Edward T. Chang, MD; Robert Powell, DO; Tyler Reese, MD
Leader & Faculty Development Fellowship Program, Madigan Army Medical Center, Joint Base Lewis-McChord, WA

DEPUTY EDITOR
Gary Asher, MD, MPH
Family Medicine Residency Program, University of North Carolina at Chapel Hill

doi: 10.12788/jfp.0667

Can these salt substitutes prevent complications of hypertension?

This study suggests the blood pressure–lowering effects of potassium-enriched salt substitutes may reduce cardiovascular morbidity and mortality.

PRACTICE CHANGER

Consider recommending potassium-enriched salt substitutes for appropriate patients with hypertension to reduce blood pressure (BP) and risk for related cardiovascular (CV) events or mortality.

STRENGTH OF RECOMMENDATION

A: Based on a systematic review and meta-analysis of controlled trials.[1]

Yin X, Rodgers A, Perkovic A, et al. Effects of salt substitutes on clinical outcomes: a systematic review and meta-analysis. *Heart*. 2022;108:1608-1615. doi: 10.1136/heartjnl-2022-321332

ILLUSTRATIVE CASE

A 47-year-old man in generally good health presents to a family medicine clinic for a well visit. He does not use tobacco products and had a benign colonoscopy last year. He reports walking for 30 minutes 3 to 4 times per week for exercise, although he has gained 3 lbs over the past 2 years. He has no family history of early coronary artery disease, but his father and older brother have hypertension. His mother has a history of diabetes and hyperlipidemia.

The patient's physical exam is unremarkable except for an elevated BP reading of 151/82 mm Hg. A review of his chart indicates he has had multiple elevated readings in the past that have ranged from 132/72 mm Hg to 139/89 mm Hg. The patient is interested in antihypertensive treatment but wants to know if modifying his diet and replacing his regular table salt with a salt substitute will lower his high BP. What can you recommend?

Hypertension is a leading cause of CV morbidity and mortality worldwide and is linked to increased dietary sodium intake. An estimated 1.28 billion people worldwide have hypertension; however, more than half of cases are undiagnosed.[2] The US Preventive Services Task Force recommends screening for hypertension in adults older than 18 years and confirming elevated measurements conducted in a nonclinical setting before starting medication (grade "A").[3]

Cut-points for the diagnosis of hypertension vary. The American Academy of Family Physicians,[4] the Eighth Joint National Committee (JNC 8),[5] the International Society of Hypertension,[6] and the European Society of Cardiology[7] use ≥ 140 mm Hg systolic BP (SBP) or ≥ 90 mm Hg diastolic BP (DBP) to define hypertension. The American College of Cardiology/American Heart Association guidelines use ≥ 130/80 mm Hg.[8]

When treating patients with hypertension, primary care physicians often recommend lifestyle modifications such as the Dietary Approaches to Stop Hypertension (DASH) diet. Other lifestyle modifications include weight loss, tobacco cessation, reduced daily alcohol intake, and increased physical activity.[9]

Systematic reviews have shown a measurable improvement in BP with sodium reduction and potassium substitution.[10-12] More importantly, high-quality evidence demonstrates a decreased risk for CV disease, kidney disease, and all-cause mortality with

lower dietary sodium intake.[13] Previous studies have shown that potassium-enriched salt substitutes lower BP, but their impact on CV morbidity and mortality is not well defined. Although lowering BP is associated with improved clinical impact, there is a lack of patient-oriented evidence that demonstrates improvement in CV disease and mortality.

The Salt Substitute and Stroke Study (SSaSS), published in 2021, demonstrated the protective effect of salt substitution against stroke, other CV events, and death.[14] Furthermore, this 5-year, cluster-randomized controlled trial of 20,995 participants across 600 villages in China demonstrated reduced CV mortality and BP reduction similar to standard pharmacologic treatment. Prior to SSaSS, 17 randomized controlled trials demonstrated a BP-lowering effect of salt substitutes but did not directly study the impact on clinical outcomes.[13]

In this 2022 systematic review and meta-analysis,[1] Yin et al evaluated 21 trials, including SSaSS, for the effect of salt substitutes on BP and other clinical outcomes, and the generalizability of the study results to diverse populations. The systematic review included parallel-group, step-wedge, and cluster-randomized controlled trials reporting the effect of salt substitutes on BP or clinical outcomes.

STUDY SUMMARY

Salt substitutes reduced BP across diverse populations

This systematic review and meta-analysis reviewed existing literature for randomized controlled trials investigating the effects of potassium-enriched salt substitutes on clinical outcomes for patients without kidney disease. The most commonly used salt substitute was potassium chloride, at 25% to 65% potassium.

The systematic review identified 21 trials comprising 31,949 study participants from 15 different countries with 1 to 60 months' duration. Meta-analyses were performed using 19 trials for BP outcomes and 5 trials for vascular outcomes. Eleven trials were rated as having low risk for bias, 8 were deemed to have some concern, and 2 were rated as high risk for bias. Comparisons of data excluding studies with high risk for bias yielded results similar to comparisons of all studies.

The meta-analysis of 19 trials demonstrated reduced SBP (–4.6 mm Hg; 95% CI, –6.1 to –3.1) and DBP (–1.6 mm Hg; 95% CI, –2.4 to –0.8) in participants using potassium-enriched salt substitutes. However, the authors noted substantial heterogeneity among the studies ($I^2 > 70\%$) for both SBP and DBP outcomes. Although there were no subgroup differences for age, sex, hypertension history, or other biomarkers, outcome differences were associated with trial duration, baseline potassium intake, and composition of the salt substitute.

