

# Medical foods for lowering homocysteine in hypertensive patients

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## KEYWORDS

blood pressure, homocysteine, hypertension, L-methylfolate, NAC, n-acetylcysteine

## 1 | INTRODUCTION

In a recent commentary, Elias and Brown<sup>1</sup> review the history of skepticism about the value of homocysteine for preventing hypertension and stroke. They argue that this skepticism is not supported by recent literature. This paper was stimulated by a recent comprehensive review of the literature on this topic by Smith and Refsum.<sup>2</sup> Prior to these papers, a commentary and review by Skeete and DiPette<sup>3</sup> provided evidence for the value of homocysteine-lowering in the treatment of hypertension. Elias and Brown<sup>1</sup> supported this conclusion. Both papers emphasized that more work is needed to clarify the beneficial effects of lowering homocysteine.

Elias and Brown<sup>1</sup> argue that lowering of homocysteine is useful for managing treatment-resistant hypertension (TRH), in conjunction with anti-hypertensive drugs. Ten million individuals in the United States alone suffer from TRH.<sup>4</sup> TRH is hypertension not effectively managed with three or more antihypertensive drugs including a diuretic.<sup>4</sup>

Elias and Brown,<sup>1</sup> among others, have discussed specific vitamins for effectively lowering homocysteine and hypertension, that is, vitamin B2, vitamin B6, L-methylfolate, and vitamin B12. However, they did not recommend optimal combinations of these vitamins in a single pill or capsule. The availability of optimal combinations of vitamins for the safe and effective lowering of homocysteine is important to the busy physician who may not have time to discuss lists of vitamins. Patients, especially those taking multiple drugs, would be helped if the number of pills to be taken daily could be minimized by consolidating homocysteine-reducing vitamins into a single prescribable

product. In this paper, we offer our opinion on homocysteine-lowering products that may be useful in lowering blood pressure. Our concerns are safety, efficacy, and compliance. There are drugs available for lowering homocysteine but they are difficult to safely use, that is, Folic Acid and Cystadane. We discuss three medical foods (defined below) with dual benefits of homocysteine and blood pressure lowering. These medical foods are only available to the patient under direct physician supervision.

It is important to state that we do not recommend dietary supplements for homocysteine lowering. Some dietary supplements are advertised for the lowering of homocysteine without a prescription or physician supervision but in absence of data supporting their claim. Such claims are not permitted by the Food and Drug Administration (FDA). Their purity and safety are often suspect.<sup>5</sup> We limit our recommendations for lowering homocysteine to medical foods as defined by the FDA.

## 2 | MEDICAL FOODS

The FDA defines medical foods as oral products administered under the supervision of a physician intended for the dietary management of a disease or condition with established distinctive nutritional requirements.<sup>6</sup> They are “intended for dietary management of a patient who, because of therapeutic or chronic medical needs, has impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients, or who has other special medically

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determined nutrient requirements, the dietary management of which cannot be achieved by the modification of the normal diet alone" (pp 3–4).<sup>6</sup> Medical foods are not drugs, they are natural food constituents in higher concentrations than found in the diet, manufactured to high purity standards, and only available from physicians or pharmacies.<sup>6</sup>

In addition to meeting the general criteria for medical foods, ideally the medical foods for homocysteine would contain vitamin B2, riboflavin; vitamin B9, L-methylfolate; and n-acetylcysteine, NAC. In the next section, we discuss their dual benefits of homocysteine and hypertension reduction, explaining why L-methylfolate is safer and more effective for lowering homocysteine than folic acid.

### 3 | KEY INGREDIENTS: L-METHYLFOLATE, RIBOFLAVIN, AND NAC

Du et al. argue that folic acid effectiveness for homocysteine reduction is less than ideal.<sup>7</sup> In their prospective cohort study almost half of the trial participants failed to reach a modest goal of 15  $\mu\text{mol/L}$  when treated with folic acid. Study participants with certain polymorphisms of methylene tetrahydrofolate reductase, MTHFR, and methyltetrahydrofolate-homocysteine methyltransferase reductase, MTRR had the highest risk of folate therapy failure. *MTHFR* C677T, *MTHFR* A1298C, *MTRR* rs1801394, and *MTRR* rs162036 are associated with impaired folate metabolism.<sup>7</sup> Patel and Sobczynska-Malefora reviewed folic acid toxicity with respect to the common dihydrofolate reductase polymorphism *DHFR19del*, which impairs the conversion of folic acid into active L-methylfolate. *DHFR19del* further accounts for the failure of folic acid to maximally reduce homocysteine reported by Du et al.<sup>7,8</sup>

