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New Evidence for Homocysteine Lowering for Management of Treatment-Resistant Hypertension

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American Journal of Hypertension, Volume 35, Issue 4, April 2022, Pages 303–305, <https://doi.org/10.1093/ajh/hpab194>

Published: 22 December 2021

Topic: hypertension, homocysteine, hypertension refractory

Issue Section: Commentaries

Treatment-resistant hypertension is a topic of great importance and the subject of editorial comments in the *American Journal of Hypertension*.^{1,2} Homocysteine is an intermediate compound in the vitamin regulated One Carbon Methylation pathway which affects glutathione, methionine, and nitric oxide metabolism. Elevated homocysteine, triggered by genetic mutations or insufficient body stores of active vitamins B6, B12, folate, riboflavin, indicates oxidative stress and is associated with impaired nitric oxide synthesis causing small vessel vasoconstriction in the central nervous system.^{3–5} High homocysteine (defined later) is also a risk factor for hypertension.⁶

THE CONTROVERSY

As early as 2002, papers recommending the reduction of plasma homocysteine levels as an approach to managing treatment-resistant hypertension appeared in the literature.^{5,7} Shortly afterwards, studies criticizing the efficacy of folic acid for homocysteine reduction to prevent death from cardiovascular disease and stroke were published in the *New England Journal of Medicine* (NEJM), leading to general skepticism of the value of this treatment for cardiovascular and neurovascular disease.^{8,9} In fact, as Spence has noted, Bonaa, at the 2005 meeting of the European Society for Cardiology, essentially proclaimed that there was no future for

homocysteine and vitamin research, i.e., that this research was dead.^{10,11} However, Bonaa's pronouncement, and its flawed interpretation, continue to meet with many objections.

Spence, in a landmark editorial, declared that the funeral for homocysteine lowering treatment is premature.¹¹ We agree. Lowering homocysteine does not currently receive the attention it deserves for treatment-resistant hypertension.

A recent review by Smith and Refsum summarized the major problems with antifolate argument, which argues against the efficacy of homocysteine reduction⁶: (i) the study periods were too short; (ii) the studies were limited to individuals with preexisting vascular disease; (iii) homocysteine levels were often estimated rather than measured and insufficiently lowered; and (iv) positive outcomes of stroke prevention were *a priori* discounted and downplayed.

In addition to taking issue with studies arguing against efficacy of homocysteine, Smith and Refsum muster an impressive array of papers indicating that supplements, with sufficient amounts of nondietary sourced vitamins B2, B6, folate, and B12 are associated with lowering of homocysteine levels safely, and that this is associated with reduction of adverse cardiovascular and neurologic events, as well as improved cognitive performance in the cognitively impaired.⁶

Space does not permit a review of all the studies establishing the links between high homocysteine values and hypertension, but a major meta-analysis study will suffice. Zhong *et al.*¹² report a meta-analysis and review involving 11 studies (4,830 cases of essential hypertension). Homocysteine (defined differently in various studies) was statistically significantly associated with blood pressure for the odds ratios based on all subjects in the study: odds ratio = 1.36, 95% confidence interval: 1.02–1.80. Because of small numbers of study participants in the individual studies contributing

to the analysis, and the defining of “high” homocysteine with different homocysteine values, analyses of result for the individual studies were not meaningful.¹² We discuss the need for standardization of values representing high homocysteine later in this paper.

We hope that Smith and Refsum’s updated findings with renewed emphasis on treatment-resistant hypertension will encourage reconsideration of homocysteine management as an important component of multimodal approaches for addressing this disease.

H-HYPERTENSION

The term H-hypertension was introduced into the literature recently by Chinese investigators who were describing the synergistic relations between elevated homocysteine and hypertension in Chinese populations. Li *et al.*^{13,14} have defined H-hypertension as blood pressure values above 140/90 mm Hg accompanied by homocysteine values of ≥ 10 μmol .

H-hypertension with elevated all-cause mortality (ACM) is not unique to Chinese populations.¹⁵⁻¹⁷ Zhao *et al.* established that elevated homocysteine in hypertensive older American patients predicted the increased risk of ACM.¹⁶ For every 1 $\mu\text{mol/l}$ increment of increase, there was an 8% increased risk of ACM and 7.15% increased risk of cardiovascular disease mortality in hypertensive participants. Fan *et al.*, in an extensive meta-analysis, confirmed the association of elevated homocysteine and ACM suggesting chronic cardiovascular disease exacerbation and the linkage.¹⁷

The concept of H-hypertension is old wine in new bottles, but the term serves to increase our awareness on the relationship of homocysteine with hypertension. This is important for effective management of treatment-resistant hypertension.

WHAT IS NORMAL HOMOCYSTEINE?

