

19 K Potassium	20 Ca Calcium
37 Rb Rubidium	38 Sr Strontium

## Potassium

### Introduction

Potassium is the main cation (i.e., a positively charged electrolyte) in intracellular fluid, with a concentration approximately 30-fold greater than found in extracellular fluids.

In contrast to potassium's role as an intracellular cation, sodium acts as the primary extracellular cation. Together, these two cations maintain the electrical potential across cell membranes; however, to

accomplish this physiological task, an appropriate balance of potassium and sodium is required. Potassium researchers recommend a diet that maintains an optimal sodium-to-potassium ratio of 1:5 or less.<sup>1</sup> Otherwise, a chronic state of cation imbalance exists in an individual.

In addition to this role in maintaining cell membrane electrical gradients, potassium plays a role in energy metabolism and fluid and acid-base balance; is required for optimal cardiac, adrenal, and renal function; and promotes muscular and neurological function.<sup>2</sup>

Potassium supplementation has been shown to be effective in treating hypertension and in the prevention of recurrent nephrolithiasis.

### Pharmacokinetics

Dietary and supplemental potassium are well absorbed in the gastrointestinal tract. Potassium transport into cells is promoted by insulin and catecholamines. Most potassium is excreted via the kidneys, although some is eliminated via the gastrointestinal tract.<sup>3</sup>

### Mechanisms of Action

Potassium's mechanism of action is primarily related to its role in maintaining membrane charge potentials, osmotic balance, and acid/base balance.

Potassium's mechanism of action in hypertension is thought to be a consequence of impacting sodium elimination and the renin-angiotension system, having a vasodilatory effect, improving baroreceptor and possibly insulin sensitivity, and enhancing catecholamine function and metabolism.

## Deficiency States and Symptoms

Potassium is responsible for normal electrical excitability of muscle tissue. Many of the signs and symptoms of potassium deficiency can be related to the role of potassium in membrane excitability: muscle weakness, arrhythmias, autonomic insufficiency, continuous thirst, vertigo, nervous disorders, and constipation.<sup>4,5</sup> Because potassium is necessary in normal skeletal muscle function, hypokalemia will manifest as a vague type of myalgia, an aching sensation often alleviated by positional changes; however, the symptoms return quickly – similar to symptoms of restless leg syndrome. Cramping may be prominent, along with localized muscular swelling and stiffness.<sup>2</sup>

Potassium's role in acid/base balance can influence kidney function. Potassium deficiency causes intracellular acidosis and ammonium ions are formed in the urine, causing tissue damage and increasing protein needs. If protein intake is low, potassium deficiency will cause muscle atrophy because skeletal muscle will be catabolized to provide nitrogen for ammonia production in the kidney. Urinary tract infections may occur in potassium deficiency as a result of acidification with ammonia in the renal medulla. Chronic elevation of renal ammonia as a result of chronic potassium deficiency has also been shown to damage the kidney.<sup>4</sup>

A number of conditions induce potassium deficiency, including prolonged fluid loss from perspiration, vomiting, or diarrhea; hypothermia; protein-modified fasts; diabetic ketoacidosis; insulin shock; alcoholism; excessive caffeine, salt, or sugar consumption; villous adenoma; and anorexia and bulimia.<sup>2</sup>

## Clinical Indications

### *Hypertension*

Epidemiological studies have shown a correlation with high potassium diets and lowered risk of stroke and hypertension.<sup>6</sup> Multiple studies have shown potassium supplementation of 2.5-5.0 grams daily has a significant effect on hypertension.<sup>7-10</sup> A recent meta-analysis of 33 randomized, controlled studies of potassium supplementation in 2,609 hypertensive subjects revealed supplementation had a significant effect in lowering both systolic and diastolic pressures.<sup>11</sup> Even though the effect was small, -3.11 mmHg systolic and -1.97 mmHg diastolic, the effect was consistent throughout the meta-analysis and the authors conclude increased potassium intake is recommended for both preventive and therapeutic approaches to hypertension, especially in those unable to reduce sodium intake. Recent studies in elderly subjects taking 2.5 grams potassium chloride daily had even greater effects – a drop of 12-15 points in systolic pressure in four weeks of treatment.<sup>8,9</sup> These studies compare favorably with results of antihypertensive medications in elderly populations.<sup>10</sup>

