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Polymorphism of genes encoding homocysteine metabolism–related enzymes and risk for cardiovascular disease

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Abstract

The aim of this review is to present a general overview of the relationships among homocysteine metabolism, polymorphism of the genes encoding homocysteine metabolism–related enzymes, and the nutrients influencing the plasma homocysteine level. Combining these factors creates a profile of an individual's susceptibility to complex diseases associated with hyperhomocysteinemia. Homocysteine is an amino acid derived from the demethylation of methionine. Hyperhomocysteinemia is associated with an increased risk of several complex diseases, including cardiovascular diseases. The level of plasma homocysteine depends on the combined effects of genetic and environmental factors. Polymorphisms of genes encoding homocysteine metabolism–related enzymes, such as methylenetetrahydrofolate reductase, methionine synthase, methionine synthase reductase, and cystathionine β-synthase, influence plasma homocysteine concentration and thereby cardiovascular health. On the other hand, homocysteine metabolism may be modulated by dietary intake of the nutrients involved in homocysteine metabolism (ie, folates, vitamin B_6, and vitamin B_{12}). Thus, the appropriate health-promoting doses of these nutrients may vary among certain groups of individuals, depending on their genotypes and other risk factors for complex diseases. Better understanding of the relationship between genotype and nutrition influencing the plasma total homocysteine level and cardiovascular health may improve the cardiovascular diagnostic tests (ie, measurement of biologic markers). It could be possible to define the level of progression, severity, and susceptibility to disease much earlier than it is done now. In conclusion, the introduction of combined dietary and pharmacologic treatment would be possible at the initial stages of disease.

Keywords: Cardiovascular disease; Gene polymorphism; Folic acid; Homocysteine metabolism; Human; Hyperhomocysteinemia; Vitamin supplementation

Abbreviations: CAD, coronary artery disease; CBS, cystathionine β-synthase; CVDs, cardiovascular diseases; Hcy, homocysteine; MS, methionine synthase; MTHFR, methylenetetrahydrofolate reductase; MSR, methionine synthase reductase; MTR, methyltetrahydrofolate-homocysteine *S*-methyltransferase; MTRR, 5-methyltetrahydrofolate-homocysteine methyltransferase reductase; PLP, pyridoxal 5′-phosphate; SAM, *S*-adenosylmethionine; tHcy, total plasma homocysteine; THF, tetrahydrofolate.

1. Introduction

It is currently believed that polymorphisms of multiple genes and multiple environmental factors contribute to a complex trait. Cardiovascular diseases (CVDs) are complex diseases that are proclaimed to be the major public health problems in developed countries [1]. In addition to the well-known risk factors for CVD, such as high blood pressure, unfavorable lipid profiles, and smoking, hyperhomocysteinemia also seems to influence cardiovascular health in humans. Epidemiologic studies present convincing evidence

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that hyperhomocysteinemia is associated with increased risk of various diseases, such as those of a cardiovascular nature. Most of these studies suggest that a significant association is observed for total plasma homocysteine (tHcy) levels above 12 to 15 μmol/L. Experimental data suggest that homocysteine (Hcy) could impair normal cellular and physiologic functions [2-4]. It is known that B-group vitamins can lower plasma Hcy concentration, but the results of folic acid supplementation intervention trials, designed to reduce Hcy level, are inconsistent [5]. Nutrigenetic studies, namely, studies that analyze the relationship between genotype, diet, and individual susceptibility to diet-related diseases, may help in determining doses of nutrients regulating the metabolic pathways affecting plasma Hcy concentration. This review describes Hcy metabolism and its genetic and environmental (nutritional) determinants. Associations between polymorphisms of genes encoding Hcy metabolism–related enzymes, plasma Hcy level, and individual CVD risk are discussed. The last section of the review outlines our current understanding of how vitamin supplementation influences plasma Hcy concentration.

2. Homocysteine

Homocysteine (2-amino-4-mercaptobutyric acid), first described by Butz and du Vigneaud [6] in 1932, owes its name to its structure and the resemblance it bears to cysteine, as it is its next higher symmetrical homologue. Homocysteine is composed of sulfhydryl, amino and carboxyl groups, and 3 more carbon atoms [7].

