Potassium Intake and Stroke Risk
A Review of the Evidence and Practical Considerations for Achieving a Minimum Target

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In recognition of a growing body of evidence in support of the benefits of increasing potassium (K+) intake, the World Health Organization (WHO) has, for the first time, issued recommendations for a target daily dietary intake for K+ of ≥90 mmol (conversion for potassium (K+) 1 mmol=39 mg, for sodium (Na+) 1 mmol=17 mg) for adults. In doing so, they state that “the successful implementation of these recommendations would have an important public health impact through reductions in morbidity and mortality, improvement in the quality of life for millions of people, and substantial reductions in health-care costs.” This article reviews the evidence underpinning this recent guidance with specific emphasis placed on reduction of stroke risk. It also briefly explores the methods by which this target may be achieved in those at high risk of stroke.

Stroke and Blood Pressure Lowering
Stroke is the third most common cause of death in developed countries and annually, accounts for 10% of all deaths worldwide. Of the 15 million strokes happening each year, 5 million are fatal and another 5 million result in permanent disability. Stroke is the principal cause of acquired disability, the second cause of dementia, and the fourth cause of disease burden. The economic burden of stroke is high and, because of aging populations and increasing prevalence of stroke risk factors, is almost certain to increase. Prevention is key to reducing both the personal and economic burden of stroke and could dramatically ameliorate the rate of death and disability if effectively implemented.

Long-term blood pressure (BP) lowering after stroke or TIA confers substantial benefit to both hypertensive and normotensive patients by reducing the risk of recurrent stroke and other vascular events. Presently, for secondary prevention of stroke, achieving a target BP of 130/80 mmHg with a combination of any available antihypertensive drugs is recommended. Despite this, there is consistent evidence to suggest that BP is poorly controlled in a proportion of this high-risk population are likely to be complex, emergent populations of both difficult-to-treat and resistant hypertensives are likely to contribute to this effect, as is the side-effect profile associated with commonly prescribed antihypertensives. Therefore, novel approaches of BP lowering within this population may be particularly useful, especially if they possess a unique mechanism of action or exhibit an improved side-effect profile.

Prevention by Nutrition
The effect of excess salt (sodium (Na+)) intake on BP, cardiovascular disease, and stroke is well established, and salt reduction programs comprise a central tenet of public health initiatives internationally.

It has been known since the 1950s that the sodium-potassium ratio (Na+:K+) may be a more important predictor of BP and hence cardiovascular and stroke risk than Na+ intake, per se. That is, that a low Na+:K+, achieved through proportionately low Na+ and high K+ intakes, may predict lower BP, cardiovascular, and stroke risk. Despite this, public health initiatives to date have focused exclusively on salt reduction policy, and yet there is growing evidence to suggest that increasing K+ intake could be equally beneficial.

What Do We Learn From Human Evolution?
It is important to consider our intakes of Na+ and K+ in the light of our evolutionary history because discordance between our modern-day diet and the diet under which our genome was selected may provide insight into fundamental mechanisms of chronic disease pathogenesis.

The Neolithic revolution, of ≈10000 years ago, saw a move away from traditional hunter-gatherer practices and the introduction of human settlement, agriculture, and animal husbandry. These practices mark the beginning of a period of profound change to the composition of the human diet and the availability of various foods, culminating in today’s modern diet. These changes have occurred over an evolutionarily minute timescale and are in conflict with our genetically determined biochemistry, which has evolved over a protracted length of time.

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With specific reference to Na⁺ and K⁺ intakes, prehistoric Na⁺ consumption may have been as low as just 10 mmol day⁻¹, and K⁺ consumption is thought to have been as high as 200 to 300 mmol day⁻¹. As a consequence, the human genome has been selected, within this environment, to provide an appetite for Na⁺ consumption along with its retention. However, because of the abundance of K⁺ in the prehistoric diet, no such mechanisms have evolved in its case.

Today, Na⁺ and K⁺ intakes vary considerably between both individuals and populations. The gold standard method for evaluating Na⁺ and K⁺ intake is via 24-hour urinary collection as the mass of these electrolytes ingested through the diet is largely excreted in the urine during the following 24-hour period. A large international cross-sectional study performed in the 1980s demonstrated daily Na⁺ excretion to be as high as 242.1 mmol and daily K⁺ excretion to be as low as 23.4 mmol in some populations. Weighted means of all participating centers yields average daily excretion for Na⁺ and K⁺ of 156.0 mmol and 55.2 mmol, respectively. These values give a Na⁺:K⁺ of 2.8 compared with an estimated value of ≈0.05 for the prehistoric diet. Although rare in the modern world, there are small populations of traditional hunter-gather societies subsisting on diets of traditional unrefined foods and which yield Na⁺:K⁺ values comparable with those of the prehistoric diet. Within such societies, individuals do not exhibit a rise in BP with age and the incidence of hypertension overall is <1%; stroke is similarly rare.

