Homocysteine — is it still an important risk factor for cardiovascular disease?

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INTRODUCTION

Homocysteine (Hcy) is an aminoacid discovered in 1932, and a relation between high Hcy level and atherosclerosis and thrombosis was suggested by a finding of premature atherosclerosis and thromboembolism in 2 children who died due to a massive stroke [1]. Research on association between Hcy and atherothrombosis was pioneered by McCully [2]. This was followed by observational studies, both retrospective and prospective, which suggested a causal relations [3]. Blood Hcy level is reduced by supplementation with folic acid, vitamin B_{12}, and vitamin B_6, as these vitamins participate in the metabolism of this toxic aminoacid [4, 5]. A negative correlation was found between folic acid and Hcy levels [6].

However, previous clinical trials of supplementation of these vitamins yielded negative results, i.e. showed no reduction in cardiovascular (CV) events. Recently, these studies were critically reviewed by Ntaios et al. [5] and Debreceni and Debreceni [7, 8]. These intriguing findings continue to puzzle researchers who attempt to clarify this issue. Thus, we also would like to review this interesting topic for our readers.

HOMOCYSTEINE METABOLISM

Metabolism of Hcy has been well established [3–5, 9]. In the body, Hcy is produced from methionine, an essential aminoacid from animal sources. Initially, methionine is transformed to S-adenosylmethionine (SAM) by methionine adenosyltransferase. SAM is demethylated to S-adenosylhomocysteine (SAH) which is then hydrolysed to Hcy.

Metabolism of Hcy may undergo along two pathways. With abundant methionine supply, Hcy is transformed into cysteine (transsulphuration). This reaction is catalysed by cystathionine β-synthase (CBS), a cofactor of which is vitamin B_6. Cysteine is used for glutathione synthesis or is metabolised into taurine. If methionine levels are low, Hcy is metabolised back to methionine by accepting a methyl group (remethylation). Donors of the methyl group include 5-methylenetetrahydrofolate (5-methylene-THF, a folic acid derivative) and betaine. Vitamin B_{12} is a cofactor of remethylation with 5-methylene-THF, and the latter is produced in a reaction catalysed by 5,10-methylenetetrahydrofolate reductase (MTHFR). Remethylation of Hcy with betaine is mediated by betaine-homocysteine methylotransferase. High levels of Hcy are mostly associated with reduction of remethylation, while folic acid and vitamin B_{12} increase remethylation.

In summary, folic acid and vitamins B_{12} and B_6 are necessary as cofactors of enzymes mediating Hcy metabolism. Vitamin deficiencies and/or decreased enzyme activity are associated with decreased breakdown and increased cellular level of Hcy [4]. As a toxic substance, Hcy is removed into plasma. Normally, only trace amounts of Hcy are excreted with urine. Homocystinuria is an inborn error of metabolism which is characterised by markedly increased plasma Hcy levels and largely increased urinary Hcy excretion.

DEFINITION OF HYPERHOMOCYSTEINAEMIA

Due to rapid metabolism, Hcy level is usually low. Hyperhomocysteinaemia is characterised by blood Hcy levels above 15 μmol/L [9]. Levels in the range of 16–30 μmol/L are considered modestly elevated, levels in the range of 31–100 μmol/L are moderately elevated, and levels above 100 μmol/L are considered severe hyperhomocysteinaemia [9]. The latter are found in severe inborn errors of Hcy metabolism. Some authors defined hyperhomocysteinaemia as levels > 12––14 μmol/L. According to Stanger et al. [4], increased Hcy levels (> 12 μmol/L) are seen in 5–10% of the general population and in up to 40% of patients with vascular disease. Statistics for Poland are unfavourable, as Hcy level was above 12 μmol/L in 26% men and 16% women aged 20–74 years [10].

