NUTRITION REVIEW

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Electrolytes and Cardiovascular Disease Risk

Abstract: *The relationship between sodium intake and blood pressure is a well-studied phenomenon; however, the impact of sodium intake on cardiovascular disease risk and mortality is controversial. Recent studies conclude that weak evidence exists to support sodium restriction for the prevention of cardiovascular mortality in normotensive and hypertensive adults, suggesting that sodium restriction may be an ineffective strategy for disease prevention. Further evidence points to the importance of balancing sodium and potassium intake, a balance commonly achieved with a healthier diet containing greater quantities of fruits and vegetables. The purpose of this article is to highlight dietary strategies that may prove to be more effective in reducing cardiovascular disease risk. Limitations of current methods used to estimate nutrient intake are described as they relate to this topic. Further research is needed to advance understanding of various aspects of dietary intake that are health protective and allow for the development of more effective public education strategies.*

Keywords: sodium; potassium; cardiovascular disease risk

Electrolytes, including sodium, potassium, and chloride, play a significant role in regulating body fluid balance. Physiologically, each of these charged ions is tightly regulated through the action of multiple systems within the body.[1] Of particular importance, sodium is an essential nutrient responsible for the regulation of the extracellular fluid compartment and subsequently, vasodilation.[2] Through this mechanism, sodium intake (as sodium chloride, or salt) has been shown to correlate with blood pressure, and it has been proposed that the increase in blood pressure from a high-sodium diet is causally linked to risk of cardiovascular disease (CVD).[3] As a result of this link, current recommendations from the American College of Cardiology (ACC) and American Heart Association (AHA) support limiting daily sodium intake in healthy adults to 1500 mg/d to reduce disease risk.[4]

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Average daily sodium intake varies based on a range of factors, including age, dietary habits, socioeconomic status, and culture.[5,6] Estimates of daily intake in the United States are 3400 mg/d, well in excess of current ACC/AHA recommendations.[7] Federal guidelines, including Healthy People 2020, recommend the restriction of sodium intake (generally defined as intake below 2300 mg/d) to decrease the risk of adverse health outcomes, including elevated blood pressure, CVD, and stroke.[7] The connection between sodium intake and blood pressure is a well-studied phenomena: A recent meta-analysis revealed that sodium reduction (defined as a 2300 mg/d reduction) is associated with a 7.7 mm Hg (95% CI: −10.4, −5.0) and 3.0 mm Hg (95% CI: −4.6, −1.4) reduction in systolic (SBP) and diastolic blood pressure (DBP), respectively, in hypertensive adults. A weaker reduction was found in SBP (1.46 mm Hg; 95% CI: −2.7, −0.2) and DBP (.07 mm Hg; 95% CI: −1.5, 1.4) in normotensive adults when reducing sodium intake.[8] The weak reduction in blood pressure in normotensive adults has led to questioning whether recommendations for sodium restriction below 2300 mg/d will lead to a decrease in health risk and subsequent reduction in mortality.[9]

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When examining the effect of reduced sodium intake on adverse health outcomes, Welsh et al[10] recently concluded that studies on sodium restriction below 2300 mg/d are insufficient to support the notion of a decreased risk of heart disease, stroke, or all-cause mortality in the general population. Similarly, a Cochrane review of studies on sodium restriction supported this conclusion that weak evidence exists to support sodium reduction for the prevention of cardiovascular mortality in normotensive and hypertensive adults.[11] Even a meta-analysis based on stratified ranges of sodium intake indicated a decreased risk of CVD (hazard ratio [HR] = 0.90; 95% CI: 0.82-0.99) and all-cause mortality (HR = 0.91, 95% CI: 0.82-0.99) from normal sodium intake compared with low-sodium (defined as <2645 mg/d) diets.[12] Taken together, these data support the notion that sodium restriction may be an ineffective strategy for disease prevention.

