Diet or Additional Supplement to Increase Potassium Intake: Protocol For An Adaptive Clinical Trial

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Study protocol

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Abstract

Background

High blood pressure is the leading cause of cardiovascular disease worldwide. The prevalence of high blood pressure is steadily rising, with the growing and ageing population. Many medicines are available to decrease blood pressures successfully, as well as many non-medical options, such as dietary changes and exercise. There is a marked preference amongst patients, reiterated in a Hypertension Canada report, for more research into methods for controlling blood pressure without medicines or to reduce the burden of taking many pills to control high blood pressure. Indeed, effective options do exist, especially with diet, specifically decreasing sodium and increasing potassium in diet. Current public health outreach mostly focusses on sodium intake, even as the potassium intake in diet remains low especially in the Western world. Excellent data exist in the published research reporting that increasing potassium intake, either as diet or even as supplements, reduces blood pressure and reduces risk of cardiovascular outcomes such as stroke. However, the advice most often provided is to ‘eat more fruits and vegetables’ which does not get translated into concrete change.

Methods

We propose to do a clinical trial in two stages, with an adaptive trial design. In the first stage, participants with high blood pressure and proven low potassium intake (measured on the basis of a 24 hour urine collection) will get individually tailored dietary advice, reinforced by weekly supportive phone/email support. If at 4 weeks, there has not been a desired increase in potassium intake, they will be prescribed an additional potassium supplement. Testing will be conducted again at 4 weeks post initiating the potassium supplement, to confirm the efficacy of the potassium supplement. Final measurements will be planned at 52 weeks to observe and measure the persistence of the effect of diet or additional supplement. Concurrent measurements of sodium intake, blood pressure, participant satisfaction, and safety measures will also be done.

Discussion

The results of the study would help determine the most effective method of increasing potassium intake, thus reducing blood pressure, need for blood pressure lowering medicines, at the same time potentially increasing participant satisfaction. The current guidelines recommend changes in diet, not supplement, to increase potassium intake, hence the two stage design will only add supplements if the most rigorous dietary advice does not work.

Trial registration:
This study has been registered on ClinicalTrials.gov identifier NCT03809884, registered on January 18, 2019. URL: https://clinicaltrials.gov/ct2/show/NCT03809884

Background

Hypertension is the leading cause of death and disability in Canada and globally. Apart from a wide choice of pharmacological agents, multiple lifestyle modifications, in particular an increase in potassium intake by diet or as a supplement, have been shown to be efficacious in reducing blood pressure[1–3]. An increase in dietary potassium is recommended by the World Health Organization[4], the American Heart Association/American College of Cardiology[5] and Hypertension Canada[6, 7]. Despite this, potassium intake remains stubbornly low in western world, including in Canada. Similar to the relative slowness in behaviour change with reducing sodium, the reason why trials of efficacy may not have translated into change is that the interventions in the trials of dietary modification have not been feasible (including supervised intake of meals and/or provision of meals) to be used in clinical practice. In contrast to behavioural modification required for increasing potassium intake in food, namely change in dietary habits, addition of potassium supplements might be an easy to implement alternative[8, 9]. The advocacy of potassium supplements has not made it into any guidelines despite robust data of their efficacy, and the public enthusiasm for consuming health supplements.

Increasing potassium intake itself is a robust, but often overlooked, means of decreasing blood pressure[9, 10]. Increasing dietary potassium intake has an inverse association with lowering blood pressure and can impact cardiovascular disease. Systematic reviews and meta-analyses of randomized controlled trials on the effect of increased potassium intake on blood pressure (BP) show significant decreases in systolic and diastolic BP with increased potassium intake[8–12]. Globally, hypertension is the leading risk factor for mortality, accounting for 13% of death, and also being the leading cause of disability worldwide, according to the Global Burden of Disease studies[13–15]. Research on lifestyle habits to reduce blood pressure, without involving pharmacotherapy has been identified as a top research priority by Hypertension Canada[1].

