A new report on sodium and health found recent evidence is insufficient to support recommended dietary intake levels. The Institute of Medicine (IOM) analysis—Sodium Intake in Populations: Assessment of Evidence—has ignited a debate about whether salt restriction is linked to health benefits, especially for at-risk individuals (1).

Recent studies selected by the IOM offered inconsistent or insufficient evidence that a daily sodium intake of 1500 mg (for certain patient subgroups) or 2300 mg (for the general population) reduced the risks of cardiovascular disease or premature mortality.

The IOM also concluded that a two-tiered approach to sodium intake—one recommended level for patient subgroups and another for the general population—was not warranted. Patient subgroups included those 51 years or older, African Americans, and individuals with kidney or cardiovascular disease, diabetes, or hypertension.

Discussion has centered on the narrow focus stipulated by the Centers for Disease Control and Prevention (CDC), which commissioned the review. The IOM excluded literature using surrogate markers, namely blood pressure, concentrating instead on studies using direct health outcome end points. Yet the relevance of this evidence has been questioned over unconventional clinical approaches or methodological limitations. Because of the contentious reaction, the authors felt it necessary to clarify their findings in a recent *JAMA* article (2).

Although affirming the association between higher sodium intake and increased cardiovascular risk, the report’s remaining conclusions conflict with current dietary guidelines and contradict the IOM’s previous recommendations on sodium and health (3,4). Its publication comes as Americans’ addiction to salt remains undiminished, with average consumption holding steady at 3400 mg/day in spite of multiple initiatives to reduce excessive intake.

To understand the controversy surrounding the IOM’s findings, *ASN Kidney* provides a thorough look at the issue.

**Ultrasound Therapy May Help Prevent and Treat Acute Kidney Injury**

By Tracy Hampton

Acute kidney injury is one of the most common and serious complications of hospitalized patients. Yet there are no FDA-approved therapies for this disorder except dialysis, and potential drug therapies are associated with a number of adverse effects.

“There is an important gap in our ability to address this problem,” said Mark Okusa, MD, of the University of Virginia. Okusa and his colleagues may have stumbled upon a solution when they unexpectedly discovered that ultrasound exposure provides a simple, portable, noninvasive, and nonpharmacological approach to prevent acute kidney injury and long-term kidney fibrosis. Their findings were published recently in the *Journal of the American Society of Nephrology*.

**Ultrasound alone**

Working with Joseph Gigliotti, PhD, also of the University of Virginia, and others, Okusa has been developing an ultrasound-based method to deliver drugs specifically to the kidney to prevent or treat ischemia-reperfusion injury. This type of injury contributes to tissue damage and reduced glomerular filtration rate in some patients who undergo major surgery, which can deprive the kidneys of normal blood flow. In addition to de-
An emphasis on direct health outcomes

Although literature has shown that decreasing sodium intake can reduce blood pressure (BP) in people with CKD, it is difficult to determine if salt restriction could influence the risk for adverse health effects. The agency asked the IOM to evaluate studies investigating the effects of sodium restriction on health published since the institute’s 2005 report on dietary intake (5).

A 12-member committee—including experts in epidemiology, nutrition, hypertension, and nephrology—examined the health effects of restricting sodium in the general population and patient subgroups. Unlike previous reviews, the IOM only included literature reporting on the direct health effects of reduced sodium intake (e.g., cardiovascular events or premature death), and only reviewed evidence published after the prior report.

“The IOM’s narrow charge excluded studies investigating the effects of reduced intake on blood pressure, a key determinant of health and the largest determinant of preventable mortality worldwide,” said Lawrence Appel, MD, an internist and director of the Welch Center for Prevention, Epidemiology and Clinical Research at Johns Hopkins University. John Forman, MD, MSc, a nephrologist at Montefiore Medical Center in the Bronx, NY, noted “much of the recent literature supports the J-curve model, where the risk for adverse health effects is greatest at the highest and lowest ends of sodium intake.” Changes in renin-angiotensin and triglycerides or insulin resistance can occur with very low sodium levels, and all these factors have to be taken into account when assessing cardiovascular risk, she said.

But Appel, lead author of the DASH (Dietary Approaches to Stop Hypertension) study (6) noted that in the study “a reduction in sodium to 1500 mg/day had no effect on LDL cholesterol and other lipid.” The IOM cautioned the unconventional clinical approach in several studies from one group differed greatly from U.S. care standards and thus may not be generalizable. Several experts contacted for this article also raised concerns about these studies’ unorthodox methods, including regimens of high doses of diuretics concurrent with fluid restriction. Uncertainty about this evidence was heightened after a meta-analysis including two of these papers was retracted “on the ground that the reliability of the data on which it is based cannot be substantiated (7).”

