

Serum Potassium, Potassium Intake & Outcomes in Health and Disease: Dietary Interventions for Potassium Management

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DISCLOSURE SLIDE

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Adjusted Mortality^{*} by Serum K⁺ Level, Patients 45–64 Yr and ≥65 Yr With and Without Comorbid Illness



Evaluated through de-identified medical records (2007-2012) of individuals with 22 serum K readings (Humedica, Cambridge MA). Spline analyses were performed to assess mortality at 0.1 mEq/L increments of serum K* after adjusting for covariates and interactions. Comorbid patients are those diabetes, heart failure , chronic kidney disease stages 3-5, cardiovascular disease, or hypertension.
Pitt B, et ak AHA 2014



HAZARD RATIOS OF ALL-CAUSE FOR PREDIALYSIS SERUM K CATEGORIES IN 21,013 INCIDENT MHD PATIENTS OBSERVED FOR UP TO 3 YR







OVERVIEW

- Potassium homeostasis: Renal and non-renal mechanisms
- Potassium intake and blood pressure in non-CKD patients
- Potassium intake in advanced CKD: what is known, and unknown and clinical implications
- Conclusions





Brown RS. Am J Med. 1984;77(5A):3-10

NON-RENAL DETERMINANTS OF POTASSIUM EXCRETION

- Circadian rhythm effect on renal function
- •Posture: can influence urine flow rate and sodium excretion
- •GI absorption and secretion
- Hepatic influence of potassium homeostasis



NORMAL POTASSIUM BALANCE AND RENAL POTASSIUM EXCRETION

Western diet: 70 mmol potassium per day
Intestine absorbs all ingested potassium and delivers it to the liver for processing
Minimal amounts of potassium is excreted in feces



NORMAL POTASSIUM BALANCE AND RENAL POTASSIUM EXCRETION

- Principal defense against chronic potassium imbalance is renal potassium excretion:
 - Free filtration at the glomerulus
 - Extensive proximal tubular reabsorption
 - Highly regulated secretory process in the distal convoluted tubule and segments of the cortical and medullary collecting duct
 - Principal cells (75% of the collecting duct cells) mediate sodium reabsorption and potassium excretion



NORMAL POTASSIUM BALANCE AND RENAL POTASSIUM EXCRETION

- The kidney excretes sufficient mmol of potassium to maintain total body balance
- The collecting duct is the major site that responds to increased potassium intake and is subject to several regulatory influences
- Renal outer medullary potassium (ROMK) channel: secrete potassium under normal tubular flow conditions and are inserted into or internalized from the luminal membrane depending on the demand for potassium secretion.



ACTIVE POTASSIUM SECRETION IN THE COLON: CKD ADAPTATION

- In CKD patients, active K⁺ secretion into the colon is increased
 20 70 mEq/day (normal = 10 mEq/day)

 - Increased BK channel concentration on the apical surface of colonic epithelial cells
 - Surface cells: <u>short term</u> (adaptive) response to high K⁺ diet (aldosterone dependent)
 - Crypt cells: long term response to CKD elevated K⁺ levels (cAMP dependent)
 - Independent of plasma K⁺ concentration or aldosterone





FEEDBACK CONTROL OF POTASSIUM BALANCE



FEEDBACK CONTROL OF POTASSIUM BALANCE

- In response to a high-potassium meal that includes glucose, pancreatic insulin secretion activates skeletal muscle and liver Na-K-ATPase, which moves potassium (Na/K exchange) from the plasma to the intracellular fluid of these cells.
- This mechanism minimizes the postprandial increase in plasma potassium concentration.
- In order to maintain balance, the amount of potassium consumed in the meal (minus the small amount lost in the feces) is excreted into the urine.

DeFronzo R.A. et al. Am J Physiol, 238 (1980), pp. E421-E427.



FEEDBACK CONTROL OF POTASSIUM BALANCE

- When an increase in potassium consumption increases plasma potassium concentration sufficiently, it triggers aldosterone synthesis and release from the adrenals, which stimulates the activity and synthesis of Na-K-ATPase and luminal potassium channels in collecting duct principal cells to secrete the excess potassium
- Aldosterone also enhances potassium excretion in the distal colon.
- This latter function can be extremely important in the adaptation that occurs when renal function is compromised.

