Hypertension

CONTROVERSIES IN HYPERTENSION

Blood Pressure Control Should Focus on More Potassium: Controversies in Hypertension

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Hypertension is the leading modifiable risk factor for cardiovascular disease, and a higher intake of dietary sodium is associated with a higher level of blood pressure (BP).[1,2] Nonpharmacological means of lowering BP are a top priority from patients and providers, and lowering of dietary sodium has been a mainstay of hypertension guidelines for several decades.[3] However, the spotlight on dietary sodium has resulted in dietary potassium becoming the neglected ion (see Table 1 for a summary). In this commentary, we will make the case for the costarring role of potassium in the regulation of BP supported by mechanistic studies, epidemiological data, and randomized clinical trials (RCTs) (all summarized in Table 2).

SODIUM AND HYPERTENSION

There is a consensus among prominent public health and scientific organizations (including the World Health Organization [WHO], the US Department of Agriculture, and the European Food Safety Authority) to endorse a reduced dietary intake of sodium for the general population.[4–6] To this end, the WHO recommends a dietary intake <2000 mg of sodium per person per day (equivalent to 5 g of salt or 86 mmol of sodium),[4] the US Department of Agriculture a daily maximum of 2300 mg/d,[5] and the European Food Safety Authority a maximum of 2000 mg/d.[6]

Sodium and BP

One of the foundational trials for these recommendations was the DASH-Sodium trial (Dietary Approaches to Stop Hypertension),[7] which was a feeding study with randomization to DASH or control diets with high, medium, or low sodium intake (about 3300, 2400, and 1500 mg/d, respectively) for 30 days. The effect of low-sodium diet (in comparison to high-sodium diet) was about −3.0/−1.6 mm Hg lower systolic BP (SBP) and diastolic BP among participants already on the DASH diet. In a systematic review and meta-analysis for the WHO,[8] pooled data from RCTs showed that reduced sodium intake led to lowering of SBP by 3.4 mm Hg (95% CI, 2.5–4.3) and by 4.1 mm Hg (95% CI, −5.15 to −2.96) in patients with hypertension. Thus, the magnitude of the mean difference of SBP and diastolic BP reduction with sodium reduction is relatively modest. This is noteworthy when considering the degree to which patients need to modify their diets to achieve the requisite reduced sodium intake, as compared with substantial BP-lowering effect from a single pharmacological agent such as a thiazide or thiazide-like diuretic—in a meta-analysis, hydrochlorothiazide and chlorthalidone were shown to cause a reduction in SBP by −17 and −23 mm Hg with median doses of 33.0 and 25.0 mg, respectively.[9]

Sodium and Clinical Outcomes

Whether this lower sodium intake translates to important clinical outcomes is the more important question, and it has mixed results. The WHO systematic review from Aburto et al[8] reported on associations in 5 RCTs and 14 cohort studies between sodium intake and all-cause mortality, incident fatal and nonfatal cardiovascular disease, and coronary heart disease, all of which were nonsignificant ($P>0.05$). Indeed, there were insufficient RCTs to assess the effect of reduced sodium intake on mortality and morbidity.[8] A 2014 Cochrane review[10] also

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Table 1. Important Differences Between Dietary Modifications of Sodium and Potassium Intake

	Decreased sodium intake	Increased potassium intake
Effect on systolic blood pressure	≈3.4 mm Hg[8]	≈3.5 mm Hg[19]
Effect on systolic blood pressure in patients with hypertension	≈4.1 mm Hg[8]	≈5.3 mm Hg[19]
Effect on clinical outcomes	Insufficient data from randomized controlled trials[8]	24% relative risk reduction in stroke[19]
Implementation	Difficult to implement effective sodium restriction strategies[53]	Easier to recommend increasing intake of higher potassium-rich food such as fruits and vegetables than restricting elements in diet
	Modern-day diet includes processed food, which is high in sodium concentration[24]	Potassium supplementation is another option if dietary modifications are challenging
	Low-sodium dietary options are typically more expensive	

