JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 70, NO. 23, 2017
ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2017.10.019

EDITORIAL COMMENT

Is a DASH of Salt All We Need?*

Thomas J. Wang, MD, Deepak K. Gupta, MD

Hypertension is the most common chronic disease worldwide, affecting 1 billion individuals and contributing to 1 in 8 deaths per year (1). It causes substantial morbidity and mortality, as a major risk factor for heart failure, stroke, coronary artery disease, renal dysfunction, and blindness. The prevalence of hypertension is increasing and uncontrolled hypertension remains a common problem (2,3). Therefore, effective, widely available, low-cost, and sustainable strategies are needed to prevent and treat hypertension.

Lifestyle modification, including diet, is a cornerstone for the prevention and treatment of hypertension (4). Reducing dietary sodium below that of typical diets eaten around the world lowers blood pressure (5). The DASH (Dietary Approaches to Stopping Hypertension) diet, comprised of fruits, vegetables, low-fat dairy products, and foods low in saturated fat and cholesterol, has also been shown to reduce blood pressure (6). In the DASH-sodium randomized crossover trial, combining the DASH diet with low sodium was additive for lowering blood pressure (7).

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In this issue of the *Journal*, Juraschek et al. (8) report a secondary analysis of the DASH-sodium trial. Their principal finding was that 30 days of a combined DASH+low sodium (1,150 mg) diet, compared with 30 days of a typical "American" non-DASH+high sodium (3,450 mg) diet, lowered blood pressure the most among individuals with the highest baseline blood pressure. Compared with the non-DASH+high sodium diet, the DASH+low sodium diet reduced systolic blood pressure by averages of 5, 7, 10, and 21 mm Hg among subjects with baseline systolic blood pressures of <130, 130 to 139, 140 to 149, and ≥150 mm Hg, respectively. Diastolic blood pressure was reduced by 4, 2, 4, and 8 mm Hg among subjects with baseline diastolic blood pressures of <80, 80 to 84, 85 to 89, and ≥90 mm Hg, respectively.

The DASH-sodium trial continues to provide intriguing data. The magnitude of blood pressure reduction achieved by the combined DASH+low sodium diet was comparable with or exceeded that of pharmacologic monotherapy observed in prior trials (9). The magnitude of blood pressure lowering was dramatic (>20 mm Hg systolic) in those with the highest baseline blood pressure. This is congruent with patterns found for other therapies (e.g., lipid and glucose lowering), namely, the highest risk individuals derive the most benefit from interventions. Whether the present findings also reflect greater salt-sensitivity among those in the highest blood pressure strata, residual confounding by unmeasured characteristics, or other mechanisms is unclear.

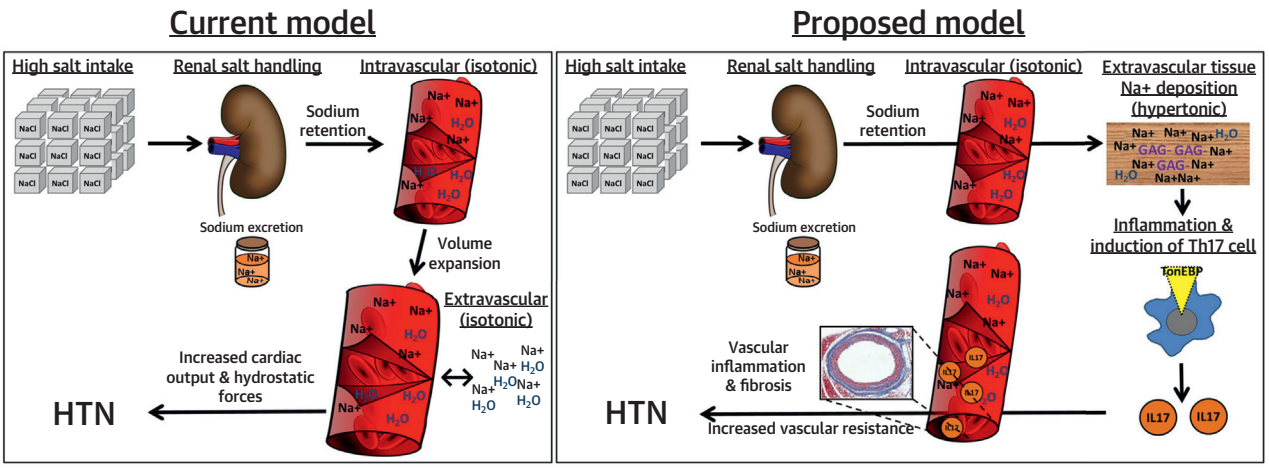
At the other extreme, subjects with the lowest baseline blood pressure would not be expected to experience a large reduction in blood pressure, in part because of a "floor" effect, (i.e., the body defends against hypotension). Nevertheless, it is notable that subjects with baseline systolic blood pressures <130 mm Hg had an average 5 mm Hg reduction in systolic blood pressure on the DASH+low sodium diet (8). In the context of existing evidence that each 5 mm Hg increment in systolic blood pressure is associated with a 25% greater risk of vascular mortality, the potential clinical impact of DASH+low sodium in the pre-hypertension group is substantial (10).

