Salt Intake and Reductions in Arterial Pressure and Proteinuria
Is There A Direct Link?

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The preponderance of the medical literature supports the concept that modest or moderate dietary salt restriction enhances the blood pressure lowering responses to most antihypertensive medications and may permit either dose reduction or, in a few cases, complete drug withdrawal. Moreover, reduction in salt intake has a permissive action on the antiproteinuric responses of angiotensin converting enzyme inhibitors and nondihydropyridine calcium channel blockers. It does not, however, affect proteinuria in those receiving dihydropyridine calcium channel blockers. The importance of selecting out those individuals who can most benefit from dietary salt modification (the “salt sensitive” groups of hypertensive patients) is important. Prospective randomized clinical studies are needed to assess the correlation between dietary salt intake and renal endpoints, such as time dialysis. This will be particularly important in different demographic groups that may have a greater predisposition to salt sensitivity, such as elderly or obese hypertensives, hypertensives of black or Hispanic descent, and those with non-insulin-dependent diabetes mellitus. © 1996 American Journal of Hypertension, Ltd. Am J Hypertens 1996;9:200S-206S

KEY WORDS: Salt, diet, antihypertensive therapy, drugs, salt sensitivity.

High salt intake is known to worsen preexisting hypertension. This is especially true for a subgroup of individuals who are “salt sensitive.” Conversely, a reduction in salt intake to less than 4 g/day reduces elevated arterial pressure and blunts increases in this surrogate endpoint. These observations make it likely that certain individuals have an impaired pressure-natriuresis response or a greater vascular responsiveness to salt and, hence, are potentially at a higher risk for developing hypertension.

A better understanding of the relationship between dietary salt intake and the vascular reactivity that correlates with blood pressure changes will help investigators understand the physiologic impact of salt. To this end, studies have evaluated the contribution of vasoactive hormones as well as both the renin-angiotensin-aldosterone and sympathetic nervous systems in the context of salt intake and arterial pressure changes. Additionally, recent studies have evaluated the renal hemodynamic effects of sodium in different disease states. These findings consistently demonstrate that salt sensitive patients have reduced renal plasma flow and increased glomerular filtration fraction as well as proteinuria in response to increasing dietary salt. Moreover, mounting evidence supports a deleterious relationship between salt sen-
sitivity and abnormalities of carbohydrate and lipid metabolism.\textsuperscript{13, 15}

Microalbuminuria is associated with an increased risk of both cardiovascular and renal mortality among diabetic patients.\textsuperscript{16, 17} Sodium intake is known to affect proteinuria levels in animal models of diabetes mellitus.\textsuperscript{11} Moreover, sodium intake also affects the antiproteinuric response of certain antihypertensive agents, such as angiotensin converting enzyme (ACE) inhibitors, and nondihydropyridine calcium channel blockers.\textsuperscript{19, 20} The mechanism of this effect is uncertain.

This paper will review the results of studies that evaluate the impact of salt intake on both the antihypertensive and antiproteinuric properties of various antihypertensive drugs. This is important, especially in light of recent data demonstrating that salt sensitivity may be a marker for cardiovascular risk clustering, particularly in blacks and diabetics.\textsuperscript{14, 15}

SALT AND ANTIHYPERTENSIVE DRUGS

The effect of various antihypertensive drugs varies with regard to the mechanism of blood pressure reduction as well as their influence on proteinuria.\textsuperscript{21, 22} These mechanistic differences may have important long-term implications regarding an individual's risk for blood pressure related cardiovascular and renal diseases.

The relationship between dietary salt intake and the antihypertensive effect of various drugs has been explored in numerous clinical trials.\textsuperscript{23-32} These studies have led to the long-standing belief that reduced salt intake potentiates the hypotensive effect of most antihypertensive agents. However, the magnitude of blood pressure lowering varies across drug class and is more pronounced with certain agents at lower drug doses among "salt sensitive" individuals.\textsuperscript{33, 34} The threshold of dietary salt intake below which the hypotensive effect of antihypertensive agents is accentuated and above which an antihypertensive effect is antagonized remains to be established.

