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Reduction in plasma homocysteine level in patients with rheumatoid arthritis given pulsed glucocorticoid treatment

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High levels of homocysteine are commonly found in patients with rheumatoid arthritis (RA), thus accounting, at least in part, for the high rate of mortality for cardiovascular events in these subjects.[1–5] The mechanisms responsible for hyperhomocysteinaemia in RA are not clear. However, drugs such as methotrexate and sulfasalazine affect homocysteine metabolism, interfering with vitamin metabolism and absorption.[1 3 5] Furthermore, an increased use or accelerated catabolism of vitamin B6 has been shown in chronic inflammatory diseases, particularly RA.[2 6–8]

Recently, it has been shown that rats treated with cortisol have plasma homocysteine levels lower than controls.[9] Glucocorticoids increase the activity of betaine-homocysteine methyltransferase, which transforms homocysteine in methionine with consumption of betaine as methyl donor coenzyme.[10] Moreover, steroids may produce genomic inhibition of several cytokines, leading to an increased availability of vitamin B6.

The effect of glucocorticoids on homocysteine plasma level was evaluated by high performance liquid chromatography (HPLC) in nine patients with active RA (eight women, one man; mean (SD) age 53.4 (16) years) with a mean (SD) duration of disease of 10.6 (8) years, in an open, uncontrolled pilot study. Serum folate (by radioimmunoassay (RIA)), vitamin B12 (RIA), vitamin B6 (HPLC), betaine (HPLC), creatinine (Syncron Chemical System LX 20, Bechman), and C reactive

Table 1 Changes in serum levels of the variables under study. Values are expressed as mean (SD)

	Baseline	2 Weeks	3 Months	6 Months
Homocysteine (normal range <15 µmol/l)				
µmol/l	13.1 (3.5)	11.0 (3.6)***	10.6 (2.7)***	9.6 (2.7)***
Δ %		–16.9	–18.3	–26.0
Creatinine (normal range 50–110 µmol/l)				
µmol/l	58 (18)	64 (9)	65 (18)	65 (18)
Δ %		+8.6	+9.1	+8.9
Folate (normal range 3–17 ng/ml)				
ng/ml	6.3 (3.3)	6.7 (5.0)	6.8 (3.0)	6.7 (2.0)
Δ %		+6.0	+6.4	+5.8
B12 (normal range 200–950 pg/ml)				
pg/ml	498.4 (155)	478.2 (142)	484.5 (231)	498.9 (218)
Δ %		–3.7	–3.1	+1.2
B6 (normal range 4.3–17.9 ng/ml)				
ng/ml	5.7 (2.8)	6.2 (3.6)	5.7 (2.4)	5.7 (2.5)
Δ %		+8.4	+0.3	–0.1
Betaine (normal range 20–144 µmol/l)				
µmol/l	49.7 (21)	42.7 (24)	38.1 (20)*	35.0 (18)**
Δ %		–11.5	–19.1	–25.3
CRP (normal value <5 mg/l)				
mg/l	35.7 (15)	20.9 (13)*	23.9 (10)	24.2 (11)
Δ %		–42.3	–29.2	–30.3

Wilcoxon's test for paired data. *p<0.05; **p<0.01; ***p<0.001. n=9.

protein (CRP) (Syncron Chemical System LX 20, Bechman) were also evaluated. Current treatment included methotrexate (n=7, mean dose 10.7 mg weekly), corticosteroids (n=6, mean dose 7.7 mg daily), and sulfasalazine (n=1, mean dose 1500 mg daily). All patients had normal renal function and vitamin plasma levels, and they were not affected with any concomitant infections or neoplasms or cardiovascular diseases.

After obtaining informed consent, all subjects underwent treatment with three 1 g methylprednisolone intravenous administrations every other day. During the observation period patients with RA continued receiving their usual treatment. Patients, including those treated with methotrexate, did not receive vitamin supplementation or continuous non-steroidal anti-inflammatory drug (NSAID) treatment. Measurements were performed on fresh blood samples before the first drug infusion, and two weeks, three months, and six months after the onset of the treatment.

Patients with RA given steroid pulse therapy showed an early and progressive reduction in homocysteine plasma level. A similar decrease was also seen in the betaine plasma level In contrast, CRP, after an initial reduction, showed a longlasting steady state period. No significant changes in creatinine and vitamin status were seen (table 1). A significant correlation was found between the mean values of homocysteine and betaine (fig 1). Interestingly, homocysteine plasma levels in the three patients not resuming oral steroids after the glucocorticoid intravenous bolus, tended to return to baseline (−17%, −12.5%, −11.3%, after two weeks, three months, and six months, respectively), whereas in the six patients continuing to receive steroids orally, homocysteine plasma levels decreased further (−16.3%, −21.4%, −36.2%, respectively).

Our results show that glucocorticoid pulse therapy is associated with a rapid and longlasting decrease in the homocysteine plasma level in patients with active RA with a possible impact on cardiovascular risk. Indeed, continuing oral treatment with low dose glucocorticoids seems to stabilise the effects on homocysteine metabolism of a single cycle of high dose administration of steroids, which in turn would "switch on" the metabolic cascade of homocysteine.

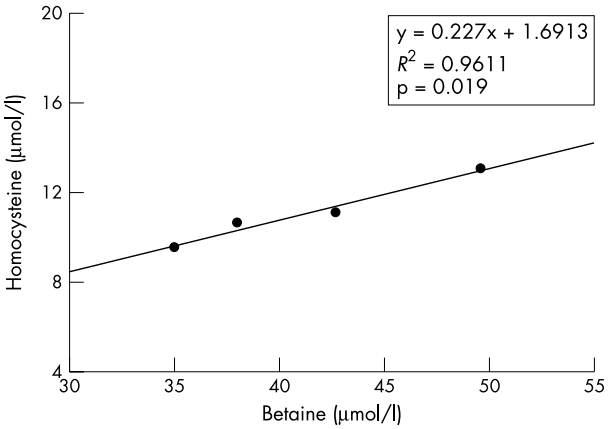

Figure 1 Correlation between the mean values of homocysteine and betaine in plasma. Statistical analysis by the Spearman's correlation coefficient.

Although our data seem to suggest a role for the betaine-homocysteine methyltransferase pathway, the observation that CRP tended to decrease as a possible expression of the reduced activity of the disease, does not allow us to rule out the possibility that lower levels of inflammation related humoral factors may contribute to the observed reduction in homocysteine.

The major limitations of our study is that it was open and uncontrolled, and with a small number of patients. A larger study, also including a control group of patients with RA, is now in progress.

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