W. Wang. Annu Rev Physiol, 66 (2004), pp. 547-569.

G. Giebisch, R. Krapf, C. Wagner. Kidney Int, 72 (2007), pp. 397-410.



FEEDBACK CONTROL OF POTASSIUM BALANCE

- If potassium intake is very low or urinary potassium excretory losses are excessive, plasma potassium concentration decreases and the feedback regulation is invoked, redistributing potassium from intracellular fluid to plasma thereby minimizing hypokalemia.
- Concomitantly skeletal muscle becomes insulin-resistant to potassium (but not glucose) uptake even before plasma potassium concentration decreases, which acts to blunt the shift of potassium from plasma into the cell.

A.A. McDonough, J.H. Youn. Semin Nephrol, 25 (2005), pp. 335-342.



FEEDBACK CONTROL OF POTASSIUM BALANCE



Murray Epstein and Meyer D. Lifschitz. KI Reports (2016) 1, 43–56.





- After hypokalemia ensues, the expression of skeletal muscle Na-K-ATPase α2 isoform decreases, which facilitates a net potassium "leak" from intracellular fluid to the plasma.
- The low plasma potassium concentration suppresses adrenal aldosterone release; as a result the kidney can reclaim essentially all but about 1% of the filtered potassium.

A.A. McDonough, J.H. Youn. Semin Nephrol, 25 (2005), pp. 335-342.



FEEDBACK CONTROL

 This renal potassium conservation involves downregulation of potassium secretion by means of the ROMK channels in cortical collecting duct principal cells. In conditions of potassium depletion, potassium reabsorption can occur in the collecting duct. This appears to be mediated by upregulation in the apically located H-K-ATPase on intercalated cells.

Dubose TD, et al. Am J Physiol 1995; 269:F500-F507.



- The "feed-forward" control mechanism subserving potassium homeostasis posits that even minor changes in dietary potassium intake, which are insufficient to alter plasma concentrations of either potassium or aldosterone, and consequently insufficient to activate feedback control, are capable of evoking rapid changes in renal potassium excretion through "feed-forward" mechanisms
- Thirty years ago, Rabinowitz and associates conducted a series of elegant experiments in sheep, which demonstrated that potassium intake in food or potassium placed into the rumen (sheep stomach) was associated with a large and significant increase in urinary potassium excretion.



- They showed that the increase in urinary potassium excretion was not related to an increase in serum potassium or glomerular filtration rate and thus the increase in urinary potassium excretion was not a consequence of an increase in filtered potassium, but rather tubular potassium excretion.
- They demonstrated that aldosterone was not responsible for this by either (i) showing there was no change in plasma aldosterone concentration, (ii) infusing aldosterone and showing it did not alter the effect, or (iii) giving an early aldosterone antagonist (potassium canrenoate), which also did not alter the effect.



- Similarly, when urine flow rate or sodium excretion was altered or urine pH was altered, the effect persisted. They concluded as follows: "The efferent factors involved in this regulation remain to be determined."
- "They do not appear to be aldosterone, urine flow, sodium excretion, or acid/base status, nor do changes in plasma potassium appear to be necessary or sufficient to produce the changes in potassium excretion associated with meal intake or fasting."



 They concluded: "The presence of receptors located at some point prior to the systemic circulation, which sense enteric potassium levels and influence renal potassium excretion"



FEED FORWARD

- Qualitatively similar findings have been seen in humans.
- During a water diuresis, intake of potassium led to an increase in urinary potassium excretion within 20 minutes, at a time when neither plasma potassium nor aldosterone had increased.
- Experiments further substantiated the existence of a GI-renal kaliuretic signaling axis in humans that is capable of mediating potassium excretion independent of changes in the serum potassium concentration and aldosterone.

Calò L, et al. Nephron 1995;69:253-258.



POTASSIUM INTAKE AND BLOOD PRESSURE IN NON- CKD PATIENTS

 Low dietary potassium intake (below 40 mEq/day [1.5 g/day]) has been associated with an elevation in blood pressure and an increased risk of stroke, as well as an increase in risk of chronic kidney disease.

Aburto NJ, et al. BMJ 2013; 346:f1378. Araki S, et al. Clin J Am Soc Nephrol 2015; 10:2152.



HIGH POTASSIUM DIET

- In contrast to the rise in blood pressure associated with a lowpotassium diet, potassium supplementation lowers the blood pressure significantly in hypertensive patients and insignificantly in normotensive patients.
- The magnitude of change has been illustrated in systematic reviews that included meta-analyses of both randomized trials and cohort studies

Aburto NJ, et al. BMJ 2013; 346:f1378.



HIGH-POTASSIUM DIET

 In one meta-analysis, the effect of potassium supplementation on blood pressure was greater in Blacks than in whites. Urinary potassium excretion in blacks is consistently less than in whites. This difference is due in part to less dietary potassium intake in Blacks

Aviv A, et al. Hypertension 2004; 43:707. Turban S, et al. J Am Soc Nephrol 2008; 19:1396.