found there was only weak evidence of benefit of dietary advice and reduced dietary sodium for cardiovascular mortality and cardiovascular events in both hypertensive and normotensive populations given insufficient study power—it concluded that the estimates of clinical benefits from advice to reduce dietary salt are imprecise with requirement of further well-powered studies needed to increase this precision. A 2018 systematic review[11] similarly showed that evidence was insufficient to draw conclusions regarding associations of sodium intake levels and risk of cardiovascular disease, coronary heart disease, or stroke morbidity and mortality.

Table 2. Landmark Studies for Na and Potassium Intake in Hypertension

Name	Study details	Effect on BP	Effect on clinical outcomes	Significance
INTERSALT[1]	n=10 079 in 52 centers from 32 countries; cross-sectional field study of randomly sampled participants	Na intake associated with slope of BP with age but not median BP or prevalence of hypertension (except in 4 centers)	Not studied	First large international study to examine the association of Na intake and BP; susceptible to ecological fallacy
PURE[51,59]	n=101 945 from 17 countries; large-scale epidemiological cohort study	Higher BP, 1.5/0.5 for every g/d Na excretion, nonlinear with increased BP effect over 5 g. Lower BP, −1.1/0.1 mm Hg for every g/d increase in potassium excretion	U-shaped curve: Na excretion ≥7 g/d associated with 15% increased risk of CV outcomes; Na excretion <3 g/d also associated with 27% increased risk of CV outcome; linear effect of increased potassium intake with CV outcomes (range from 14% lower at 1.5–2 g/d, 22% lower at >3 g/d)	Largest international study suggesting no benefit to Na reduction in improving clinical outcomes; critiqued for use of morning spot urine samples to estimate 24-h Na excretion
DASH-Sodium Trial[7]	n=412 participants; randomized cross-over trial to foods with high, intermediate, and low levels of Na	Low-Na diet compared with high-Na diet, −3.0/1.6 mm Hg lower BP in those on DASH diet and − 6.7/3.5 mm Hg lower BP in those on control diet	Not studied	Clear demonstration of magnitude of BP lowering with DASH and low-Na diets in the setting of perfect adherence
Aburto et al[8]	Systematic review and meta-analysis; 14 cohort studies; 37 RCTs reporting BP effect, and 5 RCTs reporting clinical outcomes	Pooled effect from RCTs of Na lowering −3.4/1.5 mm Hg	Insufficient RCT data for clinical outcomes From cohort studies, higher Na intake associated with 24% higher stroke but nonsignificant effect on mortality and major adverse CV events	Most comprehensive synthesis quantitating the net effect of Na intake on BP and clinical outcomes (until the SSaSS trial)
Aburto et al[19]	Systematic review and meta-analysis; 11 cohort studies; reporting BP and clinical outcomes	Pooled effect t from RCTs of increasing potassium intake −5.9/3.8 mm Hg	From cohort studies, higher potassium intake associated with 24% lower stroke; associations between higher potassium intake and incident CV disease (RR, 0.88) or CHD (RR, 0.96) not statistically significant	Most comprehensive synthesis quantitating the net effect of potassium intake on BP and clinical outcomes (until the SSaSS trial)
SSaSS[44]	Open-label, cluster RCT in 600 villages in rural China (20 995 participants); randomized to salt substitute (75% NaCl+25% KCl) or table salt (100% NaCl)	Mean difference in BP with intervention: −3.3/0.7 mm Hg	Salt substitute resulted in 14% lower rate of stroke, 13% lower rate of major adverse CV events, and 12% lower all-cause mortality	Largest RCT with clinical outcomes; salt substitute decreased Na intake by 8% and increased potassium intake by 57% from baseline

BP indicates blood pressure; CHD, coronary heart disease; CV, cardiovascular; DASH, Dietary Approaches to Stop Hypertension; INTERSALT, International Cooperative Study on Salt and Blood Pressure; KCl, potassium chloride; Na, sodium; NaCl, sodium chloride; PURE, Prospective Urban Rural Epidemiology; RCT, randomized control trial; RR, relative risk; and SSaSS, Salt Substitute and Stroke Study.