There is strong evidence to suggest that increasing dietary K⁺ intake reduces BP and stroke risk and this is, in part, the justification for the current guideline for daily K⁺ intake issued by the WHO. Although the best understood mechanism of action is BP-lowering through reduction of the Na⁺:K⁺ ratio, there is good evidence to suggest that K⁺ may be protective of stroke via other processes.

**BP Reduction**

The INTERSALT study collected international cross-sectional data including BP as well as 24-hour urinary K⁺ and Na⁺ excretion from >10000 participants in 52 centers. These results showed a negative association between K⁺ excretion (proxy for its intake) with BP. Moreover, the rate at which BP increases with age is negatively associated with K⁺ intake and positively so with the Na⁺:K⁺ ratio, thus suggesting delayed progression of age-dependent hypertension in populations with high K⁺ diets.

Recent meta-analyses of prospective studies, all including a measurement of K⁺ intake and outcomes of stroke and cardiovascular disease, demonstrate a 24% lower relative risk for stroke with an average higher K⁺ intake of 42.1 mmol day⁻¹ (Figure). A separate meta-analysis evaluated fruit and vegetable intake, which is positively correlated with K⁺ intake. This analysis demonstrated lower relative risk for stroke of 11% and 26% for those consuming 3 to 5 and >5 portions of fruit and vegetables per day, respectively, when compared with those consuming <3 portions per day. Although increasing the portions of fruit and vegetables consumed will confer several changes to the composition of the diet, this meta-analysis adds weight to the argument for the protective effects of K⁺ against stroke.

A recent meta-analysis included randomized controlled trials comprising ≥2 groups of participants where the intervention group had a higher K⁺ intake than the control group and where this was achieved either by supplementation or dietary modification. This analysis demonstrated that an increase in K⁺ intake significantly decreases BP by 3.49 mm Hg systolic and 1.96 mm Hg diastolic, respectively. When the achieved K⁺ intake was 90 to 120 mmol day⁻¹, the BP reductions were 7.16 and 4.01 mm Hg for systolic and diastolic, respectively. The BP reductions were shown to be independent of the baseline K⁺ intake, and the largest decrease in BP was observed in those consuming the largest quantity of Na⁺, perhaps because of modification of the Na⁺:K⁺ ratio.

Siani et al successfully increased the K⁺ intake of a group of well-controlled hypertensives through providing dietary advice. Antihypertensive medication was reduced in a stepwise manner during a 1-year period, providing that BP targets were maintained. At 12-month follow-up, BP was controlled with <50% of initial antihypertensive therapy in 80% of the subjects in the intervention group, compared with just 29% of the subjects in the control arm. These data demonstrate the feasibility of BP-lowering through increasing K⁺ intake.

**Animal Experiments**

The BP-lowering effect of increased K⁺ consumption can be demonstrated convincingly in animal models. Experiments in these models also support the existence of additional...
mechanisms of action for stroke prevention. Tobian et al26 investigated the effects of increased K+ consumption in spontaneously hypertensive stroke prone rats. In this model, when fed a high Na+ diet, the mortality rate is high and death principally occurs as a result of stroke (thromboembolic and hemorrhagic). By supplementing the same diet with K+, either with the chloride or citrate salt, mortality was reduced by 98% from 83% to 2% at 16 weeks of feeding for the control and supplementation groups, respectively.26 K+ supplementation significantly reduces BP in this model; however, the reduction in mortality is still observed between BP-matched pairs, suggesting the mechanism of action to be multifactorial.27

To identify possible BP-independent mechanisms, Rigsby et al28 fed low and high K+ diets to normotensive Wistar Kyoto rats. This study demonstrated improved cerebrovascular structure in the high K+ group, specifically increased luminal and outer diameters of the middle cerebral artery. This study also evaluated the effect of K+ supplementation on experimentally produced cerebral ischemia and demonstrated significant reductions in the physical size of the resulting cerebral infarct in the high potassium group.

