Clinical review

Fortnightly review

Beneficial effects of potassium

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Epidemiological and clinical studies have shown that potassium intake has an important role in regulating blood pressure in both the general population and people with high blood pressure.[1] High potassium intake may have other beneficial effects independent of its effect on blood pressure—for example, reducing the risk of stroke,[2–4] preventing the development of renal vascular, glomerular, and tubular damage,[5] decreasing urinary calcium excretion,[6] reducing formation of kidney stones,[7] and reducing demineralisation of bone (osteoporosis).[8–11] In this article we discuss the evidence for these and other benefits of a high potassium intake.

Summary points

- Increasing potassium intake lowers blood pressure in both hypertensive and normotensive people
- Increasing potassium intake and reducing sodium intake are additive in lowering blood pressure
- High potassium intake reduces the risk of stroke and prevents renal vascular, glomerular, and tubular damage
- Increasing potassium intake reduces urinary calcium excretion, which reduces the risk of kidney stones and helps prevent bone demineralisation
- Increasing serum potassium concentrations reduces the risk of ventricular arrhythmias in patients with ischaemic heart disease, heart failure, and left ventricular hypertrophy
- The best way to increase potassium intake is to eat more fresh fruit and vegetables

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Methods

We obtained information on the effects of potassium by conducting a Medline search, reviewing reference lists in original and review articles, and communicating with experts in the respective fields.

Blood pressure

The large international study of electrolytes and blood pressure (Intersalt) showed that potassium intake, as judged by 24 hour urinary potassium excretion, was an important independent determinant of population blood pressure. A 30-45 mmol increase in potassium intake was associated with an average reduction in population systolic blood pressure of 2-3 mm Hg.[12] Many clinical trials have shown that increasing potassium intake lowers blood pressure both in people with high blood pressure and, to a lesser extent, in those with normal blood pressure.[13] Most of these trials have used slow release potassium chloride, which is convenient for a double blind study.[14] However, the best way to increase potassium intake is to increase consumption of foods high in potassium, particularly fresh fruit and vegetables.[15 16]

Two areas of controversy remain about the relation between potassium intake and blood pressure. One is whether sodium and potassium intake, which have opposite effects on blood pressure, have additive effects when potassium intake is increased and sodium intake is reduced. The Intersalt study showed that blood pressure was directly related to sodium intake and inversely and independently related to potassium intake. Some small clinical trials have indicated that increasing potassium intake had less effect on blood pressure when sodium intake had been reduced. However, the dietary approaches to stop hypertension study, in which fruit and vegetable consumption was increased with a consequent increase in potassium intake from 37 mmol/day to 71 mmol/day, showed a large fall in blood pressure despite sodium intake being fixed at a low intake of 130 mmol/day.[15] A recently published study by the same group clearly showed an additive effect of increasing potassium and reducing sodium intake.[17]

The other area of controversy is whether potassium chloride has a greater or lesser effect on blood pressure than other potassium salts. Potassium in fruits and vegetables is present with phosphate, sulphate, citrate, and many organic anions including proteins rather than as potassium chloride. However, a comparison of the dietary study[15] with clinical trials of potassium chloride[13] indicates that the fall in blood pressure obtained by increasing intake of fruits and vegetables is similar to that found by increasing potassium chloride intake.

Stroke

The main risk factor for stroke is increased blood pressure. As increasing potassium intake lowers blood pressure, it is difficult to separate the effects of potassium on stroke that are mediated by blood pressure and those that might be mediated by a direct effect of potassium. However, studies in rats found that a high potassium intake caused a large reduction in deaths from stroke even when blood pressure was precisely matched between those on the high and low potassium intakes. This strongly supports a direct protective effect of potassium on stroke.[18]

In a 12 year prospective study, Khaw and Barrett-Connor found that a 10 mmol increase in daily potassium intake was associated with a 40% reduction in deaths from stroke among 859 men and women.[2] This relation was independent of other dietary variables and of other known cardiovascular risk factors, including blood pressure. More recently, studies in two much larger cohorts, the US health professional men (43 738 men)[3] and the US nurses (85 764 women),[4] showed a high potassium intake was related to a lower risk of stroke. Importantly, there was a dose-response relation (fig 1).[3]