The initial mechanism of blood pressure reduction by thiazide diuretics was postulated to relate solely to salt and water depletion. However, subsequent clinical studies demonstrated that dietary salt loading diminished their hypotensive response, whereas reduced dietary salt enhanced diuretic-induced blood pressure reductions.\textsuperscript{24-26} Moreover, thiazide diuretics in low doses (12.5 mg/d) reduce blood pressure through their vasodilator action, an effect independent of natriuresis.

Not every study, however, has demonstrated this impact on blood pressure reduction with salt restriction in the presence of diuretic therapy.\textsuperscript{37-39} Reasons for this discrepancy include the fact that combining salt restriction and diuretic therapy could enhance a person's appetite for salt through activation of the renin-angiotensin system and thereby paradoxically increase a neurohumoral system known to increase arterial pressure and thirst. This proposal, however, is not supported by the data of Bing et al who followed 32 diuretic-treated patients for 2 years and noted no increase in 24-h urinary sodium excretion (a reflection of dietary salt intake), and no tendency for blood pressure to increase.\textsuperscript{32} However, since these patients were not profiled in terms of their blood pressure responses to dietary salt, interpretation of these data is difficult. Achievement of good blood pressure reductions in other studies employed more stringent dietary salt restriction, <50 mEq/day; this is an unrealistically low level of intake for most ambulatory hypertensive patients.\textsuperscript{9}

Blood pressure reduction employing a combination of salt restriction and a \( \beta \)-blocker has also demonstrated conflicting results. Ewertman et al performed a double blind cross-over study to examine the interaction between a low salt diet and a \( \beta \)-blocker on blood pressure reduction.\textsuperscript{27} This group provided evidence that the combination of a low salt diet and \( \beta \)-blockade reduced blood pressure more than the drug with a high salt diet (−28.5 mm Hg with low salt diet versus −21.3 mm Hg with high salt diet; \( P < .05 \)). However, this observation was not confirmed by Kimura and colleagues who failed to show a potentiation of blood pressure reduction with a low salt diet added to the \( \beta \)-blockade.\textsuperscript{28} Unfortunately, since different types of patients were examined in these two studies, no firm conclusions may be reached.

Short-term studies demonstrate that angiotensin converting enzyme (ACE) inhibitors, like \( \beta \)-blockers, are effective in reducing blood pressure among patients with high plasma renin levels.\textsuperscript{9, 28, 33, 35, 36} However, there are no long-term studies that demonstrate a relationship between pretreatment renin levels and antihypertensive response of ACE inhibitors. Moreover, recent data suggests that pretreatment plasma renin levels do not predict the antihypertensive response to the ACE inhibitor trandolapril in either black or white hypertensives.\textsuperscript{37} Thus, these agents have effects on blood pressure that may have more to do with their effects on other factors than renin, such as bradykinin. Nevertheless, sodium restriction potentiates the antihypertensive effects of ACE inhibitors.\textsuperscript{39, 37} Clinical trials, although limited in number, further support this contention. They demonstrate consistent additive antihypertensive effects of reduced salt diet in combination with ACE inhibitors.\textsuperscript{9, 28} Additionally, one study demonstrated that when salt was added back to the diet the antihypertensive effect of the ACE inhibitors were markedly blunted.\textsuperscript{38}

There is scant published data assessing the antihypertensive activity of sympatholytic agents, nonspecific vasodilators, such as hydralazine, or minoxidil, \( \alpha \)-blockers, or angiotensin II receptor antagonists in relation
to dietary salt intake. However, there is information assessing the utility of dietary salt restriction with calcium channel blocker therapy. Paradoxically, some of this clinical data suggest that greater dietary salt intake potentiates the antihypertensive properties of calcium channel blockers. Nicholson et al demonstrated that, with the same dose of verapamil, patients receiving a high dietary salt intake had relatively greater reductions in blood pressure compared to those on a low salt diet. This could be explained, however, by the fact that the baseline blood pressure was higher with greater dietary salt; thus, the absolute fall in blood pressure reduction observed was larger than on the lower dietary salt intake. Moreover, the absolute level of blood pressure reached was lower on a reduced salt intake.

