Adverse effects of short-term, very-low-salt diets in subjects with risk-factor clustering\textsuperscript{1–3}

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ABSTRACT Obesity is associated with risk-factor clustering, including risk factors for hypertension, hyperinsulinemia, resistance to insulin’s lowering of glucose and fatty acid concentrations, and a complex dyslipidemia. Obese hypertensive subjects are presumed to be salt sensitive because of the antinatriuretic actions of insulin. However, in our studies obese hypertensive subjects aged < 45 y were not more salt sensitive than were lean individuals. Subjects with the greatest evidence for risk-factor clustering had higher renin and aldosterone concentrations, which increased with salt restriction. The greater rise of fatty acids and activation of the renin-angiotensin system may explain the larger elevations of blood pressure, insulin, and triacylglycerol with salt restriction in high-risk subjects than in low-risk subjects. Regardless of mechanism, the adverse effects of short-term, very-low-salt diets in high-risk subjects suggest that continued moderation in advice for universal salt restriction is appropriate. \textit{Am J Clin Nutr} 1997;65(suppl):671S–7S.

KEY WORDS Salt, obesity, insulin, renin, aldosterone, blood pressure

INTRODUCTION Cross-cultural data suggest that restricting sodium intake to < 20–50 mmol/d might prevent a substantial proportion of hypertension (1–3). Because sodium restriction to < 50 mmol/d is difficult to achieve in free-living, acculturated individuals (4), many studies with very-low-salt diets are limited in duration to 3–14 d. The blood pressure response to short-term, very-low-salt diets is heterogeneous, with many subjects showing reductions, no change, and even increases (5–7). The heterogeneous blood pressure responses to salt restriction may reflect in part different biological subsets rather than spontaneous blood pressure variability alone (1, 8). For example, other studies have shown that salt sensitivity is reproducible and is associated with characteristic changes in the renin-aldosterone axis as well as heritable traits (9–12).

The assumption that very-low-salt diets are without risk conflicts with evidence that this intervention can induce neurohumoral activation and raise insulin, total and low-density lipoprotein cholesterol, triacylglycerol, uric acid, and creatinine concentrations and blood pressure (13–19). Some deleterious effects of salt restriction may be more apparent in salt-resistant subjects with high renin concentrations and risk-factor clustering (5, 11, 16, 19). During salt restriction, salt-resistant subjects often display more intense activation of the renin-angiotensin system and vasoconstriction than do salt-sensitive subjects (5, 16, 11, 19–21), which may contribute to a rise in blood pressure (5, 11, 15, 19) and adverse metabolic effects (16, 19, 22). Although not conclusive, these data suggest that the potential for harm in some persons warrants continued moderation regarding advice for salt restriction in all.

POTENTIAL EXPLANATIONS FOR DISCORDANT ADVICE ON UNIVERSAL SALT RESTRICTION

The benefits of salt restriction have received considerable attention and have merit (1–4). This review focuses on some potentially adverse effects of salt restriction that have received much less attention. Before embarking on this discussion, we review issues that may partially explain the controversy over the benefits and risks of salt restriction.

Biological versus physiologic variability Many epidemiologists view the blood pressure effects of salt restriction as relatively homogeneous and conclude that differences between salt-resistant and salt-sensitive groups reflect the physiologic variability of blood pressure rather than true differences in biological response (1, 8). Indeed, heterogeneous groups respond as a whole with a reduction of blood pressure in response to salt restriction. Consequently, universal salt restriction is comprehensible if physiologic variability alone explains the interindividual differences in blood pressure responses to this dietary intervention.

Other evidence, however, indicates that biological differences between individuals may contribute to heterogeneity in blood pressure responses to salt restriction (5–8, 10–19). Salt-sensitivity status has a relatively high degree of reproducibility (10, 11). Different methods for defining salt-sensitivity status tend to identify the same individuals as either salt sensitive or salt resistant (23). Salt-sensitive subjects manifest abnormal-

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ties in modulating the activity of and responsiveness to the renin-angiotensin system that are plausibly linked to the pathophysiology of salt sensitivity (12, 24, 25). Salt-sensitive and salt-resistant groups of subjects are also distinguishable genetically (9, 12). Although blood pressure variability complicates determination of salt-sensitivity status for individuals, biological differences between subjects should not be overlooked in universal guidelines for salt restriction.