Advocating high potassium intake either in the form of diet or as use of a potassium supplement to the diet may pose a risk in certain populations. However, except in individuals with advanced chronic kidney disease or other conditions impairing renal potassium handling, adaptive mechanisms are triggered that allow for excretion of excess potassium in the urine[16–18]. Thus, increasing potassium intake, as part of the diet or as a supplement, has little adverse effects in most populations[9, 12]. In this adaptive trial, we will test the effectiveness of dietary counselling, followed by additional potassium supplementation in those in whom dietary counselling is ineffective. The objective of this study is to determine an effective strategy for increasing potassium intake in hypertensive individuals with low potassium intake.

Methods

Study design and setting
The study design is a single-center, single arm clinical trial, with an adaptive design of two possible sequential interventions. Focused and individualised dietary counselling to increase potassium intake will be the initial intervention amongst hypertensive individuals with low potassium intake. This study and patient recruitment will take place in a referral hypertension clinic at a tertiary care teaching hospital. Patients with difficult to control hypertension are referred to this clinic, and all patients undergo evaluation of their sodium and potassium intake with a 24 hour urinary collection.

**Study population and timeline**

In this trial, all patients with low dietary potassium intake will be eligible for enrollment. The study coordinator will screen patient for eligibility and obtain informed consent. Patients known to be at risk for hypokalemia or hyperkalemia will be excluded. The estimated duration for this study is four years.

**Inclusion criteria:**

(1) Hypertension (either on treatment, any level of BP; or not on treatment with an ambulatory blood pressure monitoring (ABPM) with daytime systolic blood pressure (SBP) > 140 or diastolic blood pressure (DBP) > 90)

(2) Aged 18 and greater

(3) 24 Hour Urine potassium < 60 mmol

**Exclusion criteria:**

(1) serum potassium < 3.3 or > 5.1 mmol/L

(2) Glomerular filtration rate (GFR) < 45 ml/min/1.73m²

(3) Primary hyperaldosteronism

(4) Pregnancy

(5) Psychiatric disorder which, in the opinion of the investigator, would interfere with the study, or inability to give consent

(6) Severe Liver disease

(7) Metabolic Alkalosis (HCO₃ > 32 mmol/L)

(8) Exclude patients who need to be started on renin-angiotensin-aldosterone blockade in the next 3 months

(9) Gastrointestinal Disorder (delayed gastric emptying, dysphagia, gastric/duodenal/oesophageal ulcers)
Interventions

Part 1: Counselling:

All enrolled patients will undergo a 1:1 counselling with a registered dietitian (with possible inclusion of family members, as appropriate). The dietitian will undertake an assessment of the comorbidities (eg. diabetes), dietary intake, dietary habits (eg. eating out, food preparation, socio-cultural aspects) and provide an individually tailored strategy to increase potassium in the diet. Secondly, on a weekly basis, the dietitian will contact the patient by telephone, or electronically (as preferred by the patient) to reinforce the advice and provide support and advice as necessary. Patients who are successful in increasing potassium to desirable levels at 4 weeks (see outcomes below) will continue to have follow up for one more year.

The counselling will be individualised, and focused on addition of food ingredients or items to increase potassium intake, rather than a complete overhaul of the participant lifestyle.

Part 2: Potassium supplementation:

Patients who are not able to successfully increase their potassium intake at 4 weeks with dietary counselling will be enrolled into Stage 2. They will receive oral potassium supplementation in the form of 50 to 100 mmol of potassium citrate (25 to 50 ml of the liquid elixir). This dose of potassium is well tolerated in hypertension (reported adverse events, at < 1% frequency and not different from placebo, are change in bowel habits, belching and flatulence, and abdominal cramps with the current wax matrix–based and microencapsulated or coated microcrystal-containing preparations with extended release characteristics)[9, 19]. There are no reports of hyperkalemia reported in trials using this dose in a similar population[9, 12]. Potassium at this dose and formulation has excellent (> 90%) bioavailability[19]. This dose of potassium also should be effective in increasing urinary potassium to desired levels.