MacGregor et al hypothesized that greater dietary salt intake may boost intracellular calcium concentration, thus enhancing the vasorelaxing properties of calcium channel blockers. Some investigators have demonstrated a reduced efficacy of calcium channel blockers in lowering blood pressure in salt restricted patients or even elevation of blood pressure in others. However, these clinical studies have not addressed the salt sensitivity status of the patients in making these observations. In a separate study, patients who were found to be more salt sensitive had a greater hypotensive response to calcium channel blocker therapy compared to salt resistant patients.

In the Treatment of Mild Hypertension Study (TOMHS), the antihypertensive properties of five different drug classes in black participants were evaluated. They observed significant differences in antihypertensive efficacy between different classes of drugs depending on salt intake. The black participants, presumably salt sensitive as suggested by the work of Luft and Weinberger, responded most effectively to therapy with either a diuretic, calcium channel blocker, or a β-blocker with intrinsic sympathomimetic activity, as compared to therapy with an ACE inhibitor or an α-blocker. However, these studies did not address whether higher doses of these drugs might result in greater efficacy of blood pressure reduction in the presence of different sodium intakes. Both black and white patients who ingested less salt experienced a potentiation of the antihypertensive effect of most drugs used in the study. These data suggest that reduced dietary salt intake potentiates the antihypertensive effect of most antihypertensive drugs in patients with stage I hypertension. Thus, modest salt restriction facilitates blood pressure reduction in most hypertensive populations, particularly those who are salt sensitive (eg, older, obese, and black populations). Nevertheless, the link between the blood pressure lowering efficacy of salt restriction during antihypertensive therapy with any drug class has not been established. Lastly, calcium channel blockers may possess more robust antihypertensive properties in the face of high salt intake compared to other drugs.

Clinical trials have also studied whether or not dietary salt restriction facilitates reduced antihypertensive medication requirements. For the most part, clinical research has demonstrated improved withdrawal from a number of different antihypertensive therapies with modest dietary salt restriction. However, this has been particularly apparent in patients who are overweight and presumably more salt sensitive. Moreover, other studies have demonstrated that modest dietary salt restriction (urinary sodium excretion < 80 mEq/day) can be helpful in reducing the amount of antihypertensive medication ingested by the patient. This observation is further supported by a recent study that demonstrated that a modest reduction in dietary salt intake (urinary sodium excretion reduced from 156 to 106 mEq/day) resulted in a marked improvement in controlled blood pressure without returning to medication compared to patients not reducing their dietary salt.

**DIETARY SALT AND ANTIPROTEINURIC RESPONSE TO ANTIHYPERTENSIVE DRUGS**

The kidneys avidly conserve serum proteins. Ten to fifteen kilograms of serum proteins pass through the renal microcirculation daily. A daily excretion of < 150 mg appears in the urine. The glomerular capillary endothelial barrier is relatively impervious to most proteins because of its size, negative electrical charge, and the rigidity of individual proteins. However, an increase in urinary protein excretion can occur if there is damage to the glomerular capillary filtering barrier, an increase in glomerular capillary pressure, or increased plasma concentration of proteins. Further, decreased tubular reabsorption of filtered proteins or increased renal tubular secretion of proteins into the urine may also cause clinically detectable proteinuria.

Increased urinary protein excretion has been shown to be an independent predictor of cardiovascular morbidity and mortality in patients with essential hypertension. Moreover, proteinuria has prognostic implications for progressive loss of renal function, particularly among patients with diabetes mellitus.