Salt as the dominant issue in hypertension

Factors in addition to salt intake distinguish primitive societies from more highly acculturated lifestyles. However, most attention has been directed to salt consumption as the primary factor accounting for cultural differences in the prevalence of hypertension. One report indicates that inhabitants of Kotyang, Nepal, consume at least as much salt as do citizens of many Western civilizations (26). However, blood pressures of Kotyang inhabitants do not rise with age and the prevalence of hypertension in this population is extremely low (1.4%). On the basis of this observation, differences of salt intake are probably not the major factor determining blood pressure differences between people living in Kotyang and more industrialized societies such as the United States. Rather, these data suggest that other factors, perhaps acting in concert with salt, are responsible for the striking differences in the prevalence of hypertension and age-related changes of blood pressure. Foremost among these are differences in body mass index and adiposity, dietary sugar, and physical activity (26).

Weight loss and salt restriction

If salt is the dominant pathogenetic factor in hypertension, then salt restriction is a logical unimodal intervention for the treatment and prevention of hypertension. Severe (< 1 g NaCl/d) and moderate (4–6 g/d) salt restriction lower blood pressure in hypertensive subjects (27, 28). Modest salt restriction can also lower blood pressure in people with high-normal values, particularly as age increases (8, 29, 30). However, weight loss causes the same lowering of blood pressure in obese subjects with mean blood pressures averaging in the high-normal range when salt restriction is either minimal (120 mmol/d) or marked (40 mmol/d) (31). The combination of weight loss with either diuretics or β-blockers was more effective than the combination of salt restriction with either treatment in reducing blood pressure and overall cardiovascular risk as well as in improving quality of life (32). These data, when combined with those from other studies, including the report from Kotyang, Nepal, suggest that factors such as adiposity and weight may be more important than sodium intake in determining risk for hypertension.

Safety and risks of salt restriction

One assumption underlying the recommendation for universal salt restriction is that even if this intervention does not lower blood pressure in everyone, it causes no harm (1). However, results of the Trial of Antihypertensive Interventions and Management suggest that modest salt restriction combined with antihypertensive therapy may not be entirely benign regarding quality of life (32). Moreover, some salt-resistant subjects have more active renin-angiotensin systems and a rise of blood pressure even in response to a relatively modest salt restriction to 70 mmol/d (5). Long-term adverse metabolic effects of salt restriction have not been proven (4), which may reflect a complex interplay of nutritional and lifestyle factors. Subjects consuming less salt tend to have lower intakes of energy, fat, and sugar. Societies with very low salt intakes generally have extremely low-fat diets, high levels of physical activity, and low body mass indexes, which would be associated with favorable metabolic effects. Another point not often considered among potential risks is that efforts to bring the population mean sodium intake to 70–100 mmol/d would result in variable adherence, with some individuals achieving considerably greater than the mean degree of salt restriction.

In our studies, the hyperinsulinemic effect of a diet containing 20 mmol NaCl/d was similar at both 1 and 2 wk in separate studies of obese, hypertensive subjects (21, 22). In another report, a more modest salt restriction to 2 g/d was also associated with greater insulinemia during a standard oral glucose challenge in hypertensive patients (13). Solomon Islanders with habitually greater sodium intakes have lower uric acid values than do Islanders with lower sodium intakes (33). These findings agree with evidence that uric acid concentrations increase with short-term salt restriction (14, 16). Plasma renin activity of Yanomamo Indians who have extremely low lifelong salt consumption is comparable with that of subjects with similar short-term salt restriction (34). Several studies identified a rise of serum cholesterol with short-term, very-low-salt diets (14, 16, 17, 19). In the Multicenter Isradipine Salt Trial, modest salt restriction to ~100 mmol/d for 1 mo was associated with a small but significant rise in total cholesterol from baseline values (35). Collectively, these data suggest that very-low-salt diets as an isolated intervention have potentially adverse short-term effects and raise the possibility that some of these effects may occur with less severe salt restriction and may be sustained.

WHO MAY BE HARmed BY SODIUM RESTRICTION?

Although diuretics and salt restriction are not identical interventions, both induce an initial volume depletion that is counterbalanced by activation of the renin-angiotensin system. In general, subgroups with less active renin-angiotensin axes, such as elderly people and black hypertensive patients, have more favorable blood pressure responses (6, 8, 19), fewer adverse effects (16, 21), and better outcomes with diuretics and salt restriction than diuretics and salt restriction without active renin-angiotensin systems (36–42). These tendencies are consistent with observations that diuretics as initial therapy for hypertension significantly reduce mortality only in people older than 50 y (37, 38). Moreover, results from trials with diuretics as initial therapy in elderly hypertensive subjects showed a reduction in total cardiovascular as well as coronary mortality (39). Both the Multiple Risk Factor Intervention Trial and the Hypertension Detection and Follow-up Program (HDFP) showed that diuretics as initial therapy in white men with baseline electrocardiographic abnormalities were associated with a > 60% increase in coronary mortality (43); total cardiovascular mortality also tended to be greater in this high-risk subgroup (36, 41). In contrast, diuretic treatment of black men in the HDFP with baseline electrocardiographic abnormalities was associated with nearly a 70% reduction in total cardiovascular
mortality (36). In the HDFP, diuretics did not appear to adversely affect cardiovascular mortality in women with or without baseline electrocardiographic changes.

