Journal of Clinical and Biomedical Sciences

Editorial

Hyperhomocysteinemia: The Continuing Saga

Harish Rangareddy[1*], Shashidhar K N[2]

1. Associate Professor, Department of Biochemistry, Sri Devaraj Urs Medical College, Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar.
2. Professor HOD, Department of Biochemistry, Sri Devaraj Urs Medical College, Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar.

Hypertension is a measurand of modern civilized life. It is estimated to be 25.3% with greater prevalence in men (27.4%) than women (20.0%).[1] Cysteine a non-essential glucogenic amino acid and invivo sulphur containing amino acid is formed in methionine metabolism with many biochemical reactions. The dimeric form of cysteine is homocysteine, or it can form 'protein-bound' homocysteine with disulphide bonds.[2] Studies have associated mild-to-moderate elevations in homocysteine with diagnosed coronary disease, myocardial infarction, cerebrovascular disease, carotid intima-media thickness and arterial disease of the lower extremities.[3,4,5,6] Observational data concluded that each 5-µmol/L increase in total homocysteine levels conferred the same increase in risk for vascular disease as a 20-mg/dL increase in total cholesterol level.[7]

Hyperhomocysteinemia linking atherosclerosis is still a puzzle probably due to abnormal endothelial function and thromboembolism. Homocysteine is known to decrease the activity of lysyl oxidase by binding with Cu^{2+}. This blended hydroxyl lysine from lysine affects the cross linking and maturation of collagen in the vasculature.[8]

During the oxidative deamination of lysine, lysyl semialdehyde is formed which is involved in the cross linking of collagen fibers by Schiff's base formation.[9] Lysyl semialdehyde reacts with both homocysteine and homocysteine affecting the collagen maturation leading to vascular remodeling and enhances the risk of thromboembolism.

Studies have reported a positive association between homocysteine levels and mild elevations in serum homocysteine may contribute to elevated blood pressure.[10] In hypertensive individuals the risk associated with hyperhomocysteinemia and vascular events have been observed to be stronger.[11]

Serum homocysteine levels have been further studied in essential hypertensive patients. Extension of the homocysteine estimation in first degree relatives needs to be evaluated. Studies carried out in India on homocysteine in first coronary event, diabetes mellitus, stroke and healthy individuals have revealed a paucity of data on consanguineous relatives with hypertension.[12, 13]

Essential hypertension in families and circulating homocysteine levels may represent the maladaptive interplay between human genome and vascular disease. Inter individual blood pressure variation in the population has a documented genetic basis, focusing the first degree relatives.[14] Despite heritability of essential hypertension in many family studies the variability is considered to be genetically determined. Variances may be attributable to shared and unshared environmental factors, diet and lifestyle habits.[15,16]

Much of the knowledge on essential hypertension and its genetic association needs to be addressed in the current scenario as the circulating levels of homocysteine in first degree relatives of hypertensive individuals provide an evidence which in turn will pave the way for further knowledge to be acquired in the future through genetic studies as to ascertain the probable polygenic etiology of hypertension. Alterations in circulating levels of homocysteine in first degree relatives of hypertensive enhance the risk of vascular diseases, increasing the morbidity and mortality. Exploring this shall provide new evidence towards the multi factorial causation of hypertension and also contribute towards vasocclusive disease risk reduction in predisposed individuals.

Homocysteine levels in circulation can be reduced by drugs and nutritional intervention to reduce the heart attacks and strokes. Estimation of circulating homocysteine in first degree relatives of hypertensive will be a novel marker enhancing the screening performance for vascular disease with other cardiovascular risk factors in combination. Since, the circulating levels of homocysteine can be lowered with drugs or vitamins there is a feasibility of formulating a combination drug using generic components like folic acid, Vitamin B6, Vitamin B12 and L-arginine.[17]

This formulation with the lowest side effects will be well tolerated and have a huge public health merit.

Homocysteine estimation in high risk population shall

i) Help early detection and treatment of essential hypertension.
ii) Contribute to the evidence for genetic basis of essential hypertension.
iii) Hint towards a radical preventive strategy of intervention suggesting the formulation of a combination drug of generic levels that decreases the homocysteine levels.
iv) Enhance scope for research in the realm of molecular biology.
v) Derive a level of policy making by health care authorities to include as a routine and mandatory test.

