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The role of homocysteine, folate and other B-vitamins in the development of atherosclerosis

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SUMMARY. The role of homocysteine, folate and other B-vitamins in the development of atherosclerosis. Recently, elevated homocysteine blood concentrations have been identified as an independent risk factor for the development of atherosclerotic lesions. The amino acid homocysteine is metabolized in the human body involving the vitamins folic acid, B12 and B6 as essential cofactors and coenzymes, respectively. There is an inverse relationship between the status of the relevant B-vitamins and the homocysteine blood concentration. Supplementation of these vitamins results in a significant reduction of the homocysteine level. Nutritive amounts seem to be sufficient to obtain this reduction, even in the case of elevated homocysteine levels.

INTRODUCTION

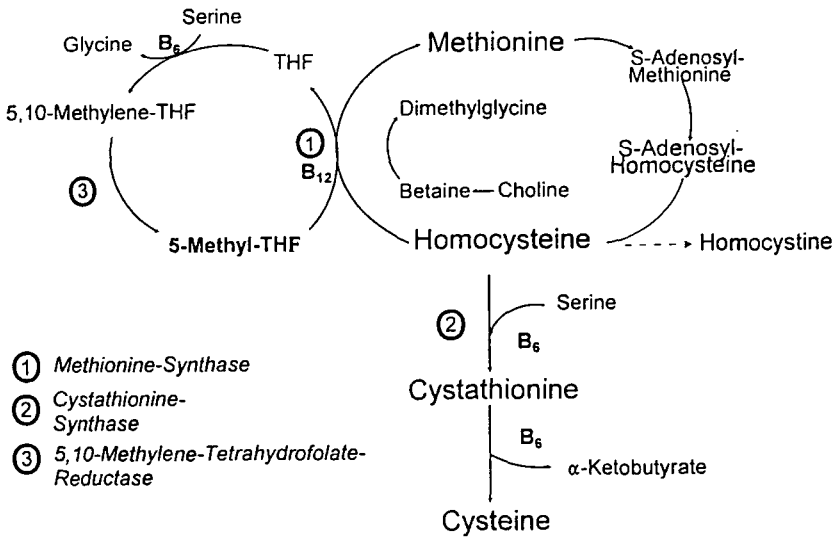
Atherosclerotic diseases like coronary heart disease (CHD) and stroke still are the leading causes of death in the Western World. A variety of risk factors have been associated with the development of atherosclerotic diseases. Among them are hypertension, hypercholesterolemia, smoking and hyperlipidemia, which together account for about 50% of the cases of CHD. However, there must be additional reasons for CHD, since half of the cases cannot be explained by the presence of the established risk factors.

For several years, the amino acid homocysteine has been discussed as a potential risk factor for the development of atherosclerotic diseases. The discovery of homocystinuria in 1962 draw first attention to the association between elevated homocysteine blood levels and the occurence of vascular diseases. In this inborn error of metabolism, homocysteine is accumulated in the blood. This leads to partial oxydation of homocysteine to homocystine, which is then excreted via the urine. If untreated, affected individuals develop large atheroslcerotic lesions as well as thromboembolic events early in life and often die before the age of 30 from stroke or myocardial infarction.

METABOLISM OF HOMOCYSTEINE

In the organism, homocysteine is exclusively derived from the essential amino acid methionine and is not taken up via the diet. Homocysteine can be remethylated to methionine or catabolized to cys-

FIGURE 1
Metabolism of homocysteine



teine (Fig. 1).Three vitamins of the B-group are involved in the metabolism of homocysteine: Folic acid as 5-methyl-tetrahydrofolic acid (5-methyl-THF) is the donor of the methyl group required for the remethylation reaction. Vitamin B12 functions as coenzyme in this reaction. The formation of cysteine requires 2 enzymes for which vitamin B6 in the form of 5-pyridoxal-phosphate (PLP) serves as coenzyme.

RELEVANCE OF HOMOCYSTEINE FOR THE DEVELOPMENT OF ATHEROSCLEROSIS

From observations of extendend and early-onset vascular lesions in homocystinuric patients the question arose if homocysteine levels as seen in the general population would be associated with the development of atherosclerosis. Subsequently, several studies examined the association between (moderately) elevated homocysteine levels and the risk for atherosclerosis. In case-control studies, a high percentage of patients with CHD showed elevated homocysteine levels. Clarke et al.(1) found high homocysteine levels in 42% of patients with cerebrovascular diseases, 28% of patients with peripheral vascular diseases and 30% of cases with coronary vascular diseases. However, none of the healthy control persons showed an elevation of homocysteine blood concentration. Others found that the mean homocysteine level of patients with coronary, peripheral and cerebrovascular diseases was significantly higher than that of comparable controls (2-9).

Despite differences in study design, there is a striking agreement between the numerous studies on this topic. So far, there are 38 studies investigating the association of elevated homocysteine levels and risk for atherosclerotic diseases. Of these 38 studies, 34 did find such an association (10). It was also shown that elevated homocysteine levels are an independent risk factor for the development of atherosclerotic diseases (1,7,9,11,12). In other words, even in the absence of other, established risk factors like hypertension, smoking or hypercholesterolemia an increase in homocysteine concentration alone can be responsible for the development of atherosclerosis.

There seems to be a graded increment in the risk of atherosclerosis with increasing homocysteine levels. It is now accepted that a treshold indicating a significantly elevated risk for persons with homocysteine concentrations above that value does not exist. Calculations show that the risk for coronary disease is elevated by 60% for men and 80% for women with every 5 mmol/l increase in homocysteine levels (10).

Upon comparison of data on the relevance of various risk factors it becomes evident that homocysteine plays an important role as risk factor for atherosclerotic diseases (1,10). It is thought to be at least equally important as elevated cholesterol levels (10).

