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Prevalence of myocardial infarction is related to hyperhomocysteinemia but not influenced by C677T methylenetetrahydrofolate reductase and A2756G methionine synthase polymorphisms in diabetic and non-diabetic subjects

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Abstract

Background: Hyperhomocysteinemia has emerged as a novel risk factor for myocardial infarction (MI). Some mechanisms proposed to explain its relationship with coronary events are also shared by major coronary risk factors. We examined whether C677T methylenetetrahydrofolate reductase and A2756G methionine synthase polymorphisms could affect the relative risk for MI.

Methods: A sample of 196 individuals was divided into four groups (diabetics with MI, n=43; diabetics without MI, n=50; non-diabetics with MI, n=47; non-diabetics without MI, n=56) and compared regarding the prevalence of the polymorphisms, risk factors, and biochemical parameters.

Results: Higher prevalence of hyperhomocysteinemia was found in MI patients (p<0.05 vs. non-MI subjects), in males (p<0.001 vs. female) and in those ≥ 65 years (p=0.01 vs. <65 years). Homocysteine was negatively associated with HDL-C (p<0.05) and glucose, although results did not reach significance (p=0.06). Similar distribution of studied polymorphisms was seen in all groups, which presented normal folate and vitamin B12 serum levels.

Abbreviations: DM, diabetes mellitus; Hcy, homocysteine; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; MI, myocardial infarction; MS, methionine synthase; MTHFR, methylenetetrahydrofolate reductase; Non-DM, non-diabetic; RBC, red blood cell; RF, risk factor; FH, family history of premature CHD.

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Conclusions: Higher homocysteinemia was predominantly observed in men, presenting low HDL-C, and at advancing age. Methylenetetrahydrofolate reductase and methionine synthase polymorphisms did not contribute to risk assessment in diabetic and non-diabetic subjects presenting normal folate levels.

Keywords: Diabetes mellitus; Myocardial infarction; Homocysteine; Polymorphisms; Methylenetetrahydrofolate reductase; Methionine synthase

1. Introduction

Since the past decade, some inherited disorders of methionine metabolism were reported and correlated to higher homocysteine plasma levels [1,2]. Early evidence that hyperhomocysteinemia contributes to a variety of vascular disorders, including premature coronary disease, cerebral and peripheral vascular disease was firmly established based on several retrospective, prospective and cross-sectional studies [3–6].

Diabetes mellitus has been widely recognized as a major risk factor for coronary artery disease and, at the present time, diabetics are considered at high risk for coronary events independently of prior evidence of atherosclerotic disease [7,8]. Diabetes shares many common mechanisms of plaque development with hyperhomocysteinemia, such as those related to endothelial dysfunction, thrombosis and oxidative stress [9,10].

Plasma homocysteine is either converted into cysteine via the transsulfuration pathway mediated by cystathionine beta synthase or it is re-methylated to form methionine by a folate and vitamin B12 dependent enzyme, methionine synthase. This enzyme catalyses the re-methylation of homocysteine to methionine by concurrent demethylation of 5-methylenetetrahydrofolate to tetrahydrofolate [11,12].

Polymorphisms of these key enzymes involved in homocysteine metabolism may add to the risk of coronary events. Recently, methylenetetrahydrofolate reductase (MTHFR) C677T and methionine synthase (MS) A2756G polymorphisms were reported to produce controversial effects in homocysteine plasma levels, which may be dependent on folate intake. For MTHFR C677T polymorphism, subjects who are heterozygous for the T allele have a 12% increase in homocysteine levels, whereas TT individuals have 30% higher levels, compared to CC genotypes [13]. For MS polymorphism less data is available, but it has been reported a protective effect for the G allele on homocysteine levels [14,15].

A 24-year follow-up of the population study of women in Gothenburg, with 1,368 women aged 38–60 years revealed that the relative risk for myocardial infarction (MI) and death due to MI was higher among those in the higher quintiles of homocysteine compared with the lower quintiles [16]. Hyperhomocysteinemia has been also considered a strong predictor of cardiovascular mortality in patients in hemodialysis [17]. In addition, it has been reported that among diabetics, homocysteine levels may be dependent on the glycaemic control [18].

Therefore, taking into account the higher prevalence of diabetes in the modern societies, and the increased importance of homocysteine as an emerging risk factor for coronary disease, we aimed our study to verify the importance of two common polymorphisms and homocysteine plasma levels in the prevalence of myocardial infarction, in diabetic and non-diabetic individuals.

2. Materials and methods

2.1. Subjects

A case control study was carried out on 196 consecutive outpatients from the Lipids, Atherosclerosis and Vascular Biology Laboratory of the Federal University of Sao Paulo. The local Ethics Committee approved the protocol and all patients gave written informed consent to participate in the study. Patients were enrolled according to the presence of either type 2 diabetes mellitus (DM) or prior myocardial infarction (MI), defined by the American Diabetes Association [19], and the World Health Organization [20] criteria, respectively. Study groups were characterized