REVIEW

Targeting the Dietary Na:K Ratio—Considerations for Design of an Intervention Study to Impact Blood Pressure

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ABSTRACT

Despite medical, dietary, and lifestyle recommendations and drug advancements, hypertension persists as among the most prevalent noncommunicable diseases in the US population, and control remains elusive. Uncontrolled hypertension may increase the risk of serious illness from various other health challenges, including cardiovascular and renal responses. Adoption of a healthy diet is a consistent core element of lifestyle modifications that are recommended for mitigation of hypertension. The dietary sodium-to-potassium ratio is recognized as having promising potential in the regulation of blood pressure. In fact, the understanding of the relation between this ratio and blood pressure was documented as a key evidence gap in the 2019 National Academies of Sciences, Engineering, and Medicine report that revised recommended intake levels for both sodium and potassium. Although notable animal and human evidence supports this point, fundamental to developing a specific dietary recommendation for a sodium-to-potassium ratio is a well-designed human intervention trial. The successful translatability of such a trial will require careful consideration of study elements, including the study population, duration, blood pressure measurement, and dietary intervention, among other factors. This paper addresses these decision points and serves as supporting documentation for a research group or organization with the interest and means to address this important data gap, which will undoubtedly be foundational for advancing dietary guidance and would inform the next iteration of Dietary Reference Intakes for sodium and potassium. *Adv Nutr* 2021;00:1–9.

Statement of Significance: Altering the sodium-to-potassium ratio (Na:K) of the diet has potential for blood pressure management. This paper addresses a key evidence gap identified in the 2019 National Academies of Sciences, Engineering, and Medicine (NASEM) Sodium and Potassium Dietary Reference Intakes report by providing considerations and recommendations for the design of a human intervention trial critical for understanding the relation between dietary Na:K and blood pressure.

Keywords: hypertension, sodium, potassium, sodium-to-potassium ratio, Na:K ratio, Dietary Reference Intakes

Background and Hypothesis

On 7 October 2020, Surgeon General VADM Jerome M Adams issued a Call to Action urging Americans to recognize and address hypertension control as a national public health priority, noting that uncontrolled hypertension increases the risk of numerous chronic diseases and may increase risk of serious illness from coronavirus disease 2019 (COVID-19) (1). In this Call to Action, African Americans were highlighted as having the highest incidence of hypertension and lowest rates of controlled hypertension.

Among other elements, a core lifestyle modification mentioned in the Call to Action was adoption of a healthy diet. It is generally recognized that such a diet should not exceed recommended intake levels for sodium. A large body of evidence links high dietary sodium intake to elevated blood pressure and increased risk of cardiovascular and kidney disease. In tandem with sodium, dietary potassium plays a well-established role in blood pressure regulation (2). Over the past several decades, little progress has been made toward reducing population-level sodium intake, and the

potassium intake of Americans consistently is below the level that is recommended (3).

The mechanisms of potassium and sodium interaction to impact blood pressure and the amount of dietary potassium that would be required to improve blood pressure given a designated level of dietary sodium intake are not well understood. Characterization of the relation between the dietary sodium-to-potassium ratio (Na:K) and health was identified as a key research gap in the 2019 Sodium and Potassium Dietary Reference Intakes (DRI) report, which set revised recommended intake levels for both nutrients for the United States and Canada (2).

Intakes of sodium and potassium at recommended DRI levels, as compared with lower intake of potassium at the same sodium intake level, moderate blood pressure in prehypertensive individuals (4). Gijsbers et al. (5) showed that supplemental potassium combined with a relatively low-sodium diet benefited blood pressure among individuals with prehypertension. In comparison, the investigators in the Prospective Urban Rural Epidemiology (PURE) Study concluded that a significant relation between estimated intakes of sodium and potassium and blood pressure was nonlinear and most often observed in study participants consuming a high-sodium diet, having hypertension, and of increased age (6). The latter study should, however, be interpreted with caution, because estimations of individual cation intakes were based on spot urine samples and may, as such, have introduced significant bias (7), whereas Gijsbers et al. validated intake using 24-h urine collection. Compared with regular salt (i.e., 100% sodium chloride), potassium-enriched salt substitutes reduce blood pressure and have been found to lower cardiovascular mortality among elderly men in Taiwan (8). An ongoing study in which a provided salt substitute is intended to both reduce sodium and increase potassium intake should provide data to understand effects of an altered intake ratio on several cardiovascular endpoints (9). At present, determining appropriate intake levels on a population basis is complicated by the existence of a finite number of randomized controlled trials with results generalizable to the "healthy population" and a larger number of observational studies that are methodologically limited for this purpose (10). Finally, Jackson et al. (11) found a clear linear association ($P = 0.006$) between Na:K and systolic blood pressure using 24-h urinary collections and dietary intake data in NHANES 2013–2014. Those in the top quartile of the ratio had about a 6 mm Hg greater systolic blood pressure than those in the lowest quartile.

