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Editorial

Is High Plasma Homocysteine a Direct Cause of Cardiovascular Disease and Mortality?

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▸ See the article "Association Between Plasma Homocysteine Level and Mortality: A Mendelian Randomization Study" in volume 53 on page 710.

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As is well known, since McCully reported the clinical observation linking high plasma homocysteine with vascular disease in 1969,[1] abundant observational epidemiologic evidence has demonstrated the hyperhomocysteinemia is associated with an increased risk of cardiovascular disease (CVD).[2-4] Homocysteine is a sulfur-containing amino acid formed during the metabolism of methionine, which is metabolized by 1 of 2 pathways: remethylation and transsulfuration. In remethylation cycle, homocysteine is salvaged by the acquisition of a methyl group in a reaction catalyzed by vitamin B12 (cobalamin)-dependent methionine synthase. N^5-methyl-tetrahydrofolate is a methyl donor in this reaction, and N^5, N^{10}-methylenetetrahydrofolate reductase (MTHFR) functions as a catalyst in remethylation process. In transsulfuration pathway, homocysteine condenses with serine to form cystathionine in a reaction catalyzed by vitamin B6 (pyridoxine)-dependent cystathionine β-synthase (CBS). Cystathionine is hydrolyzed to form cysteine, which may in turn be incorporated into glutathione or metabolized to sulfate and excreted in the urine. Therefore, hyperhomocysteinemia is caused either by genetic defects in the enzymes involved in homocysteine metabolism such as MTHFR and CBS, or by nutritional deficiencies in vitamin cofactors such as folate, vitamin B12 and vitamin B6.[4]

Despite abundant observational epidemiologic evidence, it is unclear whether hyperhomocysteinemia is a mechanistic risk factor with a direct causal effect for CVD or only risk indicator without any direct effects. In fact, even when strong statistical associations are measured between an exposure and outcome, causal conclusions are rarely justified by a traditional analysis. This is because it is never certain that all confounders of the association have been identified, measured, and appropriately adjusted. In particular, it is difficult to overcome this shortcoming when genetic variants are likely to be involved in causal relationships. Mendelian randomization (MR), which has been widely used in recent studies, is a novel alternative approach to infer the causality of lifelong risk factors (exposure) on diseases (outcome) using genetic variants as instrumental variables.[5]

In this issue of the *Korean Circulation Journal*, Choi et al.[6] demonstrated improved causal inference by reducing residual confounding and other biases through MR design in the prospective Korean population-based Namwon cohort. The observed homocysteine level was positively associated with all-cause mortality and cardiovascular mortality in conventional multivariate analysis. However, this association was not significant in MR analysis.[6]

The contents of the report are the author's own views and do not necessarily reflect the views of the *Korean Circulation Journal*.

The results of this study are consistent with the recent data. In a recent meta-analysis of prospective studies in general population, the risk of all-cause mortality increased by 33.5% for each 5 μmol/L increase in homocysteine.[7] However, there was significant heterogeneity among studies. This heterogeneity is an important confounder, and it could be due to differences in folate intake patterns, serum folate levels, or MTHFR distribution caused by point mutation in MTHFR biding site (MTHFR C677T), or CBS deficiency among study populations. In addition, the intervention trial for preventive effect of reduced homocysteine on premature death has not been significant in randomized clinical trial. One meta-analysis study reported that folate supplementation has no statistically significant effect on premature all-cause death and CVD.[8] And, a third update of the Cochrane review reported uncertain effects of homocysteine-lowering interventions in preventing cardiovascular events, suggesting that hyperhomocysteinemia should not be regarded as an independent risk factor.[9]

Furthermore, several recent MR studies have failed to provide a causal link between hyperhomocysteinemia and various CVDs including coronary heart disease, acute myocardial infarction, systolic and diastolic blood pressure, atrial fibrillation, congestive heart failure or cardiomyopathy.[10] Based on current evidence, high plasma homocysteine level is unlikely to act as a mechanistic risk factor with a direct causal effect for CVD.

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