Potassium-enriched salt substitutes were associated with reduced total mortality (risk ratio [RR] = 0.89; 95% CI, 0.85-0.94), CV mortality (RR = 0.87; 95% CI, 0.81-0.94), and CV events (RR = 0.89; 95% CI, 0.85-0.94). In a meta-regression, each 10% reduction in the sodium content of the salt substitute was associated with a 1.5–mm Hg greater reduction in SBP (95% CI, –3.0 to –0.03) and a 1.0–mm Hg greater reduction in DBP (95% CI, –1.8 to –0.1). However, the authors suggest interpreting meta-regression results with caution.

Only 2 of the studies in the systematic review explicitly reported the adverse effect of hyperkalemia, and there was no statistical difference in events between randomized groups. Eight other studies reported no serious adverse events related to hyperkalemia, and 11 studies did not report on the risk for hyperkalemia.

WHAT'S NEW

High-quality data demonstrate beneficial outcomes

Previous observational and interventional studies demonstrated a BP-lowering effect of salt substitutes, but limited data with poor-quality evidence existed for the impact of salt substitutes on clinical outcomes such as mortality and CV events. This systematic review and meta-analysis suggests that potassium-supplemented salt may reduce BP and secondarily reduce the risk for CV events, CV mortality, and total mortality, without clear harmful effects reported.

CONTINUED

Consistent reduction in BP and clinical outcomes across diverse populations and regions suggests potential worldwide benefit from the use of potassium-enriched salt in appropriate patients.

CAVEATS

Some patient populations, comorbidities excluded from study

The study did not include patients with kidney disease or those taking potassium-sparing diuretics. Furthermore, the available data do not include primary prevention participants.

Subgroup analyses should be interpreted with caution due to the small number of trials available for individual subgroups. In addition, funnel plot asymmetry for studies reporting DBP suggests at least some effect of publication bias for that outcome.

Although BP reduction due to salt substitutes may be small at an individual level, these levels of reduction may be important at a population level.

Although BP reduction due to salt substitutes may be small at an individual level, these levels of reduction may be important at a population level.

CHALLENGES TO IMPLEMENTATION

For appropriate patients, no challenges anticipated

There are no significant challenges to implementing conclusions from this study in the primary care setting. Family physicians should be able to recommend potassium-enriched salt substitutes to patients with hypertension who are not at risk for hyperkalemia, including those with kidney disease, on potassium-sparing diuretics, or with a history of hyperkalemia/hyperkalemic conditions. Salt substitutes, including potassium-enriched salts, are readily available in stores. JFP

References

1. Yin X, Rodgers A, Perkovic A, et al. Effects of salt substitutes on clinical outcomes: a systematic review and meta-analysis. *Heart*. 2022;108:1608-1615. doi: 10.1136/heartjnl-2022-321332
2. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet*. 2021;398:957-980. doi: 10.1016/S0140-6736(21)01330-1
3. USPSTF. Hypertension in adults: screening. Final recommendation statement. Published April 27, 2021. Accessed September 18, 2023. www.uspreventiveservicestaskforce.org/uspstf/recommendation/hypertension-in-adults-screening
4. Coles S, Fisher L, Lin KW, et al. Blood pressure targets in adults with hypertension: a clinical practice guideline from the AAFP. Published November 4, 2022. Accessed September 18, 2023. www.aafp.org/dam/AAFP/documents/journals/afp/AAFPHypertensionGuideline.pdf
5. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507-520. doi: 10.1001/jama.2013.284427
6. Unger T, Borgi C, Charchar F, et al. 2020 International Society of Hypertension global hypertension practice guidelines. *Hypertension*. 2020;75:1334-1357. doi: 10.1161/HYPERTENSIONAHA.120.15026
7. Mancia G, Kreutz R, Brunstrom M, et al; the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension. 2023 ESH Guidelines for the management of arterial hypertension. Endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH). *J Hypertens*. 2023; Jun 21. doi: 10.1097/HJH.0000000000003480
8. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:e13-e115. 10.1161/HYP.0000000000000065
9. National Center for Health Statistics. National Ambulatory Medical Care Survey: 2014 state and national summary tables. Accessed June 27, 2023. www.cdc.gov/nchs/data/ahcd/namcs_summary/2014_namcs_web_tables.pdf
10. Huang L, Trieu K, Yoshimura S, et al. Effect of dose and duration of reduction in dietary sodium on blood pressure levels: systematic review and meta-analysis of randomised trials. *BMJ*. 2020;368:m315. doi: 10.1136/bmj.m315
11. Filippini T, Violi F, D'Amico R, et al. The effect of potassium supplementation on blood pressure in hypertensive subjects: a systematic review and meta-analysis. *Int J Cardiol*. 2017;230:127-135. doi: 10.1016/j.ijcard.2016.12.048
12. Brand A, Visser ME, Schoonees A, et al. Replacing salt with low-sodium salt substitutes (LSSS) for cardiovascular health in adults, children and pregnant women. *Cochrane Database Syst Rev*. 2022;8:CD015207. doi: 10.1002/14651858.CD015207
13. He FJ, Tan M, Ma Y, et al. Salt reduction to prevent hypertension and cardiovascular disease: *JACC* state-of-the-art review. *J Am Coll Cardiol*. 2020;75:632-647. doi: 10.1016/j.jacc.2019.11.055
14. Neal B, Wu Y, Feng X, et al. Effect of salt substitution on cardiovascular events and death. *N Engl J Med*. 2021;385:1067-1077. doi: 10.1056/NEJMoa2105675