To move forward on the research need identified in the 2019 DRI report regarding linking dietary Na:K to blood pressure–related health outcomes, (2) an expert group was convened by the International Life Sciences Institute, North America [in 2021, ILSI North America evolved to become the Institute for the Advancement of Food and Nutrition Sciences (IAFNS)], on 26 August 2020. The group's objective was to outline the design considerations for a human intervention trial targeting clarity on the relation between the dietary Na:K ratio and blood pressure. This article summarizes those considerations and can serve as supporting documentation for a research group or organization with the interest and means to address this gap. Information generated in such a trial may be critical in the continuing struggle to reduce hypertension prevalence and related medical costs in the United States and worldwide.

A research study to elucidate the role of the Na:K ratio in blood pressure management must address several considerations: the target study population characteristics and size, study design, the range of dietary Na:K ratios to study in a controlled fashion, protocols for blood pressure measurement, and desired end points, namely preventing normotensive individuals from developing elevated blood pressure (formerly called prehypertension), preventing individuals with elevated blood pressure from transitioning into hypertension, and/or lowering blood pressure in individuals with stage 1 or stage 2 hypertension (7). This paper addresses each decision in turn, outlining the considerations and potential consequences.

Issues and Knowledge Gaps in Sodium, Potassium, and Health: Summary of DRI Committee Findings and Relevance

The DRIs are positioned for a generally healthy population and were established with data from normotensive individuals. The 2019 DRI report on sodium and potassium (2) identifies major knowledge gaps and research needs regarding assessing dietary sodium and potassium intakes that complicate determination of the relation between these nutrients (e.g., Na:K and blood pressure regulation) (**Table 1**).

DRI reports include well-established guidance around the Estimated Average Requirement (EAR), RDA, Adequate Intake (AI), and Tolerable Upper Intake Level (UL), as well as a new metric introduced in the 2019 DRI report on sodium and potassium, the Chronic Disease Risk Reduction (CDRR) level (12). The committee reviewing the DRIs for sodium and potassium rated the strength of the body of evidence for both causality and intake response using a Grading of Recommendations Assessment, Development, and Evaluation (GRADE) evidence synthesis methodology (13). The CDRR for sodium for adults, 2300 mg/d, represents "the level above which intake reduction is expected to

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Abbreviations used: AHRQ, Agency for Healthcare Research and Quality; AI, Adequate Intake; CDRR, Chronic Disease Risk Reduction; DASH, Dietary Approaches to Stop Hypertension; EAR, Estimated Average Requirement; TRUE, Ternational consoRtium for qUality research.

TABLE 1 Knowledge gaps and research needs regarding the relation of sodium to potassium, and health, as reflected in the 2019 report "Dietary Reference Intakes for Sodium and Potassium"[1]

Knowledge gap	Select research needs
Explore potassium and sodium in relation to each other and other dietary components	• Explore the relation between the Na:K ratio and outcomes and surrogate markers (e.g., blood pressure) for cardiovascular risk at different doses of potassium and sodium intake and assess whether the ratio is a better measure than either nutrient alone. • Identify individual-level attributes that affect the urinary Na:K ratio (e.g., age, race/ethnicity, BMI, genotype) and determine how that information can be used to calibrate adjustment equations. • Determine if and how the infradian rhythms of urinary potassium and sodium excretion reflect the Na:K ratio. • Improve statistical methods for estimating the distribution of the usual intake for the Na:K ratio.
Explore opportunities in the food supply	• Develop novel solutions, including through technological innovations, to decrease sodium in the food supply.

[1] Data from reference 2.

reduce chronic disease risk, within an apparently healthy population."

