Homocysteine (Hcy) Follow-Up Study

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Manuscript submitted 10th July, 2006

Manuscript accepted 12th October, 2006

Clin Invest Med 2007; 30 (1): 21-25.

Abstract

Background: Hyperhomocysteinemia confers an increased risk of coronary artery disease, stroke, and deep vein thrombosis, and is a strong predictor of mortality among patients with ischemic heart disease.

Purpose: To determine the long term clinical outcome of patients with risk factors to atherosclerosis with high concentrations of homocysteine (Hcy).

Methods: 89 patients with one or more risk factors for atherosclerosis, whose plasma total Hcy concentrations were measured, were followed for 5 years. Patients were interviewed and underwent a clinical examination in the outpatient clinic. Their medical records were reviewed in the last 5 years including smoking habits, medications, other diseases (hypertension, diabetes mellitus, hyperlipidemia) and their management. SPSS was used to describe and explore possible relationships between Hcy concentration, other diseases, medications and the clinical long term outcome.

Results: All men with normal Hcy concentrations ($10.76 \pm 1.71 \mu\text{mol/L}$) survived during the 5 years' follow up, while 5 of the men with high Hcy concentrations ($21.27 \pm 5.37 \mu\text{mol/L}$), died (17%) ($P < 0.05$). In women Hcy concentration did not affect survival. No association was found between diabetes mellitus, hypercholesterolemia, hypertension and Hcy. Long term treatment with Beta Blockers, ACE inhibitors, Calcium Channel blockers, and especially with Aspirin prevented death and changed

the natural history of patients with high Hcy concentrations ($P < 0.05$).

Conclusions – Hyperhomocysteinemia may have an effect on survival in men.

Long term treatment with Beta Blockers, ACE inhibitors, Calcium Channel Blockers, and especially with Aspirin – prevented death and changed the natural history of patients with high Hcy concentrations.

It has been demonstrated (the Physicians' Health Study) that moderately high concentrations of plasma homocysteine (Hcy) are associated with subsequent risk of myocardial infarction independent of other coronary risk factors.¹ Hyperhomocysteinemia confers an increased risk of coronary artery disease,¹⁻³ stroke,⁴ and deep vein thrombosis,⁵ and is a strong predictor of mortality among patients with ischemic heart disease.⁶ It is likely that the vascular manifestations are caused by elevated serum concentration of Hcy, because it is toxic to vascular endothelium,^{7, 8} can potentiate the auto-oxidation of low-density lipoprotein (LDL) cholesterol,^{9, 10} and promotes thrombosis.¹¹⁻¹⁵

Our purpose was to determine the long term outcome of patients with risk factors to atherosclerosis with high concentrations of Hcy, and whether medical management may affect their natural history.

Methods

This was a prospective study of 89 patients that were admitted to the Internal Medicine department 5 years ago with one or more risk factors for atherosclerosis (but had no documented cardiovascular disease), whose plasma total Hcy concentration was measured by ELISA methods. All the patients were followed for 5 years and, in order to summarize the data, they were interviewed and underwent a clinical examination in the outpatient clinic, and their medical records were reviewed thoroughly.

Student's t-test, X^2 test and Fisher test were used for the binary outcome variables as the dependent variables.

Results

There were 53 men (60%) and 36 women (40%) with a mean age of 67.44 ± 11.8 yr. Hcy concentrations $> 14 \mu\text{mol/L}$ were considered a high concentration. 24 men (45%) had normal Hcy concentrations (mean $\pm$ SD - $10.76 \pm 1.71 \mu\text{mol/L}$), and 29 men (55%) had higher than normal concentrations (mean $\pm$ SD - $21.27 \pm 5.37 \mu\text{mol/L}$). There were 15 women (42%) with normal Hcy concentrations (mean $\pm$ SD - $9.26 \pm 1.98 \mu\text{mol/L}$) and 21 women (58%) with high Hcy concentrations (mean $\pm$ SD - $19.55 \pm 6.19 \mu\text{mol/L}$) (Table 1).