Outcomes

The primary outcome will be a successful increase in potassium intake to > 90 mmol/day as estimated from the 24 hour urinary sample at 4 weeks. The secondary outcomes are persistence of increase in potassium intake (to > 90 mmol/day) at 1 year. For examination of safety, the following outcomes will be specifically examined: hyperkalemia (as defined as a serum potassium > 5.1 mmol/L) at 4 weeks after initiation of dietary counselling, at one and 4 weeks after starting potassium supplements, one week after dose escalation/dispensing, and at 12 months in everyone; and gastrointestinal side effects (change in bowel habits, belching and/or flatulence; abdominal pain or cramps). Additional patient reported adverse effects will also be measured and reported. Serious adverse events will be captured and reported as per regulatory requirements.

Blinding
The trial design is open label, given that behavioural change is difficult to blind. However, numerous safeguards will be in place to minimize actual bias in the data collected.

**Blinded assessment of outcomes:**

The primary outcome in this trial is a change in potassium intake, as measured by 24 hour urinary potassium. This is an objective measure however, and the laboratory personnel measuring the values will not be aware of which intervention is ongoing when they perform the measurement.

**Ascertainment and Follow-up plan:**

In order to minimize ascertainment bias, all patients, irrespective of the group, will have similar measurement schedule. Nevertheless, we will study the frequency of loss to follow-up and reasons thereof.

**Measurements**

The dietary intake of potassium will be assessed using 24 hour collection of urine. There is a very close relationship overall between urinary potassium excretion and dietary potassium intake. There is a circadian variation\[20\] (more potassium excretion in the day than at night) which will be overcome with a 24 hour urine collection. Twenty four hour urinary sodium and creatinine (to assess for accuracy of collection) will also be measured for all participants at baseline, 4 weeks and 52 weeks (end of study). In addition, participants who enrol into Stage 2 may have additional 24 hour urinary collection at 9 weeks and 14 weeks after initiation of the potassium supplement/dose escalation. Blood will also be collected at the same time points for measurement of kidney function and electrolytes (creatinine, sodium, potassium, total CO2, chloride). As an additional safety measure, serum potassium will be measured one week after starting potassium supplementation, one week after dose escalation and one week post each re-dispensing visit. Blood pressure will be measured using automated oscillometric measurements and 24 hour ambulatory monitoring. Additional assessment of adherence to supplement (apart from 24 hour urine measures) will be made on the basis of returned pills/bottles. Patients satisfaction will be assessed using a simple 3 question survey (see supplementary material).

**Sample size and analytical plan**

The study goal is to estimate the success rate of the dietary intervention, as well as the success rate of the two-stage approach. Dietary counselling alone will not exceed this degree of increase which was seen with supervised intake and meal provision, but there are no robust data to support an estimate of its effect. However, potassium supplementation at the dose proposed would very likely result in achieved potassium intake of > 90 mmol/day in all participants. A sample size of 100 participants will allow us to able to estimate both success rates to within a margin of error of at most 5%. At 4 weeks, there should be little loss to follow up; however we estimate this to be about 20% to be conservative. Thus this trial will enrol 120 participants.
The primary outcome is a simple proportion of the participants who are able to achieve an increase in potassium intake. Secondary outcomes of the proportion of participants with persistent adequate potassium intake at 52 weeks, and safety outcomes, will also be reported as proportions. For the secondary outcomes of change in sodium, potassium and blood pressure, mean differences will be calculated and reported, and a paired t-test will be used to compare for statistical significance. There will be no interim analysis.

The proportions will be summarized as absolute numbers and percentages. Continuous outcomes will be reported as mean (and 95% confidence intervals). A p value of < 0.05 will be used for the paired comparisons of the continuous outcomes (i.e. secondary outcomes of change in sodium, potassium and blood pressure).