The extensive work performed by Young et al29,30 is based on a premise that diets high in K+ result in an increased extracellular [K+], which is nonetheless within the physiological range, and that low K+ diets result in a relative and asymptomatic K+ depletion. This concept is supported by the observation that total body K+ and extracellular [K+] are positively associated. The detailed work of this group has aimed to assess how increased extracellular [K+], achieved through increased intake, may be protective of stroke through inhibition of vascular atherosclerotic lesion formation and progression. In this series of in vitro and in vivo studies, compelling evidence has been accumulated, demonstrating the following effects of increased extracellular [K+]: decreased vascular smooth muscle cell proliferation, decreased vascular smooth muscle cell migration, decreased free radical formation, reduced low-density lipoprotein–cholesterol oxidation, and decreased platelet aggregation. These findings support a role of increased K+ intake in prevention of thrombus formation, a major cause of ischemic stroke.29

Achieving a Minimum Intake Target for Potassium
Several approaches may be adopted to achieve a minimum daily intake target for K+; these are considered below.

Dietary Modification
Dietary modification is likely to represent an effective method to increase K+ intake in both a primary and secondary prevention setting. Appropriate dietary modification would involve substituting K+-low foods for fruits, vegetables, beans, and nuts, as seen in the Dietary Approaches to Stop Hypertension diet.1,13,22 Much of this advice already forms the basis of public health programs promoting healthy eating. Despite this, adapting existing campaigns to include information specific to high-K+ diets is likely to further bolster support, and the inclusion of K+ contents on food labeling would be a practical measure enabling individuals to make healthier food choices.

The generally high cost of achieving a minimum daily intake of K+ through dietary change may be an important obstacle for the socially deprived and as such may widen health inequalities. Therefore, dietary advice should be carefully tailored to local populations and individuals for primary and secondary prevention, respectively.

Use of Salt Substitutes
Salt substitutes are commercially available salt mixtures, in which a proportion of the sodium chloride is substituted for potassium and magnesium salts. Subsequently, the use of these products in place of salt can effectively reduce sodium consumption while concurrently increasing potassium intake. The use of such substitutes in place of salt has been shown to effectively lower BP in subjects in rural China.33 Moreover, although some difference in flavor is detectable, salt substitutes have been shown to be acceptable to such a population.34 The BP reduction achieved through the use of salt substitutes in rural China can be attributed to the fact that a large proportion of dietary salt is added to food in the home. However, this is not true of much of the economically developed world where the majority of dietary salt is contained within processed foods, added at the point of manufacture.34

The use of salt substitutes as a method to increase K+ intake may therefore have varying impact according to geographical region. In the developing world, salt substitution could represent an important public health intervention in both a primary and secondary prevention setting. In economically developed countries, salt substitution in the home may be more appropriate as a supplementary measure, targeting secondary prevention or those of high cardiovascular risk. As a public health intervention, the use of salt substitutes by the food industry should be considered, for example, in bread production, where salt use is particularly high.35 Fortification of appropriate foods with K+ is a similar method, which could have an important public health impact.

Potassium Supplementation
Secondary prevention targets those with the highest risk of stroke and with proportionately worse outcomes. Therefore, a strategy of targeted oral K+ supplementation may be justified in this setting. Supplementation with a K+ salt, such as potassium chloride (KCl), represents a cheap intervention to easily achieve a minimum daily target and is likely to be acceptable to patients in the setting of secondary prevention. K+ supplementation trials to date have demonstrated no adverse effects with daily prescriptions of between 25 and 104 mmol.36 Moreover, K+ supplementation, particularly through the use of slow-release formulations, is generally considered safe.37 Hyperkalemia is most likely to occur because of renal insufficiency rather than excessive intake and, as such, monitoring of renal function should be performed during supplementation.

K+ supplementation for secondary stroke prevention represents a clear research opportunity. However, to date no randomized controlled trial has aimed to demonstrate feasibility, safety, or BP lowering in a cohort of patients with stroke. The evaluation of these outcomes is clearly a prerequisite to a study of definitive end points (stroke recurrence). Additional
research in this area should aim to evaluate the potential benefit of different daily doses of K\(^+\) on the above outcomes, and the evaluation of the use of different K\(^+\) salts (ie, citrate, bicarbonate, and chloride) is also warranted.

**Conclusions**

Animal, epidemiological, and clinical evidence points to an important role that K\(^+\) intake may play both in contributing to the pathophysiology of stroke (low intake) and as an effective intervention tool (higher intake) for both primary (dietary increase) and secondary (supplementation) prevention of stroke and its complications. Randomized clinical trials are needed to support the potential, highly cost-effective, clinical guidelines for the prevention of stroke recurrence.

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