Obesity, Diabetes mellitus and Methylenetetrahydrofolate reductase mutations: Deadly combinations? How to approach them?

Journal of Diabetes and Endocrinology Research Research Article

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Submitted : 20 Nov 2020 ; Published : 30 Nov 2020

Introduction

Obesity and diabetes mellitus (DM) are important independent risk factors for the development of cardiovascular disease (CVD). Obesity is the leading risk factor for type 2 diabetes. The Centers for Disease Control and Prevention report that 32% of white and 53% of black women are obese. Women with a body mass index (BMI) of 30 kg/m^2 have a 28 times greater risk of developing diabetes than do women of normal weight. The risk of diabetes is 93 times greater if the BMI is 35 kg/m^2. The presence of DM can increase a woman's risk of heart disease 2-fold. In addition, the presence of diabetes overshadows the protective effects of the premenopausal state [1]. Obesity is common, serious, and costly. The prevalence of obesity was 39.8% and affected about 93.3 million of US adults in 2015-2016 [2]. The estimated annual medical cost of obesity in the United States was $147 billion in 2008 US dollars; the medical cost for people who have obesity was $1,429 higher than those of normal weight [3]. Regarding diabetes mellitus (DM), it's a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation. In 2014, 8.5% of adults aged 18 years and older had diabetes. In 2016, diabetes was the direct cause of 1.6 million deaths and in 2012 high blood glucose was the cause of another 2.2 million deaths [4].

The clustering of certain metabolic factors (e.g., abdominal obesity, dyslipidemia and elevated blood pressure), that define the metabolic syndrome (MS), has been documented to identify patients at increased risk for type 2 DM, as well as CVD and overall mortality [5,6]. The MS is a growing health problem worldwide with an estimated prevalence in developed countries of 25-35% in adults, in parallel with the increasing prevalence of obesity and diabetes [7].

An elevation of serum homocysteine level (Hcy) is generally accepted as an independent and graded risk factor for various pathologies, including vascular diseases, neural tube defects, Alzheimer disease, and pregnancy complications between others [8].

Methylenetetrahydrofolate reductase (MTHFR) by catalyzing the conversion of 5, 10 methylenetetrahydrofolate to 5-methyltetrahydrofolate, is a pivotal enzyme in folate metabolism that regulates the proportional usage of one-carbon units between methylation reactions and nucleic acid synthesis. The C677T MTHFR gene polymorphism results in a reduced specific MTHFR activity (~34% residual activity in T677T, ~71% residual activity in C677T relative to C677C) [9].

The MTHFR gene polymorphisms were also found to be associated with body mass index (BMI)-defined obesity and lean mass, sustaining a linkage of body mass index (BMI) and lean mass to chromosome 1p36, where the MTHFR gene is located [10,11].

Cardiovascular disorders, obesity, type 2 diabetes, peripheral neuropathy, and others are related to high Hcy levels and MTHFR mutations so they are responsible of high morbidity and mortality globally. Many patients benefit from diet programs, exercises, genetic screening, serum Hcy levels, and folate supplementation to treat their condition inclusive as prevention. Studies involving a larger study population and different ethnic groups and genetic counseling are required.

Evidence-Based Data

Di Renzo, et al. performed a study where the examined the role of the C677T MTHFR gene polymorphism in the response to diet in the management of metabolic syndrome [9]. They investigated the body composition and metabolic factor changes after a hypocaloric balanced diet (HBD), in Italian obese women affected by metabolic syndrome (MS). Forty-four obese women affected by MS were eligible for the study. A HBD for 12 weeks was assigned. Study participation included a complete

screening for dietary habits, anthropometry, body composition, blood biochemical markers and C677T MTHFR polymorphism genotyping. In the 81% of the total population a loss of Total Body Lean was observed. A significative loss ($p \leq 0.05$) of Total Body Lean was observed in the 47% of T (−) carriers and in the 53% of T (+) carriers. Their data provide the basis for personalized dietary recommendations based on the individual's genetic makeup and nutritional status. MTHFR genetic variations analysis would be an innovative tool for the nutritional assessment.

Pirozzi, et al. evaluated the frequencies of the angiotensin converting enzyme (ACE) gene insertion/deletion (I/D) and MTHFR gene C677T polymorphisms in obese patients with and without type 2 DM [12]. These polymorphisms were analysis by polymerase chain reaction in 125 patients with obesity, 47 (DM) and 78 (Control Group). No significant difference was found on comparing the DM and Control Groups in respect to the genotypic frequencies of the polymorphisms - (II: 13.3% vs. 12.0%; ID: 37.8% vs. 37.3; DD: 48.9% vs. 50.7%; CC: 36.2% vs. 39.0%; CT: 46.8% vs. 49.3%; TT: 17.0% vs. 11.7%), and alleles (I: 32.2% vs. 30.7%; D: 67.8% vs. 69.3%; C: 59.6% vs. 63.6%; T: 40.4% vs. 36.4%) and their synergisms in the pathophysiology of T2DM. On analyzing the DM Group, there were no significant differences in the presence of complications. In this population of Brazilian obese patients, no correlation was found between the ACE and MTHFR polymorphisms in the development of T2DM. In the group with diabetes, there was also no relationship between these polymorphisms and comorbidities.