Sodium restriction alone may play an insignificant role in disease risk, though the question remains of whether examining sodium alone may be too reductionist in identifying causes of disease. For example, in the Prevention of Renal and Vascular End Stage Disease (PREVEND) study, authors examined the relationship between sodium and chloride, the anion commonly associated with sodium in table salt. Measures of urinary excretion showed a tightly bound relationship between sodium and chloride excretion ($r = 0.96$, $P < .001$), and a Cox proportional hazards analysis could not separate these ions in predicting the risk of hypertension. In contrast, urinary excretion of potassium was weakly related to chloride excretion ($r = 0.51$, $P < .001$). This led to the conclusion that the intake of electrolytes should be viewed together when assessing the role and subsequent risk of disease development.[13] Support for this claim is reflective of real-world settings in which people eat whole foods instead of their constituent parts, and the role of these various levels of electrolyte intake may be more predictive of health outcomes.[14]

Studies examining the interrelationship between electrolytes support the concept that consumption of potassium may have an influential role on blood pressure and CVD development beyond that of sodium intake alone.[15-17] In an 18-country ecological study, greater intakes of potassium (>3.0 g/d) were found to be associated with lower risk of mortality and CVD, independent of sodium intake.[18] Potassium has further been found to partially attenuate the relationship between sodium and blood pressure.[19] These findings prompt the assessment of potassium intake and, more comprehensively, the ratio between sodium and potassium as focal areas that may have a prominent role in supporting cardiovascular health.[16,17,20,21]

Mechanistically, potassium may influence the development and progression of cardiovascular related outcomes, including stroke,[16] through inflammation pathways,[17,20] arterial stiffness[20] or blood pressure.[21] In a cross-sectional study of hypertensive adults (aged 40-70 years), individuals with the highest ratio of sodium to potassium (>4.39 mmol) were found to have greater markers of inflammation and vascular damage. Measures of C-reactive protein ($r = 0.77$, $P < .001$) and carotid-femoral pulse wave velocity ($r = 0.41$, $P < .001$) significantly correlated with the ratio of sodium and potassium as measured by 24-hour urinary excretion.[20] In a systematic review examining sodium and potassium in relation to blood pressure, 6 out of 13 randomized control trials (RCTs) and 8 out of 11 observational studies that considered the sodium/potassium ratio found stronger effects for the ratio than either ion independently.[21] Additionally, a meta-analysis of observational cohort studies indicated that a 1-unit increase (mmol) in the dietary ratio of sodium to potassium is associated with a 22% higher risk of stroke.[17] Specifically, a ratio greater than or equal to 2.26 mmol significantly increased the risk of cardiovascular events (HR = 2.19, 95% CI: 1.16-4.14).[22] These findings highlight the importance of a balanced intake of electrolytes to reduce disease risk in the general population.

Public health efforts to lower the incidence of cardiovascular events have led to initiatives aimed at improving the sodium/potassium ratio; early strategies have focused on the use of potassium salts (KCl) in place of traditional salt consisting of sodium (NaCl).[23] Potassium salts have been found to reduce SBP and DBP in both hypertensive and normotensive population groups, with greater reductions present among those with hypertension at baseline.[15,24] Reductions in SBP have been documented to range from 5.58 mmHg (−4.09 to −7.08 mm Hg) on average in a review of studies using a potassium and sodium combination compared with a normal diet including sodium chloride.[15] In a recently published randomized intervention in Peru, use of a 25% potassium salt substitute corresponded with reductions in SBP of 1.29 mm Hg ($P = .04$) in a population sample and by 1.92 mm Hg ($P = .006$) in a subgroup of participants with hypertension.[25] Decreasing incidence of CVD (13.1 per 1000 persons vs 20.5 per 1000 persons) have also been reported in a randomized intervention of adult males receiving a 50% potassium salt substitution.[24] However, the authors noted only modest reductions in sodium intake within this experimental group. This reinforces the question as to whether overall increases in potassium intake, reductions in sodium intake or the overall ratio between electrolytes has the greatest mechanistic influence on blood pressure and CVD outcomes.

