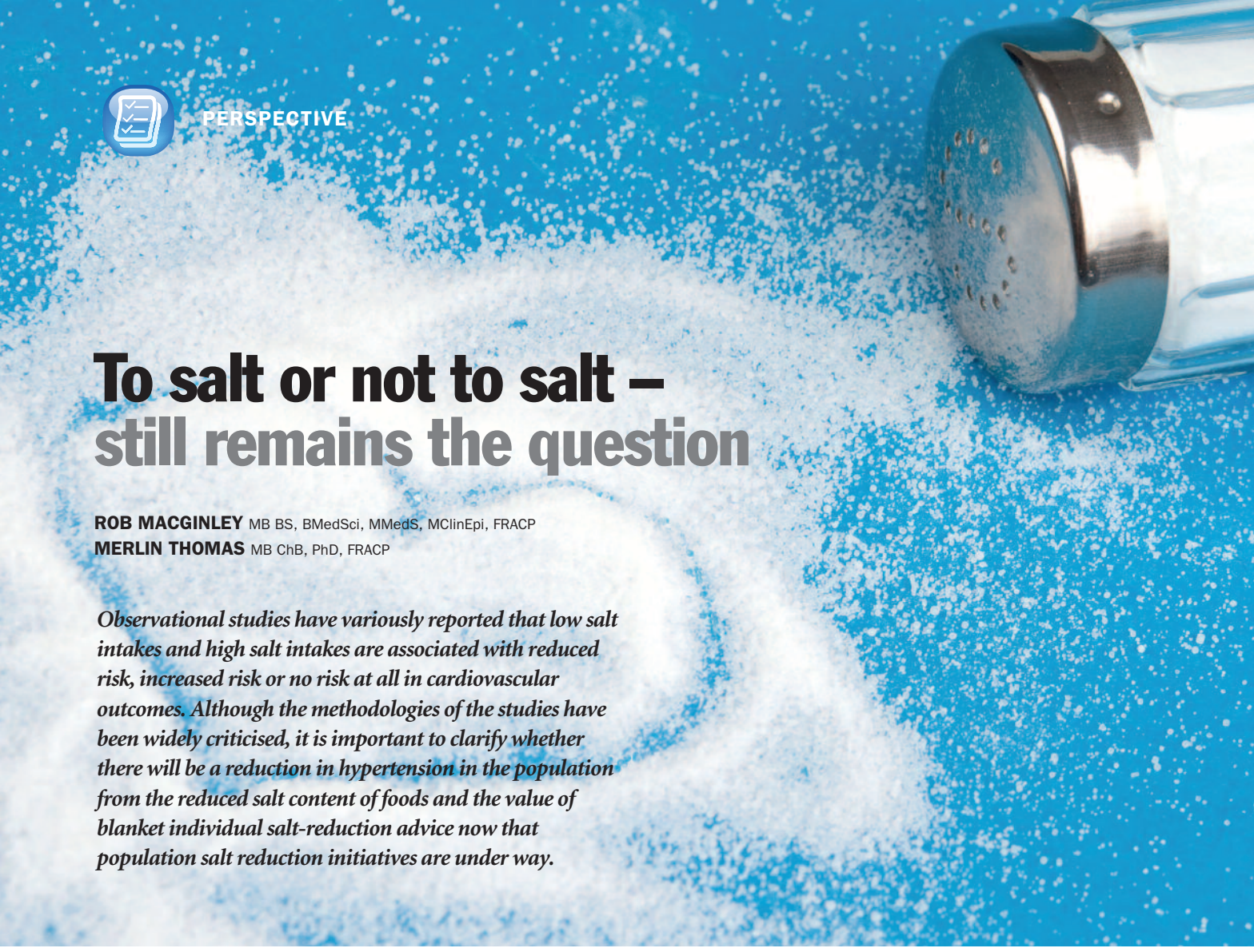

To salt or not to salt – still remains the question

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Observational studies have variously reported that low salt intakes and high salt intakes are associated with reduced risk, increased risk or no risk at all in cardiovascular outcomes. Although the methodologies of the studies have been widely criticised, it is important to clarify whether there will be a reduction in hypertension in the population from the reduced salt content of foods and the value of blanket individual salt-reduction advice now that population salt reduction initiatives are under way.