CAUSES OF HYPERHOMOCYSTEINAEMIA

Hyperhomocysteinaemia may be caused by: 1) genetic defects involving such enzymes as MTHFR, methionine synthase and cystathionine β-synthase; and 2) deficiency of cofactors of Hcy-metabolising enzymes, i.e. folic acid, vitamins B_6 and B_{12}, disturbing transsulphuration and remethylation processes. Other causes may also exist.

One of the most common genetic causes of hyperhomocysteinaemia, occurring at large rates in various population, are polymorphisms of the MTHFR gene which result in impaired remethylation. They are responsible for mild and moderate hyperhomocysteinaemia, i.e. Hcy levels in the range of 16–24 μmol/L and 25–60 μmol/L, respectively [9]. Of these polymorphisms, the most common reason for moderate hyperhomocysteinaemia is a point mutation (nucleotide 677) in the coding region of the MTHFR gene [11]. It is believed that severe hyperhomocysteinaemia and classic homocystinuria results from a homozygous CBS deficiency.

However, the leading cause of hyperhomocysteinaemia is folic acid and/or vitamin B_{12} deficiency due to inadequate intake, impaired gastrointestinal absorption, and administration of certain medication such as cyclosporin, methotrexate, fibrates, L-DOPA, and carbamazepine [4, 5]. Populations at risk of vitamin deficiency include the elderly, pregnant women, postmenopausal women, and patients with chronic kidney disease, malabsorption syndromes, and cancer.

Additional factors associated with an increased Hcy level include hypothyroidism, diabetes, hypertension, lipid disorders, alcohol abuse, smoking, and coffee intake [9].

EPIDEMIOLOGICAL EVIDENCE LINKING HOMO-CYSTEINE WITH CARDIOVASCULAR DISEASE

In a meta-analysis of 27 retrospective observational studies that included about 4000 subjects, hyperhomocysteinaemia (defined as levels above 90th or 95th percentile in the control group) was shown to be a risk factor for atherosclerotic CV disease [12]. In this analysis, a 5 μmol/L increase in Hcy level was associated with an increase in the rates of coronary artery disease by 60% in men and 80% in women, similarly to the effects of cholesterol level increase by 0.5 mmol/L. An independent association between hyperhomocysteinaemia and atherosclerotic vascular disease was confirmed in the European Concerted Action Project that included 750 patients with ischaemic heart disease (IHD) and 800 control subjects [13]. In subjects with Hcy level ≥ 80th percentile, the risk of IHD was increased 2.2-fold compared to those with Hcy level < 80th percentile.

Results of prospective cohort studies are unclear. Some indicated a significant positive association between elevated Hcy level and coronary artery disease [14–17] and stroke [17, 18] but others not, such as Physicians Health Study [19], Multiple Risk Factor Intervention Cohort [20], Atherosclerosis Risk in Communities [21] and North Karelia Project [22]. Flour

fortification with folic acid has been suggested as a factor that affected negative results of the more recent studies [23].

In contrast, an association between hyperhomocysteinaemia and an increased risk of IHD was found in a meta-analysis of prospective observational studies (Homocysteine Studies Collaboration) [24]. An increase in Hcy level by 25% (i.e., about 3 μmol/L) was significantly associated with an 11% increase in IHD risk and a 19% increase in stroke risk.

Some but not all epidemiological studies showed that increased Hcy level is a risk factor for total mortality, coronary mortality, or CV mortality. Due to these discrepant findings, Chinese authors have recently performed a meta-analysis of 12 prospective observational studies (duration of follow up 4.1 to 14 years) that included 23,623 subjects [25]. In those with the highest compared with the lowest Hcy levels, the risk of all-cause deaths was increased by 93% (relative risk [RR] 1.93, 95% confidence interval [CI] 1.54–2.43, p < 0.001), coronary deaths by 66% (RR 1.66, 95% CI 1.12–2.47, p < 0.012), and CV deaths by 68% (RR 1.68, 95% CI 1.04–2.70, p = 0.033). In addition, each increase in Hcy level by 5 μmol/L was associated with a 27% increase in total mortality (RR 1.27, 95% CI 1.03–1.55, p = 0.023), a 52% increase in coronary mortality (RR 1.52, 95% CI 1.26–1.84, p < 0.001), and a 32% increase in CV mortality (RR 1.32, 95% CI 1.08–1.61, p = 0.006). Most studies except for 2 included older adults (above 50 years of age). The authors concluded that the results of this meta-analysis suggest that elevated Hcy levels are an independent predictor of future CV deaths and all-cause deaths in the general population.