Gara, et al. studied 31 obese compared to 22 no obese children. Hcy level was assessed by fluorescence-immunoassay; folate and vitamin B12 by radioimmunoassay [13]. C677T and G80A mutations were detected using pyrosequencing. There were no differences in Hcy levels between obese and no obese, (10, 34 ± 4, 86µmoll/l vs11, 00 ± 4,26µmoll/l). They found no difference for the allelic frequencies of the C677T polymorphism (29.03 % vs 30.95 %) and of the G80A polymorphism (64.52 % vs 59.52 %). Mean levels of Hcy, folic acid and vitamin B12 were not significantly different according to MTHFR and RFC genotypes. They demonstrated no difference in Hcy, folates, vitamin B12 levels and allelic frequencies of C677T and G80A polymorphisms in MTHFR and RFC genes between obese and no obese Tunisian children. These two polymorphisms don't seem to have any impact on homocysteine, folate and vitamin B12 status in the two populations.

Regarding insulin resistance and obesity in adolescents related to MTHFR mutation, Frelut, et al. studied one-hundred and thirteen obese (BMI = 39.1 ± 6.4 kg/m^2) adolescents aged 14.4 ± 1.5 years and information on growth obtained from individual health records was available at birth (n = 107), 1 (n = 102), 2 (n = 106), 4 (n = 91) and 8 (n = 73) years of age [14]. Fifty-nine subjects were heterozygote (CT, 52.2%) and 8 were homozygote for the mutation (TT, 7.0%). Birth weights were lower in TT (2.95 ± 0.48 kg, p = 0.004) than in CC (3.34 ± 0.43 kg) and CT (3.38 ± 0.50 kg) subjects, as well as birth lengths (CC: 0.50 ± 0.02 m, CT: 0.50 ± 0.02 m, TT: 0.47 ± 0.03 m, p = 0.01). These differences persisted until 1 year of age. Median and mean fasting glycaemia were similar. Insulin levels were higher in TT (median: 26.4 UI/mL) than in CC (median: 15.0 UI/mL) or CT (median: 16.0 UI/mL) (p = 0.017) subjects, as well as HOMA IR (p = 0.04). Body composition, blood pressure, plasma lipids, homocysteine and leptin concentrations were similar among the three genotypes in both boys and girls. The common 677 C->T mutation seems therefore to represent a link between altered early growth and enhanced degree of insulin resistance that occurs later in obese adolescents.

Regarding diabetic patients, prevalence of the 2 heterozygous polymorphisms of the thermolabile MTHFR gene (CT and AC) was encountered more commonly in patients with diabetes mellitus than in the healthy controls ($p<10^{-3}$) [15]. Subjects who had significantly higher Hcy levels than the control subjects; however, there was no statistical difference in plasma Hcy values between carriers of mutant genotypes (CT/TT for C677T and AC/CC for A1298C) and wild types (CC and AA) in patients with diabetes. Retinopathy was found to be a vascular complication in patients with either the 677CT or the 1298 (AC+CC) genotype more commonly than in those with the wild-type genotypes ($p=0.003$; OR=3.2, 95% CI, 1.4 to 7.4; $p<10^{-3}$; OR=5.9, 95% CI, 2.7 to 13). Only patients who carry the A1298C mutation (AC+CC) are at risk for at least 1 complication ($p=0.002$). Double heterozygous mutants were at the greatest risk for retinopathy and for suffering at least 1 complication ($p<10^{-3}$).

Diabetic peripheral neuropathy (DPN) is also studied in MTHFR mutations. Wu, et al. demonstrated that subgroup analysis by country indicated that the MTHFR 677 C>T polymorphism may be the main risk factor for DPN in Turkey under four genetic models [16]. ACE D>I mutation was correlated with DPN in Japanese and Pakistani populations in most groups. The relationships of MTHFR 677 C>T and ACE I/D polymorphisms with DPN patients presented in this meta-analysis support the view that the MTHFR and ACE genes might play an important role in the development of DPN. Meanwhile, Jiménez-Ramírez, et al. carried out a study and sixty-seven percent (67%) of participants carry at least one of these MTHFR polymorphisms [17]. No deviations from Hardy-Weinberg equilibrium were detected. The genotype and allele frequencies showed statistically significant differences between participants and controls ($p<0.0001$ and $p=0.03$, respectively). Results suggest that 1298A>C but not 677C>T is associated with DPN susceptibility in this cohort ($p=0.018$). Different patterns of allelic dissimilarities are observed when comparing our cohort vs. the three parental ancestries. After sorting individuals by their carrier status, no significant associations were observed between these genetic variants (independently or combined) and any of the biochemical markers (HbA1c, folate, vitamin B12, homocysteine). They concluded that the prevalence of major MTHFR variants in Puerto Rican patients with DM is first time ever reported. The study provides further evidence on the use of this genetic marker as an independent risk factor for DPN.

Conclusions and Recommendations

Obesity, Diabetes, and MTHFR polymorphisms are linked together and carries a high risk for the society globally as well as higher costs in healthcare. From disease management and prevention perspective, these studies have demonstrated that genetic screening for the polymorphisms, serum folate and Hcy levels, and aggressive nutritional evaluation and management

should be applied to decrease the morbidity and mortality with this combinations. Also, important actions for risk factor management in the primary prevention of cardiovascular disease in healthy individuals are needed.

Personalized lifestyle medicine can provide solutions to chronic health , in particularly obesity, diabetes, metabolic syndrome, and diseases related to MTHFR mutations, by harnessing innovative and evolving technologies based on recent discoveries in genomics, epigenetics, systems biology, life and behavioral sciences, and diagnostics and clinical medicine. A comprehensive, personalized approach to medicine is required to promote the safety of therapeutics and reduce the cost of chronic disease. Personalized lifestyle medicine may provide a novel means of addressing a patient's health by empowering them with information they need to regain control of their health.

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