*MTHFR* folate polymorphisms are known to be associated with increased homocysteine and risk of hypertension.<sup>7–11</sup> Unlike folic acid, L-methylfolate is unaffected by *DHFR* and *MTHFR* polymorphisms and has superior effectiveness for lowering homocysteine, even in patients with advanced renal disease.<sup>8,10–12</sup> L-methylfolate is a natural food folate with no upper limit safety concerns, unlike folic acid, with the dual benefit of lowering blood pressure.<sup>8,12,13</sup> This suggests that future folate trials should use L-methylfolate rather than folic acid.

Riboflavin and n-acetylcysteine, NAC, are also associated with dual homocysteine and blood pressure reduction.<sup>1,10,11,14</sup> Ischemic stroke is a dreaded complication of hypertension. Thus, it is important to note that NAC also reduces thrombolysis and stroke volume without increasing hemorrhagic complications.<sup>14,15</sup>

In view of this literature, we are of the opinion that L-methylfolate, riboflavin, and NAC should be part of non-drug strategies for lowering homocysteine in hypertensive patients.

### 4 | RECOMMENDATIONS

Based on our criteria and the literature, we recommend three medical foods for lowering homocysteine: Metanx®, Cerefolin® NAC, and Ocufofolin®. Table 1 summarizes their contents.

Metanx®, developed for peripheral neuropathy, contains the active natural forms of vitamins B6, L-methylfolate, and methyl B12. Fonseca et al. validated its homocysteine lowering benefit.<sup>16</sup> However, Metanx® lacks vitamin B2 and NAC.

Cerefolin® NAC, developed for cognitive impairment, contains L-methylfolate, methylB12, and NAC. Shankle et al. found a significant lowering of homocysteine in a prospective study that showed reduction of ischemic white matter atrophy in the brain.<sup>17</sup> However, it lacks riboflavin and B6.

Ocufofolin® was developed to reduce ocular ischemia, oxidative stress, and retinal microvascular disease. It contains multiple antioxidants including NAC and the active forms of vitamins B2, B6, L-methylfolate, and methylB12. Ocufofolin® has been shown to increase blood flow in the retina and conjunctiva of diabetic retinopathy patients.<sup>18</sup> A study of 24 diabetic patients taking one Ocufofolin® daily documented a 30% reduction of homocysteine.<sup>19</sup> We have seen the reduction of homocysteine from 47 to 15  $\mu\text{mol/L}$  in a patient after 3 months of three Ocufofolin® daily.

In our opinion, Metanx®, Cerefolin® NAC, and Ocufofolin® are safe and effective for lowering homocysteine.<sup>16–19</sup> The second author of this paper has successfully used all three.

### 5 | BLOOD PRESSURE AND MEDICAL FOODS

The growing evidence that homocysteine and blood pressure are positively related,<sup>1–3,7,9,11–14,20–22</sup> lends support to our argument that the products discussed above (Table 1) will very likely be effective in lowering blood pressure. Skeete and DiPette<sup>3</sup> suggested the mechanism underlying a positive relation between the two: high homocysteine (levels > 10  $\mu\text{mol/L}$ ) "produces hypertension and cardiovascular disease ... through homocysteine mediated damage to vascular smooth muscle and endothelial cells." (p 1171).