Another potentially related observation is that renin emerged as a predictor of cardiovascular mortality in men but not in women (44). In men, 24-h urine sodium at an early visit was inversely correlated with subsequent coronary mortality (42). These observations suggest, but given multiple potential confounders do not prove, that low-sodium diets and diuretics, which activate the renin-angiotensin system, may increase mortality in some high-risk groups.

Renin as a risk factor or risk marker for cardiovascular disease

Some evidence suggests that renin is a cardiovascular risk factor (44, 45) and that angiotensin may contribute to cardiovascular target organ changes and complications (46, 47). However, if an activated renin-angiotensin system was a necessary and sufficient condition for cardiovascular events, then Yanomamo Indians, who have long-term, extraordinary activation of the renin-angiotensin system (34), would be expected to succumb from a greater rate of cardiovascular crises. This has not, to our knowledge, been reported.

Although activation of the renin-angiotensin system by volume depletion may not have major adverse effects on cardiovascular risk in subjects who already are at low risk, this may not be the case in subjects at higher risk. For example, evidence suggests that angiotensin has greater effects on cell growth and proliferation when combined with other metabolic components of the risk-factor cluster. Another possibility is that renin correlates with cardiovascular events, particularly in men, by virtue of an association with cardiovascular risk-factor clustering. In a study by our group, 29 subjects, all < 45 y old, were subdivided by cardiovascular risk-factor clustering, as defined by body mass index, waist-to-hip ratios, elevated insulin and triacylglycerol concentrations, and reduced high-density-lipoprotein cholesterol and indexes of insulin-mediated glucose disposal (19). Subjects with the most evidence for risk-factor clustering had greater renin and aldosterone concentrations with both high- and low-salt diets (Figure 1).

Salt restriction to 20 mmol/d for 1 wk raised 24-h ambulatory blood pressure in the high-risk subjects and produced responses similar to those among subjects who already had marked increases in renin and aldosterone concentrations (20). Salt restriction to 10 mmol/d for 1 wk raised 24-h ambulatory blood pressure in the high-risk subjects and produced responses similar to those among subjects who already had marked increases in renin and aldosterone concentrations (20). Salt restriction to 10 mmol/d for 1 wk raised 24-h ambulatory blood pressure in the high-risk subjects and produced responses similar to those among subjects who already had marked increases in renin and aldosterone concentrations (20).

Several studies have observed that salt restriction increases insulin sensitivity by improving glucose disposal (21). Salt restriction to 10 mmol/d for 1 wk raised 24-h ambulatory blood pressure in the high-risk subjects and produced responses similar to those among subjects who already had marked increases in renin and aldosterone concentrations (20).

Fatty acids: the possible proximal mediator of the adverse response to salt in subjects with risk-factor clustering

The reciprocal connection between insulin and the renin-aldosterone axis may be superseded by a more proximal abnormality in resistance to the antilipolytic actions of insulin. In high-risk subjects, fatty acid concentrations were greater with the high-salt than the high-salt diet despite a 72-pmol/L (10 μU/mL) rise in fasting insulin with salt restriction (19). In normal subjects, a 72-pmol/L elevation of insulin above fasting concentrations is sufficient to suppress fatty acids by 70% (50). Consequently, salt restriction may induce a marked resistance to insulin’s fatty acid–lowering actions in abdominally obese subjects with risk-factor clustering.