At present, no sensitive biomarker of sodium requirements has been identified, observational studies have limitations, and available balance studies do not offer sufficient data for determining sodium requirements. The DRI committee determined that insufficient evidence exists to establish sodium EARs and RDAs and median population intakes cannot be used because they exceed the sodium CDRR.

Relative to the CDRR for sodium, the committee considered, in depth, cardiovascular disease incidence and mortality associated with systolic and diastolic blood pressure. The strength of evidence for relations between reduction in sodium intake and reduction in chronic disease risk is moderate for daily sodium intakes >4100 mg and up to 5000 mg, strong at 2300–4100-mg intakes, and low at intakes of 1000–2300 mg. Few trials have examined the impact of sodium intake <1000 mg/d.

Similar to sodium, no sensitive biomarker has yet been identified for determining potassium requirements and available balance studies fail to rigorously measure intake and all forms of loss. Therefore, the DRI committee found insufficient evidence to establish EARs and RDAs for potassium; median intakes in apparently healthy groups of people were deemed appropriate for establishing AIs. The 2019 DRI for potassium was set at 3400 mg/d for men and 2600 mg/d for women.

The findings of the 2019 DRI committee regarding potassium and blood pressure/hypertension describe moderate-strength evidence for causal association, but insufficient evidence for an intake-response relation, calling for more evidence on potassium and sodium in relation to each other and to energy intake. Additionally, potential interactions with other nutrients in a complex food supply make it difficult to trace a single nutrient of any kind to a health outcome. An Agency for Healthcare Research and Quality (AHRQ) systematic review noted that changes in potassium often impact calcium and magnesium intakes (14). Interactions between intakes of sodium, potassium, calcium, and magnesium and their effects on blood pressure regulation have not been fully characterized.

Considerations for Study Design to Elucidate the Na:K and Blood Pressure Relation

Defining the study population

The overarching purpose of the study and its findings is perhaps the most important consideration toward selection of a study population. For example, a study that is positioned as substantiation toward future DRIs requires stratification with normotensive individuals and individuals at various stages of hypertension with and without other chronic diseases, as well as a definition for a "healthy" population. A study with a public health focus on a high-risk population (i.e., individuals with hypertension) carries implications of making changes for 1 specific at-risk group rather than population-wide. Defining an appropriate study population in the face of high chronic disease prevalence is among the greatest challenges, especially if the purpose of the study is aimed at prevention in a "healthy" population. The target population for dietary sodium and potassium intervention typically has a high incidence of hypertension and cardiovascular disease, as well as type 2 diabetes and overweight or obesity. Medication use in this population impacts sodium and potassium excretion, while diet counseling as part of medical nutrition therapy is targeted to alter sodium and potassium intakes. Hence, selection of a suitable study population involves numerous considerations (**Table 2**).

Salt sensitivity is a physiological trait by which the blood pressure of some members of the population exhibits changes parallel to changes in salt or sodium intake. Factors that might influence salt sensitivity include sex, age, degree of adiposity, ethnicity, and chronic disease; genetics also may play a role (15). Individuals with hypertension tend to be more salt sensitive, as do African Americans and older adults (16, 17). The prevalence of hypertension and chronic kidney disease already is high in the baseline population of many communities who could benefit from intervention, including those with a high prevalence of salt sensitivity. Individuals who are at risk from consuming a high-sodium and/or low-potassium diet include those from groups considered to be sodium sensitive (age >60 y, African American or Hispanic American), with sodium-sensitive disease states

TABLE 2 Considerations for the design of a human intervention trial investigating the relation between dietary Na:K and blood pressure[1]