It is important to note that we have not found any long-term studies or observational trials of these or any other medical foods evaluating blood pressure. Nevertheless, there are several lines of indirect evidence that the medical foods shown in Table 1 may be effective for lowering blood pressure if one considers their ingredients. Three key ingredients are riboflavin, L-methylfolate, and NAC. As previously noted, they are associated with dual activity: lowering homocysteine and blood pressure.<sup>10–14</sup> Ocufofolin® also contains other vitamins and antioxidants associated with lowering blood pressure, at least modestly, improving vascular endothelial health, and potentially reducing stroke severity in one or more studies.<sup>12,15,23</sup>

Our arguments for the potential effectiveness of Metanx®, Cerefolin® NAC, and Ocufofolin® in lowering blood pressure do not obviate the need for observational studies and trials with these medical foods. There have been conflicting findings with regard to the relationship between homocysteine and blood pressure.<sup>21</sup>

Commenting on these mixed findings, Skeete and Dipette<sup>3</sup> point out that the conflicting evidence surrounding the relation between homocysteine and blood pressure may be based on different subpopulation responses to the vitamins or that the vitamins themselves

**TABLE 1** Recommended medical foods for lowering of homocysteine

Product	Metanx®	Cerefolin® NAC	Ocufolin® <sup>a</sup>
<b>Classification</b>	Medical Food	Medical Food	Medical Food
<b>Form</b>	Tablet/Capsule	Tablet/Capsule	Capsule
<b>Key Ingredients for Homocysteine Reduction</b>			
Vitamin B12 (cobalamin)	2.0 mg Methylcobalamin	2.0 mg Methylcobalamin	1.5 mg Methylcobalamin
Vitamin B9 (folate)	3 mg L-methylfolate	6 mg L-methylfolate	2.7 mg L-methylfolate
Vitamin B6 (pyridoxal/pyridoxine)	35 mg Pyridoxal 5-phosphate		9 mg Pyridoxal 5-phosphate
Vitamin B2 (riboflavin)			30 mg Riboflavin
N-Acetylcysteine		600 mg	540 mg
<b>Other Ingredients</b>			
Vitamin B1 (thiamin)			4.5 mg Thiamine
Vitamin B5 (pantothenate)			15 mg Pantothenic Acid
Vitamin C (ascorbic acid)			135 mg
Vitamin D3 (cholecalciferol)			112.5 mcg
Vitamin E (d-alpha tocopherol)			15.08 mg
Zinc			80.25 mg
Copper			2 mg
Selenium			60 mcg
Lutein			10.05 mg
Zeaxanthin			2.1 mg
Proprietary	90.314 mg of Algae-S Powder (Schizochytrium)	90.314 mg of Algae-S Powder (Schizochytrium)	None

<sup>a</sup>Three capsules/day are recommended.

may intrinsically lower blood pressure independently of homocysteine, but that this hypothesis is difficult to test. We argue that, from a clinical perspective, we win either way if vitamins per se, their homocysteine-lowering effects, or a combination of both result in lowered blood pressure and reduced stroke. In the text above we submit evidence that in the common subgroups of *MTHFR c677t*, *DHFR19del*, and renal failure, these specific vitamin combinations lower both homocysteine and blood pressure.<sup>7,8,10-15</sup>

## 6 | SUMMARY AND CONCLUSIONS

We argue the need for single products, pills or capsules, containing multiple ingredients to lower both blood pressure and homocysteine. We recommend that they be medical foods to assure purity and efficacy.

Minimally, they should contain L-methylfolate. Ideally, they would also contain riboflavin and NAC.

We conclude that Metanx®, Cerefolin®, and Ocufolin® are safe and effective products for lowering homocysteine, with the likely additional benefit of lowering blood pressure in important subgroups of hypertensive patients, even in patients with advanced renal failure. We encourage further studies of their ingredients to address blood pressure, homocysteine, and stroke. We encourage the development of new products with these ingredients and others to lower homocysteine and blood pressure in the hypertensive individual.

## AUTHOR CONTRIBUTION

Merrill F. Elias and Craig J. Brown are equal co-authors to all aspects of this manuscript. Descriptors: homocysteine: blood pressure; hypertension; L-methylfolate; n-acetylcysteine,NAC; riboflavin.

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None.

## CONFLICTS OF INTEREST

Merrill F. Elias Disclosures: None. Merrill F. Elias Conflicts of Interest: None. Craig J. Brown Disclosures: Craig J. Brown is a stockholder and managing partner for Global Healthcare Focus, a nutraceutical company focused on addressing retinal ischemia. He participated in the formulation and development of Ocufofin, a medical food. Craig J. Brown Conflicts of Interest: None.

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