Access to medical records and study data will be limited to authorized personnel listed on the study delegation log or permitted by the study agreement. Access to electronic data will be password protected and auditable, electronic data will be stored on a hospital network with firewall and security back-up measure in place, and paper copies of the study data will be stored securely in locked cabinets and in locked offices.

**Adverse events**

The qualified investigator will follow adverse events with start dates occurring any time after informed consent is obtained until 7 days (for non-serious adverse events) or 30 days (for severe adverse events) after the last day of study participation. At each study visit, the investigator (or designee) will inquire about the occurrence of adverse events (AE)/serious adverse events (SAEs) since the last visit and record in participant research record and case report form. Events will be followed for outcome information until resolution or stabilization.

**Data Safety Monitoring Board**

This study will be monitored by an independent Data Safety Monitoring Board (DSMB), consisting of a Clinical Epidemiologist, a Nephrologist, and a Biostatistician. The DSMB will be immediately informed of any SAEs which may potentially be related to the study intervention. Other SAEs will be reviewed during regular DSMB meetings. Interim reports, prepared by the data management team for the study, for review by the DSMB will include data on recruitment, compliance, adverse effects, baseline comparability and treatment comparisons. An agreed upon review package which contains the appropriate data summary by treatment will be provided by the study statistician for the purposes of these reviews.

**Discussion**

There is unequivocal evidence on the efficacy of potassium intake in lowering blood pressure and subsequent cardiovascular outcomes. However, the trials have not resulted in change in practice due to a lack of data on the most effective methods to implement this change. Our adaptive trial design, with
sequential intervention of the dietary counselling, followed by additional supplementation in those in whom diet alone is ineffective, represents an easy to implement intervention. This might bridge the efficacy to effectiveness implementation gap. A 5 mm Hg decrease in systolic blood pressure, as reported with additional potassium effect in meta-analyses, translates into one less antihypertensive medication. Thus, the results of this trial have the potential for a very large scale impact at a public health, as well at an individual level. Lifestyle habits to improve blood pressure and decrease medication burden have been already identified as high level research priorities by patients in work done by Hypertension Canada and others. We hope the results of this trial, once completed and reported, will provide useful and actionable information for public health in this sphere.

**Trial Status**

The trial has received ethics approval from Ottawa Health Science Research Ethics Board (OHSN-REB) on February 5, 2019. Trial screening and recruitment has begun in January 2020, with anticipated completion in 2023. Protocol version and date: Jan 15, 2021, V1.

**List Of Abbreviations**

BP
Blood pressure, ABPM:Ambulatory blood pressure monitoring, DSMB:Data safety monitoring board, GFR:Glomerular filtration rate, SBP:Systolic blood pressure, DBP:Diastolic blood pressure, TOH:The Ottawa Hospital, AE:Adverse events, SAE:Severe adverse events.

**Declarations**

**Ethics approval and consent to participate:**

This trial has received approval from the OHSN-REB (Protocol ID: 20180873-01H). The research ethics board registration with ClinicalTrials.gov will be informed and amended if protocol modification is necessary. Eligible patients will undergo informed consent before participating in the trial.

**Consent for publication:**

Not applicable.

**Availability of data and materials:**

Supplementary material including a simple 3 question survey.

**Competing interests:**

None of the investigators, research staff, sponsor or the institution has any conflicts of interest with the research involved.
Funding:

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Authors’ contributions:

SH, MR, DF and GK contributed to the study concept. SH, MR, DK, TR, and GK contributed to the analytic plan. JK and SH drafted the first paper and wrote the revision and the final manuscript. All authors made substantial contributions to the conception and design of the trial. All authors of this study read and approved the final manuscript.

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References

1. Leung AA, Daskalopoulou SS, Dasgupta K, McBrien K, Butalia S, Zarnke KB, et al. Hypertension Canada's 2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults. Can J Cardiol. 2017;33(5):557–76. doi:10.1016/j.cjca.2017.03.005. PubMed PMID: 28449828. Epub 2017/04/30.

