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Importance of Nutrient Intake on Blood Pressure, Salt Sensitivity, and Health Outcomes

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In his 1998 international award winning article in the journal *Science* [1] that was entitled "*The (Political) Science of Salt*" Gary Taubes concluded "… if there was ever a debate in science, the issue of salt's effects on blood pressure is it." In the decade that has intervened since Taubes documented this contentious and often angry scientific dispute, which has spanned more than fifty years, the scientific gap between those who advocate universal sodium restriction and those who oppose it has only grown wider. The goal of this presentation is to provide a framework in which these disparate views of the scientific data in terms of health outcomes might be reconciled. In doing so, I will focus on:

- **The impact of a variety of nutrients and dietary patterns on blood pressure (BP) and mortality**
- **Salt sensitivity, its prevalence, variability, and relationship to nutrients and dietary patterns**
- **Salt restriction's impact on known risk factors for cardiovascular disease (CVD) other than BP**
- **The relationship among salt intake, dietary patterns, and cardiovascular and all-cause mortality.**

The initial evidence that dietary patterns rather that salt should be the focus of public health nutritional recommendations to reduce BP came in a 1984 *Science* paper from our lab [2]. The findings from that analysis of the US Government's First National Health and Nutrition Examination (NHANES I) identified a protective effect of calcium, potassium, and phosphorus on developing high BP. More importantly, it identified a dietary pattern comprised primarily of fruits, vegetables, and dairy products which the US Government has subsequently designated the DASH diet as the dietary pattern associated with the lowest blood pressures and weight in the US adult population. A number of subsequent analyses of NHANES I, NHANES III, and NHANES IV have confirmed that index report. Numerous observational studies from outside the US have also identified a similar pattern as being protective against high BP in other nationalities.

While a number of intervention studies in humans have documented a significant BP benefit of diets rich in the nutrients calcium, potassium, and magnesium, the definitive intervention trial supportive of the DASH diet was published in 1997 in the *New England Journal of Medicine* [3]. The Dietary Approaches to Stop Hypertension (DASH) Trial demonstrated a clinically important impact on the blood pressure of both hypertensive and normal individuals. In the former it lowered BP over 11 mm Hg systolic and 5 mm Hg diastolic pressure, a therapeutic effect comparable to anti-hypertensive drugs, in the words of the authors. In an observational study in over 40,000 US women, Kant et al. [4] found that a diet pattern consistent with the DASH diet was associated with a greater 35% reduction in all-cause and 40% reduction in CVD mortality.

The publication of the DASH Trial coincided with the publication of the largest and longest trial of moderate sodium restriction in mild hypertension, TOHPS II [5]. Over 3000 subjects were followed for up to 3 years. TOHPS II documented a minimal long-term impact on BP of sodium restriction, less than 2 mm Hg systolic and 1 mm Hg diastolic. Compared to DASH, sodium restriction had about one tenth of the impact on BP, in a range that is of questionable clinical relevance and certainly not comparable to drug management. Proponents of sodium restriction argued appropriately that for the "salt-sensitive" individual with hypertension, the benefit was potentially much greater. Meta-analyses of the multitude of previous trials of sodium modification had indeed suggested an average effect in hypertensive subjects of 3-4 mm Hg systolic, still significantly less than that of DASH.

Salt sensitivity in normal subjects and those with high BP was extensively first studied by Luft and colleagues in the mid-1970s [6]. Their landmark investigations estimated that 10-15% of normal individuals and 30-40% of hypertensives were actually sensitive to salts' effects on BP.

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Subsequent estimates by other labs confirmed these findings and extended them to note that some populations such as African Americans, the elderly and overweight were more sensitive than others. These studies also documented that salt sensitivity was quite variable in any given subject such that it was not an immutable clinical characteristic. The publication of the DASH-Sodium Trial in 2001 [7] provided the most comprehensive evidence in normal and mildly hypertensive subjects of the variability of salt sensitivity, its critical interaction with and dependence on diet quality. DASH-Sodium was similar to the original DASH Trial in design with the addition of two levels of sodium restriction either on a poor quality or DASH diet.