In several trials, a blood-pressure lowering effect of potassium chloride could be demonstrated. However, it is not known whether other potassium salts are also effective. In a randomized, cross-over trial, 12 patients with essential hypertension were treated for eight weeks with placebo and 120 mMol potassium per day. Potassium was given together with 50-percent citrate and 50-percent bicarbonate as anions. Urinary potassium excretion rose from  $61.8 \pm 8.1$  to  $166.7 \pm 21.2$  mMol/24 hours during potassium supplementation. However, blood pressure and heart rate remained unchanged when compared to placebo. Non-chloride potassium salts may not be effective in lowering blood pressure in essential hypertension.<sup>12</sup>

## *Urinary Tract Infections*

Alkalinizing the urine using potassium or sodium citrate is an established effective treatment to alleviate the symptoms of a urinary tract infection (UTI).<sup>13</sup> Although acidifying the urine is theoretically an effective bacteriostatic treatment, the use of supplemental ascorbic acid or cranberry juice at dosages commonly prescribed is ineffective at altering urinary pH.<sup>14</sup> The efficacy of cranberry juice in treating urinary tract infections appears to be through mechanisms other than acidifying the urine.<sup>15</sup> In a clinical trial of recurrent UTI in 59 children, potassium citrate was prescribed along with salt, protein, and calcium restriction due to hypercalciuria.<sup>16</sup> In 95 percent of the children, no further episodes of UTI occurred once normocalciuria was achieved. The authors hypothesize hypercalciuria may play a predisposing role for recurrent UTIs in children by promoting the formation of microcrystals that damage the uroepithelium.

## *Kidney Stones*

Potassium has therapeutic benefit in the prevention and treatment of kidney stones by decreasing urinary calcium excretion<sup>17,18</sup> and increasing urinary citrate.<sup>17</sup> Potassium chloride and potassium bicarbonate have been found to decrease thiazide-induced hypercalciuria, with greater effect from potassium bicarbonate.<sup>19</sup> Results of another study found increased urinary potassium excretion correlated with a decreased risk of stone formation in post-lithotripsy patients.<sup>20</sup>

Supplementing potassium in the form of potassium citrate may provide added benefit. The efficacy of citrate in the treatment of calcium oxalate and urate kidney stones has been well documented.<sup>21</sup> As a potassium salt, citrate raises the pH of urine and increases uric acid dissociation, thus inhibiting uric acid stone formation. Potassium citrate also decreases urinary excretion of calcium and inhibits growth and precipitation of calcium phosphate and calcium oxalate crystals in the urine.<sup>22</sup> A recent study assessed the effect of potassium citrate in preventing recurrences of kidney stones in 64 patients, who were followed 24-60 months after initial incident.<sup>23</sup> Compared to a control group who received no prophylaxis (46.2% recurrence), or a group with intermittent prophylaxis (30% recurrence), those on potassium citrate had only a 7.8-percent recurrence rate.

Potassium citrate has also been found to be effective in prevention of stone formation in patients with renal polycystic disease, in children with distal renal tubular acidosis complicated by hypercalciuria, and the prevention of renal complications at the time of glaucoma treatment with acetazolamide.<sup>24</sup> In other studies with potassium citrate, inhibition of recurrent stone formation was seen in 70-75 percent of patients.<sup>24</sup> In combination with magnesium citrate, potassium citrate has been shown to be even more effective in promoting an alkaline pH in the urine.<sup>25</sup>

### ***Congestive Heart Failure***

Tissue potassium deficiency is well documented in congestive heart failure.<sup>26</sup> However, due to concomitant magnesium deficiency, potassium replacement alone might not correct potassium deficiency in this condition.<sup>27</sup> Similar to chronic electrolyte depletion resulting from body fluid loss or malnutrition, magnesium repletion is necessary to correct tissue potassium deficits.<sup>28</sup>

### ***Insulin Resistance***

Evidence suggests a diet inducing potassium depletion results in a resistance to insulin action at post-receptor sites, a resistance that is reversed when potassium is resupplied.<sup>29</sup>

Currently no information is available on potassium supplementation under other circumstances; however, this mineral appears to have a close association with insulin resistance and merits future investigation.