It is clear in clinical trials that there are differing effects of antihypertensive drugs on urinary albumin excretion in hypertensive patients with and without kidney disease. A large intake of dietary salt raises urine protein excretion not only through its influence on systemic blood pressure but also through effects on glomerular hemodynamics and possibly through structural changes of the glomerulus. The ACE inhibitors and angiotensin II receptor antagonists are the antihypertensive agents that most consistently reduce proteinuria regardless of their
blood pressure lowering effect or the presence or absence of kidney disease.\textsuperscript{21} The antiproteinuric effect of ACE inhibitors can be documented in patients with micro- or macroalbuminuria, as well as in individuals with much greater urinary protein excretion. However, none of these clinical studies have consistently addressed the impact of dietary salt consumption on proteinuria during ACE inhibitor therapy. An important paper by Heeg et al demonstrated that increasing dietary salt intake can virtually abolish the antiproteinuric effect of ACE inhibitors.\textsuperscript{16} This group showed that increasing dietary sodium consumption, from 50 mEq/day to 200 mEq/day, completely attenuated the antiproteinuric effect of lisinopril. This blunted antiproteinuric response to the higher salt diet occurred in the absence of any blood pressure differences. In this study of patients with macroproteinuria (mean value of 6.4 ± 2.4 g/day) and hypertension (mean arterial pressure 104 ± 11 mm Hg), those who received the ACE inhibitor showed a 3% ± 3% reduction in blood pressure (89 ± 8 mm Hg to 87 ± 8 mm Hg) when going from a high salt to a low salt diet. However, there was a 52% ± 14% reduction in proteinuria during the transition from the high salt to low salt diet. Consequently, the effect of dietary salt on the antiproteinuric effect of ACE inhibitors cannot be ascribed solely to changes in systemic blood pressure. Accordingly, it is also well known that both the antihypertensive and antiproteinuric effects of ACE inhibitors are enhanced by sodium depletion.\textsuperscript{70,29,30,61} Thus, it can be postulated that the specific beneficial renal effects with ACE inhibitors might be greatest in the presence of a relatively low salt diet. Since the majority of patients consume approximately 160 mEq/day of sodium in their diet,\textsuperscript{1} an effort to encourage dietary salt restriction should be made when one uses an ACE inhibitor, both to reduce proteinuria as well as to augment the blood pressure lowering effect.

This same group of Dutch investigators provides evidence that the addition of diuretic therapy facilitates the antiproteinuric effects of ACE inhibitors even in the presence of a high salt diet.\textsuperscript{61} Moreover, this potentiating effect was not related to further reductions in blood pressure. This study also supports previous findings that the addition of a diuretic to an ACE inhibitor provides substantial reductions in blood pressure that, over the long term, should confer renal protection. Unfortunately, there is only one study that documents this association. Moreover, the differences in blood pressure between the high salt diuretic and nondiuretic groups were statistically different. Thus, further studies are needed to solidify this association.

With recent evidence that ACE inhibitors markedly slow progression of nephropathy in the patient with diabetes mellitus, it becomes more important for clinicians to focus on the optimal clinical use of ACE inhibitors. Some of the heterogeneity in the literature regarding differing antiproteinuric responses of the ACE inhibitors may be directly related to differing dietary salt intake. It may also be possible that those patients who derive optimal benefit from ACE inhibitors may ingest the least amount of dietary salt.

Nondihydropyridine calcium channel blockers (diltiazem and verapamil) may also have utility in reducing urinary protein excretion in hypertensive patients with kidney disease.\textsuperscript{21,62,84} Since the original reports were published over 7 years ago demonstrating that these agents reduce proteinuria to a similar extent as ACE inhibitors, other investigators have confirmed these findings.\textsuperscript{16,67,68} One clinical study has also demonstrated that the addition of an ACE inhibitor to a nondihydropyridine calcium channel blocker provides even greater antiproteinuric effect than either drug given alone.\textsuperscript{83} This occurred despite comparable reductions in systemic blood pressure with the individual monotherapies.

As with ACE inhibitors, salt intake affects the antiproteinuric effects of nondihydropyridine calcium channel blockers. A prospective cross-over study of non–insulin-dependent diabetic subjects with nephropathy, given either nifedipine GITS (gastrointestinal system) or diltiazem CD for blood pressure control and randomized to either a high (250 mEq/day) or low sodium (56 mEq/day) diet, showed divergent antiproteinuric effects.\textsuperscript{67} Sodium intake did not affect proteinuria if a dihydropyridine calcium channel blocker, such as nifedipine GITS, was used. Conversely, the nondihydropyridine diltiazem reduced proteinuria in the presence of a low salt diet, but this response was significantly blunted in the presence of a high salt diet. Moreover, this response was independent of the change in blood pressure reduction.