At the population level, very few individuals consume high levels of potassium (>3.5 g/d) in combination with lower levels of sodium (<2 g/d) intake. For this reason, it is inappropriate to make conclusions about the risk of cardiovascular outcomes in such a group. Intake of electrolytes more reflective of a balanced diet with moderate sodium (2-3 g/d) and high potassium (3.5 g/d) intake present the lowest risk of unfavorable cardiovascular events and mortality and may be more realistic for the general public.[16] These findings, along with the previous studies on the sodium/potassium ratio suggest a synergistic effect between sodium and

potassium on lowering blood pressure and improving CVD outcomes.[20] It is also possible that lower sodium intake coupled with higher potassium intake represents a proxy for an overall higher quality diet, one more consistent with greater fruit and vegetable consumption.[16] It is important that future work examines this relationship between sodium and potassium as synergistic electrolytes more closely.

To further our understanding of the role that each of these ions plays with regard to cardiovascular health, it is critical that rigorous measures of sodium and potassium intake are developed. Additional prospective studies controlling for confounding factors such as diet quality and ethnicity are also necessary.[17] Future research should aim to address the following areas where gaps in knowledge exist.

Improving Measures of Electrolyte Intake

The estimation of overall dietary sodium intake is limited by how accurate existing assessment methods are in predicting actual sodium intake.[26] Commonly utilized methods for quantification of electrolyte intake in research studies include biochemical testing and self-report. Food frequency questionnaires (FFQ), which require individuals to report dietary intake as a method to estimate nutrient intake, are a cost-effective strategy for large population sampling but pose a challenge in providing accurate information.[26] Problems with either 24-hour or weekly dietary recalls include the error in reporting due to misreporting,[27] biased reporting of foods consumed,[28] or significant variation in day-to-day food intake,[29] all of which can reduce the accuracy of these recall methods. For example, some studies have reported accurate sodium and inaccurate potassium intake[30] whereas others have presented the opposite; inaccurate sodium and accurate potassium intake.[31]

Though less prone to user bias, 24-hour urinary sodium excretion measures as an indicator of nutrient intake may also have limited accuracy. In a controlled diet experiment with fixed nutrient intake, daily urinary sodium excretion varied significantly between adolescent females matched for post menarcheal age, height, and weight.[32] Additionally, during a recent simulated Mars mission, participants with relatively constant daily food intake exhibited an infradian rhythm in excretion of sodium, potassium, and chloride. The authors highlighted the importance of the renin-angiotensin-aldosterone system (RAAS) in regulating these factors daily, underscoring the importance of multiple urinary measurements to accurately reflect dietary nutrient intakes.[33] Further recommendations from the International Consortium for Quality Research on Dietary Sodium/Salt (TRUE) suggest urinary measures taken over multiple years to more accurately reflect sodium levels reflective of normal dietary intake.[34] Due to the limitations of a single urinary measure, further research into the causes of daily variations in electrolyte excretion is warranted. Well-controlled studies assessing long-term electrolyte excretion are also necessary to further the understanding of electrolyte intake and health outcomes.

Dietary Pattern Assessment

Over the past few decades, researchers have called for a consideration of dietary patterns rather than individual nutrients or foods to estimate dietary impacts on health. As individuals do not consume nutrients in isolation, ignoring the interactions between nutrients as part of a whole food can hinder the understanding of the relationship between eating and health. The effects of any one nutrient, such as sodium, on a health outcome, such as blood pressure, may be confounded by the effects of other nutrients consumed in conjunction.[35,36] Overall, dietary patterns may further diminish the effects of any one nutrient on health[35]; sporadic consumption of a food is less likely to have an effect on long term health compared to foods consumed habitually over many years.[36]

Literature considering the consumption of dietary patterns (eg, Mediterranean diet, "prudent diet") higher in fruit and vegetables compared with those high in energy-dense foods (eg, "Western diet") have repeatedly demonstrated associations between fruit and vegetable intake and beneficial health outcomes.[35,36] Considering the whole diet in addition to sodium intake may better inform our understanding as to how sodium alongside other nutrients such as potassium affects cardiovascular outcomes. Well-designed prospective studies examining changes in the sodium/potassium ratio and impact on blood pressure or CVD outcomes will greatly improve the setting of future dietary recommendations.