Comparison of risk factors and clinical characteristics between elevated and normal Hcy concentrations is shown in Table 2.

Patients with Hcy concentrations $> 14 \mu\text{mol/L}$ had higher concentrations (mean $\pm$ SD - $20.5 \pm 5.7 \mu\text{mol/L}$) than patients whose Hcy concentrations were within normal limits (mean $\pm$ SD - $10.2 \pm 1.9 \mu\text{mol/L}$) ($P < 0.0001$). Patients within the high Hcy concentration were older (mean $\pm$ SD - 70.2 ± 11.4 yr) than patients with normal Hcy concentration (mean $\pm$ SD - 63.9 ± 11.6 yr) ($P < 0.05$). However, when sex was studied, old age was an independent risk factor only for men and not for women.

Men whose Hcy concentrations were within normal values (mean $\pm$ SD - $10.76 \pm 1.71 \mu\text{mol/L}$) all survived during the 5 year follow up, while 5 of the men

with high Hcy concentrations (mean $\pm$ SD - $21.27 \pm 5.37 \mu\text{mol/L}$) died (17%; $P < 0.05$).

No correlation was found in women between Hcy concentration and survival.

Using two ways analysis of variance, no main effect was found for diabetes mellitus type II and for sex. There was no interaction between sex and diabetes mellitus type II. No main effect was found for hypercholesterolemia and for sex nor was there an interaction between sex and hypercholesterolemia. There was no main effect for hypertension and for sex nor was there an interaction between sex and hypertension.

Hcy and chest pain

No effect was found between chest pain, and for gender nor was there an interaction between sex and chest pain. No effect was found for CVA and for sex nor was there an interaction between sex and CVA.

The effect of medical management on the clinical outcome:

Among patients with high Hcy concentrations treatment with statins did not affect the clinical outcome during the 5 years' follow up. The same was true for folic acid and vitamin B12. However, long term treatment with Beta Blockers, ACE inhibitors, Calcium Channel blockers, and especially with Aspirin – prevented death and changed the natural clinical history of patients with high Hcy concentrations ($P < 0.05$) (Table 3).

Discussion

In our study only men were clinically affected by high Hcy concentrations during the 5 year follow-up. Men whose Hcy concentrations were normal survived during the follow up, while 5 of the men with high Hcy concentrations died (17%) ($P < 0.05$). No such correlation was observed between Hcy concentration and survival in women, between Diabetes Mellitus type II, Hypertension, CVA and Hcy concentrations.

Homocysteine concentrations are a function of MTHFR C677T genotype; all patients with Hcy con-

TABLE 1 Homocysteine concentrations and sex

	Hcy < 14 μ mol/L	Hcy>14 μ mol/L	Total
Male	n=24(45%) Mean=10.76 μ mol/L SD=1.71	n=29 (55%) Mean=21.27 μ mol/L SD=5.37	n=53(100%) Mean=16.51 μ mol/L SD=6.68
Female	n=15(42%) Mean=9.26 μ mol/L SD=1.98	n=21(58%) Mean=19.55 μ mol/L SD=6.19	n=36(100%) Mean=15.26 μ mol/L SD=7.06
Total	n=39(44%) Mean=10.18 μ mol/L SD=1.94	n=50(56%) Mean=20.54 μ mol/L SD=5.73	n=89(100%) Mean=16.00 μ mol/L SD=6.83