There are critical differences in the interpretation of the findings from DASH-Sodium between advocates of sodium restriction and those with a more moderate view of salt's effects on health. An important fact in interpreting the data is that the DASH-Sodium participants were skewed heavily towards being salt sensitive, i.e. overweight, African American, elderly, and hypertensive. In spite of that fact, once the subjects began consuming the DASH diet, even severe sodium restriction had no added benefit except in overweight, older, hypertensive, African American females [8]. Thus the introduction of fruits, vegetables, and low-fat dairy (DASH diet) essentially eliminated salt sensitivity even in hypertensive individuals. These findings, however, are not the interpretation that the DASH-Sodium investigators have promoted or governmental agencies have emphasized in their guidelines. Instead, without justification, advocates of sodium restriction have used this trial to argue for universal sodium restriction, regardless of blood pressure status [9]. This position, now supported by a number of national and international bodies, has occurred even though numerous meta-analyses and the results of the DASH-Sodium trial itself do not support the conclusion that sodium restriction is effective for normal individuals or for most hypertensive subjects.

Sodium restriction has a variety of effects beyond blood pressure on other risk factors for CVD. These include weight, insulin resistance, angiotensin II, the sympathetic nervous system, diet quality and physical activity. For each of these risk factors, the preponderance of the evidence indicates that moderate or greater sodium restriction is associated with an adverse impact. Weight control is impaired, insulin resistance increases, angiotensin II levels are raised, sympathetic activity is increased, diet quality is harder to achieve, and maximal exercise capacity may be impaired. None are improved with sodium restriction. Thus, while BP may be decreased in 30-40% of individuals with sodium restriction, the impact on these other CVD risk factors in both salt-sensitive and salt-resistant individuals may offset any potential benefit.

That question has been addressed in a number of trials where the impact of sodium restriction was not simply assessed by its effect on BP, but by its impact on the only endpoint that actually matters if societies are to promote universal sodium restriction, all-cause mortality. This issue was first addressed by Alderman et al. in 1995 [10]. In subsequent studies from a number of laboratories around the world, the weight of the evidence indicates that either all cause mortality increases or that there is no net mortality benefit of lower sodium diets. Two studies stand out in this regard. Alderman and colleagues [11] reported the NHANES II Follow-Up cohort of over 7100 adult Americans followed for 13 years. They noted that those individuals whose reported sodium intake was below the current US recommendation of 2300 mg there was a 37% increase in CVD and a 28% increase in all-cause mortality after all appropriate adjustments. Shimazu et al. [12] reported on 40,000 Japanese followed for 7 years and found that while a high salt, traditional Japanese diet was associated with an increase in BP, CVD mortality was actually reduced by 27%.

Thus the majority of reports document an adverse impact of sodium restriction even though BP may be improved in the

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sub-set of individuals who are salt sensitive. These findings are in stark contrast to what has been documented for individuals who consume a better quality diet as opposed to those who restrict their sodium. The findings of Kant et al. [4] noted above were supported by a subsequent study of over 3000 young American adults at high risk of developing CVD who were followed for 10 years. The CARDIA Trial ([13]) reported that a diet rich in dairy foods and food groups consistent with the DASH diet was associated with dramatic reductions in multiple risk factors for CVD. These included weight, insulin resistance, lipid disorders, and high blood pressure, a striking benefit on multiple risk factors for CVD and opposite of the generally accepted impact of sodium restriction on many of these same factors.

The following conclusions can be derived from the body of evidence presented:

- A dietary pattern rich in fruits, vegetables, and low-fat dairy compared to sodium restriction has a:
  - Beneficial impact on multiple risk factors of CVD that is opposite of that of sodium restriction
  - Significantly greater, universal benefit on BP, CVD mortality, and all-cause mortality
- The DASH diet eliminates salt sensitivity in the majority of individuals at risk
- Salt sensitivity is not an immutable trait, but likely a marker of a poor quality diet
- National and international nutrition policies intended to improve BP, CVD, and all-cause mortality should emphasize increasing fruits, vegetables, and low-fat dairy foods, and not sodium restriction which may be associated with an increase in both CVD and all-cause mortality in the general population.

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