Many public health messages have clear and indisputable links to health, such as reducing sugar and fat intakes and cigarette smoking and the subsequent reduction in cardiovascular disease (CVD). There is also a robust association between dietary sodium intake and hypertension, sodium intake being excessive in today's society through the consumption of processed foods. This has lead to government, industry and advocacy groups launching projects to decrease the population sodium intakes to much lower levels via both food industry measures and salt reduction messages.

Unfortunately for the salt reduction public health message, controversy still rages regarding its utility in consistently improving health outcomes. A series of observational studies, in a range

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Key points

- **Government, industry and advocacy groups are launching projects to decrease the population sodium intakes in our community with the aim of lessening cardiovascular disease (CVD) linked to excessive salt consumption.**
- **Selected populations, including people with heart failure and those with long-term diabetes, may have an excessive response to severe salt restriction. Caution is advised in these populations when reducing sodium intake.**
- **The population program of salt reduction is separate to the individualised prescription of salt restriction. A primary care physician should act based on the patient in front of him or her.**
- **At an individual patient level, a healthy diet – and particularly one that has a low salt content – is essential and is likely to improve blood pressure control and also have extensive overall health benefits.**
- **Patients who already have a very high CVD risk will need a slow and gradual reduction in their salt intake to lessen nutritional issues and ensure counter-regulatory physiological responses are in balance when the low-salt diet is commenced.**

of different settings, have variously reported that low salt intakes and high salt intakes are associated with reduced risk, increased risk or no risk at all in cardiovascular (CV) outcomes. Although the studies have been widely criticised because of the potential confounding and selection bias, it has now become crucial, at the time when population salt reduction initiatives are under way, to clarify whether hypertension in the population will be reduced from these initiatives and the value of individual salt-reduction advice. Lowering blood pressure (BP) is immensely important because hypertension is the leading cause of CVD in our community.

This article aims to objectively review the evidence 'for and against' universal recommendations for sodium restriction and to navigate a pragmatic solution for clinicians to apply in their everyday practice for the individual.

Historical sodium intake

Human evolution required adaptations to conserve salt when on a very low salt diet (below 0.25 g/day) and thus physiologically we are salt conservers foremost.[1] However, the advent of civilisation led to enormous changes in the human diet, outpacing our thrifty adaptations for life in the wild. Since the early Chinese discovery of the food preservation value of salt, early civilisation colonised the world using it, Romans taxed it, and by the 1870s it had reached its peak of importance.[2] A sharp decline in the importance of salt, and the amount of it eaten, then commenced, due to the commercial application of refrigeration to food preservation. More recently, however, dietary salt intakes have increased by about 200 to 300% as a result of the increased processing of food and the use of salt in this for preservation and also taste enhancement.[3]

The epidemic of diabetes has been widely attributed to a thrifty phenotype exposed to caloric excess. In much the same way, the modern epidemic of hypertension has been laid at the door of our inherited predisposition to eat and retain sodium in a world where salt is no longer a scarce commodity in our diet.[4] Nowadays, some 9 to 12 g of salt needs to be handled each day by our physiological processes, particularly in the kidneys. Although about half of us successfully achieve this, adaption may not be easy for the other half, particularly those who have salt-induced hypertension and those with chronic diseases, in whom BP control is made more difficult by these high salt diets.