Element	Consideration
Objectives	
Contribution toward DRI, DGA	Higher level of evidence required for DRI vs. public health implications for DGA
Applicability/generalizability	Impact of baseline BP, demographics, sodium sensitivity, health status
Population	
Demographics	Age, sex, race/ethnicity, socioeconomic status
Health status	Normotensive, elevated blood pressure, or hypertension; controlled vs. uncontrolled hypertension; salt sensitivity; presence of sodium sensitive disease states
Recruitment	Duration, community resources, identification of comparison population, estimated dropout rate
Dietary intervention	
Na:K ratios	Intervention and comparison ratios
Diet	Dietary guidance vs. food provision
	Strategies for diet control and monitoring of compliance
	Consideration of confounding nutrients and other components in food
	Participant compliance
	Standardized lead-in diet
Food sources of potassium	Adjusting for inconsistencies in nutrient databases and for nutrient content variability in foods over time
Sodium reduction, potassium substitution, or both	Food alone vs. potassium substitution, sodium substitutes
Potassium supplementation	Form, level, palatability, food and beverage applications
	GI tolerance
	Avoiding hyperkalemia
Outcome measures	
Blood pressure	Office vs. out-of-office
	Ambulatory vs. self
	Frequency of measurement
	Staff resources
	Participant compliance
	Additional measurements (cardiac output, central BP from pulse-wave analysis, systemic vascular resistance)
Assessment: timing and frequency	Repeated measures, comparison of the final outcome measure or full longitudinal repeated-measures comparison
Twenty-four urine for sodium, potassium, other outcomes	Single collection vs. multiple collections
Secondary	Bioimpedance
	N-terminal-pro-B-type natriuretic peptide
	Renin-angiotensin-aldosterone system peptides
	Sodium MRI (e.g., skin, muscle)
	Macrophage/monocyte depolarization
	T-lymphocyte subsets
	Vascular inflammation
	Vascular remodeling
	Left ventricular mass
Design	
Type of trial	Crossover
	Parallel-group
	Factorial design
	Adaptive "dose-finding" design[2]
Potential stratification factors	Baseline sodium consumption, BP, kidney function, ethnicity, salt sensitivity
Sample size	Dependent upon choice and variation of outcome measure, number of assessments, analytic strategy, trial design
Duration	Shorter (2 wk) vs. longer (at least 4 and up to 6 wk)

[1] BP, blood pressure; DGA, Dietary Guidelines for Americans; GI, gastrointestinal.
[2] In an adaptive "dose-finding" design, several different levels of Na:K ratio would be used. Data from interim analyses can then be applied to select the best-performing doses for continued study. For example, begin the study with 4 possible ratios and then select the 2 best after a certain number of patients, continuing for the remaining patients.

(hypertension, edematous states, chronic kidney disease), and/or with disease states whose mortality might be increased by increasing dietary sodium and/or decreasing dietary potassium (cardiovascular disease, chronic kidney disease). Given the health disparities among communities, study subjects may need to represent a baseline community rather than one defined as "healthy" or "normal." The baseline group might consist of individuals at higher risk but with a lower prevalence of chronic diseases, and in whom a higher sodium or lower potassium diet could increase mortality risk. Socioeconomic status and ethnicity also are factors that should be taken into account.

Blood pressure measurement

Criteria should be established a priori for defining valid assessments for blood pressure measurements because data often are missing for part of the measurement period. Lack of standardization and quality control in research and clinical blood pressure measurement has contributed to the current controversy about the relation between dietary salt and blood pressure/hypertension.

Advisories offer recommendations on various aspects of blood pressure measurement. The TRUE (inTernational consoRtium for qUality research) Consortium recommended standards for assessing blood pressure in-office and out-of-office in human research with blood pressure outcomes (18). TRUE recommendations apply to human clinical and epidemiological research on blood pressure or hypertension where blood pressure is thought to be a major mediator of the research outcome. The American Heart Association's Scientific Statement on Blood Pressure Measurement includes recommendations on frequency and methodology of blood pressure measurement and on standards for monitoring (19). A systematic evidence review for the US Preventive Services Task Force suggests that ambulatory blood pressure monitoring better predicts long-term cardiovascular outcomes and should be the standard for evaluating noninvasive blood pressure measurements (20). Regardless of the method used, initial and ongoing training of technicians and health care providers on the use of validated and calibrated devices is critical to obtaining accurate blood pressure measurements.

Additional controllable factors that contribute to blood pressure variations include physiology, demographics, ethnicity, medications, underlying medical conditions, staffing, and "white coat" anxiety (21).

Determining the Na:K ratio in intervention diets

Several specific factors come into consideration when designing a trial evaluating the dietary Na:K ratio. The first is the methodology for achieving the desired ratio(s), whether by reducing sodium, increasing potassium, or both, and whether by increasing potassium solely through specific food choices or through partial ingredient replacement for sodium chloride.

Sodium intake and blood pressure have been shown to have a linear relation in some studies but a nonlinear relation in others. A 2014 meta-analysis of 103 sodium-reduction trials demonstrated that greater sodium reduction resulted in greater lowering of blood pressure, but that age, hypertension status, and race impact the relation (22).