Several prospective epidemiological studies have shown that increasing consumption of fruits and vegetables protects against stroke.[19 20] In the Framingham study, which followed up 832 middle aged men for 20 years, an increased intake of three servings a day of fruits and vegetables was associated with a 22% reduction in the risk of all stroke, and this was independent of blood pressure.[19] The US health professional follow up study and the nurses' health study also showed a significant protective effect of fruits and vegetables on ischaemic stroke.[20] In all these studies it is difficult to separate the effects of potassium from those of other nutrients contained in fruits and vegetables—for example, fibre and antioxidants. Nevertheless, the combination of the animal studies and human epidemiological studies clearly suggests that increasing potassium intake is itself important in reducing stroke, and some of this effect may be independent and additive to the effect that potassium has on blood pressure.

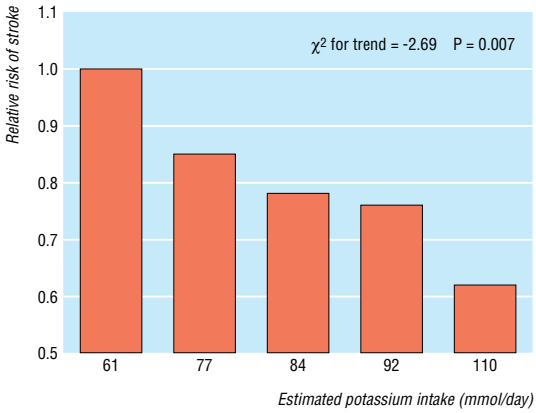

Fig 1 Potassium intake and adjusted risk of stroke among 43 738 US men aged 40 to 75 years followed for eight years. Risk was adjusted for age, total energy intake, smoking, alcohol consumption, history of hypertension, history of hypercholesterolaemia, parental history of myocardial infarction before age 65 years, profession, and quintiles of body mass index and physical activity[3]

Renal damage

Studies in hypertensive rats showed that a high potassium intake prevented renal vascular, glomerular, and tubular damage independently of blood pressure.[5 18] In humans, there is no direct evidence that potassium protects against renal arteriolar or tubular lesions that occur in either hypertension or kidney disease. If the effect is also present in humans it could be particularly important in hypertensive renal disease among black people, as this group tends to have a low potassium intake and a high prevalence of hypertensive renal failure.

Hypercalciuria, kidney stones, and osteoporosis

Increasing potassium intake reduces urinary calcium excretion and causes a positive calcium balance.[6 21] Increasing potassium intake may therefore help manage hypercalciuria. Eleven children with idiopathic hypercalciuria who were treated with potassium in the form of potassium citrate (two patients), potassium gluconate (one patient), potassium chloride (seven patients), or a high potassium diet (one patient) all had a significant reduction in their urinary calcium:creatinine ratio after two weeks.[6] By reducing calcium excretion, a high potassium intake may also reduce the risk of kidney stones.[7]

If increasing potassium intake reduces calcium excretion and causes a positive calcium balance, it may be associated in the longer term with a higher bone mass. In a cross sectional study of 994 healthy premenopausal women aged 45 to 49 years, bone mineral density in the lumbar spine and femoral neck increased with increasing potassium intake (fig 2).[8] A study of 62 healthy women aged 45 to 55 years found that a higher potassium intake was associated not only with a higher bone mass but also with lower excretion of pyridinoline and deoxypyridinoline.[9] Administration of potassium bicarbonate to 18 postmenopausal women for 18 days reduced urinary calcium and hydroxyproline excretion and increased serum osteocalcin concentration, indicating a reduction in reabsorption of bone and an increase in the rate of bone formation.[10]