MECHANISMS

 Low potassium intake may reduce sodium excretion due in part to effects of potassium deficiency on the activity of the WNK (With-No-Lysine) kinase pathway, resulting in activation of the thiazide-sensitive NaCl cotransporter

 High potassium intake increases sodium excretion. Potassium "sensing" via basolateral potassium (K+) channels in the distal convoluted tubule plays a key role in these pathways

Terker AS, et al. Cell Metab 2015; 21:39. Palygin O, et al. JCI Insight. 2017;2(18):e92331.



OBSERVATIONS IN NON-CKD PATIENTS:

- Maintenance of adequate potassium intake or the administration of potassium supplements usually lowers the blood pressure, particularly in Blacks and in patients who are not sodium restricted. Furthermore, a higher potassium intake reduces the risk of stroke.
- Some experts suggest that hypertensive patients should consume at least 120 mEq (4.7 g) of dietary potassium/day provided they do not have a predisposition to hyperkalemia. This level of potassium intake can be achieved preferably with dietary counseling.



POTASSIUM RESTRICTED DIETS ARE OFTEN ASSOCIATED WITH FOLATE DEFICIENCY

- n= 128 patients with varying degrees of CKD
- Lower serum folic acid levels, and a three fold greater frequency of folic acid deficiency among patients with CKD 3 and 4 and who were on a K-restricted diet compared to CKD 1 and 2 patients not on a K-restricted diet.

Hassan K. Therapeutics and Clinical Risk Management 2015:11:821-827.



POTASSIUM RESTRICTED DIETS ARE OFTEN ASSOCIATED WITH FOLATE DEFICIENCY

 Although there is no consensus regarding the impact of folic acid supplementation on development of cardiovascular complications, folic acid deficiency may still produce other considerable clinical disturbances (eg, hematological, neuropsychiatric, and malignant disorders) and therefore should be detected and treated.



SERUM FOLIC ACID LEVELS CORRELATED WITH ESTIMATED GLOMERULAR FILTRATION RATE (EGFR)



Hassan, Kamal. (2015).. Therapeutics and Clinical Risk Management. 11. 821. 10.2147/ TCRM.S83751.



DAILY FOLIC ACID INTAKE CORRELATED WITH DAILY INTAKE OF POTASSIUM



Hassan K. Therapeutics and Clinical Risk Management 2015;11:821-827.



NUTRIENT NON-EQUIVALENCE: DOES RESTRICTING HIGH POTASSIUM PLANT FOODS HELP TO PREVENT HYPERKALEMIA IN PATIENTS WITH CKD OR DIALYSIS PATIENTS?



- Potassium salts have been shown to result in postprandial S_K excursions in patients with chronic kidney disease (Dietary potassium intake appears to be weakly (if at all) associated with predialysis S_K in HD patients.
- Dietary potassium explained only about 2% of the variance in quarterly mean predialysis S_{K} (r = 0.14, P < .05)

Noori et al. AJKD; 2010;56:338-347.





Noori et al. AJKD; 2010;56:338-347.



 The regression line describing this relationship indicates that, as reported dietary potassium intake went from a low of 500 mg/ day to a high of 4,500 mg/day (a 9-fold difference), S_K was only about 0.4 mEq/L higher.

Noori et al. AJKD; 2010;56:338-347.



- The associations of mean reported potassium intake (mg/day) and potassium density (mg/1,000 kcal) with predialysis S_k was evaluated among 140 HD patients in the Balance Wise Study who completed 3, 24-hour dietary recalls
- No significant correlations were found between S_{K} and either absolute reported potassium intake (r = 0.06, p = .50) or potassium density (r = -0.003, p = .97).

Sevick et al. J Ren Nutr. 2016;26:149-158.



Associations of reported dietary potassium intake with predialysis serum potassium concentrations in hemodialysis patients from the Balance Wise Study



Sevick et al. J Ren Nutr. 2016;26:149-158.



- Although high predialysis S_K is used clinically to assess hyperkalemia risk and is associated with worse survival in HD patients, the lack of a correlation between reported dietary potassium intake, predialysis S_K is not, in itself, evidence that high-potassium foods do not affect hyperkalemia risk in HD patients.
- Dietary potassium intake is measured with error, and S_K reflects a complex interaction of numerous intrinsic factors, including nervous/endocrine signals (e.g., epinephrine, aldosterone, insulin), intracellular/extracellular chemical concentrations (e.g., osmolality, H+), circadian rhythms, and organ system functionality, which are influenced by environmental exposures such as diet and medications.

