

BMJ Open Effects of potassium-enriched salt substitutes on blood pressure in Iranian hypertensive patients: the protocol for a randomised, double-blind controlled trial

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ABSTRACT

Introduction Potassium-enriched salt substitutes have favourable effects on blood pressure, but it has not been tested in Iran. The present protocol is a double-blinded, randomised-controlled trial designed to investigate the effects of potassium-enriched salt substitutes on blood pressure in Iranian hypertensive patients.

Methods and analysis The primary objectives are to determine the effects on systolic and diastolic blood pressure at 3 months and 6 months. The secondary objectives are to assess the effects on serum levels of potassium, sodium, urea and creatinine; the urinary ratio of sodium to potassium; participants' attitudes toward the use of salt or salt substitutes; the recurrence of hypertensive crisis; and the occurrence and/or reoccurrence of strokes, transient ischaemic attack and cardiovascular accidents. Eligible individuals will receive the usual salt (100% sodium chloride) in the control group or salt substitute (70% sodium chloride and 30% potassium chloride) in the intervention group. A total of 500 hypertensive participants aged 40–65 years will be recruited and randomised to intervention or control groups. Potassium-enriched salt substitution in Iran will be considered to improve CVD complications and prevent deaths. Continuous and categorical baseline characteristics will be tested using the independent t-test and χ^2 test. The effect of the intervention on primary and secondary outcomes will be assessed using the intention-to-treat method and two-way mixed ANOVA models.

Ethics and dissemination This study has been approved by Alborz University of Medical Sciences (0-0-103-6369) and has received ethics approval (IR.ABZUMS.REC.1402.293). We will publish our study findings for peer-reviewed publications, conference presentations and digital stories.

Trial registration number IRCT20240121060757N1.

INTRODUCTION

Hypertension (HTN) is the most significant risk factor for cardiovascular diseases (CVD) and, in turn, death worldwide. This condition accounts for approximately 45% of the total global burden of cardiovascular morbidity

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Double-blinding of participants and researchers will reduce the risk of bias.
- ⇒ Participants' serum potassium will be assessed during the study.
- ⇒ Not administering para-aminobenzoic acid to the participants to assess the completeness of the 24-hour urine collections.
- ⇒ Not considering the additional benefits of partial salt substitution on non-cardiovascular outcomes such as gastric cancer and gastrointestinal malfunctions.

and mortality in all countries.^{1,2} Based on the predictions of the WHO, CVD will become the most abundant underlying factor of disability-adjusted life years in the near future³; HTN can also reach a prevalence of nearly 60% among adults in some populations.⁴ Studies indicate that the prevalence of HTN in many countries such as India, Middle Eastern and North African countries has reached 26%, with only 10–20% of them having achieved steady blood pressure rates.^{5–7} These numbers highlight the importance of implementing novel, low-cost interventions to improve blood pressure control in the world.

One simple yet effective method is to reduce dietary sodium intake as excess sodium intake is a significant risk factor for HTN. Usually, most international and national HTN societies recommend reducing sodium from the diet as one of the first-line HTN treatments.^{8,9} Besides reducing sodium, salt substitutes generally use potassium chloride as the primary alternative, which can increase the concentration of potassium in the blood. A previous study has shown that potassium-enriched salt substitutes (25–67% potassium chloride), compared with standard salt (100% sodium chloride), decreased average

systolic blood pressure (SBP) by 5 mm Hg and diastolic blood pressure (DBP) by 2 mm Hg.^{10 11} Also, a cluster randomised trial conducted among older Taiwanese adults indicated that potassium-enriched salt substitutes were linked to a reduced risk of mortality due to CVD.¹² Therefore, the overall potential effects of salt substitutes are due to reduced sodium intake and increased potassium intake.

