Potassium

https://open-global.kcl.ac.uk/potassium/

Date of preparation: January 2019

Contribution: Jessica Farebrother, Damon Parkington, Kerry Jones

Dr Jessica Farebrother Dr. sc. ETH Zurich, OpeN-Global Team
With:
Damon Parkington and Dr Kerry Jones PhD**,** OpeN-Global Expert Partners
NIHR BRC Nutritional Biomarker Laboratory, University of Cambridge, Cambridge UK
Website: http://www.mrc-epid.cam.ac.uk

Keywords: Cellular function, acid balance, body fluid volume, ATP, ATPase pump

Related nutrients/biomarkers: sodium

Importance of potassium for health

Potassium is an essential nutrient needed for the maintenance of body fluid volume, acid balance and normal cellular function (1, 2). Potassium is principally involved in cell membrane potential and the excitation of both nerve and muscle cells (3), and its intracellular concentration is largely dependent upon the action of the sodium-potassium ATPase pump (Na^+/K^+ ATPase pump).

A daily potassium intake of 90 mmol/day, or 3,510 mg/day, is recommended by the World Health Organization (WHO) for adults (4). A systematic review and meta-analysis of studies suggests however, that globally, average dietary intakes in many countries do not meet this recommendation (1). Yet, potassium is widely available in the diet: potassium-rich foods include green leafy vegetables, fruits especially bananas, legumes, seafood and dairy foods. Whilst a deficiency in potassium is therefore quite uncommon because of this relative dietary abundance, diets high in

processed food and low in fresh produce may be at risk of inadequate potassium intakes (1, 4), since food processing can reduce potassium content (1).

Potassium deficiency

A severe potassium deficiency, hypokalaemia, is a serum potassium concentration of <3.5 mmol/L (2). Hypokalaemia causes cardiac arrhythmias, muscle weakness and glucose intolerance (2). More common is a moderate potassium deficiency without hypokalaemia, which is characterised by an increase in blood pressure, that may in turn, increase the risk of cardiovascular disease and stroke, an increase in salt sensitivity (defined as the response of the blood pressure to a lowered sodium intake or sodium loading), an increased risk of kidney stones and a loss in bone mineral density and an increased bone turnover due to loss of calcium in the urine, reduced bone formation and increased bone resorption (2-4).

Potential benefits of an increased potassium consumption

Increased potassium intake in adults can benefit blood pressure without adversely affecting blood lipids, catecholamines or renal function (1). Increased potassium intakes might reduce blood pressure in children, though data are limited (1), and, an inverse relationship between potassium intake and risk of stroke has been suggested (1). Increasing daily potassium intakes from fruits and vegetables (alkaline foods, as opposed to meat and dairy produce, acid-forming foods) may help to reduce calcium excretion in the urine and thereby have a positive effect on bone mass and concomitant benefit on risk of osteoporosis (3). A large, longitudinal study reported that 24-hour urinary potassium excretion was inversely associated with all-cause mortality in a general population of Japanese adults aged 21 to 85 years (5).

Due to the interrelationship of potassium and sodium in the body, a one-to-one intake ratio of potassium to sodium is considered most beneficial for health (1, 6). Inadequate intakes of potassium may often be seen together with a high consumption of sodium, possibly due to dietary transitions towards a more processed diet.

Are there risks from excessive potassium intake?

Elevated potassium intakes are generally not harmful *per se* (1), the risk being restricted to patient groups with impaired urinary potassium excretion who may be at risk of hyperkalaemia if consumption increases (2). Other groups at risk are those with chronic kidney damage and certain medications, e.g. antihypertensives that block the renin-angiotensin system (angiotensin converting enzyme inhibitors or angiotensin receptor blockers) and some diuretics can cause high potassium levels if dietary intake is unchecked (3). Elderly patients with multiple morbidities and polypharmacy may be most at risk.

