Benefit assessment of dietary salt reduction: while the doctors study, should more people die?
Pasquale Strazzullo

The debate on salt and health has encompassed many generations, still in this issue of the *Journal of Hypertension*, Matyas et al. [1], on the basis of the analysis of available systematic reviews of randomized controlled trials (RCTs), conclude that there is proof of the blood pressure (BP)-lowering effect of salt intake reduction in hypertensive patients, but ‘no valid information is available to show conclusively that salt reduction is beneficial or harmful in terms of patient-relevant outcomes’ [1].

The assessment of the vast literature available on this subject by Matyas et al. is formally correct; nevertheless, their conclusions are ambiguous and such to raise a few simple questions: What has to be intended as ‘valid information’? What is meant by ‘patient-relevant outcomes’? And most important, what should we do about patients, but also about all the people (the very large majority of the human beings), whose salt intake is two, three or more times the upper level recommended by WHO [2] and more recently by the US Departments of Agriculture, Health and Human Services [3]? Anywho 001 who works in this area is well aware of the lack of RCTs of the effect of reducing sodium intake on hard cardiovascular outcomes. The same is true indeed for the effect of reducing overweight and for the effect of smoking cessation. In all these cases, the lack of a ‘conclusive’ demonstration from RCTs is justified by a number of reasons, including the occurrence of ethical problems, the methodological difficulties in assessing compliance to life-style modifications such as dietary salt reduction over a prolonged period of time, the length of observation and the size of study populations necessary to demonstrate an effect on hard outcomes and the difficulty in ensuring financial support to such a trial. Although these problems will likely hamper the possibility that this trial will ever be performed, why should we consider ‘invalid’ the information provided by prospective cohort studies, the results of which, in the large majority, are in favor of a beneficial effect of lower habitual sodium intake on the risk of cardiovascular disease [4]? How to disregard that in North Karelia, a community intervention programme of salt reduction led to a drop of over 3 g/day, which was followed by a reduction of over 10 mmHg in SBP and DBP and by a decrease of 75% in stroke and coronary heart disease mortality, despite a concomitant increase in the prevalence of obesity and alcohol consumption [5]? Why ignoring the success of the campaign implemented by the Japanese government leading to a fall in salt intake from 18 to 14 g in the north of the country, which was paralleled by a significant fall in average BP and by an 80% reduction in stroke mortality, despite increases in BMI, fat intake, cigarette smoking and alcohol consumption [6]? Should we consider invalid the ecological findings of the INTERSALT [7] and INTERMAP studies [8]? Noteworthy, this huge bulk of information comes from population-based studies, supporting the concept that an effective salt reduction programme is to be framed as a population intervention and should not be limited to hypertensive patients or even a minority thereof.

What has to be intended as ‘patient-relevant’ outcomes? Is target organ damage to be listed under this category? Probably yes, given that cardiac failure or renal insufficiency has a tremendous impact on an individual’s quality of life. Then, there is ample demonstration from RCTs of the benefit of salt intake reduction on prevention and therapy of organ damage (Table 1). A direct association has been repeatedly observed between 24 h urinary sodium excretion and left ventricular mass, to some extent independently of BP [9–11]: more important, the effect of lowering salt intake on left ventricular mass reduction in hypertensive patients has been demonstrated by at least three RCTs in mild or moderate hypertensive patients [12–14]. Population-based studies have provided evidence of the association between habitual salt intake and the rate of urinary protein excretion [15,16], which in turn predisposes to renal insufficiency [17]. A recent RCT in hypertensive black patients showed that moderate salt intake reduction, in accordance with current recommendations, significantly reduced urinary protein excretion [18]. In another trial in diabetic patients, a reduction in salt intake increased the effectiveness of angiotensin-receptor blockers on proteinuria [19]. Salt intake is a major determinant of urinary calcium excretion. Several studies showed a direct association between habitual salt intake and the risk of calcium nephrolithiasis, and an RCT of dietary salt reduction demonstrated the beneficial impact of this lifestyle modification on the rate of renal stone recurrence.
It is hard to believe that the beneficial effect of dietary sodium intake reduction on BP and on these important predictors of cardiovascular and renal outcomes does not translate to long-term benefit in terms of morbidity and mortality rates. Actually, one of the arguments put forward to refute the beneficial effects of salt intake reduction on cardiovascular outcomes is that the activation of the renin–angiotensin system (RAS) following reduction of salt intake outweighs the benefit of BP reduction [24]. In fact, there is evidence to the contrary from old and recent sources that deserve to be mentioned. The compensatory stimulation of the RAS is relatively small when reduction in salt intake is moderate and progressive over a prolonged period of time, as currently recommended by public health authorities. This has been shown by randomized trials [25], which also showed no detectable changes in sympathetic outflow under the same conditions [26]. This notwithstanding, even recently it has been claimed that habitual dietary salt intake should not be reduced to less than 120 mmol (or 7 g) a day if dangerous RAS stimulation is to be avoided [27]. Indeed, an analysis of 28 trials of moderate sodium reduction in either hypertensive or normotensive individuals has shown that, for an average reduction of dietary salt intake from 161 to 87 mmol/day (i.e. 9–5 g), plasma renin activity (PRA) increased only from 1.17 to 1.55 ng/ml per h, a quite moderate change [25]. The milestone studies of Laragh et al. [28] in the 1970s showed that half-maximal stimulation of PRA takes place at sodium intake levels of 30–50 mmol a day and that sodium intake at the level of 50 mmol a day suppresses aldosterone secretion almost completely. This evidence supports the concept that the range of RAS control mechanisms is in agreement with the dietary sodium amounts occurring in a diet containing mainly natural foodstuffs and little or no added salt. Actually, the idea that the evaluation of RAS activity may rely only on the circulating plasma levels of the system effectors angiotensin II and aldosterone is rather simplistic. It ignores the results of other pioneering studies by Brunner et al. [29] showing that sodium depletion, while increasing angiotensin II production by stimulation of renin release, also lowers vascular receptor affinity to angiotensin II, so that eventually BP is not affected at all. Confirmation of this favorable balance between the BP-lowering effect of chronic moderate salt reduction and the secondary stimulation of the RAS comes from recent studies of heterozygous individuals with loss-of-function mutations of the renal NaCl cotransporter: these individuals suffer a moderate chronic renal salt wasting because of their ion transport abnormality and have secondarily increased plasma renin levels but lower than normal BP [30]. Overall, these observations indicate that the effect of reduced body sodium content subsequent to dietary salt reduction outweighs the modest secondary activation of the renin–angiotensin–aldosterone and sympathetic nervous systems.