Conflicting “normal” values for homocysteine have long been a source of clinical confusion. Older reference values for normal are often higher than recent ones. Smith and Refsum⁶ conclude, based on considerable evidence, that homocysteine values of ≤ 10 $\mu\text{mol/l}$ are likely safe, but higher values, may benefit from intervention. ACM studies, when graphically presented reveal that any elevation above 5 $\mu\text{mol/l}$ brings increased risk of death, which continues to increase as the homocysteine increases, irrespective of “normal distributions” and may suggest optimal values lower than the upper 95%.^{6,17}

Clearly the use of different reference values for “high” homocysteine across different studies has been a source of confusion and differing findings as to the relation of homocysteine to hypertension. Standardization of reference values across studies is needed. Research on optimal definitions of high homocysteine must continue. But for now, the Smith and Refsum paper gives us new empirically based reference values.⁶

FOLIC ACID VS. L-METHYLFOLATE

Folic acid has been the only study agent chosen to reduce homocysteine and shows weak evidence for stroke prevention with no benefit for ACM and cardiovascular mortality.¹⁸ Folic acid is not bioequivalent of natural dietary folates in patients with common folate polymorphisms. It does not directly lower homocysteine, may cause renal toxicity and, unlike natural L-methylfolate, does not cross the blood brain barrier.¹⁹⁻²¹ This calls into question whether folic acid is the appropriate folate to address hypertension and neuroprotection. Which folate is the optimal agent for therapeutic outcomes? This is an important question that needs to be addressed in further studies.

HOMOCYSTEINE-DRIVEN OPPORTUNITIES FOR HYPERTENSION RESEARCH

Genome-wide studies by McNulty *et al.*³ reveal that the MTHFR gene is one of eight loci associated with blood pressure. Individuals carrying the common MTHFR C677T mutation have decreased affinity for the essential cofactor FAD (riboflavin), exhibiting higher blood pressure values than controls, with a very high risk of diagnosed hypertension. McNulty *et al.* also found significant reductions in blood pressure in randomized control studies employing riboflavin (B2) averaging 6–13 mm Hg, independent of medication.³ In another randomized trial, it was demonstrated that as little as 1.6 mg/day of riboflavin decreased systolic blood pressure more effectively than hypertensive drugs alone.⁴ They noted that a 2 mm decrease in blood pressure reduces stroke risk by 10%.⁴ Other studies reveal consistent evidence that riboflavin administration represents an underutilized approach for the treatment of resistant hypertension and stroke prevention.^{3,19}

While resistant hypertension treatment issues are central to our paper, the new homocysteine literature has important implications for addressing brain related cognitive impairment. Newer studies of managing homocysteine with high-dose vitamin supplementation also demonstrate benefits for brain preservation, cognition, and macular degeneration.⁶

BARRIERS TO DIAGNOSIS OF H-HYPERTENSION

We don't know what we don't know. Insurance companies make it difficult to test for homocysteine. Homocysteine assays are rarely included in test panels comprehensive physical examinations and thus elevations are routinely missed.

Many insurance companies now refuse reimbursement, saying the usefulness of homocysteine assays has been questioned. Criteria for

insurance approval are obscure, inconstant, and inconsistent in order to discourage patients and practitioners from investigating homocysteine-driven pathologies. The documentation and the appeal processes are exhausting. Although a patient may access homocysteine testing from an independent laboratory without insurance coverage, these tests are expensive.

Homocysteine assays should be routinely covered by insurance for the diagnosis and management of hypertension and monitored annually. The fact that it is not, making the data unavailable to the clinician, is a barrier to addressing the homocysteine component of the H-hypertension form of resistant hypertension.

SUMMARY

Reembracing the label H-hypertension, with renewed attention on homocysteine pathophysiology and more nuanced homocysteine reference intervals will clarify the current confusion. Lowering homocysteine and hypertension do not always require dangerous or expensive drugs.

Addressing how C677T riboflavin insensitivity leads to L-methylfolate depletion, homocysteine elevation, and resistant hypertension, points to an elegant and safe opportunity for attacking stubbornly resistant hypertension ultimately improving neurological and cardiovascular outcomes.^{3,4,19}

A significant literature indicates that supplements with sufficient nondietary sourced vitamins B2 (riboflavin), B6, reduced folate, and B12 can blood pressure as much as 6–13 mm Hg. Utilizing riboflavin and folate is a safe and economical therapy for reduction of hypertension and stroke.^{3,4,19}

The goal is successful management of treatment-resistant hypertension and safely reducing its consequential end organ damage to hearts, brains, and vision. It is time for action.

Craig Brown is a stockholder and managing partner for Global Healthcare Focus, a nutraceutical company focused on addressing retinal ischemia.

DISCLOSURE

The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to writing and editing this paper.

DISCLAIMER

Any views or opinions are those of the author(s) only and not of the AJH or its Editors.

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