Blood pressure and salt sensitivity

The challenge of the physiological burden of excessive salt on the kidney is a gradual rise in BP and thus a likely increase in CVD and renal disease. In experimental studies, direct effects have been demonstrated on stroke, left ventricular hypertrophy, progression of renal disease and proteinuria; these effects are independent of and additive to the effect of salt on BP.[5] It is likely, as proposed above, that hypertension originates as an inherited inability to excrete a sodium load and that its development is facilitated in the sodium-rich environment that is characteristic of our western society.[6]

Dietary salt can raise BP in salt-sensitive individuals and has been linked to premature mortality in these individuals.[7] There are many studies on the effect of salt restriction on BP. Most have found that BP can be reduced by decreasing salt intake, and the benefits are generally more pronounced in hypertensive than normotensive subjects. In the Nonpharmacological Interventions in the Elderly (TONE) study, individuals randomised to sodium intake reduction had a significant reduction in their BP, a reduction in the requirements for antihypertensive therapy and a reduction in CV events (relative risk, 0.69).[8] A recent study demonstrated that isolated systolic BP could be decreased by an average of 10 mmHg by reducing patients' sodium intake from 175 mmol/day to 87 mmol/day (measured by urinary sodium excretion; $p<0.001$).[9] In this study, BP was also significantly reduced in patients with combined hypertension, with systolic BP decreasing by an average of 7 mmHg and diastolic BP by an average of 4 mmHg after reducing sodium intake from 176 mmol/day to 98 mmol/day ($p<0.001$).

CVD reduction from salt reduction

The hypothesis that salt restriction will reduce CVD because it lowers BP is highly plausible and readily supported in salt-sensitive models and settings. A meta-analysis by Strazzullo and colleagues of 13 cohort studies showed an increase in salt intake of 5 g/day was associated with a 14% increase in CVD, and the long-term cohort data of He and MacGregor, which included a meta-analysis of randomised controlled trials, showed a sodium reduction of 100 mmol/day (equivalent to 6 g salt/day) leads to an 18% reduction in coronary artery disease.[10-12]

The long-term cohort randomised controlled studies Trial of Hypertension Prevention I and II (TOHP1, 18 months; TOHPII, 36 months), which showed 1.7/0.8 mmHg and 1.2/07 mmHg BP reduction respectively with sodium reduction, did not show any reduction in coronary events at 36 months, although 10 to 15 years later a 25% reduction in events was observed.[13] This was despite there being no difference in sodium excretion between the two arms, leading to the suggestion that it was not salt restriction but other dietary changes associated with restricting salt that may explain these differences.

From these experimental studies and epidemiological, migration, intervention, treatment, animal and genetic studies there is overwhelming evidence demonstrating that dietary salt is a major cause of raised BP and is largely responsible for the rise of BP with age. The evidence also shows that a reduction in salt intake does lower BP in many groups, thereby reducing BP-related diseases. Considering there is a high incidence of hypertension in the community and that the condition accounts for at least half of all the deaths from myocardial infarction and stroke at both the individual and population health levels, an improvement via salt reduction would be very worthwhile in principle.[3] Although there is seemingly interdependence between salt intake, salt excretion and BP, there is almost certainly a continuum with interindividual differences in BP response to dietary sodium loads being affected by many variables.

Population salt reduction

A series of papers on cost-effectiveness modelling has arisen from these studies on salt reduction. The proposal of these papers is that not only are 'lives' saved with population salt reduction strategies but governments will save money in health expenditure.[14,15] One model showed a decrease of 9.5% in population sodium intake would result in a US$32 billion saving in medical costs.[14] This level of savings from the modest reduction of salt would be as beneficial as smoking cessation.

For developing countries with limited health care resources, reducing salt intake and tobacco smoking would account for 80% of the chronic disease burden. The total cost of prevention would be US$0.09 a person for salt intake reduction, compared with US$0.26 a person for smoking prevention.[16]

Two caveats with any of the current models are the necessity of food industry co-operation and that the BP elevation risks proposed for myocardial infarction and stroke events are below the medication treatment levels of BP recommendations that exist currently.