The DASH-sodium trial also raises several provocative questions. First, how much sodium do we need

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Vanderbilt Translational and Clinical Cardiovascular Research Center, Division of Cardiovascular Medicine, Vanderbilt University Medical Center, Nashville, Tennessee. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

FIGURE 1 Current and Proposed Models for the Pathophysiologic Basis of Sodium-Induced Hypertension



The current model is that excess intravascular sodium (Na+) promotes increased plasma volume, higher cardiac output, and increased hydrostatic pressure, resulting in hypertension (HTN). The proposed model is that extravascular Na+ deposition (bound to negatively charged glycosaminoglycans [GAG-]) without commensurate water retention incites an inflammatory response mediated by interleukin (IL)-17-producing T helper 17 (Th17) cells, resulting in vascular inflammation, fibrosis, increased vascular resistance, and HTN. H2O = water.

to consume? The low sodium diet (1,150 mg ≈ 0.5 teaspoons of salt) tested in the DASH-sodium trial was substantially lower than that recommended for the general population (<2,300 mg) and below that currently recommended for high-risk groups (<1,500 mg), such as the middle-aged and elderly; black individuals; and those with pre-hypertension, hypertension, diabetes mellitus, or chronic kidney disease (5,7). However, 1,150 mg of sodium is still well above the minimal amount of daily sodium that is assumed to be necessary to maintain normotension. The Yanomamo Indians of Brazil consume an ultra-low sodium diet (<200 mg/day) and do not develop hypertension even into old age, suggesting that just a dash of salt (1/16 teaspoon ≈ 150 mg sodium) per day may be all our bodies need to maintain normal blood pressure (11). Although the safety of very-low sodium intake remains controversial, it is likely that for most people on their typical diets, even a modest reduction in sodium may be beneficial (5).

Another question central to the DASH-sodium findings is how excess dietary sodium raises blood pressure. Surprisingly, the pathophysiologic mechanisms linking sodium intake with hypertension are incompletely understood. The prevailing model suggests that excess sodium intake increases intravascular sodium, with requisite water retention and expansion of plasma volume to maintain circulating sodium concentration within a homeostatic range. The increased plasma volume increases cardiac output and hydrostatic forces, leading to higher blood pressure and vascular smooth muscle hypertrophy (**Figure 1**). This equilibrium theory, with sodium and water balanced throughout the body, necessitates an increase in body weight driven by water retention. In the DASH-sodium trial, however, changes in blood pressure with low-sodium diets occurred in the absence of changes in weight (7).

Until recently, there was little consideration of the possibility that *extravascular* sodium deposition may play a role in hypertension. Long-term studies in astronauts in a closed space station simulator environment demonstrate that sodium intake can exceed excretion for a sustained period of time, independent of water retention and weight gain (12). Experimental and human studies suggest that this excess sodium is deposited in the extravascular compartment, without commensurate water retention, resulting in a hypertonic extravascular environment (13,14). These findings oppose the conventional view that extracellular fluids readily equilibrate between the intravascular and extravascular compartments (i.e., that sodium and water are tightly linked throughout the body). Moreover, experimental data indicate that extravascular sodium can activate the immune system, including T cells, which are necessary for maintaining hypertension (15,16). Recently, the induction of pathogenic T helper 17 cells was identified as a key mediator of this process (17). T helper 17 cells secrete interleukin-17, which promotes vascular inflammation, fibrosis, and

hypertension (18). Thus, a proposed model for how sodium influences blood pressure is that excess sodium is deposited within the extravascular space, without commensurate water retention, creating a hypertonic environment that incites inflammation, vascular fibrosis, and increased vascular resistance (**Figure 1**).

A third question raised by the DASH-sodium trial is why some individuals are more salt-sensitive than others. Salt-sensitivity is multifactorial and influenced by demographic, social, environmental, dietary, genetic, and neurohormonal factors. Among black individuals, for instance, genetic variants and neurohormonal deficiencies have been reported as contributors to salt-sensitive hypertension (19–21). More recently, we demonstrated racial differences in circulating natriuretic peptides, with lower levels in black compared with white individuals (22–24). Because the natriuretic peptides are the principal counter-regulatory hormones against sodium retention, a relative deficiency in black individuals could predispose to excessive total body sodium.

The DASH-sodium trial was a landmark study that continues to be highly informative. Nonetheless, questions remain regarding how diet and sodium influence blood pressure and how to sustain dietary modifications at a reasonable cost on a broad scale. The DASH+low sodium diet is an important foundation to offer patients, but it is not enough to solve the global hypertension problem. Public policy to regulate mineral and nutrient content in processed foods, programs to promote healthy diet and physical activity, and deeper mechanistic understanding of how salt modulates blood pressure are just a few of the steps needed to reduce the global burden of hypertension.

ADDRESS FOR CORRESPONDENCE: Dr. Thomas J. Wang, Vanderbilt Translational and Clinical Cardiovascular Research Center, Division of Cardiovascular Medicine, Suite 383 PRB, 2220 Pierce Avenue, Nashville, Tennessee 37232-6300. E-mail: Thomas.j.wang@vanderbilt.edu.

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KEY WORDS inflammation, natriuretic peptides, salt-sensitive hypertension