DOI: 10.1111/jch.13073

COMMENTARY

WILEY

Relationship between homocysteine and hypertension: New data add to the debate

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Over the past 5 decades, as well as presently, the morbidity and mortality attributable to hypertension continues to be a major public health issue both at the local and global levels. Despite individual and population-based efforts to address the traditional and well-known modifiable risk factors that contribute to cardiovascular disease, including hypertension, such as reducing dietary sodium intake, weight reduction, increasing physical activity, and smoking cessation, the disease burden attributable to hypertension and its corresponding target organ damage is on the rise. This increase is associated with considerable individual, family, societal, and economic implications.

Of the multiplicity of established risk factors associated with the development of hypertension and its complications (such as heart disease, stroke, chronic kidney disease, accelerated atherosclerosis, and premature death), hyperhomocysteinemia has arguably been one of the most elusive of the proposed risk factors to convincingly link to hypertension. Multiple clinical and epidemiological studies investigating the relationship of increased homocysteine levels to hypertension have come to contrasting conclusions. As such, the debate as to the causal link between hyperhomocysteinemia and hypertension continues.

The main proposed mechanism by which hyperhomocysteinemia (generally defined as serum homocysteine levels >10 μmol/L) produces hypertension and cardiovascular disease is through homocysteine mediated damage to vascular smooth muscle and endothelial cells. This damage, in turn, leads to a loss of arterial vasodilation, vascular integrity, and thus increased blood pressure (BP) and accelerated atherosclerosis. This hypothesis has been supported by findings of both in vitro and in vivo basic science studies. Given the availability of modalities to lower homocysteine levels in humans, in particular, through the administration of inexpensive B vitamin dietary supplements, if a true link exists between hyperhomocysteinemia and hypertension, the potential implications on reducing hypertension disease burden are large and exciting.

Pertinent to the continued debate regarding the role of homocysteine in hypertension, Yang and colleagues[1] report in this issue of the Journal their study entitled "Interactions of Homocysteine and Conventional Predisposing Factors on Hypertension in Chinese Adults."[1] In this case-control study, the relationship between homocysteine levels and hypertension, as well as its interaction with additional factors, was explored. The study recruited a total of 2615 adults using a multistage sampling method. The initial observation of the study was that elevated levels of homocysteine were significantly associated with hypertension and BP (P<.05 for both). Importantly, the study demonstrated that within the population studied, factors such as age, overweight/obesity, dyslipidemia, and family history of hypertension were significantly associated (ie, played interactive roles) with the interaction between hyperhomocysteinemia and hypertension. These results led the authors to conclude that there is strong evidence for the interaction of homocysteine with these associated cofactors and the relationship to BP and hypertension. This study adds a novel approach to exploring the relationship between elevated homocysteine levels and hypertension. In addition, it may help explain some of the discrepancies seen in the previous studies on this subject, as mentioned above. It sheds light on the possibility that the relationship between hyperhomocysteinemia and hypertension is not linear or direct, but, rather, involves a more complex relationship involving the input of other key factors in select populations.

Several large observational trials, including NHANES III (the Third National Health and Nutrition Examination Survey) and a substudy of the SHEP (Systolic Hypertension in the Elderly Program) trial, demonstrated an increased prevalence of hypertension in persons with higher compared with lower homocysteine levels.[2,3] In the case of NHANES III, which provides some of the most convincing evidence for the association between hyperhomocysteinemia and hypertension, a 5-μmol/L increase in homocysteine levels (or 1 SD above the mean), was associated with a 0.7- and 0.5-mm Hg increase in systolic blood and diastolic BPs, respectively, in men and an increase of 1.2- and 0.7-mm Hg increase in systolic and diastolic BPs, respectively, in women.