It is generally agreed today that policy interventions that change the environment to make default choices healthier are more efficient than health promotion programs such as individual education as ways to improve the health outcomes for large numbers of people. Successful policy interventions often improve health at a low cost and can sometimes produce cost savings to the health care system.

Reducing the sodium content of foods makes them less palatable so implementing sodium reduction in an incremental fashion allows individuals to become accustomed to the blander taste, aiding acceptance of the lower salt content foods.

> '... individual patients will benefit from thoughtful modification of the salt content of their diet.'

The physiology of sodium reduction

In contrast with the salt-sensitive argument discussed above, physiological principals exist for the response of the body to reduced salt. For example, young normotensive adults are not generally salt-sensitive and the effects on BP arising from salt restriction in such adults are slight, or even nonsignificant. A study in young adults with type 1 diabetes showed that while one-third of patients had a fall in BP following sodium restriction, another third experienced an increase in BP and the remaining third had no change.[17]

The data from the previously described study raises the important question of why some individuals are salt-sensitive when it comes to their BP whereas others are not. One possible explanation comes from the reasons why salt increases BP at all. It is believed that when a high salt intake increases BP it does so by expanding the intravascular fluid volume because the affected individuals do not have the excretory capacity to remove a sodium load. However, the kidneys are very effective regulators of sodium balance, filtering and reabsorbing over 25,000 mmol of salt every day, losing only 0.5% of the filtered load into the urine. In healthy individuals, this loss equates almost exactly to the amount of salt in the diet (about 100 to 200 mmol/day).[18] Consequently, it represents little problem for renal function to deal with the meagre additional sodium load of a high salt diet (above 200 mmol/day), even in individuals with overt renal insufficiency. Furthermore, this means that the pathogenesis of salt-sensitivity must therefore involve a derangement or resetting of renal sodium handling, leading to an inclination to reabsorb rather than excrete excess sodium. Several candidates have been proposed, including activation of the intrarenal renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system and signalling via with-no-lysine (WNK) kinases.[19] In particular, the WNK kinase pathway represents an important molecular pathway linking the RAAS and sympathetic nervous system to the expression of urinary sodium transporters and therein renal sodium handling.[20]

Another possible explanation why some individuals are salt-sensitive when it comes to their BP whereas others are not is that sodium restriction induces feedback pathways (see below) whose job it is to maintain the BP close to its homeostatic set point. Any reduction in sodium intake results in activation of the systemic RAAS, increased sympathetic activity, increased uric acid levels and decreased insulin sensitivity.[21,22] This neurohormonal feedback is far more efficient in younger individuals than in older people, meaning any effects on BP in younger people are offset by activation of the RAAS, sympathetic nervous system and other pathways. In the elderly and in native African individuals, these feedback pathways are less potent, and the effects of salt restriction are greater. Interestingly, these latter populations also benefit less from RAAS blockade than they do from other antihypertensive interventions. Similarly, one reason why people who have been treated for hypertension may be more salt-sensitive is that their medications have blocked these feedback pathways, leaving them more open to the antihypertensive effects of sodium restriction.

Little evidence exists experimentally for these theories. In a study of salt loading followed by a two-week salt washout, Todd and colleagues showed in salt-sensitive individuals both a dose response curve to salt and, on salt deprivation, a marked renin, aldosterone and uric acid increase (unpublished data) that could represent the response of the body to reduced salt.[23]

Studies still producing evidence to the contrary

Recent clinical studies on dietary sodium and mortality include three prospective cohort studies, one in healthy middle aged

Europeans, one in patients with type 1 diabetes and the other in patients with type 2 diabetes.[17,24,25] Methodological issues, discussed below, lessen the robustness of the conclusions of these studies, but they each clearly showed that a lessened salt intake as detected by a 24-hour urine collection in a long-term cohort was associated with the outcome of increased CVD mortality. Criticisms of the European healthy cohort are that one-off 24-hour urine collection is a poor measure and the young population (below 55 years of age) had very few events (84 out of nearly 4000).[24] Other issues included that no change in urinary sodium was noticed and it was difficult to manipulate diet and age-related trends in systolic BP. The diabetic studies were criticised for similar reasons. However, these studies all suggest that there is not a supposed link between salt restriction and reduced CVD.