One strategy to account for overall dietary patterns may be to assess the ratio of sodium to potassium among normotensive adults.[21] As sodium is often present in highly processed foods, whereas potassium tends to be found in fruits and vegetables,[37] dietary patterns could be used as a reference to estimate the sodium/potassium ratio. This proxy may help inform how dietary balance contributes to reducing health risk.[21] Further exploration of dietary patterns more closely related to adverse cardiovascular outcomes through methods, including the use of a Healthy Eating Index or factor analysis[35] instead of only assessing sodium intake may further allow for more realistic intervention strategies to be determined.[38] Public health interventions targeting overall dietary patterns as opposed to a single nutrient such as sodium may be easier for the general public to understand and apply, as they more closely relate to how food is actually consumed.[35]

Shifting Guidelines Toward Proper Dietary Patterns to Improve Electrolyte Balance

As we begin to improve our understanding of the impact of dietary

patterns on health outcomes, we can shift public focus away from sodium as an individual driver of health risk and instead focus on the context of all consumed foods. Sodium restriction is notoriously difficult to achieve[3,39] and may undermine the value of specific dietary patterns conducive to improved health outcomes. Strategies to reduce the amount of sodium used in processed foods aim to improve the balance of electrolytes in the diet; however, most companies committed to reducing sodium levels as a result of strategies, including the National Salt Reduction Initiative, have failed to meet expected goals.[40] Though significant, these initiatives for sodium reduction should not be the primary focal point for public education. Instead, dietary counseling should recognize and educate individuals regarding the hidden amounts of sodium in processed foods, the importance of fruit and vegetable intake in improving sodium-to-potassium balance, and the importance of whole-food diets in achieving improved health.

Conclusion

In this issue, Razavi et al[41] examined 30-day readmission rates in heart failure patients and found dietary noncompliance (defined as failure to restrict sodium or fluid intake) to account for 26.42% of readmissions. The study explored the use of culinary medicine education as a strategy to improve dietary practices in this population in an effort to achieve recommended lifestyle modification factors to manage heart failure. Though the dietary recommendations for sodium restriction in heart failure are controversial,[42] this may be due to the difficulty in separating sodium reduction from dietary changes that improve the sodium/potassium ratio. For example, increased consumption of fruits and vegetables has been linked to numerous health benefits while also increasing the ratio of potassium to sodium. Assessing the overall impact of dietary counseling on comprehensive changes to dietary patterns may prove a more fruitful intervention in this patient population.

As an understanding of the role of dietary patterns in reducing the risk of adverse health outcomes further develops, it is clear that additional research is necessary. Refining techniques used to estimate electrolyte intake will allow for more precise measurement of sodium, potassium and other synergistic electrolytes that may influence changes in blood pressure and CVD risk. Through use of such measures in prospective studies, researchers can consider the long-term ratio of electrolytes that contributes to an increased likelihood of CVD incidence. As electrolytes are consumed within the broader matrix of foods and overall dietary patterns, guidelines surrounding dietary education will benefit from a focus on the factors that affect adoption and long-term compliance with patterns consistent with improved health outcomes. Untangling the effects of nutrients on CVD risk and translating these messages into guidelines for the general population will continue to be a vital strategy for improving health outcomes in both healthy and at-risk populations.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

Informed Consent

Not applicable, because this article does not contain any studies with human or animal subjects.

Trial Registration

Not applicable, because this article does not contain any clinical trials. AJLM

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