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Original Research

Cyclic supplementation of 5-MTHF is effective for the correction of hyperhomocysteinemia

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ABSTRACT

Folic acid supplementation is the mainstay treatment of hyperhomocysteinemia (HHcy). However, no recommendations are currently available in regard to the optimal replacement therapy. Therefore, this prospective study hypothesized that a cyclic schedule (1 month of therapy followed by 2 months of withdrawal) of 5-methyltetrahydrofolate (5-MTHF) would reduce plasma levels of fasting total homocysteine (tHcy) in patients with mild/moderate HHcy. Patients with a new diagnosis of mild/moderate HHcy were evaluated for the methylenetetrahydrofolate reductase genotype and the presence of major features of metabolic syndrome. All enrolled subjects received a cyclic 5-MTHF oral supplementation and were reevaluated after each treatment cycle for a total of 2 years. In the 246 enrolled subjects, a significant reduction of tHcy levels occurred after the first cycle of treatment (from 31.6 ± 13.6 to 14.4 ± 5.77 μmol/L, $P < .001$) and during the whole 2-year follow-up (from 31.6 ± 13.6 to 12.18 ± 3.03 μmol/L, $P < .001$). The values of tHcy returned to reference range in 117 subjects (51.3%) after the first cycle and in 198 (86.8%) during the follow-up. The risk of failure in tHcy level normalization was increased in patients with metabolic syndrome (hazard ratio [HR], 3.49; 95% confidence interval [CI], 1.46-8.36), higher baseline tHcy levels (HR, 1.045; 95% CI, 1.018-1.073), or methylenetetrahydrofolate reductase homozygous mutation (HR, 6.59; 95% CI, 2.64-16.4). This study clearly shows that a cyclic schedule (1 month of therapy followed by 2 months of withdrawal) of 5-MTHF supplementation is able to significantly reduce tHcy levels in patients with mild/moderate HHcy.

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Abbreviations: HHcy, hyperhomocysteinemia; 5-MTHF, 5-methyltetrahydrofolate; MTHFR, methylenetetrahydrofolate reductase; tHcy, total homocysteine.

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1. Introduction

Homocysteine is the main metabolite of the essential amino acid, methionine [1]. Increased plasmatic levels of fasting total homocysteine (tHcy) are determined by different genetic and dietary factors [2]. The most common cause of genetically determined hyperhomocysteinemia (HHcy) is the C677T polymorphism of the *methylenetetrahydrofolate reductase* (*MTHFR*) gene [3].

Folic acid intake is the most important dietary determinant of tHcy levels. In fact, a 5.0-mg/d folate supplementation is associated with a reduction of ≈25% in plasma homocysteine levels [4]. Folate supplementation is shown to lower tHcy proportionally to baseline tHcy levels and inversely to baseline folate levels, even in the presence of normal folate status and normal tHcy concentrations [5,6]. In addition, some data suggest that the tHcy-lowering effect of folate is greater in subjects with the C677T polymorphism of the *MTHFR* gene [7–9].

However, although a clear association between HHcy and the risk of arterial and venous thrombosis has been documented in prospective [10–16] and retrospective [17,18] studies, there are contrasting data in regard to the role of folate supplementation in controlling tHcy-related thrombotic risk [19]. In addition, no recommendations are currently available on the optimal schedule of folate supplementation in patients with HHcy. Although several studies indicate the effectiveness of folic acid either alone [20–23] or in combination with hydroxycobalamin and pyridoxine [24–26] in reducing tHcy levels, little is known about the tHcy-lowering effects of 5-methyltetrahydrofolate (5-MTHF) [9,27,28], the biologically active compound of folic acid [6,8]. Moreover, as reported in the meta-analysis by the Homocysteine Lowering Trialists Collaboration, there is a wide variability between studies with regard to the duration of folate supplementation in HHcy patients and there is little known about changes in tHcy levels after folate supplementation withdrawal [29–31].

