Potassium and Vascular Health: Good Medicine Tastes Bitter

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Sodium intake increases the circulating blood volume, and excess intake of sodium causes dysregulation in the renin-angiotensin system, leading to increased blood pressure and the development of heart failure. Reducing salt intake is thus useful for lowering blood pressure and preventing heart failure. Salt substitutes can help patients reduce their sodium intake. The epithelial sodium channel is responsible for active sodium reabsorption, which is essential for maintaining salt and water homeostasis in the body. Sodium intake through food sends a signal to the brain, and that signal is an effect of salt improving the food's flavor.

Lithium can be substituted for sodium, and lithium chloride was used as a salt substitute at one time. Lithium chloride tastes similar to sodium chloride because the epithelial sodium channels allow lithium to pass through. However, lithium chloride had side effects, such as lithium addiction. Therefore, potassium chloride has since been used as the primary salt substitute. Potassium does not pass through the epithelial sodium channels well, and it tastes bitter. Therefore, the currently available salt substitutes are a mixture of regular salt and potassium chloride, and food manufacturers have made many efforts to reduce the bitterness of potassium chloride. Higher sodium and lower potassium intakes measured in multiple 24-hour urine samples were associated with a higher cardiovascular risk¹⁾. Among individuals with a history of stroke or age ≥ 60 years with high blood pressure, the rates of stroke, major cardiovascular events, and death were reduced with the use of a salt substitute compared to the corresponding rates with the use of regular salt²⁾.

There are many reports on the relationship between serum potassium levels and cardiovascular prognosis and mortality³⁻⁷⁾. In a community-based study of elderly individuals, the 8-year follow-up of 2,065 subjects demonstrated that the rates of total and cardiovascular death were both higher in the group with low-normal serum potassium concentrations (3.5–3.8 mmol/L) compared with the group within the normal range of potassium concentrations (3.9–4.4 mmol/L) and that the serum potassium concentration was associated with U-curves for total death and cardiovascular events³⁾. In patients with hypertension, the risk of total mortality was also U-curved around a serum potassium concentration of 4.1–4.7 mmol/L⁴⁾. There have been many studies on the association between potassium and renal impairment, and meta-analyses have shown that the risk relationship between potassium and all-cause mortality demonstrated the lowest risk for serum potassium levels between 4 mmol/L and 4.5 mmol/L and a higher risk outside of the 3.5–5 mmol/L range⁵⁾. In the PARADIGM-HF study that enrolled patients with heart failure with a reduced ejection fraction, the cardiovascular mortality rate was higher in patients with serum potassium levels <3.5 or >5.5 mmol/L compared to those with levels at 4.1–4.9 mmol/L⁶⁾. In the PARAGON-HF study that enrolled patients with heart failure and preserved ejection fraction, the rates of both cardiovascular and total mortality were higher in patients with serum potassium levels <4 mmol/L compared to those with levels at 4–5 mmol/L in the estimated glomerular filtration rate <60 mL/min/1.73 m² subgroup⁷⁾. In the above studies, the appropriate concentration of potassium was different, and the risk of hypo/hyperkalemia varied among the subjects.

The relationship between potassium and vascular

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Fig. 1. Management of potassium for the prevention of cardiovascular events

ACE: angiotensin converting enzyme; ARB: angiotensin II receptor blocker; CV: cardiovascular. The relationship between CV event rate and potassium level are shown, and the potassium level at which CV events are minimized are segregated by disease (three curves).

function has been reported at least as far back as 1952⁸⁾. Friedman *et al.* showed that the administration of potassium resulted in rapid restoration of decreased peripheral vascular reactivity in a potassium-deficient rat model⁸⁾. Although Maruhashi *et al.* demonstrate in this issue that serum potassium levels of 4.5 to <5.0 mmol/L are associated with better vascular function⁹⁾, there are few reports on the relationship between potassium intake/serum potassium and vascular function. There is a U-curve relationship between serum potassium and cardiovascular events, and there is probably a similar U-curve relationship between potassium intake/serum potassium and vascular function. There are many methods for evaluating vascular function other than flow-mediated dilatation, and additional research on vascular function and potassium intake/serum potassium is needed. A major role of vascular function tests is the use of their results as surrogate markers for cardiovascular events. In the management of patients with heart failure, it is necessary to maintain an appropriate level of potassium and adjust medications accordingly to avoid dyskalemia¹⁰⁾. The appropriate value of potassium may vary depending on the subject, such as the presence of heart failure, hypertension, and chronic renal disease. Vascular function tests and potassium monitoring can thus be effective for predicting prognoses and determining the treatment effects in each individual (Fig. 1).

The treatments of heart failure and hypertension have entered a new era with the widespread use of

renin-angiotensin system inhibitors, mineralocorticoid receptor antagonists, and angiotensin receptor neprilysin inhibitors, all of which affect serum potassium levels. Vascular function tests can be expected to contribute to the reduction of cardiovascular events while taking potassium into account.

Conflict of Interest

The author declares no conflict of interest.

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