Why measure population potassium intakes? There is a relationship between over-consumption of sodium and under-consumption of potassium, both of which are important risk factors for cardiovascular disease and stroke. Recommendations to increase dietary potassium intakes may help to reduce this risk, and that of osteoporosis and kidney stones. Assessment of potassium status

is not routinely done in clinical practice (https://ods.od.nih.gov/factsheets/Potassium-HealthProfessional/)

Human biomarkers of population potassium intake and status

About 80-90% of dietary potassium is excreted in the urine, the remaining being lost via faeces and sweat (3). Losses in sweat can increase when exposed to extreme heat conditions or a high sweat production due to intense physical activity, however acclimatisation to these conditions by the body is rapid and supplementation is rarely needed (4).

Methods

Note: the following methods detail recommendations for population biomarker assessment and are not suitable for use to assess individuals or in an individual clinical setting.

Potassium excretion in 24 h urine samples

The **gold standard** for population potassium intake assessment is the measurement of potassium excreted in a 24 h urine sample (7). Though spot urine samples have been used, 24 h samples are the most reliable and practical method for assessing estimated population potassium intakes (5).

The measurement of 24 h urine potassium excretion is a surrogate for 24 h potassium intake. The concentration of potassium in a 24 h collection, usually measured in mmol/L, can be multiplied by the volume in litres of urine collected to give mmol potassium excreted in 24 h (mmol/24 h).

Example of a 24 h urine collection protocol for study participants using concomitant PABA administration to assess urine collection completeness, from UK National Diet and Nutrition Survey: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/509424/Appendix_D_field_documents.pdf

Completeness of 24 h urine samples should be assessed. Incomplete and/or under-collection of urine due to missed urine voids can result in falsely low 24-hour sodium and potassium excretion. Over-collection, beyond 24 hours, can skew results in the opposite direction (8).

Several methods are available to assess the completeness of 24 h urine collections:

- *p*-aminobenzoic acid (PABA) recovery (9);
- Urinary creatinine concentration correction (10, 11).
- Questionnaire.

PABA: PABA is a non-toxic B-complex vitamin that is thought to be fully absorbed and is readily analysed (8). PABA is an accepted measure to assess the completeness of 24 h urine collection (12). It involves the concomitant administration of 80 mg PABA tablets usually with main meals (12). The

use of PABA in national surveys has been reported in the National Diet and Nutrition Survey: assessment of dietary sodium in adults 19-64 years in England (2014) (page 15, section 2.6) (13).

Though used as an objective measure of urine collection completeness, the use of PABA is not without issue due to potential variation in excretion rate with age, non-adherence to the dosage regimen and potential interaction with medication although this is less of a problem when PABA is measured by HPLC (12, 14).

Method: Example of a 24 h urine collection protocol for study participants using concomitant PABA administration to assess urine collection completeness, from UK National Diet and Nutrition Survey: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/509424/Appendix_D_field_documents.pdf

Method: SOP for PABA analysis by HPLC (See link on https://www.open-global.kcl.ac.uk/potassium/)

Creatinine: Creatinine correction is an alternative method for 24 h urine collection completeness assessment. Creatinine values should be interpreted dependent on sex, protein intake, muscle mass, degree of malnutrition and ethnicity (10, 11). Since standard cut-offs do not widely exist, creatinine should be used with caution. For guidance on creatinine measurement, see the OpeN-Global page on Common methods, https://www.open-global.kcl.ac.uk/common-methods/.

Questionnaire: Use of a questionnaire to assess 24 h urine collection completeness is reported in the US NHANES surveys (see link below). However, standardised procedures across study fieldworkers is paramount to reduce operator variation, and rigorous and intensive protocols are required to uphold data quality, including supervised urine collection (15).

Method: Details of a 24 h urine collection protocol for study participants using a questionnaire to assess urine collection completeness, from US CDC: https://www.cdc.gov/nchs/data/nhanes/nhanes_13_14/24_Hour_Urine_Study_Procedures_Manual.pdf

Potassium excretion in Spot urine samples

Where collection of 24 h urine samples is impossible, spot urine samples may be a valuable alternative. Further, since spot samples are often routinely used in other health surveys, e.g. measurement of urinary iodine, additional assay can be easily integrated into survey or research protocols. Spot samples also remove the need for multiple visits, and therefore may be a more efficient use of resources.