Controversy Underlying Sodium Reduction

Because sodium is an essential electrolyte required for the normal functioning of the cardiovascular and multiple other organ systems, the validity of sodium restriction recommendations has been the subject of considerable discussion. Several cohort studies have suggested the possibility of a J-shaped association of sodium intake with cardiovascular events and mortality (that both high and low sodium intakes are associated with increased risk)[12]; these studies have led to considerable criticism particularly due to concern for methodological rigor on the basis of biased estimation of salt intake and reverse causation.[13] Notwithstanding the potential J-shaped curve, guidelines recommending low sodium intake are not supported by large definitive long-term RCTs that clearly demonstrate significant effects on outcomes such as mortality or cardiovascular events.[14] Many suggest that public health efforts should focus on reducing sodium intake in populations with high sodium intake (over 5000 mg/d) rather than diverting resources to promotion of low sodium intake for the entire population given the unclear benefit.[15] The only unequivocal method to ascertain that excessive sodium intake causes increased cardiovascular disease would be to study this in a large RCT of sodium reduction, which has been deemed to be impractical and costly.[16] Hence it is apt and timely to consider that focusing on potassium intake may have a more substantial impact on BP lowering and health outcomes such as reduction in cardiovascular events.

POTASSIUM AND HYPERTENSION

With the outsize focus of sodium, the role of potassium in regulating BP has been unfortunately sidelined. The landmark DASH trials revealed the importance of modifying diet by emphasizing fruits, vegetables, high fiber, and low-fat dairy products, but it is often missed that the typical DASH diet plan includes about 4700 mg (120 mmol) per day of potassium.[7,17,18] The WHO along with Hypertension Canada and the American Heart Association/American College of Cardiology guidelines has now recommended to increase potassium intake to assist in lowering BP.[19–21]

Mechanism of Potassium Lowering BP

Potassium is an important nutrient, and its role in lowering BP has to do with its function in maintaining our total body fluid volume, acid, and electrolyte balance, as well as normal cell function.[19,22] A high serum concentration of potassium leads to endothelium-dependent vasodilation by hyperpolarizing the endothelial cell via stimulation of the sodium pump and opening potassium channels.[23–25] Endothelial hyperpolarization occurs through the vascular smooth muscle cells as it leads to less cytosolic calcium, resulting in vasodilation, and thus lowering BP. Another important kidney mechanism is the development of a negative sodium balance by significant natriuresis via the downregulation of the NCC (sodium chloride cotransporter), also known as the potassium switch.[26] The natriuresis effect occurs with high potassium intake without elevated plasma aldosterone levels, thereby not promoting sodium retention in the body.[26] For this reason, it has been demonstrated that increasing potassium in the diet and receiving potassium chloride infusions result in a high sodium urinary excretion and lower BP.[26,27] Furthermore, Terker et al[28] demonstrated that high extracellular concentration of potassium in mice regulates NCC function directly, independent of any hormonal mechanism. Their experiments revealed that serum potassium affects the membrane voltage of the distal convoluted tubule cell and in turn, intracellular chloride concentration. High-potassium diet will lead to a higher intracellular chloride concentration, which will not stimulate the WNK (with-no-lysine kinase) pathway, and thereby, NCC will remain inactive. This mechanism will cause natriuresis, kaliuresis, and decrease in BP[28] (Figure 1). Many other proposed mechanisms on how potassium can influence BP have been reported, which include alterations in intracellular sodium and tonicity, modulation of baroreceptor sensitivity, vasoconstrictive sensitivity to norepinephrine and angiotensin II, high sodium/potassium ATPase activity and alteration in DNA synthesis and proliferation, and decrease in cardiac diastolic dysfunction.[23]

