species.¹ The development of an atherosclerotic cardiovascular complication is a common and serious problem for long-term survivors of organ transplantation.⁵

In renal and cardiac transplant recipients, total homocysteine is markedly raised.^{5,6,7} Data on total homocysteine in liver transplant recipients are limited,^{8,9} but have shown that levels of total homocysteine are increased. We sought to determine plasma homocysteine levels in liver transplant patients who were found to have significant cardiovascular risk factors.^{8,9}

Methods

Blood samples were drawn from 12 liver transplant patients and 12 apparently normal healthy volunteers in EDTA vacutainer tubes (Becton Dickinson). The blood was centrifuged at 3000 g for 10 minutes within

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Ann Saudi Med 24(3):201-202

30 minutes of collection and plasma was stored at -20°C until assayed for homocysteine. Plasma homocysteine was assayed on an Abbott IMX, using an automated fluorescence polarization immunoassay. Blood was also collected into vacutainers without anti-coagulant and centrifuged at 3000 g for 10 minutes after clotting. The serum was assayed for urea, creatinine, aspartate transaminase, alanine transaminase, alkaline phosphatase and g-glutamyl transferase, to assess renal and liver function. These assays were performed on a Synchron Ix20 (Beckman Coulter). All the liver transplant patients were taking tacrolimus (FK506).

Results are expressed as mean $\pm$ SD. Data were analysed using the statistical package for social sciences (SPSS) (13) and a P value of <0.05 was taken as the cut-off level of significance.

Results

All patients and controls had normal renal and liver function as evidenced by a normal urea, creatinine, transaminases, ALP, and GGT. Plasma homocysteine levels were significantly higher

Table 1. Demographics of patients and controls (mean $\pm$ SD).

Variable	Transplant patients (n=12)	Controls (n=19)
Age (years)	35.6 $\pm$ 1.9	32.6 $\pm$ 4.8
Years post-transplant	3.3 $\pm$ 1.9	NA
Homocysteine ($\mu\text{moles/L}$)	14.19 $\pm$ 5.4*	8.55 $\pm$ 2.06

* $P=0.008$

in liver transplanted patients ($P=0.008$) (Table 1). There was no correlation between the homocysteine levels and years after transplantation.

Discussion

The development of atherosclerotic cardiovascular complications is a common and serious problem for long-term survivors of organ transplantation.⁵ Increased circulating total homocysteine has been implicated as an independent risk factor for atherosclerotic disease.^{1,2} An elevated total homocysteine has been found in recipients of kidney and heart transplants.^{5,6,7}

In our study on liver transplant patients, the mean total homocysteine was significantly higher compared to the controls. This finding is in agreement with recent studies showing raised total homocysteine in liver transplant

recipients.^{8,9} Our study, however, did not show raised total homocysteine to be due to renal impairment as shown by other studies. This could be explained by the low number of patients in our study as compared to the other studies, which found renal function as the main predictor, with 35% of variability of total homocysteine explained by high creatinine.⁸ Our study confirms the finding that, as in heart and kidney transplants, liver transplanted patients have a high homocysteine level and organ transplantation may be a cause of elevated homocysteine.^{1,4}

A recent large study found that cardiovascular and cerebrovascular diseases are the second most important cause of late graft loss.¹⁰ Liver transplant patients have been found to have significant increases in other cardiovascular risk factors^{11,12,14} and our findings further add another risk factor to these patients.

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