Sample size estimates may need adjustment to provide the correct power and precision, and other conversion or correction factors (e.g. measurement of urinary creatinine) may be needed (14).

Measurements of creatinine concentration and potassium concentration in a spot urine sample combined with details of the individual's sex, weight, height and age allow application of the Kawasaki formula which estimates 24 h urine excretion (16). It is recommended that this method,

which is less accurate than using 24 h collections, can be used for population assessments provided that the sample size of the group is adequate (7).

Review the Kawasaki method: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1440-1681.1993.tb01496.x?sid=nlm%3Apubmed

Laboratory methods

Note: urine is a potential biohazard, and safety precautions should be employed at all times whilst handling or manipulating urine samples.

Sample manipulation/processing and storage

Certain anticoagulants, preservatives, drugs and organophilic compounds may affect electrolyte determinations.

Visually turbid urine samples should be centrifuged prior to analysis. Urine samples should be transferred to the required storage receptacle, e.g. Eppendorf tubes, which should be clean and free of contamination. Samples should be frozen immediately if possible. If freezing is not possible, then refrigeration is preferred until the samples can be frozen.

Urine sample stability

- *Room temperature:* Potassium is stable in urine for ≤ 14 days (17) at 15-25 °C, though this is not recommended due to bacterial growth in the urine, and operator comfort during analysis.
- *Refrigeration:* Potassium is stable in urine for ≤ 14 days (17) at 2-8 °C.
- *Frozen:* Potassium is stable indefinitely if stored frozen.
- *Freeze-thaw cycles:* Up to 6 freeze-thaw cycles, at -80 °C and up to 5 cycles at -20 °C did not affect potassium concentrations in patients with kidney disease (18).

We advise OpeN-Global users to consult relative SOPs for other biomarker analyses to be conducted in the collected urine samples to ensure all stability restrictions are considered.

Analytical methods

The gold standard method is **Inductively-Coupled Plasma Mass Spectrometry (ICP-MS)**, (link to https://www.nist.gov/sites/default/files/documents/srm/SP260-162-2.pdf , see p 7-1). This method can also be used on blood, serum and sweat.

The **Ion-selective electrode method (IES)** method is also widely accepted and adopted for several electrolyte measurements, is accurate and precise and scalable for population studies e.g.US CDC NHANES surveys:

https://wwwn.cdc.gov/nchs/data/nhanes/2013-2014/labmethods/URLT_H_R_MET_Electrolytes.pdf

Potassium in urine can also be measured using Flame Atomic Emission Spectrometry (FAES) or Atomic Absorption spectrophotometry (AAS), however these methods are seldom used.

Quality Control

ICP-MS and ISE: Standard Reference Materials (SRM) are available from the National Institute of Standards and Technology (NIST): SRM 2670a Toxic elements in urine (freeze-dried), level 1 (37.2 mmol/L) and level (41.0 mmol/L).

See https://www.nist.gov/sites/default/files/documents/srm/SP260-162-2.pdf p 7-2.
To order SRM from NIST: https://www-s.nist.gov/srmors/

ISE: CLINIQA standards used in the CDC NHANES method are available here:
http://www.cliniqa.com/Products/Details.aspx?ID=13

Confounding factors

The analysis of potassium may be biased by day-to-day intra-individual variations in potassium and in fluid intake, physical activity, the environment and medication use, including the use of diuretics. Potassium is also lost in faeces and sweat, though in temperate climates this factor is likely negligible (7), though seasonal variability could be considered in countries with appreciable summer-winter temperature differences.

Accreditation schemes

For laboratory accreditation, validation and details on availability of proficiency testing, please see the OpeN-Global page on Laboratory accreditation: https://open-global.kcl.ac.uk/accreditation/

Technical assistance

Please contact the OpeN-Global team via www.open-global.kcl.ac.uk/contact/ or write to the NIHR BRC Nutritional Biomarker Laboratory, University of Cambridge: nbl@mrc-epid.cam.ac.uk

Website: http://www.mrc-epid.cam.ac.uk

Useful links

National Academies Press, Dietary Reference Intakes for Water, Potassium, Sodium, Chloride and Sulfate (2005) https://www.nap.edu/read/10925/chapter/1

WHO Potassium intake for adults and children. Guideline (2014)
http://www.who.int/nutrition/publications/guidelines/potassium_intake/en/

NIH Factsheet for Health Professionals: Potassium https://ods.od.nih.gov/factsheets/Potassium-HealthProfessional/

References

1. Aburto NJ, Hanson S, Gutierrez H, Hooper L, Elliott P, Cappuccio FP 2013 Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. The BMJ **346**:f1378.

