Webcast

Identifying and Addressing Elevated Sodium Intake to Decrease Cardiovascular Risk: Expert Perspectives and Discussions

Part 2: Hypertension and Beyond: Impact of Sodium Across the Cardiovascular Disease Spectrum

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May 2023

Hypertension and Beyond:

Impact of Sodium Across the Cardiovascular Disease Spectrum

VIREND K. SOMERS, MD, PHD: Now I have the absolute pleasure of introducing my colleague and friend, Dr. Gregg Pressman, who as I mentioned is from the Einstein Medical Center in Philadelphia and Thomas Jefferson University. He's going to talk about hypertension and beyond, the impact of sodium across the cardiovascular disease spectrum.

GREGG S. PRESSMAN, MD, FACC, FASE: I'd like to start on a historical note and talk about this paper titled, "Treatment of hypertension vascular disease with rice diet," authored by Walter Kempner and published in the American Journal of Medicine in 1948. I'll quote from the paper. The rice diet contains in 2,000 calories not more than 5 grams of fat and about 20 grams of protein and not more than 150 mg of sodium. Further, if the sodium concentration of the plain water available is greater than 20 mg/L, distilled water should be used.

This paper created quite a stir because the subjects were patients who were severely hypertensive. It's important to remember that at that time there was very little treatment available for severe hypertension. This paper is widely considered to be the first proof that low sodium in the diet reduces blood pressure. In fact, the paper's been cited nearly 700 times.

Part of the reason it was such an important paper and had such an impact is because it was profusely illustrated with patient cases such as we see here. If we look at this graph top left, we see that with this diet, there was a rapid decrease in weight. There were rapid decreases in systolic and diastolic blood pressure. Heart size shrank. ECG polarization abnormalities resolved and retinopathy resolved. This was again at a time when we had no good pharmacotherapy for these patients.

Other epidemiological evidence strongly suggests, as already mentioned, that high salt intake leads to hypertension and in particular, the rise in blood pressure typical in western society. So if we look at these countries here, including United States, that all have high salt intake and blood pressure typically rises dramatically with age. If we look at these countries with lower salt intake, blood pressure remains fairly flat throughout life. If we now go to the bottom left, we can see that salt excretion, again, a measure of sodium intake, is linearly related to systolic blood pressure. If we look at the graph at the top right plotting salt intake by country against mortality from stroke, we again see a linear relationship strongly suggesting that high salt intake increases stroke mortality. Finally, at the bottom right, whether we look at coronary heart disease death, overall cardiovascular disease death, or all cause mortality, the hazard ratio is much higher in those with higher salt intake than lower.

This is a meta-analysis of studies comparing high and low sodium exposure. These

studies included patients with and without hypertension. Sodium ingestion was measured by looking at 24-hour urinary sodium excretion. These studies also included those that randomized patients to a normal diet versus a low salt diet or an additional sodium supplementation. In the composite, we see that there's a linear increase in systolic blood pressure according to sodium intake and that did not depend on which type of study was done. There are also linear increases in diastolic blood pressure, though a bit less than with the systolic blood pressure.

Further, when they looked at subjects with hypertension, the increase in systolic and diastolic blood pressure was dramatically more with high sodium intake than in the nonhypertensive subjects. So if you flip it around, the idea is that with a simple maneuver of reducing sodium ingestion, you can substantially lower the blood pressure in your hypertensive patients without pharmacotherapy.

That brings us to the Salt Substitute and Stroke Study, a seminal trial published in the New England Journal two years ago. This study enrolled nearly 21,000 subjects in towns in rural China. All had a history of stroke or were 60 years of age and greater with hypertension. The intervention was to introduce salt substitute to lower the sodium ingestion or have subjects continue with their regular salt ingestion. I should mention here that in China, average sodium intake is very high, amongst the highest in the world, as I'll show you later.

The primary outcome in this study was stroke and the mean followup was 4.7 years. I apologize for the size of these graphs. You can easily pick this up in the New England Journal. But the primary outcome of stroke was significantly reduced just by using salt substitute. Major adverse cardiovascular events were significantly reduced and even total mortality was reduced by a simple dietary intervention. No side effects. No cost of administering drug therapy.

What about salt and obesity? This study comes from the U.K. It looked at 458 children and 785 adults. Again, salt intake was measured by looking at urinary sodium excretion. These investigators found that for each 1 gram per day increase in salt intake, there was a 28% increase in the odds of obesity in children and a similar increase in the odds of adults. Further, a high salt intake was associated with increased body fat in the subset of patients who had body fat measured objectively. So high salt intake is associated with obesity. That doesn't mean that the salt itself is causing obesity, but probably they have a high caloric and high fat intake, along with the high salt intake.

