Effect of Serum Chloride on Mortality in Hypertensive Patients

To the Editor:

I have read with interest the large and long follow-up study by McCallum et al.1 concerning the risk of low serum chloride on the mortality in 12,968 patients with hypertension. They concluded that an increase of the serum chloride by 1 mEq/L was associated with a 1.5% reduction of the all-cause mortality, cardiovascular disease (CVD) mortality, ischemic heart disease (IHD) mortality, and non-CVD mortality after adjusting for confounding variables. The authors recognized a bias by excluding 2000 individuals without data on the serum chloride, and also accepted that the association between low serum chloride and mortality remains unclear. Although the statistical power was satisfactory and time-dependent Cox regression analysis was an appropriate method for a long-term follow-up study, I have 3 fundamental concerns about their study.

First, the authors did not use risk factors for CVD such as serum lipids for the adjustments. As compared with the recently reported insulin-related and inflammatory markers in patients with CVD, the serum cholesterol concentration had been used more widely in epidemiological studies. For example, Andersson et al.2 reported from a 2-decade follow-up study that the total cholesterol concentration was a risk factor for the development of IHD in patients with antihypertensive medication. The baseline study was conducted in 1970, and the study environment was almost the same as that for the study conducted by McCallum et al. Although the study design differed in the setting of the control population without hypertension, it also used time-dependent Cox regression analysis to predict future development of IHD. The baseline data handled the serum total cholesterol concentration.

Second, as a concern, information on antihypertensive medication was limited to the use of diuretics. About 20% of the target subjects were on treatment with diuretics, and I agree that diuretic use is important to evaluate the serum sodium and chloride concentration. In addition, a variety of hypertensive medications have been released in the market during the past decade. Because the systolic and diastolic blood pressure during the follow-up reflect the efficacy of management of hypertension, I speculate that the authors considered that the type of medication had no influence on the risk of mortality in patients with hypertension in their study. On this point, I recommend that McCallum et al include several types of medications in their Cox regression analysis and also exclude the independent variables of systolic or diastolic blood pressure to avoid multicollinearity.

Finally, the risk of stroke associated with low serum chloride concentrations did not reach statistical significance. There are some differences in the risk factors between stroke and IHD or CVD and also some differences in the risk factors depending on the type of stroke. Is this caused by the lack of power with a relatively small number of events, or is there any speculation on a different mechanism between stroke and IHD or CVD?

Anyway, the authors handled a large amount of data in this long-term follow-up study. Their study could become a leading research if it were combined with past reviews with special reference to the protective effects of statin3,4 and risk assessment of mortality in different ethnic populations.5

Disclosures

None.

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