### **Drug-Nutrient Interactions**

Medications that induce potassium depletion include aspirin, bisacodyl, choline magnesium trisalicylate, colchicine, corticosteroids, non-potassium sparing diuretics (such as thiazide diuretics), laxatives, and sodium bicarbonate.<sup>5</sup>

The botanical *Glycyrrhiza glabra* may also result in potassium loss. While it more commonly occurs with long-term use of more than 1 g glycyrrhizin daily, some people experience signs of potassium loss with lower doses.

ACE inhibitors (captopril, enalapril, ramipril, etc.) produce potassium retention by inhibiting aldosterone. Potassium supplementation with ACE inhibitors and potassium-sparing diuretics (spironolactone, amiloride, triamterene, etc.) should be approached with caution to prevent hyperkalemia.<sup>3</sup>

### **Side Effects and Toxicity**

Side effects of excessive doses may include gastrointestinal problems (nausea, stomach pain, vomiting, diarrhea, flatulence), bradycardia, hyperkalemia and consequences thereof, and respiratory problems, including difficulty breathing.

Potassium intolerance may be aggravated by concomitant use of beta-blockers, digitalis, medications that suppress aldosterone production (NSAIDs, angiotensin-converting enzyme inhibitors), potassium-sparing diuretics, and other medications that interfere with aldosterone or renin.<sup>4</sup>

Toxic effects include muscle weakness, lethargy, gastric hypomotility, paralysis, arrhythmias, cardiac conduction disturbances, and even death.

## Dosage

Potassium chloride dosages used in treating hypertension usually range from 2.5-5.0 g daily. Potassium citrate dosages in kidney stone prevention range from 1.1-3.3 g daily.<sup>2</sup> The estimated safe and adequate daily dietary intake of potassium for adults, according to the Committee on Recommended Daily Allowances, is 1.9-5.6 grams. Current guidelines do not recommend increasing potassium above the safe and adequate dietary potassium intake during pregnancy or lactation.

Oral doses greater than 18 grams daily may lead to severe hyperkalemia in people with normal kidney function.<sup>3</sup> One milliequivalent or millimole is equal to 39.09 mg.

## Warnings and Contraindications

Use with caution in subjects with renal insufficiency, since disrupted renal function might inhibit potassium elimination and result in hyperkalemia. Potassium citrate is contraindicated in struvite (magnesium ammonium phosphate) renal stone disease, peptic ulcer, gastritis, gastrointestinal bleeding, disorders of coagulation, and metabolic alkalosis.<sup>23</sup>

Care should be taken in prescribing potassium to elderly people since evidence has demonstrated the elderly to be at increased risk for hyperkalemia. This is probably a result of impaired renal elimination and deterioration of cell membrane health/function resulting in a higher amount of extracellular potassium.

Potassium supplementation with ACE inhibitors and potassium-sparing diuretics should be approached with caution to prevent hyperkalemia.

## References

1. Murray M, Pizzorno J. Nutritional medicine. In: Pizzorno J, Murray M, eds. *Textbook of Natural Medicine, Volume 1*, 2<sup>nd</sup> ed. New York, NY: Churchill Livingstone; 1999:376.
2. Schuster VL. Potassium deficiency: pathogenesis and treatment. In: Seldin DW, Giebisch G, eds. *The Regulation of Potassium Balance*. New York, NY: Raven Press; 1989:241-267.
3. Hendler SS, Rorvik D. *PDR for Nutritional Supplements*, 1<sup>st</sup> ed. Des Moines, IA: Medical Economics – Thompson Healthcare; 2001.
4. Knochel JP. Clinical expression of potassium disturbances. In: Seldin DW, Giebisch G, eds. *The Regulation of Potassium Balance*. New York, NY: Raven Press; 1989:207-240.
5. Pelton R, LaValle JB, Hawkins EB, Krinsky DL. *Drug-Induced Nutrient Depletion Handbook*. Hudson, OH: Lexi-Comp; 1999:256-257.