The first mentions of Hcy as a factor that could influence human health appeared in the 1960s, when a group of investigators from Belfast, Northern Ireland, found high concentrations of Hcy in the urine of children with mental retardation. These children also presented other characteristic features of a disease now called homocystinuria, such as growth acceleration, dislocation of ocular lenses, osteoporosis, and a tendency to develop thrombi in blood vessels [7]. Research studies concerning the last mentioned trait of homocystinuria resulted in formulation of the Hcy theory of atherosclerosis in 1975 by McCully and Wilson [8], postulating that moderate elevations of Hcy in blood may be a risk factor for atherosclerosis in the general population. A normal total plasma Hcy concentration ranges from 5 to 15 μmol/L in the fasting state; thus, by elevated concentration is meant that levels in excess of 15 μmol/L and hyperhomocysteinemia is classified as follows: mild (15-30 μmol/L), intermediate (30-100 μmol/L), and severe (>100 μmol/L) [9-11].

The incidence of hyperhomocysteinemia varies between populations and depends on age, sex, lifestyle factors (smoking, alcohol and coffee consumption, diet, usage of vitamin and mineral supplements), and genetic variability [12]. Studies indicate that the percentage of people with hyperhomocysteinemia (judged by the cutoff level for tHcy of 15 or 13 μmol/L) is 11% in Europe and 9.8% in the United States after food fortification with folic acid (compared with the prevalence of 18.7% before mandatory fortification) [13].

Bearing in mind that even mild hyperhomocysteinemia is a risk factor for CVDs, such as ischemic heart disease, stroke [14], deep venous thrombosis, myocardial infarction, cerebral infarction, and peripheral vascular disease [15]. Homocysteine is sometimes called “cholesterol of the 21st century” or “new cholesterol” [16]. However, CVDs are not the only ailments that may be caused by elevated levels of the abovementioned amino acid. It might also be a risk factor for neurodegenerative diseases, including stroke, Alzheimer disease and Parkinson disease [17], psychiatric diseases, including dementia [18] and schizophrenia [19], as well as osteoporotic fractures [20].

Despite the fact that in its structure Hcy is very similar to other amino acids, such as cysteine or methionine, which are present in proteins, Hcy is known to be a nonprotein amino acid. Studies on acid hydrolysates of human hair conducted in the 1960s did not reveal the presence of Hcy in proteins. However, at that time, analytical methods were not sufficiently precise. Nowadays, in vitro studies suggest that it can be incorporated into the polypeptide chain by indirect mechanisms. At high concentrations, it can react with nitric oxide, forming *S*-nitroso-Hcy in which form can be attached to tRNA and then to the growing polypeptide chains on ribosomes. This Hcy modification facilitates incorporation of this amino acid in the position normally occupied by methionine [21]. There is also another possible way for Hcy to be incorporated into the polypeptide chain, which seems to be of greater importance, as it explains its toxic characteristics. This is known as the Hcy-thiolactone theory [22]. It involves the conversion of Hcy to Hcy-thiolactone by methionyl-tRNA synthetase followed by Hcy-thiolactone’s acylation of protein lysine residues. The last reaction, that is, *N*-homocysteinylation, leads to protein damage [23]. Nevertheless, there are other possible metabolic pathways for Hcy to undergo, such as methylation and transsulfuration, resulting in the reduction of its levels in plasma.

3. Homocysteine metabolism

Because food contains only traces of Hcy, this amino acid is present in human cells mainly due to the demethylation of one of the essential amino acids (ie, methionine). In every mammalian cell, methionine may be incorporated into protein or may react with adenosine-5′-triphosphate, forming S-adenosylmethionine (SAM; a universal methyl donor in any transmethylation reactions), which are essential for many important physiologic functions. *S*-adenosylmethionine, when deprived of methyl groups becomes *S*-adenosylhomocysteine. Because *S*-adenosylhomocysteine is an inhibitor of enzymes catalyzing methylation reactions, it has to be removed; therefore, it is enzymatically converted to