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REVIEW

Hyperhomocysteinemia and diabetic macroangiopathy: guilty or innocent bystander? A literature review of the current dilemma

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Homocysteine;
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Vitamin therapy;
Controversy

Summary

Background: It is established from a large corpus of clinical studies that even moderately elevated plasma total homocysteine levels are associated with an increased risk for cardiovascular disease, in non-diabetic and in type 2 diabetic individuals. However, recent prospective interventions trials aimed at decreasing plasma homocysteine concentrations using vitamin supplementation (folic acid, Vitamin B-12, Vitamin B-6) were unable to demonstrate a clear preventive benefit on cardiovascular events. In this view, hyperhomocysteinemia could rather represent a marker of vascular risk than a true risk factor *per se*, as previously strongly hinted at.
Objectives: The aim of this review is to analyse the pro- and contradictory data concerning a potential pathogenic role of hyperhomocysteinemia in the development of atherosclerosis, in particular in patients with type 2 diabetes, who are at high risk of developing macroangiopathy.
Conclusions: Hyperhomocysteinemia could be a marker of atherosclerosis rather than a causal factor.

Contents

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Introduction

An impressive corpus of studies has convincingly established that even moderately elevated plasma total homocysteine (tHcy) concentrations are associated with an increased risk for cardiovascular disease (CVD) in non-diabetic and diabetic individuals [1—7]. However, conflicting results were also reported, in particular from intervention trials aimed at decreasing tHcy in relation to CVD natural history [8—11]. The aim of this review is to analyse pro- and contradictory evidence in order to determine the current relevance of hyperhomocysteinemia in clinical practice, in particular in subjects with type 2 diabetes who are at high risk for developing CVD.

Definition and metabolism of homocysteine

Homocysteine is a sulfur-containing aminoacid formed during the metabolism of methionine, an essential aminoacid provided by food. In physiological conditions, the body is able to balance both tHcy production and turnover, the latter being achieved by either remethylation into methionine (in hepatic and non-hepatic cells, including the endothelium), or transsulfuration (in hepatic cells) to cysteine via cystathionine.

Remethylation may occur by transfer of a methyl group from donor 5′-methyltetrahydrofolate (5′-MTHF) in a reaction catalysed by Vitamin B-12-dependent methionine synthase. The production of 5′-MTHF is catalysed from 5-10-MTHF by methyltetrahydrofolate reductase (MTHFR). Remethylation may also occur through an alternative pathway in the presence of betaine, that acts as methyl donor, and betaine-homocysteine methyltransferase. Transsulfuration is initiated by Vitamin B-6-dependent cystathionine β synthase [3,5,7,12].

Normal values of tHcy in the fasting state range from 5 to 15 μmol/l, although an increasing number of authors believe that the upper limit of the normal range should rather be 10—12 μmol/l [1,12,13].

Hyperhomocysteinemia: from acquired to genetic causes

Circulating levels of tHcy may be altered by both acquired and inherited factors. Thus, tHcy increases as a result of advancing age in both sexes, postmenopausal status, smoking, sedentarity, renal failure, hypothyroidism and, as a major cause, of low levels of tHcy metabolization cofactors (*e.g.* Vitamins B-9 [folic acid], B-6 and B-12). Several drugs, including fenofibrate [14], also increase tHcy concentrations (see review in refs. [3,5]).

The inherited factors include various congenital mutations or polymorphisms affecting the normal functioning of enzymes involved in homocystein metabolism. Of paramount importance is MTHFR, a Vitamin B-2 dependent enzyme that plays a key role in homocysteine/folate metabolism [15]. A missense mutation (C to T substitution at position 677 [C677T]) leads to an alanine-to-valine substitution that renders the enzyme thermolabile and less active. This leads to increased levels of tHcy in homozygous individuals, in particular when folate status is impaired [16]. We previously reported in a cohort of 80 type 2 diabetic patients with hyperhomocysteinemia (21.3 ± 6.7 μmol/l, mean ± S.D.) that MTHFR mutation in the homozygous state was present in 23% of subjects, when compared with a mere 8% in a group of subjects who exhibited normal tHcy values ($p < 0.02$) [17].

The overall prevalence estimates of hyperhomocysteinemia vary between 5 and 30% in the general population. Our own data provide prevalences figures of 17 and 31% in cohorts of type 1 and type 2 diabetic individuals [18,19].

Hyperhomocysteinemia and atherosclerosis

The main pro arguments

In non-diabetic populations

Mc Cully was the first to hypothesize that elevated tHcy could cause atherosclerosis [20]. Since that report, abundant epidemiological evidence has validated such a relationship mainly on the basis of