It is also worth mentioning that a Polish study showed an independent positive association between Hcy level and the risk of CV and all-cause deaths during 38,818.9 person-years of follow-up in the Polish general population (WOBASZ study) [26]. Relative risk of CV and all-cause deaths among subjects with highest Hcy levels (> 10.51 μmol/L) was significantly higher compared to those with lowest levels (< 8.20 μmol/L), at 1.937 (95% CI 1.051–3.569) and 1.766 (95% CI 1.197––2.605), respectively, after adjusting for 8 other risk factors.

Other Chinese authors reported a meta-analysis of prospective observational studies on the association between Hcy level and the risk of various types of stroke [27]. The meta-analysis included 9 studies with 13,284 participants. The relative risk of an ischaemic stroke in the category of highest compared to lowest Hcy level was 1.69 (95% CI 1.29-2.20). The increase in the risk of haemorrhagic stroke was not significant (RR 1.65, 95% CI 0.61–4.45) but the increase in the risk of recurrent stroke was (RR 1.76, 95% CI 1.37–2.24). For the latter risk estimate, only 2 studies provided relevant data.

As explained by the authors, this meta-analysis was inspired by the fact that although previous meta-analyses showed an association between moderately elevated Hcy levels and the risk of stroke [12, 24, 28], they were mostly based on case-control studies which makes it difficult to ascertain

whether an elevated Hcy level is a precursor or a consequence of stroke. Thus, data from prospective studies were needed. In addition, previous meta-analyses did not take into account the type of stroke.

The authors concluded that their meta-analysis showed that elevated Hcy levels increased the risk of ischaemic and recurrent strokes but not haemorrhagic strokes.

Evidence from epidemiological studies indicate that elevated Hcy levels are also associated with an increased risk of venous thrombosis [29–31]. In meta-analyses, an increase in Hcy level by 5 μmol/L was associated with a 60% increased risk of venous thrombosis (odds ratio [OR] 1.6, 95% CI 1.1–2.2), and the risk in subjects with Hcy levels > 95th percentile was increased 2.5-fold compared to controls (OR 2.5, 95% CI 1.8–3.5) [29, 31].

MECHANISMS OF ATHEROGENIC EFFECTS OF HOMOCYSTEINE

It has not been fully elucidated how Hcy affects the development of atherothrombotic events. No single coherent theory has been proposed, and studies have been fragmentary. A number of mechanisms have been suggested including intracellular production of free oxygen species, inhibition of nitric oxide synthesis, activation of thrombosis, endothelial dysfunction, monocyte activation, production of inflammatory mediators including interleukin-8 and haeme carrier protein (HCP-1), and stimulation of smooth muscle cell proliferation [32, 33]. Complex links between hyperhomocysteinaemia and atherosclerosis may also be mediated by endothelial cell DNA hypomethylation associated with accumulation of SAH [34, 35]. SAH is a strong inhibitor of intracellular methylotransferases including DNA methylotransferase. This compound is believed to be more toxic to cells, including endothelial cells, than Hcy. Its effects include induction of reactive oxygen species and reduced nitric oxide bioavailability, resulting in endothelial dysfunction.