Potassium Intake and BP

Both epidemiological studies and RCTs have demonstrated the association between high potassium intake and lowering BP.[26] For example, 3 systematic reviews with meta-analyses have suggested that high potassium intake is associated with lowering BP in adults with or without hypertension.[29–31] In 2013, Aburto et al from the WHO[19] conducted the largest meta-analysis on the impact of increased potassium intake on cardiovascular risk factors and diseases. It included 22 RCTs with 1606 participants and reported that an increase in potassium intake reduced SBP by 5.3 (95% CI, 3.4–7.2) mm Hg and diastolic BP by 3.1 (95% CI, 1.7–4.5) mm Hg in adults with hypertension.[19] With higher potassium intake (90–120 mmol/d), the reduction in SBP was even greater at 7.2 (95% CI, 1.9–12.4) mm Hg. A subsequent dose-response meta-analysis of 32 RCTs identified a U-shaped relationship between potassium intake and BP, suggesting that an adequate intake of potassium was desirable to achieve a lower BP but that excessive supplementation should be avoided, particularly in specific subgroups.[32] For instance, Gritter et al performed an analysis of the run-in phase of a clinical trial where 191

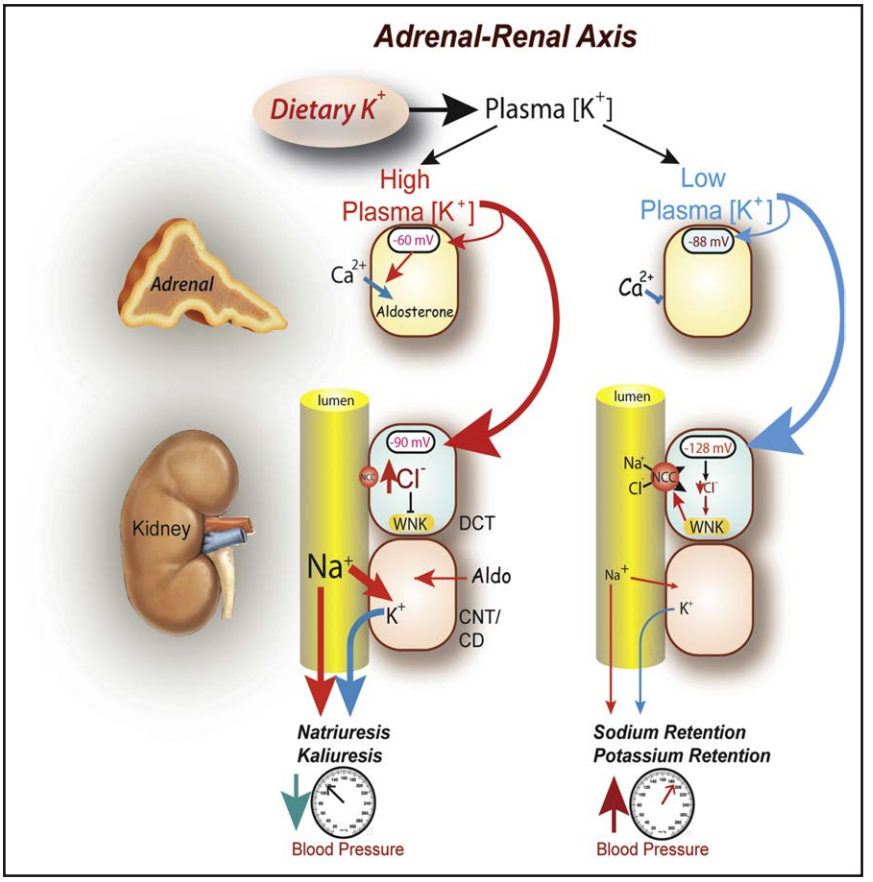

Figure 1. Schematic representation of the link between dietary sodium (Na) intake, aldosterone (Aldo), and tubular Na transport through the thiazide-sensitive NCC (sodium chloride cotransporter).
Dietary potassium (K) deficiency activates NCC even in the setting of high Na intake thus increasing Na retention and blood pressure, while increasing K intake does the reverse. This is mediated via the WNK (with-no-lysine kinase). Ca indicates calcium; CD, collecting duct; Cl indicates chloride; CNT, connecting tubule; and DCT, distal convoluted tubule. Adapted from Terker et al[28] with permission. Copyright©.