Additional support for the association between hyperhomocysteinemia and an elevation in BP includes evidence that reducing homocysteine levels by dietary B vitamin supplementation resulted in a reduction of BP. Thus, the observation of an increased prevalence of

hypertension in persons with higher than normal homocysteine levels, together with the demonstration that lowering homocysteine levels appeared to result in a reduction in BP, anchors the evidence that hyperhomocysteinemia is a risk factor for hypertension.

On the other hand, it must be noted that large population studies, including some using a retrospective design, are limited in their ability to establish causality. As a result of limitations in their design, some studies are unable to take into consideration the presence of possible confounding factors. Such factors include an increase in homocysteine and BP levels with advancing age. In addition, hypertension also leads to a reduction in renal function, a factor that significantly affects the clearance of homocysteine, resulting in potential elevations in homocysteine levels independently of BP.

In addition, arguments against the association between homocysteine and hypertension include the concept that the BP reduction seen, at times inconsistent, through B vitamin supplementation, including folic acid, might be caused by the nutritional supplements themselves. This would make it difficult to prove that the reduction in homocysteine levels was the mechanism for the reduction in BP with dietary supplementation. Likewise, further examination of the study populations in some of the trials which support the concept that reducing homocysteine levels produces BP reduction has been conflicted by the presence of significant confounding factors such as tobacco use. Tobacco use may directly cause vascular dysfunction, which could be improved by B vitamin supplementation, again independently of homocysteine.

More recently, the impact of homocysteine reduction on BP was also reexamined. In a randomized controlled trial comprising 276 participants, 65 years or older, with or without hypertension, individuals received a combination of 1000 μg of folate (L-5-methyltetrahydrofolate, calcium salt), 500 μg of vitamin B_{12} (cyanocobalamin), and 10 mg of vitamin B_6 (pyridoxine) or placebo. At the end of the first and second years of the study, homocysteine and BP levels were determined. Despite the reductions in homocysteine levels of 4.3 μmol/L at year 1 and 4.4 μmol/L at year 2, no statistically significant reduction in BP was seen.[4]

In addition, several large studies have also questioned the association between hyperhomocysteinemia and hypertension. Using the Framingham Heart Study population as its base, a large cohort trial including 2104 participants was conducted. The mean age of the participants was 57 years, predominantly women (58%), who were followed over a 4-year time period.[5] Unlike the landmark NHANES III retrospective trial, which was published 1 year prior, this study failed to show a statistically significant association between elevated homocysteine levels and an increased incidence of hypertension, following multivariable adjustment for age and sex.[5] Similarly, a prospected nested case-control trial that followed healthy male physicians at baseline and subsequently for a period of 17.5 years failed to demonstrate an increased incidence of hypertension in persons with elevated homocysteine levels.[6] In the latter study, the population of persons with hypertension was much younger (47.5±6.1 years vs 59.94±10.62 years) and leaner (body mass index 24.6±2.4 kg/m^2 vs 24.54±3.66 kg/m^2) compared with the study by Yang and colleagues.[1] These differences might contribute to the disparity in results between the two studies.

Given the new results of the study by Yang and colleagues, what is the relationship between homocysteine and hypertension presently? Although not clearly applicable in all settings, it appears that there may be certain populations in whom the interactions of other multiple factors, such as age, weight, lipid status, and family history of hypertension, result in a heightened association between homocysteine levels and hypertension. Identifying the populations that may demonstrate this heightened association and thus may benefit from the therapeutic reduction of homocysteine levels seems to be a direction to pursue. Given the increasing disease burden of hypertension, continued efforts must be made to identify nontraditional risk factors associated with the development of hypertension. Once identified, innovative and targeted treatments of these nontraditional risk factors can be developed.

ACKNOWLEDGMENTS

Donald J. DiPette, MD, is a Health Sciences Distinguished Professor of the University of South Carolina, Columbia, South Carolina.

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How to cite this article: Skeete J, DiPette DJ. Relationship between homocysteine and hypertension: New data add to the debate. *J Clin Hypertens*. 2017;19:1171–1172.
https://doi.org/10.1111/jch.13073