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COMMENT

Is renal function the key to disease risk management in elevated homocysteine levels?

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Homocysteine is a metabolic intermediate product of methionine, an essential amino acid. The metabolism of homocysteine requires B-vitamins, including folate, vitamin B6, and vitamin B12. A deficiency of folic acid and vitamins slows methionine metabolism and thus increases homocysteine. Many observational studies over two decades have reported that elevated homocysteine levels were associated with increased risk of cardiovascular disease and non-cardiovascular disease, as well as all-cause mortality [1]. Meanwhile, whether homocysteine could be a target for therapeutic intervention is controversial. For instance, folic acid and vitamin intake, which are involved in homocysteine metabolism, reduce homocysteine levels in the blood, but their efficacy in preventing diseases is uncertain [2, 3]. In addition, a Mendelian randomized analysis has reported no causal relationship between plasma homocysteine levels and coronary heart disease or acute myocardial infarction [4]. Considering these findings, homocysteine has been suspected to be a risk marker rather than a cause of disease.

Homocysteine is supposed to be a cause of impaired renal function, and furthermore, impaired renal function is a major risk factor for cardiovascular disease, however, few observational studies on the association of high homocysteine levels with cardiovascular disease have focused on renal function. The present study by Ding et al. reported a positive association of homocysteine with all-cause mortality and cause-specific mortality in Chinese hypertensive patients, and that 40% of these associations were mediated by reduced renal function [5]. Some previous studies have reported that hyperhomocysteinemia was associated with the development of chronic kidney disease (CKD) [6, 7]. In Chinese hypertensive adults, the positive association between elevated baseline homocysteine levels and odds ratio (OR) of CKD development during 4.4 years of follow-up period after adjusting for confounders including estimated glomerular filtration rate, folate and vitamin B12 levels at baseline [OR of the second tertile compared with that of the first tertile group, 1.50; 95% confidence interval (CI), 0.55 to 4.1; OR of the third tertile, 3.23; 95% CI, 1.25 to 8.35] [6]. These findings may suggest that risk assessment and the management of renal function decline for hypertensive patients with high homocysteine levels may be beneficial in preventing diseases.

Although previous intervention studies have shown the conflicting effects of homocysteine-lowering therapy on cardiovascular diseases or all-cause mortality [2, 3], some studies have indicated that homocysteine-lowering therapy is beneficial for preventing cardiovascular disease in populations with preserved renal function. In a meta-analysis of individual data from two large trials of B vitamin therapy, the VISP trial and the VITATOPS trial, the effect of cyanocobalamin (a form of vitamin B12) use on stroke events in participants with normal renal function and those impaired renal function was examined, as well as the effect of high (≥400 μg/day) and no or low-dose (20 μg daily) cyanocobalamin use [8]. This meta-analysis has demonstrated that the use of cyanocobalamin resulted in an 11% risk reduction compared with the control in participants with normal renal function [risk ratio (RR) 0.89, 95% CI: 0.83–0.96], while this effect did not show a statistical significance in participants with impaired renal function (RR 0.98, 95%CI 0.81–1.19). Additionally, participants with normal renal function and with no cyanocobalamin or low doses of cyanocobalamin resulted in a 22% risk reduction of stroke events compared with the control (RR 0.78, 95% CI 0.67–0.90), while the potential adverse effect of

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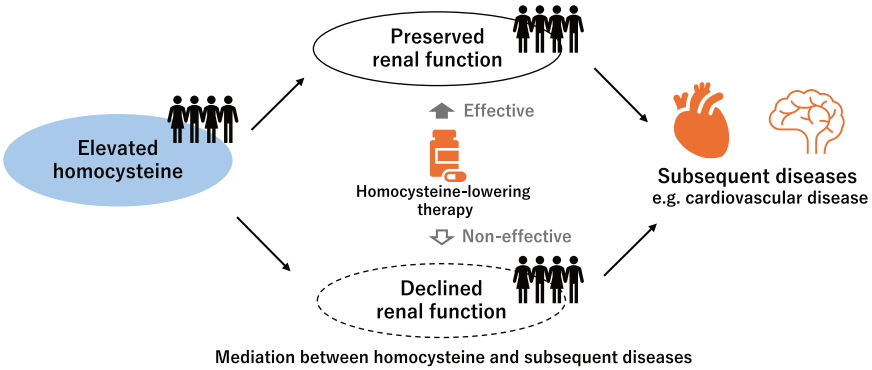

Fig. 1 Renal function may be the ley to disease risk management in elevated homocysteine levels

cyanocobalamin was shown in participants with impaired renal function exposed to high-dose cyanocobalamin (RR 1.04, 95%CI 0.84–1.27; interaction $p = 0.03$). This finding suggests the importance of preserved renal function in homocysteine-lowering therapy.

As mentioned earlier, conflicting findings in many previous studies on the effect of high homocysteine levels on diseases have led to the suspicion that homocysteine is a risk marker rather than a cause of disease. Meanwhile, several studies have suggested that renal function may be key to disease risk management in populations with high homocysteine levels (Fig. 1). Particularly, hypertension is a strong risk factor for both impaired renal function and cardiovascular disease, and therefore hypertension with high homocysteine levels may require further strict risk assessment and the management, including blood pressure control and lifestyle guidance.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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