patients with chronic kidney disease were treated with 40 mmol of potassium chloride daily for 2 weeks and found that 21 participants (11%) developed hyperkalemia (these patients were older and had higher baseline plasma potassium).[33]

Potassium Intake and Clinical Outcomes

The meta-analysis from Aburto et al also reported a 24% lower risk of stroke (relative risk, 0.76 [95% CI, 0.66–0.89]) with high potassium intake in the pooled analysis, which is the cardiovascular outcome most closely related to BP. High potassium intake was not associated with significant adverse effect on kidney function, blood lipids, or catecholamine concentrations. Another study also reported that a high potassium intake in hypertensive patients resulted in less need for antihypertensive therapy: 81% of participants needed less than half of the baseline medication, and 38% required no antihypertensive medication for BP control, as compared with 29% and 9%, respectively, in the control group.[34] Similar to the Aburto meta-analysis, cerebrovascular benefits have been demonstrated in other studies.[23] Khaw and Barret-Connor[35] conducted a 12-year prospective study that revealed an increase in potassium intake of 10 mmol/d among 859 men and women lead to 40% decline in stroke mortality. Two additional large cohort studies showed similar results from the Health Professionals Follow-Up Study (N=43 738)[36] and Nurses Health Study (N=85 764).[37] Lastly, high potassium intake has additionally revealed other cardiovascular benefits. For example, an increase in potassium intake has shown to improve time for repolarization in patients with inherited or acquired long QT.[38]

WHAT IS IMPORTANT: SODIUM OR POTASSIUM?

With regard to the relative contribution of dietary sodium and potassium, these debates are not really new. Experiments performed by Meneely and Ball[39] in 1958 suggested that animals fed toxic amounts of sodium chloride survived longer if they were concomitantly fed higher amounts of potassium chloride. Further, even experiments on Dahl salt-sensitive rats[40] have reported that higher potassium intake blunts the hypertensive effect of sodium. This would suggest that even if the sodium content of diet is high, incorporating more potassium into the diet might potentially mitigate the effect of dietary sodium, and the potassium switch mechanism discussed above might explain this protective effect. It has been observed that mortality from stroke is higher in Japan compared with the West, traditionally attributed to the higher sodium content of traditional Japanese

cuisine. However, epidemiological studies from Japan have shown that BP also correlates inversely with urinary potassium excretion and positively with the urinary Na+/K+ ratio.[41] Similar studies from the West have also identified a negative correlation between BP and urinary potassium excretion[42] or urinary Na+/K+ ratios. Lastly, an RCT from 1990 reported that the effect of supplemental potassium chloride in the setting of a low-sodium diet was modest (BP reduction of 1.9/0.6 mm Hg).[43] Similarly, in the DASH-Sodium trial, the effect of the DASH diet (which is enriched with potassium) was higher in the high sodium setting (BP reduction of 5.9/2.9 mm Hg) compared with the low sodium setting (2.2/1.0 mm Hg).[7]