Urinary calcium excretion is also associated directly with sodium intake and affected by acid-base homeostasis. To try to clarify the separate effects of potassium, sodium, and the accompanying anions, Lemann et al compared the effects of administering potassium chloride, potassium bicarbonate, sodium chloride, and sodium bicarbonate (90 mmol/day) in 10 healthy adults on fixed metabolic diets.[21] Each supplement was given for four days in random order. They also studied the effects of a reduction in potassium chloride and potassium bicarbonate in eight people. Giving potassium bicarbonate had the greatest effect on reducing calcium excretion, but potassium chloride also reduced the fasting urinary calcium:creatinine ratio significantly. Sodium bicarbonate did not affect calcium excretion, whereas sodium chloride increased calcium excretion. A reduction in potassium

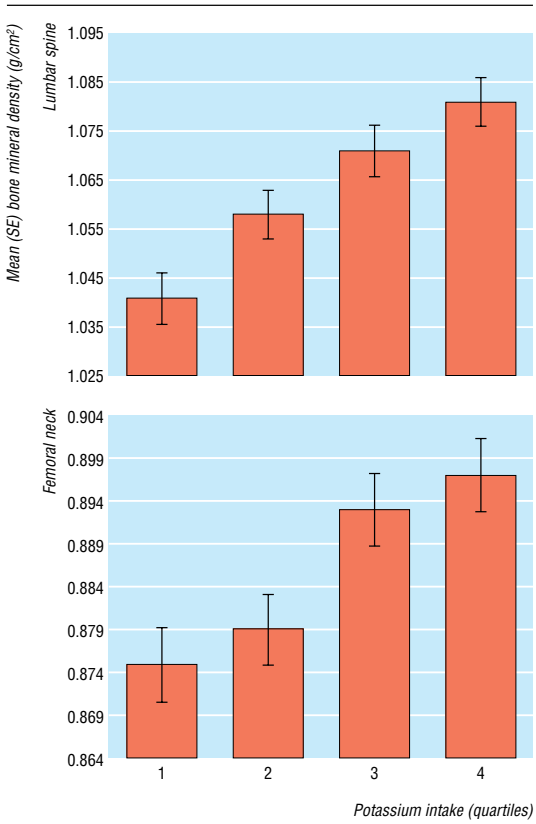

Fig 2 Average increase in bone mineral density with quartiles of energy adjusted potassium intake. Reproduced with permission[8]

chloride and bicarbonate caused an increase in calcium excretion and fasting urinary calcium:creatinine ratio to similar extents. These results show that potassium has an independent effect on reducing urinary calcium excretion and that potassium bicarbonate has a greater effect than potassium chloride. An increase in potassium bicarbonate combined with a reduction in sodium intake would probably have an additive effect.

Glucose intolerance

Glucose intolerance may occur in clinical conditions where there is severe hypokalaemia and a deficit in potassium balance such as primary or secondary aldosteronism[22] or after prolonged treatment with diuretics.[23] Correcting the underlying cause or increasing potassium intake usually improves the glucose intolerance. Further evidence to support the role of potassium in glucose tolerance comes from a study in which healthy people were placed on a low potassium diet (40 mmol/day).[24] The reduced potassium intake produced a significant fall in serum potassium and total body potassium concentrations, and this was associated with a significant decline in the amount of glucose metabolised and in the plasma insulin response to sustained hyperglycaemia. In a study that used a potassium exchange resin to reduce potassium balance, participants showed a significant impairment on intravenous glucose tolerance testing; this was corrected when potassium depletion was corrected.[25]

One prospective epidemiological study of 84 360 US women over six years showed that a high potassium intake was associated with a lower risk of developing type 2 diabetes.[26] This inverse association was attenuated among obese women.

In uncontrolled diabetes mellitus, glucose osmotic diuresis causes considerable loss of body stores of potassium, but hypokalaemia is usually absent. In fact, a few small studies have shown that intermittent hyperkalaemia is common in diabetic patients, particularly after a glucose load, because both hypertonicity and insulin deficiency impede the entry of potassium into cells.[27] However, hypokalaemia can develop when insulin is given, and patients with diabetic ketoacidosis may develop severe hypokalaemia unless potassium stores are replaced aggressively. We found no controlled studies looking at the effect of increasing potassium intake on the requirement for hypoglycaemic drugs or insulin in diabetic patients.