In contrast, the relations between dietary potassium and blood pressure have been shown to be nonlinear (23). Most studies have utilized a crossover design and studied people with untreated hypertension (23). Studies typically provided potassium as potassium chloride, with dosages of 30–120 mmol/d (1200–4700 mg/d) (23). The greatest reduction in blood pressure was observed at a potassium intake of 30–40 mmol/d (1200–1500 mg/d) and/or 90–120 mmol/d urinary potassium excretion (23). The dose–response relation between potassium supplementation and blood pressure appeared to be stronger in study populations with lower urinary potassium excretion (<75 mmol/d) at baseline (23). Similarly, the blood pressure effects of potassium supplementation were greatest in study populations with high sodium excretion at baseline (23). Stratifying based on hypertension status, potassium supplementation was associated with greater blood pressure reduction in those with untreated hypertension (23); few studies were conducted in normotensive participants. Data suggest that the impact on blood pressure can be optimized across a range of potassium intakes in the face of high sodium intake. Little gain occurs, however, by increasing potassium to >40–50 mmol/d.

Data from NHANES 2017–2018 show sodium intake in the United States at ∼3500 mg/d (152 mmol/d), which is higher than desired, and potassium intake of ∼2500 mg/d (64 mmol/d), below the recommended DRI (24). Attaining a workable and clinically meaningful Na:K ratio could call for lowering sodium to 2000 mg/d (87 mmol/d), for example, and increasing potassium by up to 2000 mg/d (51 mmol/d) for a total intake of 3500–4700 mg/d (90–120 mmol/d). Ideally, both sodium and potassium intakes would be varied, but this approach would require a series of studies. A simpler design approach, however, might be to keep sodium constant at the typical intake for Americans and raise potassium so that only 1 variable changes.

Sodium and potassium sources in study diets

Few studies have compared effects on blood pressure of increasing potassium through food sources versus potassium substitution for salt/sodium chloride, and evidence does not exist to support an effect on blood pressure of increasing potassium through food sources alone (14). Increasing potassium intake to a high-enough level through foods rich in potassium such as fruits and vegetables can be difficult, introduces variability in other nutrients, and changes diet quality. Bioavailability and uptake of potassium from food compared with potassium compounds must also be considered. When the bioavailability of potassium in potatoes and potassium gluconate was compared in a randomized controlled trial enrolling young and healthy men, no difference in bioavailability (assessed by AUC of serum potassium) was evident (25).

Likewise, few studies have evaluated simultaneous changes in sodium and potassium intake. Newberry et al. (14) noted a lack of evidence of a moderating effect of increasing dietary potassium on the blood pressure–lowering effect of sodium reduction compared with sodium reduction alone. However, blood pressure reduction in salt-substitute trials where sodium chloride is partly replaced by potassium chloride generally is greater than what is expected from sodium reduction alone, but the interactions among the sodium, potassium, and chloride ions are not yet fully understood. The potential effects of chloride or other alterations in dietary cations/anions on blood pressure merit consideration.

The Dietary Approaches to Stop Hypertension (DASH) test diet included fruit, vegetables, low-fat dairy, and other nutrient-rich foods while keeping sodium constant (26, 27).

In a later study, Svetkey et al. (28) randomly assigned subjects to either the DASH diet or a typical American diet in a parallel-group design and at each of 3 sodium intake levels in a crossover design. Systolic blood pressure dropped most among those following the DASH diet and consuming the lowest level of sodium.

One step toward designing an intervention diet could be to re-evaluate previous studies in terms of their Na:K ratios. This should be conducted in light of changes in the food supply over the past 20 y following the original DASH studies. Today's food supply provides more protein and fiber and less sugar, *trans* fat, saturated fat, and sodium (29, 30). Sodium intake has not dropped over 20 y, however, because consumers are eating more calories and it is well demonstrated that sodium intake tracks with caloric intake (31).

Diet design could manipulate the top dietary sources of sodium. In the United States, 71% of sodium intake comes from processed and restaurant foods and 11% is added at the table and while cooking (32). Top food sources of sodium include deli meat, bread, sandwiches, pizza, burritos and tacos, soups, and savory snacks. These and others could be targets of reformulation to lower sodium and increase potassium (32).