What about atherosclerosis? This is a population-based study from Sweden published this year involving nearly 11,000 subjects. Again, sodium intake was estimated by urinary sodium excretion. All subjects had parotid ultrasound performed and coronary CTA. Increased 24-hour sodium ingestion was associated with an increase in the number and severity of carotid plaques, an increase in the coronary artery calcium score, and an increase in the severity of coronary artery stenosis. These associations were mainly mediated by blood pressure.

If we look in this country, this is from the NHANES study or the National Health and Nutrition Examination Survey, nationwide study that's been ongoing for many years. This paper looked at that first cohort, which included 5,000-some overweight subjects, 5,000-some non-overweight subjects, and had a nice, long followup of 19 years. In this case, the end point of interest was incident heart failure. There were 413 cases in the non-overweight group and much more in the overweight group. In that overweight group, the relative risk of developing heart failure was 1.3 with high sodium intake, meaning they were 1.43 times more likely to develop heart failure, and looked at another way, 43% more likely just on the basis of a high sodium intake. Furthermore, there was a graded increase in risk, especially prominent in the group with the highest salt intake.

Let's talk a bit about the pathophysiology of this. This is a very interesting study in a small group of normotensive volunteers who spent two weeks taking placebo and two weeks taking salt tablets. They were crossed over in a blinded fashion. Four-arm blood flow was measured by venous plethysmography and endothelial-dependent vasodilation was assessed using intra-articular injection of acetylcholine. Endothelial independent vasodilation was measured using injection of nitroprusside. Finally, they used color M-mode echocardiography to assess diastolic function.

Not surprisingly, daytime systolic blood pressure was significantly higher with salt loading. This is only two weeks' worth of salt loading. Further, if they looked at the four-arm blood flow, here's the placebo group. We see within injection of acetylcholine you get a nice increase in blood flow mediated by endothelial release of nitric oxide. However, with salt loading this response was markedly depressed. By contrast, sodium nitroprusside injection caused the same amount of vasodilation, whether they were receiving the salt loading or not, and we know nitroprusside dilates the smooth muscle directly without the endothelium involved. This means that salt loading somehow poisons the endothelial response to acetylcholine and the vessels do not dilate normally.

If you look at the color M-mode, here we're looking at the slope of this inflow into the left ventricle, indicated by this yellow line. The closer to vertical, the more normal the diastolic function. These are the patients with salt loading. You can clearly see that their left ventricular diastolic function is impaired, and that's due to increased left ventricular stiffness.

Here’s a study published last year looking at sodium ingestion and biomarkers. The authors noted that population-based studies have shown reduced cardiovascular events when patients follow a heart-healthy diet and that heart-healthy diet--in this case, the DASH diet--typically includes a sodium restriction. They studied in this paper a combination of that heart-healthy diet and different levels of sodium reduction in the diet, which we won't go into. But suffice it to say, sodium reduction alone reduced N terminal proBNP. Combining that with the heart-

healthy diet in a randomized fashion--so this was the DASH sodium diet--it studied patients who were hypertensive.

The investigators noted a statistically significant reduction in high-sensitivity cardiac troponin I with the combination of the DASH diet and low sodium and a decrease in high-sensitivity CRP with the DASH diet and the low-sodium ingestion. They concluded that this combination of low sodium in a heart-healthy diet reduces inflammation as indicated by CRP and it reduces subclinical myocardial damages indicated by troponin I release. So these are direct effects of dietary manipulation on systemic inflammation and subclinical myocardial damage.

What about renal function? Here's a population-based study out of Japan of subjects starting with a normal estimated GFR. The outcome of interest was impaired kidney function developing over the course of the study, and a high salt intake was associated with greater incidence of kidney impairment versus lower sodium intake. This was observed to be a graded fashion according to quartiles of sodium intake. The higher the sodium, the greater the renal impairment over time.

Here's a study from the U.K. Biobank, a population-based study of subjects free of cardiovascular at baseline. They filled out a detailed dietary questionnaire, from which a modified DASH score was created, excluding the sodium intake part of the DASH diet. Then sodium intake was estimated based on the frequency with which subjects added salt to their food, ranging from never to always. The median followup was nearly 12 years and the composite outcome was ischemic heart disease events, stroke, and heart failure.