Studies in Iran show that the mean salt intake among men is 10 ± 4.8 g/day and 8.99 ± 2.93 g/day in women¹³; these numbers indicate that the current salt intake in this country is much higher than the 2-gram maximum sodium intake recommended by WHO. Although some policies proposed by WHO or other organisations have resulted in the reduction of salt intake. Some of these policies are being executed at national levels, such as reformulation and labelling foods, campaigns regarding public health, promoting healthy foods and advertisements regarding lowering salt intake and giving dietary counselling; however, despite all these efforts, the usage of salt in Iran is extremely high.¹⁴ Thus, the need for strategies that reduce sodium use, such as replacing sodium chloride salt with potassium salt, can have a tremendous effect on lowering the blood pressure of the hypertensive population. In this promising strategy, regular dietary salt (sodium chloride) will be replaced by a blend of sodium chloride partially and non-sodium alternatives, such as potassium chloride as the primary replacement. These salts can substitute ordinary table salt and other products that are sources of sodium, such as some types of cheese and soy sauce. Most studies and meta-analyses have documented that salt-sodium alternatives reduce blood pressure.^{15 16} For example, a study that compared potassium-enriched salt substitutes (with 25% to nearly 70% potassium chloride) with ordinary table salt (100% sodium chloride) showed a reduction in blood pressure for both SBP and DBP (an average reduction of 5 mm Hg and 2 mm Hg, respectively).¹⁷ Based on these studies, this low-cost, effective intervention significantly reduces the blood pressure of hypertensive patients. Despite concerns regarding hyperkalaemia, the observed side effects of using potassium salts were much less than expected, making it a safe substitute for regular sodium chloride salt.^{17 18}

The consumption of common table salt in Iran is remarkably elevated. Despite studies having been done in other countries, no study has been done on the Iranian population to evaluate the effects of ordinary sodium chloride salt blended with potassium chloride salt in HTN and other outcomes that may arise as a complication of HTN. If a study proves the blood pressure-lowering effect of the aforementioned salt in the Iranian population, it will help health policymakers and officials use such blends in the entire nation to reduce HTN and control blood pressure. Therefore, this protocol presents the main methods and facts of a randomised, double-blind controlled trial: 'Effects of Potassium-enriched salt substitutes on blood pressure in Iranian hypertensive patients'.

METHODS

Aims and hypotheses

The primary aim of the present study is to compare the effect of salt substitutes on the changes in SBP and DBP in the salt substitute group and the control (regular salt) group from baseline to 3 months and 6 months later among patients with HTN in Iran. The primary hypothesis is that the salt substitute will effectively lower SBP and DBP.

The secondary aims are to determine the various effects of the salt substitute in the salt substitute group compared with the control group from baseline to 6 months later, which are as follows: the changes in the urinary ratio of sodium to potassium; participants' attitudes towards the use of salt or salt substitute; the recurrence of hypertensive crisis; and the occurrence and/or reoccurrence of strokes, transient ischaemic attack (TIA) and cardiovascular accidents. Also, another secondary aim is to compare the mean change of serum potassium levels in the salt substitute group with the control group from baseline to 6 months later. The secondary hypotheses are the improvement of the urinary ratio of sodium to potassium as well as the salt-related knowledge, attitudes and behaviours; the decrease in the recurrence of hypertensive crisis and the occurrence and/or reoccurrence of strokes, TIA and cardiovascular accidents, and finally, we hypothesise that the salt substitute will be generally acceptable to the study participants.

Study design and randomisation

This trial is registered in the Iranian Registry of Clinical Trials (IRCT20240121060757N1). The planned start date is estimated to be June 2025, and the end date is estimated to be 30 April 2026.

In this double-blind RCT, 500 hypertensive patients (aged 40–65 years) will be selected via a simple random sampling method from 6 healthcare centres in Alborz province (west of Tehran, Iran). We will randomly assign participants through a central computerised process into two groups (250 individuals in each group); one is the salt substitute group and the other will be the regular salt group. The random allocation sequence will be generated by an independent biostatistician, and thus, the study team will be blinded to the randomisation sequence. The study team members who follow-up and evaluate the outcomes will also be blinded to participants and assigned groups during the study.

This double-blind RCT with an intervention duration of 6 months will assess the effects of a subnational intervention to replace discretionary dietary salt with potassium-enriched salt substitutes (70% sodium chloride and 30% potassium chloride) on blood pressure and secondary outcomes in Iran. The evaluation will be designed as the means of evaluating the benefits of lowering blood pressure (both systolic and diastolic) and the potential, if any, consequences of hyperkalaemia.

Study sites

Alborz province is located 30 km west of Tehran, with a population of 1 400 000. The patients will be recruited

from the Shaheed Rajaie Cardiovascular Medical and Research Centre.

Sample size

According to previous studies,^{18 19} the sample size required for this study was estimated using a formula for comparing two means. By considering type I and type II errors (5% and 20%, respectively) and mean $\pm$ SD changes of DBP in the salt substitute (-0.6 ± 5.4) and salt regular groups (0.6 ± 4), the sample size was estimated to be 250 subjects in each group.

