1.1.1 ***Salt***

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1.1.1.1 Brief background—the salt issue up to 2002

Salt and its effect on human health has been a debated issue for centuries. The possible detrimental effect of salt on hypertension and blood pressure–related diseases—the "Salt hypothesis"—became of considerable interest when Kempner introduced his rice diets with exceptionally low salt intakes as a method of coping with patients with very high blood pressure.[1] Then after the second world war, Dahl and colleagues[2,3] showed that animals could be bred to reveal marked salt sensitivity, therefore suggesting that salt sensitivity was genetically inherited. Given the differential response of patients to reduced intakes of salt this also led to the concept that in humans there was a subgroup with salt sensitivity who would need to be advised to reduce their salt intake. This led to a great debate between Pickering[4] and Platt[5] as to whether one could readily distinguish a separate group in the population with higher blood pressures as a means of providing separate advice and management. Miall[6] then showed, as have many others, that there is a continuous spectrum of blood pressures within the population with a progressive increase in cardiovascular events as the systolic blood pressure rises from 115 mmHg.[7] This was traditionally considered a low-normal value. Rose then highlighted that if one sought to limit the hazards associated with high blood pressure (or indeed high blood cholesterol levels) then there is greater benefit in reducing the average blood pressure or cholesterol level of the whole population rather than focusing on a smaller group with particularly high blood pressure or cholesterol levels.[8]

Until the late 1980s progress in the salt field was hampered by small, and usually insufficiently powered, studies in humans. In addition, the estimates of salt intake in different population groups were challenged on methodological grounds. Many studies were based on interviews using food frequency questionnaires, a method with several recognised pitfalls. The gold standard remains the 24-hour sampling of urine to determine sodium excretion, a cumbersome method that is not always applicable. It was also realised that the major part of salt consumption (perhaps 70-80%) stems from processed foods[9] and often with insufficient reporting of salt content by the manufacturers.

Closer to 2002, some larger and important studies were published. The INTERSALT-study from 1988 remains the largest single study (of 10,079 individuals from 32 countries) to date reporting on the association between sodium excretion and blood pressure levels.[10] The authors reported a significant, albeit low, correlation between sodium excretion and blood pressure across populations. Similar findings based on integrated analyses were later published by Law and colleagues based on sodium excretion data from about 47,000 individuals sampled from 24 different

populations.[11,12,13] Both studies have, however, been criticised in terms of the complex methods used in taking account of country and other differences.[14,15,16]

The relevance of these studies which found correlations between salt intake and blood pressure in population groups was then amplified in 2001 by meticulous dietary studies involving testing the impact of altering specific components of the diet without weight loss in two groups with normal blood pressure and high blood pressure[17] In these DASH trials involving 412 normotensive and pre-hypertensive individuals it was shown that in the whole group reducing the salt intake to intermediate levels led to a fall in systolic blood pressure of 2.1 mmHg with a further fall by 4.6 mmHg when the salt intake was reduced to the lowest level i.e. 3g salt/day. These reductions occurred when the diets were relatively low in fruit and vegetables but high in total and saturated fat. This full 6.7 mmHg fall compared with a total fall of 3.0 mmHg when equivalent reductions in salt intake were made but when diets were higher in fruit and vegetables and low in fat. Thus salt reduction produced greater falls in blood pressure in those on less healthy diets but on each diet there was a statistically significant reduction in blood pressure. Among non-hypertensive participants who received the control diet, lower (vs. higher) sodium intake decreased blood pressure by 7.0/3.8 mm Hg in those older than 45 years of age ($P < 0.001$) and by 3.7/1.5 mmHg in those 45 years of age or younger ($P < 0.05$).[18] All subjects with higher blood pressures when starting the DASH trials showed an even greater fall of 11.5 mmHg in their systolic blood pressures i.e. equivalent to that achieved by an effective drug for high blood pressure. This implies that the more susceptible groups in society would gain even greater benefit from consuming a lower salt diet.

These changes may seem modest but were statistically very significant because of the care taken with both the dietary changes and blood pressure measurements. The blood pressure changes are observed most readily in those where no other dietary changes are made,[19] so can be taken to apply to the effects of reducing salt intake in an otherwise unchanged European diet. Although the DASH trials were short term interventions with dietary changes similar to those of the DASH trial but also involving a modest reduction in body weight for several years were already recognised as also reducing the incidence of hypertension over a five year period.[20]

Numerous major intervention studies have shown that lowering the average blood pressure of a group of adults leads to marked falls in both the incidence of myocardial infarction and strokes and in cardiovascular mortality.[21] Thus, for example, a 5 mmHg reduction in diastolic blood pressure reduces the risk of stroke by at least 34% and of myocardial infarcts by 21% and this is seen in blood pressure ranges as low as 120-130 mmHg systolic and 70-80 mmHg diastolic.

