Hyperhomocysteinemia as a Risk Factor for Coronary Atherosclerotic Disease in the Elderly

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The level of homocysteine – a product of methionine demethylation – is regulated by intracellular remethylation and transsulfuration. Through remethylation homocysteine is converted back into methionine, and through transsulfuration it is converted into cystathionine, cysteine and sulfate, excreted by the kidneys. Folic acid is the substrate of the main remethylation pathway, which is catalyzed by methionine-synthase and methylenetetrahydrofolate reductase (MTHFR), and vitamin B12 (cyanocobalamin) is the cofactor. The other pathway, exclusively hepatic, is catalyzed by betaine-homocysteine methyltransferase (BHMT). Transsulfuration is catalyzed by cystathionine beta-sinthase, and vitamin B6 (pyridoxine) is the cofactor. Under physiological conditions the remethylation cycle predominates, whereas under conditions of excess homocysteine an increase in the transsulfuration cycle occurs[1].

The hypothesis of hyperhomocysteinemia as a risk factor for atherosclerosis emerged from studies conducted in children with homozygotic homocystinuria, a rare genetic disorder that affects one in fifty to two hundred thousand newborns[2]. These patients develop premature atherosclerosis (coronary, cerebral, and peripheral) and venous thromboembolic disease, dying before thirty years of age[2,3].

Other causes of hyperhomocysteinemia include the heterozygotic form of homocystinuria (one in one hundred individuals in the general population), MTHFR deficiency (10 to 20% of the healthy population), and group B vitamin deficiencies (folic acid, B6, B12), accounting for two thirds of the cases of hyperhomocysteinemia[1]. Causes of these deficiencies include the use of drugs such as methotrexate, anticonvulsants (carmazepine, phenytoin, phenobarbital), theophylline, contraceptives, and smoking, alcoholism, and nutritional deficiencies. These deficiencies become more frequent in the elderly. This might have been a concurrent factor for the high prevalence of hyperhomocysteinemia (34%) in Taddei et al (*Arq Bras Cardiol 2005;85:166-73)*. Other factors for hyperhomocysteinemia include chronic renal failure, liver failure, neoplasias and psoriasis[1].

Several observational studies, both cross-sectional and longitudinal, have indicated high levels of homocysteine as a primary risk factor for acute myocardial

Infarction or cardiac death[1,4,5]. A similar risk prediction occurs among coronary disease patients. In 587 coronary disease patients followed for four years, a 3.8% mortality was observed among those with homocysteinemia $< 9\mu$mol/l, and a 24.7% mortality among those with values $>15\mu$mol/l. For values between 5 and 20 μmol/L, the correlation with cardiovascular mortality increased, and was more intense for values above 15μmol/l[6].

Taddei et al's study adds important information related to the elderly (65 to 88 years of age), an age range poorly considered in clinical and epidemiological studies. The cases (84) with $\geq$ 70% coronary obstruction, mean age of 72.8 $\pm$ 0.46 years, presented homocysteinemia of 14.33 $\pm$ 6.84 μmol/l, whereas the control group presented levels of 11.99 $\pm$ 4.59 μmol/l, p = 0.015. In coronary obstruction cases, the mean value of homocysteinemia was close to the upper limit of the range considered normal (5 to 15 μmol/l), suggesting that it should be readjusted to lower values. The authors proposed this readjustment based on the fact that above 14 μmol/l the estimated risk of coronary atherosclerotic disease (CAD) among this population was 2.3.

Another important point in this study is the characterization of hyperhomocysteinemia as an additional risk factor in the elderly, an age group where the prevalence of causal risk factors of cardiovascular diseases is high, as was among the patients studied, including the control cases. Thus, the prevalence of high blood pressure was 78.6% in the case group, and 87.5% in the control group; dyslipidemia, 52.4% and 30.7%; diabetes, 34.5% and 21.6%; smoking, 61.9% and 33.0%; sedentary life style, 34.5% and 21.6%; and central obesity, 60.7% and 60.2%, respectively. These data suggest the strength of the association between hyperhomocysteinemia and CAD in these patients, pointing out that more attention should be given to this problem, particularly in this age bracket.

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The type of association between hyperhomocysteinemia and atherosclerotic disease remains unclear. Although hyperhomocysteinemia is considered a cardiovascular risk factor by AHA/ACC, it is classified among the conditioning factors, because the molecular mechanisms linking homocysteinemia to atherosclerosis are unknown[7]. Recent experimental data suggest that homocysteine, even at low concentrations, stimulates the expression and secretion of monocyte chemoattractant protein-1 (MCP-1) and of interleukin-8 (IL-8) by means of the activation of intracellular oxidative processes in endothelial and smooth muscle cells, facilitating macrophage accumulation and contributing to a proinflammatory and proatherosclerotic endothelial response[8].

In Taddei et al's study (*Arq Bras Cardiol 2005;85:166-73*), the high prevalence of hyperhomocysteine also in the control group (37.3%) suggests, in the elderly, a high risk potential that includes cerebrovascular disease, peripheral artery disease, vascular dementia, and Alzheimer's disease[1,9]. In the face of these evidences, how should hyperhomocysteinemia be treated? Its detection is still limited by technical complexity and cost, so the procedure could be reserved only for cases of atherosclerotic disease in the elderly or in patients with no causal risk factor, personal or family history of premature atherosclerosis, low intake of group B vitamin, and presence of comorbidities, and use of drugs associated with hyperhomocysteinemia[1].

In relation to the treatment, the efficacy of the administration of folic acid and vitamins B6 and B12 in the significant reduction of cardiovascular events is not yet proven, as demonstrated by the VISP study ("Vitamin Intervention for Stroke Prevention")[10]. This first randomized, controlled, double-blind clinical trial did not show a significant reduction either in the two-year mortality or in the combined endpoint of stroke, CAD, and death both in the group (1,814) treated with higher doses of folic acid and vitamin B6 and B12 (2.5 mg, 25.0 mg and 0.4 mg, respectively), and in the group (1,835) treated with low doses (0.02 mg, 0.2 mg and 0.006 mg). However, another study – the VITATOPS – with a more proper study design including approximately eight thousand patients is still in progress[11].

The preliminary and general measure for the treatment and prevention is the correction of nutritional habits, with a diet rich in vegetables, green vegetables, fruits, cereals, white meat of poultry, fish, and fortified flour, which are sources of these vitamins[1].

For vitamin supplementation, the AHA Nutrition Committee[3] recommends a 0.4 mg folic acid, 2 mg vitamin B6, and 6 μg vitamin B12 daily intake. Nevertheless, in patients with an adequate diet, supplementation with folic acid alone at 1 to 5 mg/day doses has been empirically used and well tolerated, with a 40 to 50% reduction in homocysteinemia within six weeks.

The current treatment target is homocysteinemia < 13 μmol/l[12]. However, in this group of elderly subjects, the 11.99 μmol/l mean suggests lower levels as a therapeutic goal to be confirmed.

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