Study population

Adults aged 40–65 years with HTN diagnosed by a health professional will be eligible for participation. Individuals and all their household members will sign a written consent to participate in the trial (online supplemental form 1). Participants will be excluded if they use potassium supplements and have acute or chronic kidney disease (CKD) according to self-report or baseline lab tests.

We will randomly assign 500 participants to two groups, including intervention by a salt substitute ($n=250$) and the control group (regular salt, $n=250$). Participants meeting the eligibility criteria will be recruited from the Shaheed Rajaie Cardiovascular Medical and Research Center, a referral cardiovascular hospital, in the Alborz province (west of Tehran, Iran). The study physicians will check the existence of HTN in participants and inquire about the presence or absence of severe kidney diseases that could result in hyperkalaemia by using potassium-enriched salts.

Patient and public involvement

There was no direct patient or public involvement in the design and development of the study protocol.

Inclusion criteria

Participants aged 40–65 years with confirmed HTN (having measured SBP ≥ 135 mm Hg) and, alternatively, those under treatment with antihypertensive medications can participate in the study. Only participants with written informed consent from both themselves and all their household members can participate in the study (due to the nature of our study, household members of the study participants also consume the blended salt). Only those who mainly consume their home-cooked food are eligible to participate in the study.

Participants who meet the eligibility criteria will be recruited from healthcare centres throughout Alborz province, west of Tehran, Iran. A study physician will verify the validity of self-reported HTN and inquire about the presence or absence of severe kidney disease. Additionally, the physician will determine the absence or presence of self-reported kidney disease among the participant's household members, considering that salt substitutes may increase the risk of hyperkalaemia in patients with kidney disease.

Exclusion criteria

Since there are concerns regarding hyperkalaemia induced by using potassium-enriched salts, all of the participants themselves or any of their household members using a potassium-sparing diuretic, potassium supplements or any known acute or CKD will be excluded from the study. In participants, in addition to self-reporting, baseline lab tests will be used to determine acute and CKD. In this regard, CKD will be determined by individuals' medical records, and $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ represents CKD diagnosis.²⁰

Intervention and control

There will be face-to-face visits to all participants in their own homes by our research team. We will obtain informed consent and confirm eligibility criteria on this first visit. We will conduct a brief physical examination and record the baseline blood pressure. Afterwards, on the next visit, we will randomly assign the participants to two groups.

In this study, we will give the intervention group a blend of approximately 70% sodium chloride with 30% potassium chloride blended salt, and the control group will receive regular sodium chloride salt (100% sodium chloride).

With an estimated salt intake of nearly 8 g/day per person in Iran, we will provide the daily needs of each household with blended or regular salt based on the size of the household, and then the total amount of household consumption for the study duration (6 months) will be provided for the household. In addition, an evaluation of the remaining salt at the end of the study will be assessed to calculate the total amount of salt consumption during the study period. After the initial visits at the beginning of the study, within this 6-month duration, we will visit our participants at the beginning of the study, giving them all the needed instructions to answer all questions and attending to all their concerns, at the end of month one and the end of month 3 and month 6. We will manufacture the salt substitute according to Iran's national manufacturing standards (which require 70% sodium chloride and 30% potassium chloride). We will distribute sufficient amounts of this blended salt, free of charge, to cover household cooking, preparation and food preservation.

We will instruct our participants to report any adverse events to us during the study. We will ask our participants about the acceptability, tolerance, taste and usage of the blended salt; 24-hour urine samples shall be collected on the final study visit. All participants will receive their prescribed HTN treatment, given to them by their physician before the study, and the researchers will not intervene nor interfere with their medication. Moreover, the only intervention will be the substitution of ordinary table salt (100% sodium chloride) with 70% sodium chloride blended with 30% potassium chloride salt.

Data collection and measurements

Blood pressure analysis

At the first study visit, and then every 2 months (3rd month and 5th month), blood pressure will be measured three times for each participant using an automated blood pressure monitor (all blood pressure monitors will be from the same company and will be the same model). We will record the mean of the acquired measurements. The automated blood pressure monitors will carefully be evaluated and calibrated regularly. The examination will take place in a quiet and comfortable room in a regular comfortable chair for at least 5 min before measuring their blood pressure. The chair that we will use must support the back and arm of the participants, with their feet being flat on the floor. On the day of measurement, caffeine use, exercise, smoking and alcohol consumption will be prohibited. The participants will be instructed to empty their bladders 30 min before the measurement. During the rest of the blood pressure measurement period, speaking will be prohibited. The participant will rest for 1 min between each of the measurements. Moreover, the measurements will be taken at the same time for each subject.