Tying these 2 strands together is SSaSS (Salt Substitution and Stroke Study),[44] which was a cluster RCT conducted in 600 Chinese villages, randomized to a sodium substituted salt (75% sodium chloride with 25% potassium chloride) or usual table salt. Almost 21 000 participants with either a history of stroke or who were ≥60 years of age with high BP were enrolled. Impressively, there was a 14% relative risk reduction of stroke and a 12% reduction of all-cause mortality. Notably, the change in sodium consumption from baseline was about an 8% decrease (≈15 mmol/d) but for potassium was about 57% increase (≈21 mmol/d). Similar results were shown in Peru where a stepped-wedge cluster randomized trial was performed at a population level replacing regular salt with a combination of 75% sodium chloride and 25% KCl.[45] A total of 2376 participants were enrolled with an average reduction of 1.29 mm Hg (95% CI, −2.17 to 0.41) in SBP. Among patients without hypertension at baseline, the use of the salt substitute was associated with a 51% (95% CI, 29%–66%) reduced risk of developing hypertension compared with the control group.

Implementation Aspects

Nonpharmacological interventions like dietary changes and lifestyle modification do form an essential aspect of the management of hypertension, irrespective of the underlying pathogenesis. Though sodium reduction has been a staple of hypertension guideline recommendations, increasing potassium has now joined the table in recent years.[4,46,47] However these guidelines recommend dietary changes, and it is important to examine the practicalities of implementation of these otherwise sound recommendations.

The DASH diet is the most widely promoted as an effective way of controlling BP, but notably in the original DASH trial,[17] the participants had to consume prepared meals for breakfast and lunch at the study centers and received a packaged supper designed to fulfill study criteria. The effect seen in such feeding interventions may not be achieved in real-life settings. A systematic review[48] examined the feasibility of implementing effective sodium restriction strategies in primary care strategies. Among the 4 RCTs that reported a 24-hour urine sodium reduction as an outcome and provided sufficient details of the intervention to be reproducible, none were reported to be feasible for implementation. All the interventions in these trials are either of a feeding nature where food is provided or intense (eg, inpatient 5-day counseling), which would be impractical for clinical care. A recent feasibility trial investigated whether intensive behavioral and dietary counseling would result in a significant and sustained dietary change. Three hundred seventy-three participants were recruited, and though there was a small change in dietary change (difference between groups, ≈17 mmol/d as measured by 24-hour urine), this was not sustained at 2 years, with no changes in BP, 24-hour urine sodium, or any other parameters measured.[49]

This is not surprising once we understand that there are several hidden sources of sodium. The National Health and Nutrition Examination Survey data show that the average individual consumes about 3440 mg/d of sodium, and the major contribution to this comes from commercial food processing and preparation. Additionally, low-sodium diets may be more difficult to implement either in terms of cost to buy or time to prepare. In an analysis from another National Health and Nutrition Examination Survey, the mean DASH accordance score (with 40 being the highest) was only 20.7, and a significant difference in diet cost across quintiles of DASH accordance, with mean daily cost in the top quintile being higher than the bottom quintile by $1.30.[50] This is several times higher than the lowest dose of a thiazide diuretic, which costs pennies a day and produces greater BP lowering with little behavioral change necessary.[50] On the other hand, it might be easier to increase the potassium content (rather than decrease in sodium) in diet so that it can offset the harmful effects of sodium. Similar to sodium, it is interesting to note that worldwide, the consumption of potassium is also suboptimal. In North America and Europe, the average potassium intake is 2.5 to 2.7 g/d, while in Africa and South America, it is only around 2 g/d, and Asian populations eat <2 g of potassium per day.[51]

Approaches to Increasing Potassium Content in Diet

Potassium content from a particular source is dependent on other factors such as the method of preparation, carbohydrate content (promotes insulin secretion, which can reduce potassium availability), and simultaneous intake of other food items, which may influence potassium metabolism. For example, the potassium content of fresh green beans is reduced by 15% with soaking, 33% with cooking, and 46% with soaking and cooking.[52] In addition, potassium supplements may be used in individuals unable to meet requirements through

diet. Poorolajal et al[53] conducted a meta-analysis of 23 RCTs studying the effect of potassium supplementation on primary hypertension for a minimum of 4 weeks. They concluded that potassium supplementation did reduce BP significantly as well (pooled effect, −8.9/6.4 mm Hg). An ongoing trial will examine whether dietary changes are sufficient to increase potassium intake to the required 90 mmol/d or additional potassium supplements are necessary.[54]