The differential changes of fatty acids may contribute to the greater adverse effects of salt restriction in high-risk than low-risk subjects (Figure 3). For example, the rise of vascular resistance with salt restriction in obese salt-resistant subjects (21) may be mediated in part by greater vascular α-adrenergic tone (61); fatty acids can raise vascular resistance and augment α-adrenergic reactivity (54, 55). Ambulatory blood pressures increased more in high-risk than in low-risk subjects with salt restriction (19); fatty acids raise blood pressure (54). The integrated insulin area during the oral-glucose-tolerance test, which is strongly correlated with insulin-mediated glucose disposal in clamp studies (56), rose more in high-risk than in low-risk subjects with salt restriction; fatty acids induce insulin resistance by impairing glucose use in skeletal muscle (57), the major site of glucose disposal, which could drive a compensatory hyperinsulinemia. Moreover, fatty acids impair hepatic insulin clearance (58), which would further augment peripheral hyperinsulinemia (62). Triacylglycerol also rose more with salt restriction in high-risk subjects; fatty acids increase hepatic

In Figure 1, the plasma renin activity and plasma aldosterone concentrations in subjects consuming low- and high-salt diets were grouped by composite scores for variables in the risk-factor cluster. *Significantly different from the low-score group, P < 0.05. †Significantly different from the medium-score group, P < 0.05. Reprinted by permission of Elsevier Science (19). Copyright 1994 by American Journal of Hypertension Inc.
production of very-low-density, triacylglycerol-rich lipoproteins (59).

The greater rise of renin and aldosterone in high-risk subjects is one feature that does not fit with fatty acids being the primary pathogenetic factor for the greater adverse effects of salt restriction in high-risk subjects because fatty acids suppress renin and aldosterone (63, 64). We postulate that the rise of fatty acid concentrations with salt restriction in high-risk subjects contributes to their greater hyperinsulinemia, which, in turn, drives renin and aldosterone production (48, 49). This hypothesis is indirectly supported by positive correlations between insulin and both renin and aldosterone for subjects consuming low-salt diets (Figure 4) (19).

Vascular response to salt restriction

The past decade we have witnessed an extraordinary growth of interest in the contribution of hemodynamic, neurohumoral, and microvascular factors to metabolic abnormalities, with a focus on insulin-mediated glucose disposal (60, 66–69). Although these arguments are provocative, significant limitations remain (69). Our combined evidence indicates that most people have greater insulin concentrations during very low salt intake (20 mmol/d) than during high salt intake (200 mmol/d) regardless of salt-sensitivity status (16, 21, 22). This rise of insulin with salt restriction may constitute an adaptive counterregulatory response, because insulin has direct antinatriuretic actions and augments aldosterone production (49, 70, 71). Nevertheless, on the basis of the fundamental logic that some blood flow is essential to normal metabolic function, differential changes of vascular resistance with salt restriction may contribute to a tendency for greater adverse metabolic effects in the salt-resistant subset. More specifically, salt-resistant subjects, as a group, undergo vasoconstriction with salt restriction, whereas salt-sensitive subjects as a group undergo vasodilation (7, 21, 61). In salt-resistant subjects, the vasoconstriction with salt restriction and vasodilation with salt feeding are sustained for several months (7, 20). Theoretically, the long-term vasoconstriction in response to low-sodium diets in salt-resistant subjects might contribute to more sustained adverse metabolic effects than in salt-sensitive subjects who undergo vasodilation (60, 65, 67–69).

SUMMARY

In many hypertensive subjects, blood pressure dysregulation is mediated not only by an excess consumption of salt, but also by a complex interplay of environmental and genetic factors. All populations appear to have a relatively comparable prevalence of hypertension with acculturation. The comparable and relatively high risk of hypertension and other components of the risk-factor cluster in populations with access to excess saturated fat, sugar, and sedentary leisure time suggests that these genetic factors must have some survival value (72, 73). Although selective and focused recommendations such as salt
restriction for a complex lifestyle problem are appealing from a public health perspective, we have significant concerns about universal salt restriction given the potential for harm in some individuals. There is less concern about limiting the population sodium intake to the 3000 mg/d advocated by the American Heart Association, which lies just slightly below the lower limits of the natural salt appetite defined by Folkow and Ely (74), particularly if this restriction is part of a healthy lifestyle change including reducing excessive intakes of energy, fat, and sugar and becoming less sedentary.

Of particularly concern are salt-resistant subjects, particularly those younger than 45 y, with clustering of multiple risk factors and markers and in whom the potentially adverse metabolic effects of salt restriction are not counterbalanced by a decline of blood pressure (16, 19). For some of these individuals, the risk of adverse metabolic effects of salt restriction may be further compounded by a rise in blood pressure. Although this concern is based largely on short-term studies, other evidence, cited earlier in the review, suggests that some potentially adverse effects of salt restriction may be sustained. Longer-term interventions with modest sodium restriction as an isolated intervention in subjects at high risk for adverse effects could prove instructive and might disprove the results of the short-term studies. However, the principal of “first do no harm” favors continued moderation in advice for universal salt restriction.

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