Dietary assessment

We will ask the participants to fill out a 3-day 24-hour dietary recall to assess dietary intake during each visit. Each participant should fill out dietary recalls for each week with the typical number and details of meals. Then, data will be analysed by Nutritionist IV software (First Databank, San Bruno, California, USA) modified for Iranian food.

Urine analysis

We will instruct our participants on how to collect a 24-hour urine sample in detail. They are also instructed not to change their usual lifestyle and dietary habits. At the first and last visit (baseline and 6 months), we will provide our participants with new containers to collect 24-hour urine samples. After this 24 hours, we will collect the containers, and to make sure that the process was done as instructed, we will assess the total urine volume. If the total 24-hour urine volume is less than 500 mL or greater than 6000 mL, the participant will be asked for another 24-hour urine sample after instructing them in detail once more. To assess urine electrolytes, we will be using automated electrolyte meters to measure urine sodium and potassium concentrations. Based on the sodium and potassium concentrations in the urine samples, we will calculate the amount of salt usage among our participants using the following formulas^{21 22}:

Sodium (in g) = ((Urine sodium concentration (in g/L)) * 2.54) * (Urine volume (L)).

Potassium (in g) = ((Urine potassium (in g/L)) * 1.91) * (Urine volume (L)).

Furthermore, within the last visit, the participants will be asked about the taste, attitude and usage of salt. We will calculate discretionary salt intake by asking our

participants about the salt added during food preparation and prior to consumption.

Primary and secondary outcomes

The primary outcomes are assessing the effect of the salt substitute on the change in SBP and DBP from baseline to 3 months and 6 months, compared with the group receiving the regular salt. Secondary outcomes include the 24-hour urinary sodium and potassium excretion, the urinary ratio of sodium to potassium and serum creatinine from baseline to 3 months and 6 months after the initiation of the study. Also, the number or percentage of individuals who develop hyperkalaemia and hypokalaemia will be reported. Along with hyperkalaemia and hypokalaemia, the occurrence of CVD events will be presented as a safety outcome such as the recurrence of hypertensive crisis, the occurrence and/or reoccurrence of strokes, TIA and cardiovascular accidents. Last but not least, the mean of blood pressure, the acceptability, usage, tolerance and taste of the blended salt and attitudes regarding it will be assessed.

Statistical analysis

Continuous and categorical variables will be presented as means with SD and numbers with percentages, respectively. Continuous and categorical baseline characteristics will be tested using the independent t-test and χ^2 test. Missing data will be imputed using the multiple imputation method. The effects of the intervention will be assessed using the intention-to-treat method. The effect of the intervention on primary and secondary outcomes, including SBP and DBP over time (baseline, 1 month, 3 months and 6 months), will be assessed using two-way mixed analysis of variance (ANOVA) models. There will be adjustments for multiple comparisons for SBP and DBP. The intervention's effect on acceptability and salts' usage will be assessed using independent t-tests and χ^2 tests, respectively. A p value <0.05 will be considered statistically significant. All statistical analyses will be performed in STATA software (V.14).

DISCUSSION

This trial is the first RCT of a salt substitution intervention among individuals with HTN in Iran. We will recruit 500 eligible participants among whom the hypotheses can be examined in this study.

In the past two decades, the prevalence of HTN has diminished moderately in high-income countries, while it has increased significantly in low- and middle-income countries.²³ In Iran, the prevalence of HTN increased from 14.66% to 32.03% between 2009 and 2021.²⁴ Excessive sodium intake causes HTN, which is one of the most common diseases in Iran, as mentioned in the introduction. Iran has implemented some policies to control high blood pressure, including regulations on fat and salt labelling in food and reducing salt in bread. However,

the treatment, management and control of high blood pressure is still unsatisfactory.^{25 26} Therefore, due to the high prevalence of HTN and limited national resources to meet government priorities and goals, the identification of the most effective and feasible interventions seems necessary.²⁷