VITAMIN B SUPPLEMENTATION AND CARDIOVASCULAR RISK

Several large studies of vitamin B supplementation, including VISP [36], HOPE-2 [37], NORVIT [38], HOST [39], WAFACS [40], VENBIT [41]], SEARCH [42], VITATOPS [43], and SU.FOL.OM3 [44] showed no reduction in the rate of a combined endpoint of CV disease despite reduction of Hcy level, and as a result this preventive approach was abandoned. Why did these studies yield negative results despite observational data indicating an association between Hcy levels and CV risk, and the fact that administration of folic acid, vitamins B_6 and B_{12} effectively reduces Hcy level? This continues to be a puzzle and a subject of debate. Issues that have been raised include heterogeneity of clinical trial participants (mostly patients with CV disease, receiving medications used in secondary prevention), varying duration of intervention,

different vitamin doses, and in most studies, intake of grain products from flour fortified with folic acid.

In addition, meta-analyses yielded discrepant results regarding the effect of vitamin B supplementation on risk. The 2006 meta-analysis of 12 randomised clinical trials by Bazzano et al. [45], which included 16,958 subjects with CV disease, showed no significant reduction in the risk of CV disease, IHD, stroke, and all-cause mortality. Similarly, in the meta-analysis by Clarke et al. [46] (8 clinical trials; 37,485 participants), no significant reduction in CV risk was observed despite reduction in Hcy level by on average 25%.

However, a reduction in the risk of stroke was observed in meta-analyses of other authors, including Wang et al. [47], Lee et al. [48], and Ji et al. [49]. In a meta-analysis of 8 trials, Wang et al. [47] showed that folic acid supplementation effectively reduced the risk of stroke by 18% overall (RR 0.82, 95% CI 0.68–1.00) and by 25% in primary prevention (RR 0.75, 95% CI 0.62–0.90). In addition, this effect was greater in studies with duration of more than 36 months (RR 0.71, 95% CI 0.57–0.87), with a reduction of serum Hcy level by more than 20% (RR 0.77, 95% CI 0.63–0.94), and in those studies in which participants did not consume food products fortified with folic acid (RR 0.75, 95% CI 0.62–0.91).

Lee et al. [48] performed a meta-analysis of 13 studies that included 39,005 subjects. The reduction in stroke risk was 11% among participants receiving folic acid supplementation only (RR 0.89, 95% CI 0.79–0.89) and 17% among participants receiving folic acid and vitamins B_6 and B_{12} (RR 0.83, 95% CI 0.71–0.97). Also Ji et al. [49] in a meta-analysis of 14 studies with 54,913 participants found that vitamin B supplementation resulted in a significant reduction in stroke risk (RR 0.93, 95% CI 0.86–1.00) in addition to a reduction in Hcy level.

CONCLUSIONS

Based on prospective observational studies and clinical data, hyperhomocysteinaemia has been considered a CV risk factor but clinical trials of folic acid and other vitamin B supplementation showed no CV event rate reduction despite effective lowering of Hcy level. However, the effect of this therapy on the reduction of stroke risk that was observed in some clinical trials should be explored further. Of interest, introduction of food fortification with folic acid in the United States and Canada that resulted in a reduction of Hcy levels was associated with a greater decrease in stroke mortality (from –1% to –5.4% in 1998–2002), while no such change was observed during the same period in England and Wales where food fortification with folic acid did not take place [50]. In addition, it has been estimated that in the United States, fortification with 140 μg and 700 μg of folic acid per 100 g of grain products was associated with a reduction in the annual number of myocardial infarction cases by 16,862 and 88,172, respectively [51].

In summary, suggested reasons for negative results of clinical trials include the fact that some of these studies were performed in populations consuming food fortified with folic acid. Another reason may be using aspirin, statins, and other drugs for secondary prevention in both intervention and control groups. In addition, most studies were of short to moderate duration, and some of them included subjects without hyperhomocysteinaemia.

No evidence exists to support CV risk reduction by folic acid and other vitamin B supplementation to decrease Hcy levels, except for some data suggesting a possibility of stroke prevention. Thus, European experts do not recommend vitamin B supplementation in the prevention of CV disease [52], and American experts did not include Hcy among the discussed risk factors [53].

Conflict of interest: *none declared*

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