1.1.1.2 Important questions addressed 2002—2009

This review will focus on four key questions about the association between salt intake and blood pressure.

Is there a relation between salt intake and blood pressure in community studies?

Concerns were raised about whether the INTERSALT study really provided evidence for a relation between salt intake and blood pressure across different populations. Several ecological analyses have reported conflicting results as to the relation between salt intake and blood pressure levels in various population groups, but as always there are many different factors in addition to salt that may have complicated the interpretation.[22,23,24] Three Cochrane reviews of intervention studies came to somewhat conflicting conclusions. He and MacGregor based their findings on a meta-analysis of 17 trials with hypertensives and 11 trials with normotensives, and concluded that lowering of salt intake for four weeks or more would lower blood pressure in both normotensive and hypertensive subjects.[25] Hooper *et al* assessed a small number of trials (five with hypertensives and three with normotensives), while Jurgens and Graudal studied 57 trials with hypertensives and 58 trials with normotensives.[26,27] Jurgens and Graudal found that in normotensive subjects reducing salt intake induced a fall in systolic blood pressure of 1.27 mmHg, whereas in those with an elevated blood pressure the low salt diet reduced systolic blood pressure by 4.18 mmHg. Both these effects were highly significant ($P < 0.0001$). The authors concluded that these changes in blood pressure did not warrant a general recommendation to reduce salt intake in people with normal blood pressure, but their analyses were not concerned with the impact of small changes in blood pressure on cardiovascular morbidity and mortality at the population level.

Although the meticulously organised DASH trial showed a clear dose response relationship between salt intake and blood pressure in adults, a meta-analysis of 10 trials of children and three trials of infants by He and MacGregor in 2006, showed that a dose response was not evident. However, different degrees of salt reduction invariably reduced blood pressure.[28]

Additional support for the induction of higher blood pressure by salt in a graded dose dependent manner was shown in careful feeding studies in chimpanzees, a species phylogenetically close to humans.[29] The lowest and highest doses of salt used were equivalent to 0.1-1.5 g/d and 15 g/day, values equivalent to those observed in some tribal groups with practically no salt sources and in Japan where traditionally salt intakes were very high. Intakes of 15 g used to be common in Europe but further confirmation of the important graded relationship between salt intake and blood pressure came in a subsequent chimpanzee study where smaller amounts of salt ranging from the human equivalent of 2 to 12 g salt/day were used. Blood pressures returned to normal on withdrawal of the intervention with salt.[30]

In summary, reducing salt intake lowers systolic blood pressure by 3-7 mmHg (depending on age) in adults with a normal blood pressure and weight (BMI between 20 and 25 kg/m^2). There is also clear evidence that individuals with higher blood pressures reduce their systolic blood pressure to a greater degree than normotensives when salt intakes are reduced.

Mechanisms for salt induced high blood pressure

Many investigators have attributed the blood pressure raising effects of increased salt intake to an increase in the volume of circulating blood. The inherent argument was that the increased plasma sodium would lead to greater thirst, hence increased water intake, as well as a distribution of fluid from the intracellular to the extracellular compartment.[31] However, the data are inconclusive. As reviewed, short-term salt infusions into man or dogs apparently do not raise blood pressure.[32] Possible explanations for these observations might be rapid changes in arterial blood vessels leading to compensatory vasodilation and/or increased natriuresis. Other explanations for salt-induced hypertension, by mechanisms not related to blood volume changes, include possible effects of sodium on its renal excretion through direct effects on various transport systems or by mechanisms involving the arterial vessel walls.[33,34,35] Specific polymorphisms have also been identified for genes coding for transport proteins within the renal excretion systems, suggesting that individuals carrying these polymorphisms might be more prone to raised blood pressure upon increased salt intake.[36]

In summary, there is yet no universally accepted explanation of how increased salt intake increases blood pressure. Several mechanisms, both volume-dependent and volume-independent, are likely to play a role.

Salt-sensitivity – still a concept to consider?