2. US Institute of Medicine, Food and Nutrition Board 2005 Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate. The National Academies Press, Washington D.C. US.

3. Lanham-New SA, Lambert H, Frassetto L 2012 Potassium. Adv Nutr **3**:820-821.

4. World Health Organization 2014 Guideline: Potassium intake for adults and children. WHO, Geneva, Switzerland.

5. Nohara-Shitama Y, Adachi H, Enomoto M, Fukami A, Kumagai E, Nakamura S, Kono S, Morikawa N, Nakao E, Sakaue A, Tsuru T, Fukumoto Y 2018 Twenty-four-Hour Urinary Potassium Excretion, But Not Sodium Excretion, Is Associated With All-Cause Mortality in a General Population. Journal of the American Heart Association **7**:e007369.

6. World Health Organization 2003 Diet, nutrition and the prevention of chronic disease: report of a Joint WHO/FAO Expert Consultation. . WHO, Geneva, Switzerland.

7. Ovesen L, Boeing H 2002 The use of biomarkers in multicentric studies with particular consideration of iodine, sodium, iron, folate and vitamin D. European journal of clinical nutrition **56 Suppl 2**:S12-17.

8. John KA, Cogswell ME, Campbell NR, Nowson CA, Legetic B, Hennis AJ, Patel SM 2016 Accuracy and Usefulness of Select Methods for Assessing Complete Collection of 24-Hour Urine: A Systematic Review. J Clin Hypertens (Greenwich) **18**:456-467.

9. Cox L, Guberg K, Young S, Nicholson S, Steer T, Prentice A, Page P 2018 Validation of the use of p-aminobenzoic acid to determine completeness of 24 h urine collections in surveys of diet and nutrition. European journal of clinical nutrition **72**:1180-1182.

10. Middleton DR, Watts MJ, Lark RM, Milne CJ, Polya DA 2016 Assessing urinary flow rate, creatinine, osmolality and other hydration adjustment methods for urinary biomonitoring using NHANES arsenic, iodine, lead and cadmium data. Environ Health **15**:68.

11. Cogswell ME, Maalouf J, Elliott P, Loria CM, Patel S, Bowman BA 2015 Use of Urine Biomarkers to Assess Sodium Intake: Challenges and Opportunities. Annu Rev Nutr **35**:349-387.

12. Jakobsen J, Pedersen AN, Ovesen L 2003 Para-aminobenzoic acid (PABA) used as a marker for completeness of 24 hour urine: effects of age and dosage scheduling. European journal of clinical nutrition **57**:138-142.

13. Public Health England 2014 National Diet and Nutrition Survey: assessment of dietary sodium. Adults (19 to 64 years) in England, 2014.

14. McLean RM 2014 Measuring population sodium intake: a review of methods. Nutrients **6**:4651-4662.

15. Intersalt Cooperative Research Group 1988 Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. Intersalt Cooperative Research Group. BMJ **297**:319-328.

16. Kawasaki T, Itoh K, Uezono K, Sasaki H 1993 A simple method for estimating 24 h urinary sodium and potassium excretion from second morning voiding urine specimen in adults. Clinical and experimental pharmacology & physiology **20**:7-14.

17. Young DS 1997 Effects of preanalytical variables on clinical laboratory tests. 2nd ed. ed. Washington (D.C.) : AACC press.

18. Zhang Y, Luo Y, Lu H, Wang N, Shen Y, Chen R, Fang P, Yu H, Wang C, Jia W 2015 Effect of freeze/thaw cycles on several biomarkers in urine from patients with kidney disease. Biopreserv Biobank **13**:144-146.