Partial substitution of potassium chloride for salt/sodium chloride as an ingredient in food formulation is 1 approach, since a majority of dietary sodium comes from sodium-containing ingredients in processed foods. In fact, this replacement is ongoing in the food supply (33). Potassium-based ingredients can significantly change the Na:K ratio in some food products. A single ingredient change from sodium chloride to potassium chloride, for example, could reduce sodium by 30%. Many major food companies have reformulated products to lower sodium and could be potential partners for creating study-specific products. Internal studies conducted by Cargill using potassium chloride reduced the Na:K ratio from 4.8 to 1.1 in deli ham, 0.6 to 0.4 in crushed tomatoes, and 14.4 to 1.5 in chicken noodle soup (Janice Johnson, unpublished data, 2020). Use of potassium chloride in these and other food products must consider the taste limitations due to bitterness and food safety as sodium chloride is reduced (33). In addition, individuals with a history of hyperkalemia or who take an angiotensin-converting enzyme inhibitor may be required to monitor intake of potassium.

An ideal design would include a diet in which the same foods are present but the amounts of sodium and potassium are varied using potassium chloride. As potassium chloride is the most commonly used sodium chloride substitute in the US food supply, its use offers an element of practicality for application of the study results (34). The translational benefit of this approach is that food choices can be maintained, circumventing the persistent challenges with dietary behavior change. A further critical element of diet design would be to provide all foods to study participants at an energy intake needed for body-weight maintenance. This intervention approach minimizes error in estimating intakes of all nutrients, but especially of sodium and potassium.

Establishing the Na:K ratio of the intervention diet using potassium-containing compounds in place of sodium chloride allows manipulation of the Na:K ratio(s) without drastic compositional diet and nutrient changes. With the control diet as the typical American diet, a test diet could fall between the control diet and DASH, adjusting sodium and potassium levels through alternative nonsodium substitutes.

Study validation

Assessment of both sodium and potassium in a 24-h urine collection is generally considered to be superior to self-reported dietary intake or use of food-composition data to estimate daily sodium and potassium intake. Although most dietary sodium is recovered in urine, evidence indicates that approximately 77% of dietary potassium is excreted in urine (2). Urinary sodium and potassium also tend to fluctuate day by day (35, 36), so a combination of multiple 24-h urine collections or multiple spot collections will improve precision. Evidence indicates that, even with a consistent intake of sodium-to-potassium, variability in the ratio will be apparent with 24-h urine collections, even in long-term balance studies (36).

Statistical and Design Considerations

Petersen et al. (37) recently summarized guidance for the planning and conduct of statistical analyses in randomized controlled trials focused on nutrition research questions. Many of these general considerations have relevance for the study of interest here. This section focuses on design options that will affect choices for statistical analysis.

Study duration needs to be long enough for a measurable response to the studied dietary intervention. The AHRQ systematic review commissioned for the DRI panel included studies of at least 4 weeks minimum intervention duration (14), although DASH observed differences at 2 weeks (14). Blood pressure usually changes within 2 wk and then restabilizes. Follow-up after the diet period ends, however, can be challenging if participants return to their prior lifestyle and diet. A longer duration might also be needed to observe changes in other surrogate cardiovascular and blood pressure–related outcomes.

The choice of primary study outcome influences statistical design consideration. If measuring systolic blood pressure, for example, a final measurement could be considered at the conclusion of the study for analysis or incorporated into longitudinal repeated measures in the primary analysis. Longitudinal repeated-measures analysis is more powerful but comparison just at the final point in time may be preferable for participant burden and may be a better measure of the true treatment effect of the diet.

A 2- to 4-wk run-in period with a standardized diet establishes energy intake needs, identifies subjects who are unable to comply with the diet, and provides a diet buffer in advance of measuring baseline blood pressure. Data may

require adjustment to account for lapses in adherence and to estimate a treatment effect if subjects were perfectly adherent.

A crossover design offers the presumed advantage of requiring fewer study subjects. It is statistically efficient because participants serve as their own control, reducing random variability (38). Shortfalls include the potential for order and/or carryover effects, the need for a washout period between treatments, challenges in switching diets, possible unblinding from different tastes (i.e., saltiness) between treatments, and differential dropout between arms. This design is appropriate only if little dropout is expected.