The term "salt-sensitivity" was coined in order to possibly identify individuals susceptible to lowering of blood pressure upon reductions in salt intake. Conceptually, the term appeared fruitful. However, despite numerous attempts to reach a unifying standardisation, there are still wide differences in how salt sensitivity is defined, and it has been hard to obtain reliable results when performing repeated tests on salt sensitivity.[37,38,39] Given the inability to identify a separate group of hypertensive individuals, other than by taking arbitrary definitions of what constitutes a raised blood pressure, and recognising that multiple genes with potentially different mechanisms are involved in the control of blood pressure, it is currently unwise to consider the identification of specific salt-sensitive sub-groups within society as a practical strategy for tackling the major public health problem of hypertension.

In summary, it has not been possible to agree on a definition of the term salt-sensitivity, and in any case, such a definition is of little practical use and neglects the important benefit that could arise should the whole population reduce its average salt intake.

1.1.1.3 Does increased salt intake lead to increased mortality or morbidity of blood pressure-related diseases (stroke and other cardiovascular disorders)?

Hypertension, in addition to being classified as a disease itself, is the major risk factor for stroke, and a substantial risk factor for cardiac diseases.[40] Ischaemic heart disease and cerebrovascular disease are the most important risk factors for death and disability in high-income countries.[41] WHO has calculated that a global salt-reduction strategy could prevent about 8.5 million deaths worldwide.[42]

Definitive proof that reducing salt intake selectively reduces the burden of cardiovascular disease is unrealistic, as it would require major long term randomised trials with very high costs and major logistical difficulties.

Notwithstanding this, in the late 1990s and early in this decade a number of short-term studies were performed and in recent years there have been follow-ups of some of them. Complicating many of these studies were heterogeneous study populations, e.g. inclusion of both normotensives and hypertensives as well as people with normal and elevated body mass index, confounding factors that have been more or less adequately statistically handled. Also, the chosen interventions have in many studies varied from a mere reduction in salt intake to a combined change in several lifestyle factors including diet and physical activity.

The intervention PREMIER-trial showed that a combination of the DASH-diet, in addition to modifications of several lifestyle factors, increased the prevalence of optimal blood pressure (< 120 mmHg systolic and < 80 mmHg diastolic) to 35% compared with 19% among those who were only given usual advice about nutrition and physical activity.[43]

The randomised Treatment of Hypertension in Older Persons (TONE) intervention study from 1998 showed that, in a modest-sized and relatively short term study, marked effects were seen in terms of blood pressure and the reduced need for medication. A reduction in salt intake of as little as 1.8 g/day or less among elderly (60-80 years), led to a significant decrease in the main outcome measure (a composite measure of hypertension, use of anti-hypertensive treatment or cardiovascular event) compared with a control group (relative hazard ratio 0.69; 95% CI 0.59-0.81), in particular among obese participants. However, the small reduction in cardiovascular events in the lower salt intake group was insufficient to achieve statistical significance in this small, short term trial.[44]

A Finnish study prospectively followed two cohorts from 1982 and 1987, respectively, until 1995. For each 100 mmol greater sodium excretion/24-hour (equivalent to a 6 g/day difference in salt intake) the hazard ratios for coronary heart disease and other cardiovascular disease were 1.51 (95% CI 1.14-2.00) and 1.45 (1.14-1.84), respectively. Interestingly, the frequency of acute stroke was not significantly associated with increasing sodium excretion.[45]

The Trials of Hypertension Prevention (TOHP) study prospectively followed adults with prehypertension recruited from 1987 to 1988 and from 1990 to 1992. This was a randomised trial lasting 1-3 years testing the effects of various lifestyle interventions

including reductions in salt intake. Data collected 10-15 years after enrolment were presented in 2007 and showed a 25% reduction (relative risk 0.75; 95% CI 0.57-0.99) among those who had reduced their salt intake between 33 and 44 mmol/24-hr (equivalent to a 2.5-3g reduction in salt intake) compared to the controls.[46] The authors also found that a higher potassium intake was associated with a reduction in the frequency of cardiovascular disease and this is in keeping with the well-recognised effect of dietary potassium in countering the hypertensive impact of sodium.[47] Numerous studies have shown that increasing potassium intake lowers blood pressure, so it is not surprising that in the DASH study, where there was a selective increase in potassium-rich fruit and vegetables, there was a clear reduction in blood pressure in the normotensives and a greater fall in the hypertensives among those allocated to the intervention diet.[48,49] The DASH study also suggested the usefulness of urinary potassium excretion as an index of fruit and vegetable consumption and blood pressure reduction.