Role of the Food Industry

The emphasis on behavior modification and dietary change is somewhat misplaced once we consider the source of sodium and potassium in diet. A systematic review examined studies that quantified discretionary (salt added during cooking or at the table) and nondiscretionary sources of salt and those that provided information about the food groups contributing to dietary salt intake.[55] From the 80 studies from 34 countries included, they reported that the source of salt varies across the world. For instance, in China, sodium intake is dominated by salt added in cooking and at the table, but this is not true for North America, Europe, and Australia where <25% of sodium is from a discretionary source (Figure 2). Thus, the implementation of guidelines will require different pathways, focusing on individual actions in some countries and other actions in other countries. The nondiscretionary sources refer to sodium added in food processing and food preservation, which guidelines do not touch. There does appear to be interest in this area from the food industry, with research from the food industry showing that sodium substitution in prepared foods can be achieved while maintaining taste.[56] Additionally, the US Food and Drug Administration decided in 2020 to allow potassium chloride to be labeled as potassium salt thus paving the way for easier addition of potassium or substitution of sodium with potassium in processed food.[57] Given the robust results from the SSaSS trial, in places where the source of sodium is discretionary, that is, added in the kitchen/household, the increased use of the salt substitute should be encouraged.

There is concern with respect to the safety of making these changes, especially if they are made by the food industry at a population and not individual level such as the risk of hyperkalemia in individuals with impaired potassium excretion. A modeling study[58] examined the risks and benefits of lowering sodium intake through potassium enriched salt substitution. This study used comparative risk assessment models to estimate the effects of replacing discretionary dietary salt with potassium enriched salt substitutes (20%–30% potassium chloride) in China. It concluded that such a substitution