TABLE 2 Risk factors and clinical characteristics and Hcy concentrations

p-value	Hcy $\geq$ 14 (n=50)	Hcy<14 (n=39)	
0.012	70.2 $\pm$ 11.4	63.9 $\pm$ 11.6	Age (yr)
0.7	29 (58%)	24 (62%)	Male
0.0001	20.5 $\pm$ 5.7	10.2 $\pm$ 1.9	Homocysteine
0.3	41 (82%)	35 (90%)	Survival
0.6	24 (48%)	21 (54%)	DM type II
0.5	31 (62%)	27 (69%)	Chol+
0.2	0 (0%)	2 (5%)	TG+
0.4	44 (88%)	32 (82%)	HTN+
0.9	8 (16%)	6 (15%)	Smoke+
0.7	25 (50%)	21 (54%)	Simovil
0.1	21 (42%)	23 (59%)	β block
0.5	20 (40%)	13 (33%)	ACE-1
0.5	20 (40%)	13 (33%)	Ca block
0.8	37 (74%)	28 (72%)	Aspirin
0.1	6 (12%)	1 (3%)	Folic Ac
0.6	2 (4%)	1 (3%)	Vit B12
0.9	39 (78%)	31 (80%)	Chest pain
0.6	19 (38%)	17 (44%)	Cor Ang
0.07	2 (4%)	6 (15%)	CABG
0.4	2 (4%)	3 (8%)	PVD
0.6	13 (26%)	12 (31%)	CVA

TABLE 3. Treatment and survival among patients with high Hcy concentrations

P	Died (n=9)	Survived (n=41)	Medication
1.000	4	21	no
	5	20	yes
0.0001	8	5	no
	1	36	yes
0.576	9	35	no
	0	6	yes
1.000	9	39	no
	0	2	yes

centrations > 30 mgr/l had the MTHFR C677T homozygous substitution. Elevated Hcy concentrations were identified in smokers and in coffee drinkers, with the degree of elevation dependent on MTHFR C677T genotype.¹⁶ Between 1984-1995 serum samples were collected from 11,846 participants in cardiovascular surveys in Japan. By the end of 2000 - 150 people had strokes. Compared with control subjects, the 150 patients who had a stroke, hemorrhagic (n=52) or ischemic (n=98), had higher mean values of total Hcy than patients who did not have stroke. The multivariate odds ratios of Hcy (after adjustment for body mass index, smoking, alcohol intake, hypertension, serum cholesterol, and other cardiovascular risk factors) were 2.99 for total stroke, 3.89 for ischemic stroke, 3.36 for lacunar infarction, and 1.63 for hemorrhagic stroke.¹⁷ In our study no such effect was found – no correlation was observed between Hcy concentration and the development of CVA later on.

Another prospective follow-up cohort study examined serum Hcy in relation to mortality and morbidity from coronary heart disease in 1,368 women. For the fifth Hcy quintile, relative risk was 1.86 for acute myocardial infarction (AMI) and 5.14 for death due to AMI. These differences both for AMI and for death due to AMI were apparent after 15 years of follow-up.¹⁸ In our study women were not affected at all from high Hcy concentrations – in any of the parameters that were studied (survival, chest pain, CVA). In a study that examined Hcy concentration in

patients with coronary artery disease it was found that patients with coronary artery ectasia and coronary artery disease had higher Hcy concentrations than controls.¹⁹

On the other hand, in a prospective, nested, case-control analysis involving 97 cases of sudden cardiac death (SCD) among apparently healthy men enrolled in the Physician's Health Study, only baseline CRP concentrations were associated with the risk of SCD over the ensuing 17 years of follow-up. In contrast to the positive relationship observed for CRP, neither Hcy nor lipid concentrations were significantly associated with risk of SCD.²⁰

Long term treatment with Beta Blockers, ACE inhibitors, Calcium Channel Blockers, and especially with Aspirin may affect and improve the long term survival of patients with high Hcy concentrations. This finding is very important and may have an important clinical implication on long term management of patients with high Hcy concentrations.

The small sample size is a limiting factor, and in order to have better answers and to verify our results larger studies should be done, with an extended duration of follow-up.

Conclusions

Hyperhomocysteinemia may have an effect on survival in men. Men with high Hcy concentrations were older, and 17% of them died during the 5 years' of follow up. Women were not affected from high concentrations of Hcy. Medical intervention with Beta Blockers, Calcium Channel Blockers, ACE inhibitors, and especially with Aspirin improved long term survival in patients with high Hcy concentrations. Thus, the natural history can be changed with medical conservative management.

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