Population-based intake recommendations

The IOM found no health benefits, and instead the potential for adverse health outcomes, by restricting daily sodium intake to between 1500 mg and 2300 mg for patient subgroups—particularly those with CKD, diabetes, and cardiovascular disease. They also concluded evidence did not support treating patient subgroups differently from the general population.

“In aggregate these high-cardiovascular risk groups comprise a majority of the U.S. population, which is a disturbing statement,” said Hummel, “but that doesn’t mean the reduction in sodium restriction will be similarly effective in all subgroups.” He observed that dietary modification research is inherently challenging. “It’s hard to measure intake, gauge adherence to dietary recommendations, and sustain adherence over time.”

“From a population perspective it’s easier to have one goal instead of a two-tiered approach,” said Appel, but evidence for the lower intake goal is based on blood pressure studies excluded by the IOM. “There is strong evidence that middle-aged and older adults and African Americans are especially sensitive to the blood pressure lowering effects of sodium reduction. In fact, sodium reduction has tremendous potential to reduce racial disparities in blood pressure-related cardiovascular disease,” he said.

Target ranges for dietary sodium were not requested by the CDC.

Sodium effects on the kidney

Only two of the 38 studies examined the effects of sodium restriction on the kidney. One was a post-hoc analysis (Heer-sink et al. (12)) of two well-performed large randomized trials of diabetically nephropathic patients treated with sodium intake by a 24-hour urine collection, Forman said. “It showed that low sodium intake was associated with a lower rate of adverse events (compared with a higher sodium intake) among those patients taking an angiotensin receptor blocker (ARB).”

“Yet the IOM failed to include another post-hoc analysis of the RIMPRI (Rampiril in Non-Diabetic Renal Failure) randomized trial (which included patients with non-diabetic kidney disease) that showed similar results (although patients received angiotensin-converting enzyme [ACE] inhibitors rather than ARBs) (8),” said Forman. Another study missed by the IOM’s study, McGuill and colleagues’ post-hoc analysis of the HEMO randomized trial—found a high sodium intake in hemodialysis patients was associated with increased mortality (9).

“Thus, in patients with both diabetic and nondiabetic renal disease receiving angiotensin inhibition, the data suggest that patients who consume less sodium have better outcomes,” Forman said.

“Since most nephologists will treat their patients who have diabetic and nondiabetic kidney disease with either ACE inhibitors or ARBs, the evidence (although observational) suggests that a low sodium diet is better.”

Although omitted from their analysis, the IOM surveyed research reporting proteinuria and renin-angiotensin-aldosterone system (RAAS) biomarkers. Increasing sodium intake increases sodium consumption was linked to CKD progression.

“Most of the studies on proteinuria are consistent—the more salt you consume, the more proteinuria you have,” said Appel. “I think there’s a reasonable case to be made for lower salt intake in kidney disease, but acknowledge the need for more evidence.”

Evidence using the RAAS biomarker was less conclusive, with reduced sodium levels increasing plasma renin activity (PRA), a proposed predictor of cardiovascular disease. “PRA goes up when blood pressure or blood volume goes down, it’s a counteregulatory response,” said Appel. “Some believe it’s an important biomarker, but it’s a risk correlate, it’s not causal.” He pointed to the Yonamorni Indians in Brazil who consume little salt, have high PRA levels, but very little vascular disease (10), and evidence for diuretics (ACE inhibitors and Lipid-Lowering Treatment to Prevent Heart Attack Trial) where a diuretic arm (which raises PRA) and ACE inhibitor arm (which lowers PRA) experienced similar cardiovascular outcomes.

Reducing sodium in processed foods

The same week the IOM report was released, JAMA Internal Medicine published a study of sodium content in processed and restaurant foods—the source of almost 80 percent of sodium consumed in the United States. The authors concluded government regulation of sodium was needed after finding minimal declines after voluntary industry reduction measures (11).

Sodium content in processed foods and fast-food items was tracked over a 6-year period. Levels in processed food declined 3.5 percent but increased 2.6 percent in fast-food items, and individual products varying up to 30 percent.

However, reducing sodium levels creates new problems. “Phosphorus is a big concern,” said Lauren Graf, MS, RD, a renal dietician at Montefiore Medical Center. “Many low-sodium processed foods are high in phosphates, which are added as preservative and can be more harmful, especially to patients on dialysis.”

Since industry and government efforts have failed to lower sodium consumption, what could reduce the excessive intake levels in the United States? Considering the difference, suggested Singer. Knowing which foods are highest in sodium—such as bread—could help people make informed choices.