Kovesdy, C.P., et al. CJASN. 2007; 2: 999-1007



 It is possible that the association of dietary potassium intake with predialysis S_K is too weak to overcome these sources of measurement error, or that dietary potassium intake is correlated with S_K when measured in other metabolic states (e.g., postprandial, fasting).

Kovesdy, C.P. et al. Clin J Am Soc Nephrol. 2007; 2: 999–1007.



DISTRIBUTION AND EXCRETION OF POTASSIUM IN KIDNEY DISEASE

- Kidney disease has been recognized as a condition of impaired potassium tolerance for 100 years.
- In the 1940s, potassium balance studies by Winkler et al. and Keith and Osterberg demonstrated impaired renal clearance of potassium and higher S_{K} in patients with renal insufficiency after ingesting 2 to 5 g of potassium.

Winkler, A.W., et al. J Clin Invest. 1941; 20: 119–126 Keith, N.M. and Osterberg, A.E. J Clin Invest. 1947; 26: 773–783



- It was then concluded that caution should be exercised when using potassium-based diuretics in patients who were anuric or uremic (blood urea ≥ 100 mg/dL).
- In both studies, the increases in S_K were highly variable and less than predicted based on the dose and renal clearance of potassium.

Keith et al. JCI 1947;26:773-782.



 It is now apparent that a portion of ingested potassium is temporarily distributed within a secondary (intracellular) compartment, thereby buffering its effect on S_K in patients with ESRD.

Sterns, R.H., et al. Kidney Int. 1979; 15: 651–660.



• In this study, 63% to 92% of intravenous potassium (0.3 mEq/kg/hour \times 3 hours) exited the extracellular fluid, and the observed changes in S_K were consistent with a 2-compartment model with bidirectional flux between compartments.

Sterns, R.H., et al. Kidney Int. 1979; 15: 651-660.



- Several factors are known to influence intracellular/extracellular shifts of potassium, including acid-base balance.
- Hydrogen ion concentrations and S_{K} were found to be inversely correlated in HD patients (r = -0.66), and higher bicarbonate dialysate solutions resulted in more rapid S_{K} decreases.

Sterns, R.H., et al. Kidney Int. 1979; 15: 651–660



PREDISPOSITION TO HYPERKALEMIA: IMPAIRED EXTRARENAL BUFFERING





DIETARY FACTORS: ACIDOSIS, GLUCOSE, INSULIN

- The biological mechanisms linking acidosis and hyperkalemia are incompletely understood but appear to involve a complex interaction of numerous ion transporters (e.g., Na+-H+ exchanger, Na+/K+-ATPase), which help to maintain blood pH balance by indirectly leading to an exchange of H+ for K+ between intracellular and extracellular compartments.
- Insulin is another key determinant of potassium distribution in the body. Although insulin is generally recognized for its role in macronutrient metabolism, it helps regulate potassium distribution and balance; potassium triggers and mediates insulin release
- Insulin shifts potassium into cells by stimulating Na⁺/K⁺-ATPase activity.

Aronson, P.S. and Giebisch, G. J Am Soc Nephrol. 2011; 22: 1981–1989. Hiatt, N., et al. Horm Metab Res. 1972; 4: 64–68. Gomez, M. and Curry, D.L. Potassium stimulation of insulin release by the perfused rat pancreas. Endocrinology. 1973; 92: 1126–1134. Rowe, J.W., et al. Metabolism. 1980; 29: 498–502.

DIETARY FACTORS: ACIDOSIS, GLUCOSE, INSULIN

- Because dietary macronutrients, in particular glucose, also stimulate insulin release, they can help shift potassium intracellularly.
- The rise in $S_{\rm K}$ after potassium ingestion is greatly attenuated if glucose is provided along with it
- Importantly, fasting is known to increase S_{K} in ESRD.
- In one study, the difference in the maximal change in S_K between HD patients and controls was greatly attenuated after ingestion of carbohydrates (+0.41 mmol/L \rightarrow +0.20 mmol/L).

Allon, M., et al. Am J Med. 1993; 94: 475-482.



NUTRITIONAL CHARACTERISTICS OF PLANT FOODS

- Many plants are naturally high in potassium, which make them an obvious target for dietary potassium restriction.
- In one study, the top 5 sources of potassium were beef, chicken, Mexican food, hamburgers, and legumes.
- muscle-based animal products are naturally high in potassium, and may be enhanced with potassium-based food additives that can greatly increase potassium content.