What they found was that participants who combined a DASH diet, a heart-healthy diet, with the lowest frequency of adding salt to their diet, had the lowest cardiovascular risk. In fact, the more they decreased sodium, the more the reduction in cardiovascular events.

What do we do with all of this data? Well, England initiated a nationwide salt reduction program in 2003. This resulted in a 15% reduction of salt intake by 2011. During that time, blood pressure in the population fell, and so did the incidence of ischemic heart disease deaths and stroke deaths. These look like nice correlations with the reduction in salt intake. This is observational. It doesn't prove causality, but strongly suggests that a simple maneuver of reducing sodium intake on a nationwide basis impacts mortality from two of the largest causes of death.

That leads us to the World Health Organization global report on sodium intake reduction earlier this year. In that report, the WHO recommends that each country target a reduction of 30% or more in the mean population intake of sodium. They recommend doing this by lowering the maximal amounts of sodium in processed foods and increasing standards of package labeling so that people can know how much sodium they are ingesting. In this report, by the way, they note that sodium intake ranges from a low of 2000 mg per day to a high of nearly 7000 mg per day.

So country by country, the intake varies greatly.

Now at this point, I should pause to mention that sodium and salt are not the same. Salt is sodium chloride, so 1000 mg of sodium is the equivalent of 2500 mg of sodium chloride, table salt. If you want to compare studies, you need to keep that conversion in mind. This has already been noted in the Americas--and this is all the Americas--but includes the United States. Average sodium intake per day in the population is around 3,500. Based on trends in the decade 2010 to 2019, it's not likely that's going to change very much in the future.

On the other hand, modeling based on a 1.5 gram per day reduction in salt, 584 mg of sodium by 2025 and 2.6 grams per day by 2030 are estimated to produce a reduction in global cardiovascular deaths of 2.2 million in 2025 and 7 million in 2030, just by the simple means of reducing dietary sodium ingestion.

How are we doing in this country? Here's a report from the FDA. Our current average intake is 3400 mg. The recommended maximum is 2300. This report notes that most sodium comes from food processing and not from home cooking. In fact, look at this graph here of sources of sodium. That lunchtime sandwich of yours is providing a lot of salt probably through the processed meats on that sandwich. If we look at the bad actors in our diet, added sugars, saturated fat and sodium, with the orange in these graphs indicating the percentage of the population exceeding recommended levels, we're bad. But we are especially bad when it comes to sodium ingestion.

This is the DASH diet that I mentioned earlier that is recommended by the American Heart Association. The Europeans like the Mediterranean diet, which is quite similar. It emphasizes increasing intake of vegetables, fruits, whole grains, fish and poultry, limiting fatty meats, full fat dairy, and sugar-sweetened beverages, and of course, limiting sodium ingestion to no more than 2300 mg per day. But note the asterisk; 1500 mg per day further lowers blood pressure.

Here is a graph illustrating the effects of a DASH low-sodium diet on systolic and diastolic blood pressure. Here's the dietary intervention. Here's placebo. These changes happen rapidly and are sustained. I'm going to end with something that you probably didn't know before Dr. Somers mentioned it, but this will reinforce it. I certainly didn't know this. Certain medications, particularly certain formulations have tremendous amounts of sodium in them. This is especially true of effervescent medications. Here's a list of such medications from England. Paracetamol has been mentioned. This is Tylenol or acetaminophen in this country. If you take the maximum daily dose, it's 3400 mg of sodium just from the medication, and that exceeds the recommended daily limit of 2300.

I'm going to point out now a study involving the population in England that took these particularly drugs and compared. This study compared in a nested case-control fashion subjects taking these medications in their standard formulation

versus subjects taking them in their high-sodium formulation.

They looked at odds ratios for a composite cardiovascular outcome adjusted or unadjusted for multiple other variables. There was a statistically significant increase in the composite cardiovascular outcome with the high-sodium formulation of the drugs in question. This extended to the individual endpoint of stroke. Look at the odds ratios for hypertension. Even all cause mortality in this observational study was noted to be increased significantly so in those subjects taking the high-salt formulation of these drugs as compared to the same drugs in a standard formulation.

Bringing it closer to home, this is from the Alka Seltzer website. These are the different formulations and the amounts of sodium contained in each. Because of these high amounts of sodium, the company recommends duration of use of no more than 10 to 14 days in order to limit total sodium ingestion.

With that, I'll end it and thank you for your attention.