Following this, a recent meta-analysis by Taylor and colleagues analysed seven randomised controlled trials, three in people with normal BP, two in people with hypertension, one in a mixed population of people with normal BP and people with hypertension and one in people with heart failure.[26] None of these trials was designed to test the effects of sodium reduction interventions on CV events and mortality. The studies were performed in a mixture of populations supposedly without CVD. There were 665 deaths in the roughly 6250 participants but in analysis a sustained reduction in BP was not confirmed. Unfortunately the investigators also truncated the TOHPI and TOHPII trials to 1.5 years of data rather than include the long-term results. The meta-analysis could not identify any significant CVD benefit of sodium restriction, and the authors noted that in the heart failure trial it was associated with significant mortality and morbidity. The meta-analysis suffered from mixed populations and different study designs, methods and scope of available data, and was revoked by a repeat meta-analysis, published within a month, that excluded the patients with heart failure and demonstrated an improved CVD mortality.[27] There remains the confounder of the incomplete data in the 24-hour urine collections as well. The methodologies of all the studies will be in question from the undercollection of 24-hour urines, which complicate the data. The low number of deaths provided little power to the conclusions supposed, and led to poor statistical methods. Thus, the hypothesis of individual salt restriction portending a possible poor outcome requires more comprehensive studies.

The suggestion of a possible J-curve for some individuals with different diseases in which high salt is detrimental but very low salt may also not prove beneficial has been supported by the large post-hoc analysis of two previous studies (On-Target [Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial] and Transcend [Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease]), involving some 29000 individuals.[28] The populations were very heterogeneous and the analysis results showed that CVD risk was increased among both those with the lowest levels of sodium excretion and those with levels well above current recommended levels. Again, methodological issues associated with the post-hoc analysis of studies not designed to test salt intake and CVD risk and the estimated 24-hour salt intake being determined by spot urinary salt are likely to have introduced error.[29,30]

The final argument

The final argument about restriction of salt may be dependent on the individual and the need for an individual approach. No other major nutrient story has produced such controversy. From population data and clear physiological principals, the benefits of salt reduction seem obvious and incontrovertible. The existence of small cohort studies that demonstrated a J-curve relation between BP and CV events and all-cause mortality in populations with diabetes and heart failure is akin to the evidence in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study that BP lowering did not prevent CVD outcomes and the recent paper on people with pure vascular risk showing a clear J-curve for BP targets.[31]

Dietary advice for patients

A patient handout giving advice on low sodium foods is provided on pages 23 and 24.

Conclusion

The plan is for people worldwide to have a generalised reduction in their dietary sodium intake and thus, hopefully, the noncommunicable disease epidemic of stroke particularly will lessen at a population level.[3] The most cost-effective way to achieve this appears to be reducing the salt content of processed foods to historical levels, this content having increased by 200 to 300% over the past couple of decades.

At an individual patient level, a healthy diet – and particularly one that has a low salt content – is essential and is likely to improve BP control and also have extensive overall health benefits. Patients who already have a very high CVD risk (for example, those with an activated RAAS system) will need a slow and gradual reduction in their salt intake, both to allay the negative impact on the appetite of the less tasty lower salt-content food and thereby lessen nutritional issues, and to ensure counter-regulatory physiological responses are in balance when the low-salt diet is commenced.

Hopefully the end of the salt wars is near. Population health may benefit from salt reduction at a food industry level and individual patients will benefit from thoughtful modification of the salt content of their diet. **CT**

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A list of references is available on request to the editorial office.

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