VITAMIN SUPPLEMENTATION AS A MEANS TO INFLUENCE HOMOCYSTEINE LEVELS

The metabolization and degradation of homocysteine in the body requires the presence of the vitamins folic acid, vitamin B12 and vitamin B6. A low status of these vitamins is rapidly reflected by an increase in the homocysteine blood level. Therefore, homocysteine can be referred to as a functional parameter of the vitamin nutritional status of the respective B-vitamins. Seventy-seven of 78 patients with vitamin B12 -deficiency and 18 of 19 patients with confirmed deficiency of folic acid had elevated homocysteine levels compared to a healthy control group (13). There exists an inverse relationship between homocysteine and the relevant B-vitamins: a low homocysteine level is associated with high blood concentrations of folic acid and vitamin B12 whereas the homocysteine blood concentration increases with decreasing vitamin levels (14)

EFFECTIVENESS OF THE VITAMINS TO LOWER HOMOCYSTEINE LEVELS

By supplementing the vitamins involved in the metabolism of homocysteine, the blood level of this atherogenic amino acid can be lowered. A combination of folic acid, vitamin B12 and B6 given daily in an amount 2,5-4 times the RDA was able to lower the homocysteine level significantly by 17-50% (15,16). The extent depends on the homocysteine concentration at the onset of supplementation: the higher the level, the greater the observed treatment effect.

In our own studies we were able to show that the homocysteine level could be influenced by low (nutritive) doses of the relevant vitamins even in the case of so-called "normal" homocysteine concentrations and adequate vitamin status prior to supplementation. In one of our studies, 35 female students were supplemented with a multivitamin tablet containing 400 mg folic acid, 2 mg vitamin B6 and 6 mg vitamin B12 daily. Within four weeks, the mean homocysteine level decreased significantly by as much as 21% in this group, whereas no change was observed in the control group (placebo; n= 37). Ongoing supplementation did not lead to a further reduction.

Folic acid, vitamin B12 and vitamin B6 differ in their potential to influence the homocysteine level. Vitamin B6 alone does not seem to have a lowering effect (10,15). Supplementation with vitamin B12 resulted in a decrease by 15% in men with initial elevated homocysteine blood concentrations (16). However, in this study as much as 400 mg vitamin B12 was given, which is about 133 times the daily requirement for healthy adults. Folic acid seems to play a key role in lowering homocysteine. In men, a reduction of 42% in homocysteine levels was obtained by supplementation with folic acid (0.65 mg/d) alone, which was not significantly different from the effect obtained by giving a combination of folic acid (0.65 mg/d), vitamin B12 (0.4 mg/d) and vitamin B6 (10 mg/d) (16). Similarly, supplementation of folic acid to young women was as effective in reducing the homocysteine level as a combination of folic acid and vitamin B6 (15).

In their meta-analysis, Boushey et al. (10) estimated that an increase in folic acid intake could prevent up to 50 000 deaths due to CHD in the USA. Calculations for Germany show that the death rate from CHD could be reduced by up to 15 000 depending on the intervention strategy used for increasing the uptake of folic acid (Table 1).

The key role of folic acid in lowering homocysteine is also supported by other authors (10,12,16) and can be explained biochemically: In the metabolism of homocysteine, the vitamins B6 and B12 serve as coenzymes and thus are not used up during the reaction they are involved in. Folic acid, however, functions as donor of the methyl group in the remethylation reaction and is used up quantitatively so that it has to be regenerated to 5-methyl-THF. During the remethylation reaction, the methyl group of 5-methyl-THF is transferred to vitamin B12 and after that to homocysteine to form methionine. Therefore, folic acid acts as limiting factor for this reaction and the absence of the methyl donor cannot be compensated by vitamin B12. Vitamin B12 does not seem to play a key role because it is usually present in sufficient amounts due to large stores of this B-vitamin in the body.

The minor role of vitamin B6 is thought to result from the possibility of the body to increase the remethylation rate in the case of a lack of the respective coenzyme (PLP) and thus limited degradation of homocysteine to cysteine via the transsulfuration pathway. This increase in the remethylation rate seems to sufficiently prevent an accumulation of homocysteine in the body (17).

So far it is known that nutritive amounts of folic acid are able to lower homocysteine levels in young women. This age group usually has homocysteine levels below 10 mmol/l, even though "normal" levels have not been defined yet. The homocysteine blood concentration

TABLE 1
Potential reduction of deaths from coronary heart disease (CHD) for persons aged 45 years and older based on different intervention strategies

Intervention strategy	Annual number of potentially preventable deaths	
	USA	Germany
Food fortification (flour and cereal products)	up to 50 000[1]	~ 15 000[2]
Folic acid supplements (assuming high effectiveness)	up to 28 000[1]	~ 10 000[2]
Nutrition education (assuming high effectiveness)	up to 26 500[1]	~ 8 000[2]

1 Data for USA from JAMA 1995; 274: 1049 - 1057
2 Data calculated for Germany (Pietrzik 1995)

increases with age and reaches levels of 10-15 mmol/l in healthy adults of middle age. Elderly persons show homocysteine concentrations of about 10-25 mmol/l. We assume that nutritive amounts are still sufficient to effectively lower these levels and are currently investigating this topic. However, it might be possible that elderly people require a combination of all vitamins involved in the metabolism of homocysteine since they often have a suboptimal vitamin status. Data from the Framingham study show that 30% of the patients had an elevated homocysteine level. In 67% of these patients a suboptimal vitamin status of one or more of the three B-vitamins was found and thought to be the cause for the elevation of homocysteine (18). It is also known that about 30% of elderly people have an atrophic gastritis which may lower the absorption of vitamin B12 and lead to a suboptimal status of this vitamin over time.

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