Noori, N., et al. *Am J Kidney Dis*. 2010; 56: 338–347. Sherman, R.A. et al. *Clin J Am Soc Nephrol*. 2009; 4: 1370–1373



NUTRITIONAL CHARACTERISTICS OF PLANT FOODS

- Meats are often absent from high-potassium foods lists, despite containing more potassium than the recommended cutoff (>200 mg/portion), and nearly as much or more potassium than many of the fruits and vegetables listed
- Although potassium from different foods is chemically equivalent, other nutrients in food influence potassium distribution and excretion
- Unlike meat, the metabolism of which leads to net acid production, and which are low in carbohydrates and contain no fiber, plant foods (especially fruits and vegetables) tend to yield net base production and are high in both carbohydrates and fiber.



NUTRITIONAL CHARACTERISTICS OF PLANT FOODS

 Compared with high-potassium meat, potassium-rich plant foods may promote distribution of a greater proportion of dietary potassium intracellularly (alkaline and insulinstimulating), and excretion of potassium in stool by increasing fecal bulk (dietary fiber).



IMPLICATIONS

- There are no studies demonstrating differences in S_{K} resulting from potassium ingested from animal versus plant products in HD patients.
- Recent data have suggested that alkalinizing fruits and vegetables may have a beneficial effect of reducing the progression of CKD. A study conducted in Stage 4 CKD patients found that increasing fruit and vegetable consumption for 1 year reduced metabolic acidosis and progressive kidney injury without increasing S_K.
- Unfortunately, due to concern regarding hyperkalemia, this study specifically selected only nondiabetic patients with acidemia who had $S_K \le 4.6 \text{ mEq/L}$ and did not require potassium-sparing diuretics.

Goraya, N et al. Clin J Am Soc Nephrol. 2013; 8: 371–381



HISTORICAL PERSPECTIVE

- Giovannetti and Maggiore diet included eggs and some low-nitrogen fruits and vegetables, but the majority of energy came from unsalted butter and lard, vegetable oils, sugar, honey, and maize and wheat starch.
- Despite the relatively low potassium content of these diets (~2,000 mg/day), patients were prone to developing hyperkalemia.
- The etiology of hyperkalemia was unknown but thought to involve acidosis and reduced urinary clearance of potassium.
- Regardless of the cause, treatment included potassium restriction to about 1,000 mg/day as a prudent, albeit unproven measure.

Giovannetti, S. and Maggiore, Q. Lancet. 1964; 1: 1000–1003. Shaw, A.B., et al. Q J Med. 1965; 34: 237–253. Berlyne, G.M., et al. Nephron. 1965; 2: 129–147. Franklin, S.S., et al.. J Am Med Assoc. 1967; 202: 477–484.



REALITY

- HD patients consistently report mean dietary potassium intakes well below the proposed upper limit of 3,000 mg/day and less than non-CKD matched controls
- Lower intakes of fruits and vegetables and other plant-derived compounds (e.g., dietary fiber, vitamin C, carotenoids).
- Very few (<2%) of US adults actually consume the adequate intake for potassium (4,700 mg/day), regardless of CKD status.

Kalantar-Zadeh, et al. J Ren Nutr. 2002; 12: 17–31 Cupisti, A., et al. Ren Fail. 2010; 32: 47–54 Therrien, M., et al. J Ren Nutr. 2014; 24: 72–80



REALITY: "RENAL DIET"

- Diet is bland and tasteless
- Too complicated
- Hard to keep track of nutrient intakes
- Potentials to impair nutrition status and quality of life
- May contribute to adverse metabolic states (e.g., oxidative stress, inflammation, metabolic acidosis, dyslipidemias)
- Conditions (e.g., constipation, hypertension) that negatively impact health of CKD patients



ADHERENCE TO A LOW POTASSIUM DIET IS SUBOPTIMAL

Many patients are already on low carb and low salt diets What's left to eat?





1. Sanghavi S, et al. Semin Dial. 2013;26:597–603.

CONCLUSIONS

- When determining the cause of hyperkalemia, it is important to consider non-dietary factors such as prolonged fasting, hyperosmolality, metabolic acidosis, tissue breakdown, constipation, and medications.
- In the absence of empirical evidence, it is of course prudent to continue to recommend low-potassium diets to CKD patients with hyperkalemia
- However, the practice of advising patients to eliminate so many plant foods from the diet may be harmful, and must be evaluated.

Pani, A., et al. Semin Dial. 2014; 27: 571-576

