

# Does the Available Literature about Hyperhomocysteinemia Cause Confusion to Clinicians?

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## ABSTRACT

**Background—Aim:** Hyperhomocysteinemia (HHcy) (typically defined as serum total homocysteine/tHcy levels  $>15 \mu\text{mol/L}$ ) has been associated with more than 100 diseases, syndromes, or outcomes. However, the current literature about the testing for or the treatment of HHcy causes confusion to clinicians. The aim of this study was to present and comment on the main causes of this confusion.

**Discussion:** The main causes of the above confusion are the important limitations of clinical trials related to the management of HHcy, the false impression that measurement of serum tHcy levels is not useful generally in clinical practice, the inability of modern diet (poor in folate and rich in methionine) to reduce the serum tHcy levels, and, finally, the consequent exclusion of identifying individuals with genetic causes of HHcy, as MTHFR C677T gene mutation.

**Conclusion:** The recommendations about the testing for or the treatment of HHcy must be clarified.

**Keywords:** Homocysteine, Hyperhomocysteinemia, MTHFR C677T, Recommendations.

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## 1. INTRODUCTION

Homocysteine (Hcy) is an intermediary amino acid formed by the conversion of methionine to cysteine. Cross-sectional and prospective studies have revealed that elevated serum or plasma total homocysteine (tHcy) levels have been associated with more than 100 diseases, syndromes, or outcomes [1]. Nonetheless, the inability of clinical trials to prove that lowering tHcy levels with B vitamin supplementation can prevent future cardiovascular events (with the possible exception of stroke) or reduce rates of recurrent venous thromboembolism, has led researchers to consider the amino acid Hcy as a disease biomarker rather than as a risk factor [1] and to exclude it entirely from the latest guidelines for the prevention of cardiovascular disease (CVD) [2], [3]. However, these guidelines include, among others, characteristics of a healthy diet: the limited consumption of methionine-rich foods like red meat and dairy products, and the increased consumption of foods rich in folate and vitamin B6 like fruits and vegetables ( $\geq 200$  gr from each one daily) [2], [3]. In this way, these diet recommendations indirectly aim to reduce the serum or plasma tHcy levels in individuals

with or without the thermolabile variant of methylene tetrahydrofolate reductase (MTHFR). It is remarkable that the current literature review about hyperhomocysteinemia (HHcy) (typically defined as serum tHcy levels  $>15 \mu\text{mol/L}$ ) is not in absolute agreement. For example, UpToDate, the most trusted evidence-based clinical decision support resource at the point of care, suggests not testing for or treating HHcy, unless homocystinuria (a rare autosomal recessive disorder) is suspected or confirmed [4], but another recent literature review concludes that values of tHcy of  $11 \mu\text{mol/L}$  or above may justify intervention [1].

These disagreements of the researchers have caused confusion amongst clinicians regarding the management of HHcy. The aim of this study was to present and comment on the main causes of this confusion.

## 2. DISCUSSION

In my opinion, the main causes of the confusion amongst clinicians regarding the management of HHcy are the following:

(a) The reliability of the related clinical studies. Several researchers support that the recommendation not to test for or treat HHcy was based mainly on clinical trials which have had several important limitations, for example, short study periods, preexisting vascular disease, and insufficient lowering of Hcy levels [1], [5]. They point out that most of the trials were conducted in countries with folic acid fortification of the food supply and primarily among participants who were not required to have elevated tHcy levels at baseline [4]. In addition, they observed that these trials were designed to lower Hcy concentrations with folic acid, but participants with normal folic acid levels were not excluded [4]. Thus, as expected all these limitations caused many clinicians concern about the reliability of relative clinical trials and to consider the management of HHcy with B vitamin supplementation necessary, especially in countries where folic acid fortification is not applied.

(b) Testing for HHcy is not useful generally. The recommendation not to test for HHcy, as well as the absence of any mention of even the term Hcy in the CVD prevention guidelines [2], [3], gives the physician the false impression that measurement of tHcy is not useful generally in clinical practice. Of course, this is not correct. It is known that tHcy measurement is necessary as additional testing for cases in which initial test results for vitamin B12 and/or folate levels are borderline (near the lower limit of normal, i.e., 200 to 300 pg/mL for vitamin B12 and 2 to 4 ng/mL for folate) or inconclusive, or if clinical findings are discordant with initial testing values, for instance, low-normal vitamin B12 level in an individual with unexplained macrocytic anemia or unexplained neurologic findings [6]–[8].

(c) Inadequate intake of folate from foods. It is known that by correcting the nutritional inadequacy of folate and vitamin B12, the serum or plasma tHcy levels will decrease in most patients [4]. For this reason, B vitamins supplementation is considered unnecessary for the treatment of HHcy as the nutritional needs for these vitamins can be covered by the recommended intake of appropriate foods. Yet in reality, the percentage of the general population meeting fruit and vegetable intake recommendations is low [9], [10]. Moreover, folate intake is strongly influenced by various methods of cooking that can degrade the natural forms of the vitamin in foods. Also, the effect cooking has on the reduction of folate content in food depends on the food itself, the cooking method, and cooking time [11]. On the other hand, heavy consumption of meat and dairy products, and excess protein intake in general, can raise tHcy levels by increasing the methionine burden [12]. Therefore, the lowering of tHcy levels through a diet poor in folate and rich in methionine, which unfortunately characterizes the modern human, cannot be achieved.

(d) Testing for MTHFR gene mutation is not useful. No measurement of serum or plasma tHcy levels obstructs the further detection of individuals with MTHFR C677T gene mutation, the most common form of genetic HHcy, which is probably associated with CVD, low serum folate, and 25(OH)D levels [4], [13]–[15]. This is very important considering that the search for T allele presence (mainly 677TT genotype) in patients exhibiting low serum folate levels with accompanying HHcy is critical for determining the appropriate folate supplement in order to

successfully decrease or normalize the elevated serum or plasma tHcy concentrations without increasing the levels of un-metabolized folic acid (UMFA) in the peripheral circulation [13]. It is recommended that folate deficiency among homozygotes (677TT genotype) patients be treated with 5-MTHF (400–800 µg daily) and not with folic acid, mainly because the 5-MTHF supplementation, in contrast to folic acid supplementation, prevents a UMFA accumulation and its potential negative health consequences [13].

### 3. CONCLUSION

The available literature about the testing for or the treatment of HHcy causes confusion to clinicians. Considering that CVD is the leading cause of death worldwide in developing and developed countries, the research on the role of Hcy in human health must be continued, while the recommendations about the testing for or the treating of HHcy must be clarified.

### DISCLOSURE STATEMENT

This study was conducted independently; no company or institution supported it financially.

### CONFLICT OF INTEREST

Author declares that he does not have any conflict of interest.

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