Cardiac arrhythmias

The relation between intracellular and extracellular potassium is important in determining the electrophysiological properties of cardiac conducting tissue. Hypokalaemia can cause prolonged repolarisation, the pathogenic factor in torsade de points, particularly in patients with ischaemic heart disease, heart failure, and left ventricular hypertrophy. Raising serum potassium concentrations may improve repolarisation in patients with inherited or acquired long QT syndromes.[28]

In patients with high blood pressure, non-potassium sparing diuretics have been shown to decrease serum potassium concentrations, which may increase the risk of arrhythmia. In the multiple risk factor intervention trial among 1403 hypertensive men who were taking diuretics, there was a 28% increase in ventricular arrhythmia for every 1 mmol/l decrease in serum potassium.[29] The Medical Research Council's mild hypertension trial also showed a significant increase in ventricular extrasystolic counts in patients taking long term thiazide diuretics compared with those taking placebo.[30] However, other studies have found no association between serum potassium and ventricular arrhythmias in hypertensive patients taking diuretics. These differences in results are probably due to small sample sizes and variations in study design, characteristics of participants, status of participants' cardiovascular system, degree of hypokalaemia, and dose, type, and duration of diuretics.

The risk of diuretic induced ventricular arrhythmia is greater in older people with organic heart disease and in those who take high dose diuretics for longer. Recent studies have focused on low dose diuretics, which have been shown to be almost as effective as high dose diuretics in lowering blood pressure but to have lesser effects on electrolyte, carbohydrate, and lipid concentrations.[31]

In patients with heart failure, the potassium balance is often disturbed. This may be due partly to diuretics but also to activation of the renin-angiotensin system in secondary aldosteronism. The reduction in serum potassium concentrations can increase the likelihood of arrhythmias, particularly those related to digoxin. Correction of serum potassium concentrations can reduce the frequency and complexity of ventricular arrhythmias and may prevent subsequent sudden cardiac death. Some of the benefits of angiotensin con-

verting enzyme inhibitors in reducing arrhythmic deaths in patients with heart failure may be due to the increase in serum potassium that occurs, and the finding that low dose spironolactone reduces sudden cardiac deaths in patients with heart failure also supports the potential role of potassium.[32] However, other mechanisms—for example, blocking the effects of aldosterone on the formation of collagen—could also play a part.

It has been suggested that patients with congestive heart failure should routinely be given potassium supplementation, a potassium sparing diuretic, or an angiotensin converting enzyme inhibitor, even if their initial potassium measurement is normal (4.0 mmol/l).[33 34] Many patients with potassium deficiency will also have magnesium deficiency, and such patients require magnesium as well as potassium to correct the imbalance and the accompanying arrhythmias.

In most studies, hypokalaemia is based on measurement of only serum or plasma potassium concentration, and this may not reflect total body potassium concentrations. For instance, hypokalaemia in many patients with acute myocardial infarction results from an influx of potassium into cells and no potassium is lost from the body. However, in chronic hypokalaemia—for example, after prolonged treatment with diuretics—there is long term loss of potassium from the body and therefore a reduction of total body potassium. It is difficult to distinguish between the disorders of total body, serum, and intracellular potassium on clinical grounds. Nevertheless, it is important to maintain the intracellular and extracellular potassium gradient that is the primary determinant of the resting membrane potential. Small changes in the intracellular:extracellular potassium ratio can greatly affect impulse generation and conduction through the heart, and potassium intake is one determinant of these changes.

Does excess potassium intake have any harmful effect?