References

1. Gupta R, Gaur K, S Ram CV. Emerging trends in hypertension epidemiology in India. J Hum Hypertens 2019;33(8):575-87.
2. Yunir E, Aziza Y A N. Serum Homocysteine as a Biomarker in Diabetes. In: Patel V B, Preedy V.R. (eds) Biomarkers in Diabetes. Biomarkers in Disease: Methods, Discoveries and Applications. Springer, Cham 2022. doi: https://doi.org/10.1007/978-3-030-81303-1_13-1
3. Wang B, Mo X, Wu Z, Guan X. Systematic review and meta-analysis of the correlation between plasma homocysteine levels and coronary heart disease. J Thorac Dis 2022;14(3):646-53.
4. Poddar R. Hyperhomocysteinemia is an emerging comorbidity in ischemic stroke. Exp Neurol 2021; 336:113541.
5. Chen A, Wu W, Gong J, Han Y, Xu G, Xie L. Association of homocysteine with carotid atherosclerosis in hypertension. J Hum Hypertens 2022;1-8.
6. Reza MS, Rahim AA, Bashar AH, Islam MS, Alam SA. Association of Hyperhomocysteinemia with Early Onset Atherosclerotic Peripheral Arterial Occlusive Diseases. Cardiovasc Res 2021;13 (2):120-7.
7. Bhargava S. Homocysteine in occlusive vascular disease. In The Clinical Application of Homocysteine. Springer, Singapore 2018:15-35. doi: https://doi.org/10.1007/978-981-10-7632-9.
8. Martínez-González J, Varona S, Cañes L, Galán M, Briones AM, Cachofeiro V, et al. Emerging Roles of Lysyl Oxidases in the Cardiovascular System: New Concepts and Therapeutic Challenges. Biomolecules 2019;9(10):610.
9. Akagawa M. Protein carbonylation: molecular mechanisms, biological implications, & analytical approaches. Free Radic Res 2021;55(4):307-20.
10. Onyemelukwe OU, Maiha BB. Relationship between plasma homocysteine and blood pressure in hypertensive Northern-Nigerians. Afr Health Sci 2020;20(1):324-337.
11. Pang H, Han B, Fu Q, Hao L, Zong Z. Association between homocysteine and conventional predisposing factors on risk of stroke in patients with hypertension. Sci rep 2018;8(1):1-7.
12. Naiksatam M, Popat VC, Chavda AD. Serum homocysteine level as a predictive marker in patients of coronary artery disease – A study of 150 cases. Natl J Physiol Pharm Pharmacol 2022;12(9):1352 -1360.
13. Chouksey D, Ishar HS, Jain R, Athale S, Sodani A. Association between serum homocysteine levels and methylene-tetrahydrofolate-reductase gene polymorphism in patients with stroke: A study from a tertiary care teaching hospital from Central India. J Med Sci [serial online] [cited 2022 Jul 3]; 2021;41(3):140-45. Available from: https://www.jmedscindmc.com/text.asp?2021/41/3/140/297429
14. Gupta-Malhotra M, Hashmi SS, Barratt MS, Milewicz DM, Shete S. Familial aggregation of first degree relatives of children with essential hypertension. Blood Press 2018 ;27(5):289-96.
15. Pickering GW. The genetic factor in essential hypertension. Ann Intern Med 1955;43(3):457-64.
16. Smirk FH. Casual, basal and supplemental blood pressures in 519 first-degree relatives of substantial hypertensive patients and in 350 population controls. Clin Sci Mol Med Suppl 1976;3:13-17.
17. Menzel D, Haller H, Wilhelm M, Robenek H. L-Arginine and B vitamins improve endothelial function in subjects with mild to moderate blood pressure elevation. Eur J Nutr 2018;57(2):557-568.

***Corresponding Author**
Dr. Harish R
Associate Professor, Department of Biochemistry,
Sri Devaraj Urs Medical College,
Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar -563101,
Mobile No : 9845955050
E-mail: harishreddy1349@gmail.com

Submitted: 11-07-2022.
Accepted: 26-07-2022.
Published: 10-10-2022.