Last, but not least, a number of careful cost–utility and cost–benefit analyses made recently available in the literature have highlighted the cost–effectiveness of dietary salt reduction if implemented as part of a population strategy of primary prevention. Table 2 reports the main findings of the most recent such studies indicating the huge savings in public health costs determined by the expected decreased incidence of hypertension and, more important, by the reduction in the incidence of fatal or disabling cardiovascular, renal and cerebrovascular events [31].

Matyas et al. recognize that there is solid evidence for health benefit when BP is reduced to recommended levels, and that, in certain patients, lifestyle changes may enable them to reduce or stop drug therapy as well:

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**Table 1** Type of evidence of the recognized effects of lower dietary salt intake

<table>
<thead>
<tr>
<th>Effect</th>
<th>RCTs</th>
<th>Cohort studies</th>
<th>Ecological studies</th>
<th>Experimental studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower rate of rise in blood pressure with age</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Blood pressure reduction in hypertension and normotension</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Decreased risk of cardiovascular events</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Decreased risk of stroke</td>
<td>X</td>
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<tr>
<td>Reduction in left ventricular hypertrophy</td>
<td>X</td>
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<tr>
<td>Reduced rate of albuminuria</td>
<td>X</td>
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<tr>
<td>Improved arterial elasticity</td>
<td>X</td>
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<td>Lower risk of calcium nephrolithiasis</td>
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</table>

**Table 2** Recent studies of cost–effectiveness of reducing dietary sodium intake

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect</th>
<th>Cost</th>
</tr>
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<tbody>
<tr>
<td>Palai and Sturm [32]</td>
<td>Salt intake reduction to 8 g/day at population level</td>
<td>18 billion dollars saved yearly</td>
</tr>
<tr>
<td>Dall et al. [33]</td>
<td>Sustained salt intake reduction of 1 g/day in uncontrolled hypertension</td>
<td>2.3 billion dollars saved yearly</td>
</tr>
<tr>
<td>Rubinstein et al. [34]</td>
<td>Salt intake reduction at salt intake</td>
<td>Very low cost – 151$ per disability adjusted life-year</td>
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<tr>
<td>Bibbins-Domingo et al. [35]</td>
<td>Salt intake reduction of 3 g/day at population level</td>
<td>10–24 billion dollars saved yearly</td>
</tr>
<tr>
<td>Smith-Spangler et al. [36]</td>
<td>Government collaboration with food industry to cut salt content of food voluntarily</td>
<td>32 billion dollars saved yearly</td>
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</tbody>
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sodium reduction is one of these measures and also the one with the greatest potential impact, given the epidemic worldwide diffusion of excess salt intake. Should we refrain from this life-saving measure and let people die of hypertension and its cardiovascular complications while waiting for the ‘mother of all trials’?

References