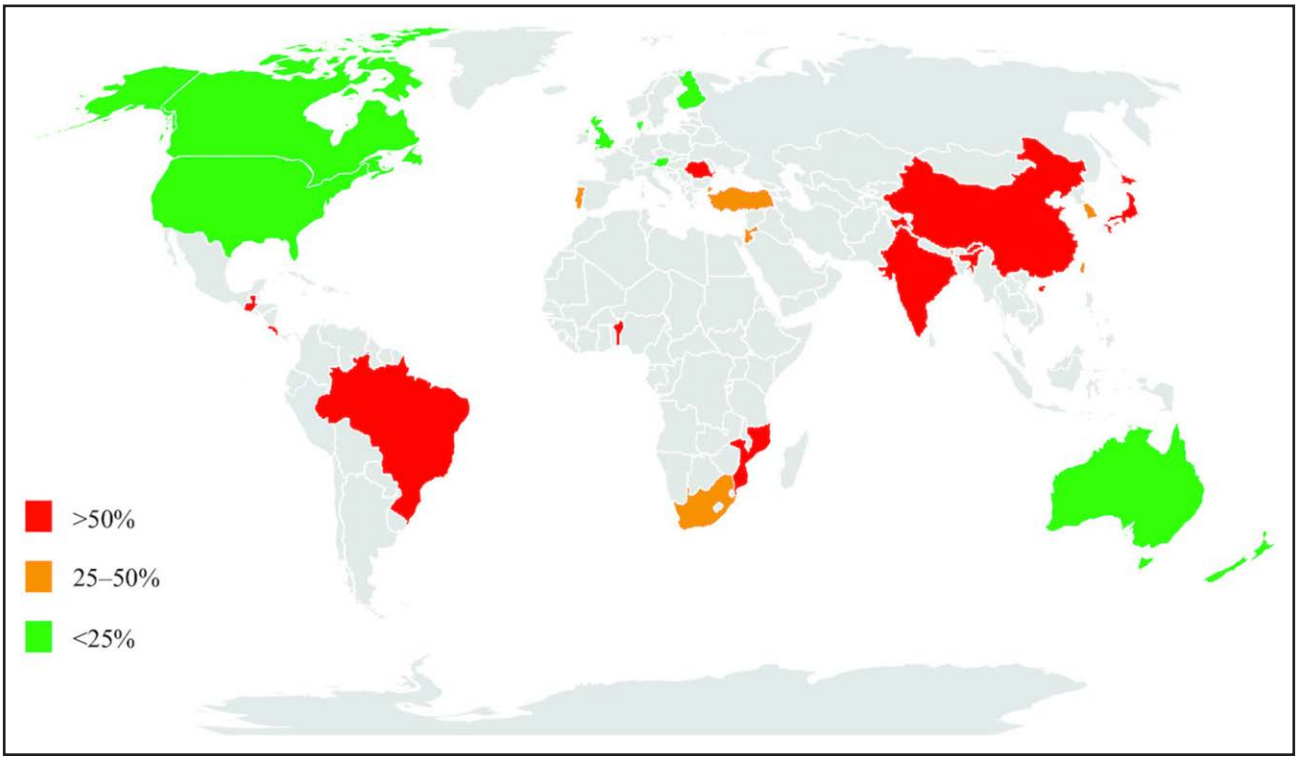

Figure 2. Contribution of discretionary sources to total dietary salt intake around the globe.
Green, <25% of dietary salt from discretionary sources; amber, 25% to 50% of dietary salt from discretionary sources; red, >50% of dietary salt from discretionary sources. No published data were available for countries shaded in gray. Adapted from Bhat et al[55] with permission. Copyright©.

could result in a substantial net benefit and prevent around 1 in 9 deaths from cardiovascular disease overall, and this benefit was maintained even in individuals with chronic kidney disease.

CONCLUSIONS

Thus, potassium intake clearly regulates BP, and a high dietary potassium intake may not only lower BP but also protect against the effects of a high sodium intake. In addition to lowering BP, increasing potassium intake also lowers risk of stroke, Lastly, implementing an increase in potassium intake in the diet has multiple pathways, including diet, supplements, and action from the food industry, in stark contrast to sodium intake, which has not budged despite decades of guideline recommendations. The time is now to elevate the status of potassium for BP control and achieve faltering targets of BP control and hypertension-related clinical outcomes.

ARTICLE INFORMATION

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Response to Blood Pressure Control Should Focus on More Potassium: Controversies in Hypertension

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Despite the compelling arguments by Chan et al, it should be noted that observational studies suggesting U-shaped and null associations between sodium and cardiovascular disease rely on self-report and spot urine. With gold standard, 24-hour urine assessments, risk associations are linear and consistent.[1,2] Also, arguments comparing sodium to pharmacological thiazides are fraught. Lifestyle and pharmacological interventions should be viewed synergistically given evidence that higher sodium intake attenuates the efficacy of thiazides[3] and lower sodium reduces blood pressure in adults with treated hypertension.[4]

There are compelling reasons for public health policy to focus specifically on sodium reduction. First, potassium exhibits heterogeneous blood pressure benefits (primarily effective in high sodium, low potassium contexts) and heterogeneous harms (patients predisposed to hyperkalemia), which argue that potassium interventions should be tailored at the patient level. Conversely, sodium is universally beneficial without known harms and thus well suited for population-wide implementation. Second, achieving potassium goals without supplementation requires consuming many fruits and vegetables and potentially unhealthy food sources. One potassium-focused grocery study relied on fruit juice to achieve potassium targets, finding no impact on BP and worsened fasting glucose.[5] Others noted higher costs with higher potassium diets.[6]

Ultimately, realignment of food subsidies to reduce fruit and vegetable costs relative to processed foods or meat products may be necessary to incentivize dietary choices that lower sodium and increase potassium. For now, industry restrictions on sodium in processed foods or warning labels on high-sodium products in stores and restaurants could be expedient and safe steps toward healthier populations.

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