6. Rouse IL, Berlin LJ, Mahoney DP, et al. Vegetarian diet and blood pressure. *Lancet* 1983;2:742-743.
7. Patki PS, Singh J, Gokhale SV, et al. Efficacy of potassium and magnesium in essential hypertension: a double-blind, placebo controlled, crossover study. *BMJ* 1990;301:521-523.
8. He J, Whelton P. Potassium, blood pressure and cardiovascular disease. *Cardiol Rev* 1997;5:255-260.
9. Fotherby MD, Potter JF. Long-term potassium supplementation lowers blood pressure in elderly hypertensive patients. *Int J Clin Pract* 1997;51:219-222.
10. Fotherby MD, Potter JF. Potassium supplementation reduces clinic and ambulatory blood pressure in elderly hypertensive patients. *J Hypertens* 1992;10:1403-1408.
11. Thijs L, Amery A, Birkenhager W, et al. Age-related effects of placebo and active treatment in patients beyond the age of 60 years: the need for a proper control group. *J Hypertens* 1990;8:997-1002.
12. Overlack A, Conrad H, Stumpe KO. The influence of oral potassium citrate/bicarbonate on blood pressure in essential hypertension during unrestricted salt intake. *Klin Wochenschr* 1991;69:79-83.
13. Kahn HD, Panariello VA, Saeli J, et al. Effect of cranberry juice on urine. *J Am Diet Assoc* 1967;51:251-254.
14. Bodel PT, Cotran R, Kass EH. Cranberry juice and the antibacterial action of hippuric acid. *J Lab Clin Med* 1959;54:881.
15. Munday PE, Savage S. Cymalon in the management of urinary tract symptoms. *Genitourin Med* 1990;66:461.
16. Lopez MM, Castillo LA, Chavez JB, Ramones C. Hypercalciuria and recurrent urinary tract infection in Venezuelan children. *Pediatr Nephrol* 1999;13:433-437.
17. Martini LA, Cuppari L, Cunha MA, et al. Potassium and sodium intake and excretion in calcium stone forming patients. *J Ren Nutr* 1998;8:127-131.
18. Lemann J Jr. Relationship between urinary calcium and net acid excretion as determined by dietary protein and potassium: a review. *Nephron* 1999;81:18-25.
19. Frassetto LA, Nash E, Morris RC Jr, Sebastian A. Comparative effects of potassium chloride and bicarbonate on thiazide-induced reduction in urinary calcium excretion. *Kidney Int* 2000;58:748-752.
20. Pierratos A, Dharamsi N, Carr LK, et al. Higher urinary potassium is associated with decreased stone growth after shock wave lithotripsy. *J Urol* 2000;164:1486-1489.
21. Pak CY, Sakhaee K, Fuller C. Successful management of uric acid nephrolithiasis with potassium citrate. *Kidney Int* 1986;30:422-428.
22. Sakhaee K, Nicar M, Hill K, Pak CY. Contrasting effects of potassium citrate and sodium citrate therapies on urinary chemistries and crystallization of stone-forming salts. *Kidney Int* 1983;24:348-352.
23. Lee YH, Huang WC, Tsai JY, Huang JK. The efficacy of potassium citrate based medical prophylaxis for preventing upper urinary tract calculi: a midterm followup study. *J Urol* 1999;161:1453-1457.
24. Zmonarski SC, Klinger M, Puziewicz-Zmonarska A. Therapeutic use of potassium citrate. *Przegl Lek* 2001;58:82-86. [Article in Polish]
25. Koenig K, Padalino P, Alexandrides G, Pak CY. Bioavailability of potassium and magnesium and citrauric response from potassium-magnesium citrate. *J Urol* 1991;145:330-334.
26. Packer M. Potential role of potassium as a determinant of morbidity and mortality in patients with systemic hypertension and congestive heart failure. *Am J Cardiol* 1990;65:45E-51E.
27. Wester PO, Dyckner T. Intracellular electrolytes in cardiac failure. *Acta Med Scand Suppl* 1986;707:33-36.
28. Altura BM, Altura BT. Biochemistry and pathophysiology of congestive heart failure: is there a role for magnesium? *Magnesium* 1986;5:134-143.
29. Norbiato G, Bevilacqua M, Meroni R, et al. Effects of potassium supplementation on insulin binding and insulin action in human obesity: protein-modified fast and refeeding. *Eur J Clin Invest* 1984;14:414-419.