Antihypertensive medications are very effective in lowering blood pressure. Moreover, behavioural patterns based on sodium reduction are also recommended to keep blood pressure under control.²³ Potassium-enriched salt, which replaces the sodium chloride in common regular salt with potassium chloride, is an effective and practical method of lowering blood pressure.²⁸ A large randomised trial in China demonstrated that potassium-enriched salt significantly reduced the risk of major cardiovascular events, stroke and premature death over 5 years compared with regular salt.²⁹ Other previous studies have shown that reduced sodium and added-potassium salt substitutes lower blood pressure.^{28 30} However, the potential risks associated with potassium-enriched salt substitutes should be considered. These risks include an elevated likelihood of hyperkalaemia and its primary adverse effects, which encompass arrhythmias and sudden cardiac death. This is particularly concerning for individuals with conditions that hinder potassium excretion, such as CKD.¹⁶ Moreover, despite salt substitution having the potential to lower all-cause and cardiovascular mortality, the evidence regarding its effectiveness in decreasing cardiovascular events and not leading to serious adverse events remains inconclusive, especially within Western populations.¹⁵

Increased dietary sodium causes HTN and CVD. HTN currently affects more than a quarter of adults and is the main global risk factor for death.³¹ The WHO recommends that adults limit their sodium intake to <2 g/day (equivalent to 5 g of salt per day).³¹ Several mechanisms play a role in the potential benefits of salt restriction. First, high salt intake increases blood volume and peripheral vascular resistance, so limiting salt intake may facilitate blood pressure reduction.³² In addition, salt restriction has been proposed as a preventative factor for the production of reactive oxygen species.³³ Moreover, the salt restriction can reduce the production of inflammatory markers.³⁴ If this study provides favourable results regarding the efficacy and acceptability of salt substitutes in Iran, the results will have important implications for the use of salt substitutes in the treatment of HTN in Iran and may also stimulate new large-scale studies testing the efficacy of salt substitutes on blood pressure lowering in other populations and locations in Iran.

Strengths of this study include the randomised controlled design, which ensured similar baseline characteristics across groups, allowing causal investigation of the effect of salt substitutes on the primary and secondary outcomes. Also, double-blinding of the intervention of participants and researchers (outcome assessors) reduces the risk of bias. The recruited

sample size allows for a 20% dropout to ensure statistical power. In addition, we will recruit from both genders, which allows the results to be generalisable. Blood pressure measurements are performed according to standard HTN guidelines using validated devices. Furthermore, although 24-hour urine collection is onerous, it is the conventional gold standard for estimating dietary sodium intake.³⁵ We also will routinely assess participants' serum potassium during the study. Although the risk of hyperkalaemia is low regarding the exclusion of patients with kidney problems, it is possible that salt substitutes can cause hyperkalaemia in some people.

Some limitations are recommended to be considered in future research. First, we will not administer para-aminobenzoic acid to the participants to assess the completeness of the 24-hour urine collection. It is likely that some of the collections will be incomplete, which may underestimate total salt intake. Also, we will not exclude patients who consume the renin-angiotensin system (RAS) inhibitors, which increase the risk of hyperkalaemia, because this exclusion limits generalisability. Therefore, this limitation will be considered in the statistical analysis. Additionally, we did not consider the additional benefits of partial salt substitution on non-cardiovascular outcomes such as gastric cancer and gastrointestinal malfunctions, which may lead to an underestimation of the net benefit of the intervention. Future studies should evaluate the benefits of potassium-enriched salt substitutes in specific subpopulations. Although the research team attempted to manage typical RCT operational challenges by developing a detailed work schedule, the current study will probably be involved in some challenges, such as maintaining the blinding of participants and study personnel and maximising adherence to the standardised protocols. Additionally, comprehensive training will be provided to study staff, particularly about blood pressure measurement, 24-hour urine sampling and the use of automated meters to measure urine electrolytes. All in all, this trial will provide data on the efficacy of reduced sodium and added-potassium salt substitution on blood pressure and its acceptability among Iranian hypertensive patients. Findings from this trial will provide much-needed new evidence of the efficacy and acceptability of salt substitutes as a possible strategy to decrease HTN in Iranian hypertensive patients.

Ethics and dissemination

This research involving humans with HTN will be conducted in Iran. This study has been approved by Alborz University of Medical Sciences (0-0-103-6369) and has received ethics approval (IR.ABZUMS.REC.1402.293). The study will be conducted in accordance with the Declaration of Helsinki and is prospectively registered at the Iranian Registry of Clinical Trials on 2024-02-17

(IRCT20240121060757N1). The results will be submitted for publication in a peer-reviewed journal and presented at one or more scientific conferences.

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Contributors ED wrote the manuscript. NKH handled the registration protocol in IRCT. EH, SS, BG, MP and ZFK will conduct the data gathering. ES will report the final results. OA and MQ planned the study and will supervise it. MQ is responsible for the overall content as guarantor.

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