Previously, we documented that a short-course (28 days) supplementation of 5-MTHF was persistently effective in reducing tHcy and increasing plasma folate levels for at least 2 months after 5-MTHF withdrawal [32]. Based on this and the studies discussed above, we hypothesized that a cyclic schedule (1 month of therapy followed by 2 months of withdrawal) of 5-MTHF supplementation is able to reduce tHcy levels in patients with mild/moderate HHcy. To assess this, we provided patients with a cyclic 5-MTHF oral supplementation for a 2-year period. We also evaluated clinical and demographic features that may have impacted the efficacy of 5-MTHF in the reduction of tHcy.

2. Methods and materials

During a 2-year period (March 2009–March 2011), all patients who were referred to the Regional Reference Center for Coagulation Disorders of Federico II University of Naples with a new diagnosis of mild/moderate HHcy without any previous exposure to folate or 5-MTHF were screened for inclusion in this study. The diagnosis of HHcy was determined by the presence of fasting tHcy levels greater than 15 μmol/L, and the severity was defined as mild (tHcy, >12 and <30 μmol/L), moderate (tHcy, ≥30 and <100 μmol/L), or severe (tHcy, ≥100 μmol/L), based on standard criteria [33].

Data regarding age, sex, height, weight, previous and/or current treatments, and major vascular risk factors were collected from all patients. According to the National Cholesterol Education Program criteria [34], definitions are as follows: abdominal obesity, waist circumference ≥102 cm for men and ≥88 cm for women; hypertriglyceridemia, triglycerides levels ≥150 mg/dL; hypercholesterolemia with low high-density lipoprotein cholesterol, total cholesterol ≥200 mg/dL with high-density lipoprotein cholesterol <40 mg/dL for men and <50 mg/dL for women; hypertension, systolic blood pressure ≥130 mm Hg and/or a diastolic blood pressure ≥85 mmHg; and impaired fasting glucose, fasting glucose ≥100 mg/dL. Patients were defined as having metabolic syndrome if 3 or more of these risk factors were present.

In each enrolled patient, tHcy levels and the presence of C677T polymorphism of *MTHFR* gene were determined, as previously described [35]. Patients were excluded if HHcy was not confirmed at the local laboratory evaluation, where tHcy was at least 100 μmol/L (severe HHcy) and in the presence of MTHFR-C677T heterozygosity. Given the known effect on tHcy levels, a simultaneous supplementation with Vitamin B group compounds was not allowed [4].

All enrolled patients were subjected to a cyclic (1 month of therapy followed by 2 months of withdrawal) 5-MTHF oral supplementation of 15 mg/d (calcium *N*5-methyltetrahydrofolate, corn starch, lactose, magnesium stearate, polyethylene glycol 6000, polymethacrylates, polysorbate 80, simethicone, sodium hydroxide, talc), and they were reevaluated after each treatment cycle (every 3 months) for 2 years. At each follow-up, tHcy levels were assessed.

The primary outcome of the study was the assessment of the percentage of patients that reached a therapeutic target (tHcy < 15 μmol/L) during the cyclic 5-MTHF supplementation. In case of achieving the therapeutic target, the cyclic 5-MTHF supplementation was continued, and the mean number of 5-MTHF supplementation cycles necessary to obtain this result was evaluated. In addition, we tested if the presence of the C677T polymorphism and features of metabolic syndrome were associated with a significantly higher tHcy or less effective supplementation therapy.

This study was approved by the Federico II University Ethics Committee and was conducted according to the declaration of Helsinki. All patients provided written, informed consent.

2.1. Statistical analyses

Statistical analysis was performed with the SPSS 16 system (SPSS Inc, Chicago, IL, USA). Continuous data were expressed as means ± standard deviation (SD); categorical variables were expressed as percentages. The *t* test and the analysis of variance with the Bonferroni post hoc test were performed to compare continuous variables. In case of variables with a skewed distribution, nonparametric tests were used. The χ^2 test with the Fisher exact test was used to compare categorical data. The cumulative rate of therapeutic target achievement (tHcy < 15 μmol/L) was described according to a Kaplan-Meier survival curve.

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