Potassium balance is normally maintained by precise physiological mechanisms that match potassium excretion to intake, mainly through the kidney but also through the gastrointestinal tract. Large loads of potassium are excreted rapidly with only a minimal increase in plasma potassium concentration. Conditions such as severe renal disease may impair the kidney's ability to excrete potassium. However, a serum potassium concentration above 5.5 mmol/l is uncommon until over 90% of renal function is lost and the glomerular filtration rate is less than 20 ml/min. However, there are other important determinants of plasma potassium, particularly sodium-potassium ATPase, hydrogen ion balance, plasma tonicity, and plasma insulin, adrenaline, noradrenaline, and aldosterone concentrations.[35] Hyperkalaemia may occur when these regulatory mechanisms are disrupted or impaired, particularly in patients with impaired renal function. In these situations, a high potassium intake may aggravate the hyperkalaemia, although the greatest danger is when potassium is given intravenously.

Additional educational resources

Cohn JN et al. New guidelines for potassium replacement in clinical practice. A contemporary review by the National Council on Potassium in Clinical Practice. *Arch Intern Med* 2000;160:2429-36

The DASH diet. http://dash.bwh.harvard.edu

Conclusions

Until recently, humans consumed a diet low in sodium (<10 mmol/day) and high in potassium (>200 mmol/day). However, increasing consumption of processed foods, which have potassium removed, combined with a reduction in fruit and vegetable consumption, has decreased potassium intake. The average consumption in most Western countries is now about 70 mmol/day.[23] An increase in potassium intake is associated with a reduction in population blood pressure, and may have other beneficial effects as outlined above. The population would benefit from an increase in potassium intake, and this would best be done by eating more fruit and vegetables as these may also have other beneficial effects on health.

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Lesson of the week

Recurrent bacterial meningitis: the need for sensitive imaging

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Sensitive imaging is needed in children with recurrent bacterial meningitis to detect cranial anatomical defects

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Recurrent bacterial meningitis in childhood is unusual and should prompt a search for immune deficiency. A variety of immunological defects may predispose to recurrent meningitis, including antibody or complement deficiency and hyposplenism. It is equally important to consider cranial anatomical defects such as skull fractures, particularly those affecting the base of the brain and extending to the sinuses and petrous pyramids.[1] Craniospinal dermal sinuses, neurenteric or dermoid cysts, occult intranasal encephaloceles, or transethmoidmeningoceles are also potential portals of entry for pathogens into the subarachnoid space.[2 3]

Encephaloceles may occur anywhere in the midline and arise from failure of closure of the embryonic neuraxis, creating a defect in the dura and cranium with or without protrusion of brain and meningeal tissue. Basal ethmoidal encephaloceles may extend into the nose and be mistaken for nasal polyps[2] or into ethmoid sinuses or orbits.

Sometimes there may be a delay in establishing a diagnosis owing to a failure to consider anatomical defects or the use of insufficiently sensitive imaging procedures. We describe two children with recurrent bacterial meningitis due to cranial anatomical defects in whom diagnosis was delayed.

Case reports

Case 1

A 9 year old boy presented with pneumococcal meningitis. Although he required ventilation, he responded rapidly to intravenous cefotaxime and penicillin. A year later he presented with a second attack, but no organism was identified in either cerebrospinal fluid or blood. A detailed immunological investigation was unremarkable (table) except for a moderately low concentration of pneumococcal antibodies (12 U/l; median 34, interquartile range 20-49). Because this was a second episode of meningitis and because he responded modestly to test immunisation with pneumovax (post-immunisation antibody level 34 U/ml), antibiotic prophylaxis was started. Abdominal ultrasonography showed a normal sized spleen, and there was no evidence of Howell-Jolly bodies in his peripheral blood.

Fifteen months before his first episode of meningitis, the patient had injured his head in a road traffic incident. A cranial anatomical defect was considered at this stage, but his original skull radiographs and cranial tomograms showed no abnormality. In the absence of a history of cerebrospinal fluid rhinorrhoea, more detailed imaging was not considered useful. He continued to remain well at follow up. Penicillin prophylaxis was stopped 18 months after his second episode of meningitis.

A third episode of meningitis occurred when he was 12, six weeks after stopping penicillin prophylaxis. Unencapsulated *Haemophilus influenzae* was cultured from his cerebrospinal fluid. A coronal thin section tomogram of the skull showed a small linear bony defect at the right ethmoid plate (fig 1). This was