2. Lawes CM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke: an overview of published reviews. Stroke. 2004;35(4):1024. Epub 2004/04/01. PubMed PMID: 15053002.

3. Padwal RS, Bienek A, McAlister FA, Campbell NR, Outcomes Research Task Force of the Canadian Hypertension Education P. Epidemiology of Hypertension in Canada: An Update. Can J Cardiol. 2016;32(5):687–94. doi: 10.1016/j.cjca.2015.07.734. PubMed PMID: 26711315.

4. WHO. Guideline. Potassium intake for adults and children. Geneva, World Health Organization (WHO). 2012.

5. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2960–84. doi: 10.1016/j.jacc.2013.11.003. PubMed PMID: 24239922.

6. Whelton SP, Blumenthal RS. Beyond the Headlines: Insights on Potassium Supplementation for the Treatment of Hypertension From the Canadian Hypertension Education Program Guidelines (CHEP). Circulation. 2017;135(1):3–4. doi:10.1161/CIRCULATIONAHA.116.024525. PubMed PMID: 28028058; PubMed Central PMCID: PMCPMC5217710. Epub 2016/12/29.

7. Leung AA, Nerenberg K, Daskalopoulou SS, McBrien K, Zarnke KB, Dasgupta K, et al. Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. Can J Cardiol. 2016;32(5):569–88. doi:10.1016/j.cjca.2016.02.066. PubMed PMID: 27118291. Epub 2016/04/28.
8. Dickinson HO, Nicolson DJ, Campbell F, Beyer FR, Mason J. Potassium supplementation for the management of primary hypertension in adults. Cochrane Database Syst Rev. 2006;(3):CD004641. Epub 2006/07/21. doi:10.1002/14651858.CD004641.pub2. PubMed PMID: 16856053.

9. Aburto NJ, Hanson S, Gutierrez H, Hooper L, Elliott P, Cappuccio FP. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. BMJ. 2013;346:f1378. Epub 2013/04/06. doi:10.1136/bmj.f1378. PubMed PMID: 23558164; PubMed Central PMCID: PMCPMC4816263.

10. Aaron KJ, Sanders PW. Role of dietary salt and potassium intake in cardiovascular health and disease: a review of the evidence. Mayo Clin Proc. 2013;88(9):987 – 95. Epub 2013/09/05. doi: 10.1016/j.mayocp.2013.06.005. PubMed PMID: 24001491; PubMed Central PMCID: PMCPMC3833247.

11. Binia A, Jaeger J, Hu Y, Singh A, Zimmermann D. Daily potassium intake and sodium-to-potassium ratio in the reduction of blood pressure: a meta-analysis of randomized controlled trials. J Hypertens. 2015;33(8):1509–20. Epub 2015/06/04. doi: 10.1097/HJH.0000000000000611. PubMed PMID: 26039623.

12. Poorolajal J, Zeraati F, Soltanian AR, Sheikh V, Hooshmand E, Maleki A. Oral potassium supplementation for management of essential hypertension: A meta-analysis of randomized controlled trials. PLoS One. 2017;12(4):e0174967. doi:10.1371/journal.pone.0174967. PubMed PMID: 28419159; PubMed Central PMCID: PMCPMC5395164. Epub 2017/04/19.

13. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, et al. Global Burden of Hypertension and Systolic Blood Pressure of at Least 110 to 115 mm Hg, 1990–2015. JAMA. 2017;317(2):165–82. doi:10.1001/jama.2016.19043. PubMed PMID: 28097354. Epub 2017/01/18.

14. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies C. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903–13. doi:10.1016/s0140-6736(02)11911-8. PubMed PMID: 12493255. Epub 2002/12/21.

15. WHO. Global health risks: mortality and burden of disease attributable to selected major risks. Geneva, World Health Organization.; 2009.

16. Rabelink TJ, Koomans HA, Hene RJ, Dorhout Mees EJ. Early and late adjustment to potassium loading in humans. Kidney Int. 1990;38(5):942–7. doi:10.1038/ki.1990.295. PubMed PMID: 2266680. Epub 1990/11/01.