Consequently, it appears that the ability of ACE inhibitors and nondihydropyridine calcium channel blockers to reduce proteinuria may, in part, rely on a permissive action of reduced dietary salt intake. Interestingly, dihydropyridine calcium channel blockers do not appear to reduce proteinuria independently of their ability to reduce systemic arterial pressure.\textsuperscript{81,66,88} This is primarily related to the inability of these agents to alter glomerular membrane permeability.\textsuperscript{67,69}

Potential mechanisms by which ACE inhibitors and nondihydropyridine calcium channel blockers may interact with salt on glomerular permeability are summarized in Table 1. Recent evidence from micropuncture and clinical studies documents that low salt diets alone do not significantly alter renal function or increase intraglomerular pressure or efferent arteriolar resistance.\textsuperscript{55,71} Moreover, recent studies in normotensive individuals demonstrates that salt restriction
does not worsen insulin resistance. Therefore, changes in proteinuria in the presence of different salt intakes probably relate to mechanisms involving alterations in glomerular membrane permeability.

CONCLUSIONS

Numerous clinical studies now demonstrate that dietary salt can have a significant impact on the antihypertensive and antiproteinuric effects of drugs. A summary of antihypertensive agents whose effects on proteinuria are salt dependent are listed in Table 2. Note, however, that other antihypertensive drugs, if they profoundly reduce blood pressure, also reduce proteinuria. Since more aggressive blood pressure reduction can benefit renal function, particularly in proteinuric patients, these observations take on particular importance in patients at risk of, or with clinically evident, kidney disease. Part of the evidence for this observation comes from an analysis of the Modification of Diet and Renal Disease (MDRD) trial. This study demonstrated that the effects of blood pressure reduction on the progression of renal disease correlated with the level of proteinuria at baseline evaluation. The greater the amount of proteinuria, the greater the need for more aggressive blood pressure reduction. More clinical trials are needed to specifically define this interaction, particularly in patients who are known to be salt sensitive and in patients who have or are at risk of developing kidney disease. Successful reductions in systemic blood pressure and reduction in urine albumin excretion are clearly important in delaying target organ damage to various vascular beds throughout the body and in the kidney.

TABLE 1. ALTERATIONS IN THE FOLLOWING RENAL PARAMETERS MAY ACCOUNT FOR A BLUNTED ANTIProTEINURIC RESPONSE TO BLOOD PRESSURE LOWERING MEDICINE IN THE PRESENCE OF HIGH SALT INTAKE

<table>
<thead>
<tr>
<th>alteration</th>
<th>effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubular secretion of protein*</td>
<td>may be reduced</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>( K_t ) may be reduced</td>
</tr>
<tr>
<td>Glomerular membrane permeability</td>
<td>( P_{a-e} ) may increase</td>
</tr>
</tbody>
</table>

*Recent evidence shows that diltiazem and nifedipine affect secretion of creatinine. They may also affect proximal tubular handling of protein in the presence of different salt intakes.

TABLE 2. ANTIHYPERTENSIVE AGENTS THAT REQUIRE A LOW SALT DIET FOR MAXIMAL ANTIProTEINURIC EFFECTS

<table>
<thead>
<tr>
<th>agent</th>
<th>effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin converting enzyme inhibitors without diuretics</td>
<td>may not be effective</td>
</tr>
<tr>
<td>Nondihydropyridine calcium channel blockers (verapamil, diltiazem)</td>
<td>may not be effective</td>
</tr>
<tr>
<td>Angiotensin II blockers</td>
<td>may not be effective</td>
</tr>
</tbody>
</table>

REFERENCES

17. Abbott KC, Sanders LR, Bakris GL: Microalbuminuria...