Graf said a broader approach was needed, stating that government initiatives focusing only on sodium reduction miss the mark. “The combination of a whole foods, fruits, and vegetables that are naturally lower in sodium and higher in fiber, antioxidants, and minerals, such as potassium, that can help lower hypertension.”

The JAMA Internal Medicine article examined only one nutrient, but the foods analyzed...
IOM on Salt
Continued from page 5

were high in transfats, saturated fat, refined carbohydrates, and chemicals. “Even if the sodium content were reduced, there wouldn’t be much health benefit,” she said.

A change in clinical approaches
Could the IOM report influence physicians’ clinical practice to treating patients with hypertension or kidney disease?
Hummel didn’t think so. “The importance of sodium restriction is so ingrained in medical practice, which is a separate question from whether sodium restriction is a good idea,” he said. “It will take more than the IOM report to change practice.”

Nevertheless, Forman believes the report and press surrounding it could likely reduce concerns about sodium intake among nephrologists and patients with kidney disease. “This is unfortunate, especially given the way the IOM considered the data.”

For nutrition dieters it depends on the patient.
“Low sodium intake is still recommended for patients on dialysis, but the IOM report could change the way that dieters counsel patients with hypertension or early stages of CKD,” Graf said.

Although pediatric nephrologists regularly encounter hypertension, one concern with excessive sodium restriction in this population is the potential for adverse consequences on growth, said Singer. “Sodium is an essential electrolyte, and children need that to grow.”

A need for more research
The IOM found the literature was limited by methodological approaches, particularly with evaluating sodium intake, and recommended further research including the health effects of sodium in combination with other electrolytes, and interactions with antihypertensives and sodium restriction on blood pressure.

Graf said future studies should look at the broader picture, including such factors as obesity and other nutrients and not just sodium intake. “The dietary aspects of cardiovascular disease are multifactorial, and we can’t just look at one single nutrient,” he said.

Appel noted that despite very good evidence linking salt intake and proteinuria, more research on salt and blood pressure in kidney disease is needed.

“Although randomized controlled trials are viewed as the gold standard, in this case the most useful studies are prospective observational studies evaluating multiple effects of sodium intake overtime because they are more reflective of reality,” said Singer.

Yet Forman thinks one or more randomized controlled trials are needed because the evidence reviewed by the IOM was observational. “Patients in the trial should have non-dialysis dependent CKD, and the end points should be ESRD and death,” he said.

Hummel suggested research into biomarkers and better measurements of sodium intake.

“A biomarker of salt sensitivity that could predict blood pressure response to sodium changes, but more importantly could be associated with a mechanism for cardiovascular disease or CKD, would be ideal,” he said.

And although 24-hour urine collection is the gold standard, there are problems with incomplete urine collections, and something that could reduce the complexity, such as a spot urine sample, would be beneficial.”

It may be difficult to move this research forward, however. The spending cuts mandated under sequestration have contracted available research funding, and it remains unknown what alternate funding sources may be available to support this science.

Singer believes they’ll be funded, especially given the overall cardiovascular burden in the U.S. health care system.

Kidney disease is a tough area to get research funded, said Appel.

“The right studies can be expensive studies ($25,000 per person or more for a feeding study), and this is a bad climate for such research,” he said. “It’s going to take a change of mindset among funding agencies to fund the right kind of studies that yield high-quality results that can be used to form guidelines.”

Hummel noted that previous studies have suffered from the misconception that sodium’s effects on health were established.

“The more studies that come out about the uncertainty in this area will help with future funding, not just in a population perspective but also high-risk subgroups.”

Despite the debate surrounding the IOM’s conclusion on lower sodium levels, the report confirms the dangers of excess sodium consumption for health. Americans’ reliance on high-sodium processed foods—42% of each food dollar is spent outside the home (11)—and steady thirst for salt raises concerns.
about a potential increase in the burden of kidney and cardiovascular disease. Under-scoring the need for more research into sodium and health, Hummel concluded “there are huge public health implications for these questions.”

References

atypical Hemolytic Uremic Syndrome (aHUS) is a genetic, chronic, systemic, and life-threatening disease that can result in vital organ failure and premature death

![Graph showing the cumulative fraction of patients free of events (CFH mutation)](image)

- 70% of aHUS patients (with the most common mutation*) die, require dialysis, or have permanent renal damage within 1 year.
- 33% to 40% of patients die or progress to end-stage renal disease with the first clinical manifestation.
- Plasma exchange/infusion (PE/PI) does not address chronic, uncontrolled complement activation, the underlying cause of TMA in aHUS.

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