17. Sarafidis PA, Blacklock R, Wood E, Rumjon A, Simmonds S, Fletcher-Rogers J, et al. Prevalence and factors associated with hyperkalemia in predialysis patients followed in a low-clearance clinic. Clin J Am Soc Nephrol. 2012;7(8):1234–41. doi: 10.2215/CJN.01150112. PubMed PMID: 22595825; PubMed Central PMCID: PMCPMC3408123.

18. Kovesdy CP, Redor DL, Mehrotra R, Jing J, McAllister CJ, Greenland S, et al. Serum and dialysate potassium concentrations and survival in hemodialysis patients. Clin J Am Soc Nephrol. 2007;2(5):999–1007. doi:/CJN.04451206. PubMed PMID: 17702709. Epub 2007/08/19.
19. Hinderling PH. The Pharmacokinetics of Potassium in Humans Is Unusual. J Clin Pharmacol. 2016;56(10):1212–20. doi:10.1002/jcph.713. PubMed PMID: 26854277. Epub 2016/02/09.

20. Mann H, Stiller S, Korz R. Biological balance of sodium and potassium: a control system with oscillating correcting variable. Pflugers Arch. 1976;362(2):135–9. Epub 1976/03/30. doi: 10.1007/BF00583639. PubMed PMID: 944420.

Figures

| TIMEPOINT                       | 0-20 months | Allocation | Post-allocation | Close-out |
|---------------------------------|-------------|------------|-----------------|-----------|
| ENROLMENT:                      | X           | 0          |                 |           |
| Eligibility screen             | X           |            |                 |           |
| Informed consent               | X           |            |                 |           |
| Counselling with dietician     | X           |            |                 |           |
| Allocation                      | X           |            |                 |           |
| INTERVENTIONS:                  |             |            |                 |           |
| Oral potassium supplementation*| X           |            |                 |           |
| ASSESSMENTS:                    |             |            |                 |           |
| 24 hours urinary collection    | X           | X          |                 | X         |
| Persistence increase in potassium intake | X            |            |               | X         |
| Safety outcome                 | X           |            |                 | X         |
| Adverse events                 | X           |            |                 | X         |
| DATA ANALYSIS                  |             |            |                 | X         |

Figure 1

Stage 1 study period content for all participants (stage 1), including the schedule of enrolment, interventions, and assessments for the Diet or Additional Supplement to Increase Potassium study. *Only apply for patients who did not increase potassium intake after stage 1.
| TIMEPOINT | ENROLMENT: Potassium supplementation* | Allocation | End of week 4 (stage 1) | 9 weeks | 14 weeks | 26 weeks | 38 weeks | 52 weeks |
|-----------|--------------------------------------|------------|-------------------------|---------|----------|----------|----------|---------|
|           | X                                    | X          |                         |         |          |          |          |         |
| INTERVENTIONS: | Oral potassium supplementation | X**        |                         |         |          |          |          |         |
| ASSESSMENTS: | 24 hours urinary collection | X          | X                       | X       |          |          |          |         |
|           | Follow-up appointment |                        | X                      | X       | X        | X        |          |         |
|           | Safety outcome |                        |                        | X       | X        | X        | X        | X       |
|           | Adverse events |                        |                        | X       | X        | X        | X        | X       |
| DATA ANALYSIS |                          |                        |                        |         |          |          |          | X       |

**Figure 2**

Stage 2 study period content for participants who failed stage 1, including the schedule of enrolment, interventions, and assessments for the Diet or Additional Supplement to Increase Potassium study. *Only if participants who failed stage 1, remains < 60 mmol/day at the end of 4 weeks (unsuccessful in increasing potassium via diet after 4 weeks). ** Potassium supplementation will be provided at a dose of 100 mmol/day (liquid solution).

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- PotassiumstudySupplementarymaterial.docx
- SPIRITCHECKLISTPotassiumstudyprotocolJan2021.doc