Attempts to consider this issue at a national level have come from analyses of the US National Health and Nutrition Examination Survey (NHANES) involving nearly 9,000 participants that were followed between 1971-75 and 1988-1994. This prospective, observational study attempted to link self-reported estimates of salt intake to the incidence of heart disease in three different surveys. All three surveys[50,51,52] tended to show an inverse relationship between the presumed intake of sodium and the individuals' subsequent mortality but all relied on a single 24-hr recall of the diet which is notoriously inaccurate before one considers the uncertain composition of salt in the foods reportedly consumed. More robust studies from Finland have shown marked secular reductions in salt intake[53] and these changes, accompanied by a substantial reduction in the dietary fat content, were accompanied by a marked fall in the average blood pressure, stroke and myocardial infarction rates of the Finnish population.[54]

So far, probably the most convincing support for a decrease in salt intake in terms of reducing blood pressure-related diseases, comes from a recent meta-analysis of 13 studies involving about 177,000 participants with follow-up periods lasting between 3.5 and 19 years. After adjustments for confounding factors, it was concluded that an increased salt intake (equivalent to a change of 6 g/day) was associated with a relative risk for stroke of 1.24 (95% CI 1.06-1.43), whereas the relative risk for other cardiovascular disease was 1.14 (95% CI 0.99-1.32).[55] Similarly long term, i.e. 10-15 years, prospective analyses of the randomised hypertension prevention trials show that the combination of advice to reduce salt intake and alter diet to improve potassium intakes was associated with a significant reduction in subsequent cardiovascular disease, i.e. myocardial infarction stroke, coronary, revascularization, or mortality from cardiovascular diseases.[56,57]

In summary, almost all large scale studies with longer term follow up and better measures of salt intake now report that reducing salt intake will contribute to a fall in average population blood pressures which will then induce a reduction in the incidence of hypertensive disorders. Individuals with prehypertension, established hypertension and those who are overweight or obese, seem to benefit the most from reducing their daily salt intake.

1.1.1.4 Recommendations

Many studies report that about 10 g of salt is consumed per day among adults in most Western European nations.[58] From a physiological point of view, as little as 1-2 g of salt per day is adequate. Most international recommendations are for 5-6 g of salt per day. WHO recommends a daily salt intake of no more than 5 g.[59] The American Heart Association and the American Dietetic Association recommend an upper intake level of 5.75 g or less per day.[60,61] The Nordic recommendations are 6 g/day for women and 7 g/day for men.[62] Some more recent recommendations have been more ambitious—in 2010 the UK's National Institute for Health and Clinical Excellence (NICE) proposed 3 g/day by 2025[63] and the US Dietary Guidelines for America 2010 propose a goal of 3.75 g/day (1.5 g/day sodium).[64]

This requires a co-ordinated government-led approach as shown by the differences in national response to efforts to reduce salt intake. Thus a recent systematic review of 38 studies with about 26,000 subjects' salt intakes in the US[65] showed that salt intakes, of approximately 9 g/day, have been virtually unchanged from 1953 to 2003, and with no particular trend for gender or ethnicity. Within that period there have been several attempts to lower salt intake in the US by using educational approaches to the population with seemingly dismal results. This contrasts, however, with national data from European studies where governments have been implemented policies involving a specific and systematic reduction in salt intakes with the food industry re-formulating its products. The reduction in salt intakes following a systematic multi-sectoral approach can be substantial[66] and is partly responsible for the 80% reduction in cardiovascular disease in Finland over the last 35 years.[54] Salt is used a vehicle for iodine fortification to eliminate iodine deficiency, and concerted action is, therefore, important to ensure that salt reduction strategies are compatible with action to improve iodine intakes.

In summary, given the available evidence it seems justified to propose an interim recommendation of maximally 5 g salt intake per day for adults, with a more ambitious longer-term goal of less than 4 g/day. International experience suggests that a reduction of salt intake should be implemented gradually and requires an integrated approach, both from public authorities and from the industry.[67]

1.1.1.5 Summary

- The precise amount of daily salt intake among adults in Europe is not known, but probably lies around 10 g.
- Falls in salt intake reduce blood pressure as do increases in the intake of potassium-rich foods such as fruits and vegetables. Recent follow-up data of randomised trials, with modest salt reductions, show clear evidence of a reduced blood pressure and a fall in cardiovascular morbidity and mortality.
- The mechanisms of how salt raises blood pressure are still being explored.
- A maximal daily consumption of 5 g/day seems reasonable for adults in the interim. In the longer term, a population goal of less than 4 g/day is proposed. In

order to achieve this goal on a population-based level, policies for a progressive decrease are needed.

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