A parallel-design study is simpler to carry out because it does not require a washout period, eliminates confusion around switching diets, and may be faster depending on the length of the recruitment and study periods. It requires a larger overall sample size, but each participant completes just 1 treatment period rather than 2 plus a washout period and therefore may be less prone to drop out before study completion.

In a parallel-group design, regression analysis offers more statistical power. A study that examines the expected difference in follow-up value between 2 individuals who start with the same value and are treated with A versus B favors regression analysis of final measurements, with control for baseline values (39). Regardless of design, any study should be powered on the smallest effect size that is considered to be clinically meaningful.

Other design options include a factorial design, which would allow simultaneous testing of multiple questions (e.g., participants assigned to an Na:K ratio and to a delivery method, e.g., food alone vs. substitution) or an adaptive "dose finding" design with 3 or more Na:K arms. The adaptive design would allow initiating the study with several candidate Na:K ratios, then using data from interim analyses to select the best-performing ratios for continued study to efficiently allocate the available patients and provide the maximum possible information about what the optimal Na:K ratio would be.

Frequentist statistical analyses and Bayesian statistical analyses are 2 major statistical approaches. The classic frequentist approach computes a *P* value testing the observed data against a null hypothesis. The Bayesian approach is more complex, specifying prior distributions for treatment effect and computing posterior effect probabilities based on the combination of prior and observed data. It is especially well suited for adaptive trials that use accruing outcome data to inform allocation and drop arms that are performing poorly—for example, one of several Na:K ratios. In addition, if overall recruitment proves to be difficult, Bayesian approaches will allow frequent interim looks for efficacy or futility of specific arms.

Discussion

Prevention and management of chronic disease with a public health rather than pharmaceutical approach is a paradigm shift for the medical community. Examination of the Na:K ratio as an effective tool for preventing and/or reducing hypertension is consistent with several objectives that support the National Heart, Lung, and Blood Institute Research Priorities: investigate factors that account for differences in health among populations; develop and optimize novel diagnostic and therapeutic strategies to prevent, treat, and cure heart, lung, blood, and sleep diseases; and optimize clinical and implementation research to improve health and reduce disease (40).

A summary of recommendations for the design and conduct of a dietary Na:K ratio intervention study is provided in **Text Box 1**. Expectations regarding the contribution of the study to the body of research on sodium and potassium guidance drive the selection of a target population. Development of a study for consideration toward dietary guidelines and/or DRIs requires a generalizable study population. Contribution to public health initiatives might be derived through an intervention in higher-risk populations. If the optimal Na:K ratio requires potassium supplementation, study findings could help support a potassium-fortification or -substitution program that would lower sodium and raise potassium in the food supply to help consumers achieve the desired ratio.

TEXT BOX 1
Priority recommendations for the design and conduct of a dietary Na:K ratio intervention study to impact blood pressure

Recommendation 1. Clearly define the study question and intended application of the outcomes as these will drive the selection of the appropriate study cohort.
- For example, a study that aims at prevention, treatment, or establishing dietary guidance may require cohorts with different phenotypes.

Recommendation 2. Clearly define outcome assessments such that they are of clinical importance and biologically meaningful.
- For example, peripheral blood pressure measures are important clinically, whereas central blood pressure may offer other important insights.

Recommendation 3. Implementation of the dietary sodium and potassium treatments must consider dietary sources, supplement sources, food supply variability, palatability, practicality and feasibility for real-life use, and other factors that will affect compliance.
- For example, KCl is commonly found in processed foods, is widely available, and can mimic some of the critical functional roles of NaCl to include microbial management, protein modification, and taste.

Recommendation 4. Consider study designs that reflect potential pitfalls such as carryover effects and compliance, to maximize resource allocation (fewest number of subjects with an adequate number of ratios of Na:K).
- For example, an adaptive design can be used to identify 2 optimal ratios of Na:K by examining interim analyses from a larger initial set of ratios.

Any public health education component based on study findings regarding the Na:K ratio will require clear explanation of the ratio as it translates into food choices and tools to help consumers make those choices. While the ratio would be relevant for its absolute numbers, it needs to be translated into practical and applied implications in food choices and the overall diet. Research on and tools for promoting choices that align with the DASH diet may provide a model for dietary guidance toward the desired Na:K ratio.

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