Benefits of water intake on kidney function in older adults: protocol for a randomized controlled trial

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Objective: The goal of this study is to evaluate the benefits of an increase in water intake guided by a mathematical formula (per kg of body weight) on kidney function in older adults.

Methods: Older adults (≥ 65 years old) cared for at the Internal Medicine Unit of a tertiary hospital will be randomized to receive or not guidance on water intake (30 mL/kg per day) after initial assessment of kidney function. After 14 days, participants will be reevaluated through clinical and laboratory examinations. Patients with uncompensated disease will be excluded. The main outcomes will be glomerular filtration rate and laboratory measures such as serum and urinary osmolality, sodium, urea, 24-h urine volume and serum creatinine, uric acid, and copeptin. The Mini Nutritional Assessment (MNA) questionnaire will be applied to participants at each visit. Categorical variables will be described as numbers of cases (%) and compared using the χ² test whereas continuous variables will be analyzed with Student’s t-test in relation to baseline measures. The Generalized Estimating Equations (GEE) method will be performed to assess differences over time and between groups. This study was approved by the Institution’s Research Ethics Committee (grant number 16-0153) and is in accordance with the Declaration of Helsinki.

Expected Results: By increasing water intake (ml/Kg) we expect to provide an improvement in kidney function in older population assessed by serum creatinine and cystatin-c applied to eGFR formulas.

Relevance: Many conditions, both organic and behavioral, can contribute to chronic dehydration states in older adults. To mention, decreased ability to concentrate urine, reduced kidney mass, blood flow, and glomerular filtration rate (GFR) along with changes in sensitivity to hormones such as renin, vasopressin and natriuretic peptide can generate water imbalance, leading to dehydration. For being simple and inexpensive, this strategy may be broadly used and bring several health benefits to older adults.

Keywords: water intake; older adults; kidney function.

Abstract

How to cite this article: Falcetta MRR, Rocha GBM, Daudt LR, Bublitz AK, Menegolla MP, Borges RP, et al. Benefits of water intake on kidney function in older adults: protocol for a randomized controlled trial. Geriatr Gerontol Aging. 2022;16:e0220004. https://doi.org/10.53886/gga.e0220004

Resumo

Palavras-chave: ingestão de água; idosos; função renal.
INTRODUCTION

One of the greatest cultural achievements of a people is the aging of the population, reflecting an improvement in living conditions. The percentage of people over the age of 60 years is increasing around the world. According to a projection by the United Nations, 1 in 9 people worldwide is 60 years of age or older, and this proportion is estimated to increase to 1 in 5 by 2050.

Aging is associated with cell growth and differentiation processes, resulting from the interaction between genetic characteristics and individual, environmental, and sociocultural variables that comprise an individual's lifestyle. These processes are usually characterized as progressive decrease in functional reserve, reducing responsiveness to challenges and leading to functional overloads that may result in pathological processes.

Body water regulation is one of the metabolic processes that undergo major changes through the years. An important feature of this dysregulation is the perception of thirst, which significantly contributes to a high prevalence of dehydration in the older population, causing a decline in kidney function. Conditions that lead to chronic dehydration states in older adults can be frequent. To mention, a decreased ability to concentrate urine and decreased kidney mass, blood flow, and glomerular filtration rate (GFR). Furthermore, changes in sensitivity to hormones such as renin, vasopressin, and atrial natriuretic peptide can generate water imbalance, leading to dehydration. This population may also have a decrease in thirst and an intentional decrease in fluid intake for reducing voiding frequency and urinary losses.

Metabolic changes in body water homeostasis can influence and lead to chronic dehydration states through reduced vasopressin. Functional impairments in this population, such as issues with mobility, autonomy, and memory, can restrict access to liquids. The use of many medications, which is common in this age group, can also add risks for dehydration: these include diuretics, renin-angiotensin-aldosterone system inhibitors, laxatives, and psychoactive drugs. In a subgroup of patients with diabetes mellitus, polyuria and changes in vasopressin release can be aggravating factors for chronic dehydration, contributing to chronic kidney disease.

Dehydration in adults aged 60 years or older is associated with important pathological conditions, including urolithiasis, constipation, asthma, cardiovascular disease, diabetes, and cancer. In this population, dehydration can also contribute to impaired cognitive function, kidney disease, low blood pressure, and infections. Dehydration can be classified into hypertonic, isotonic, and hypotonic, according to the relationship between water and salt loss. Age is also an independent risk factor for both hypernatremia and hyponatremia. Studies indicate mortality rates of up to 40–50% associated with dysnatremia (any alteration in sodium levels) and dehydration in this population. The best measure for assessing kidney function is GFR. The most accurate way to measure GFR is by using a marker that has a constant production rate and is freely filtered, not reabsorbed or secreted by the renal tubules, nor metabolized or eliminated by extra-renal pathways. Analyses of substances such as inulin, 51Cr-EDTA, or iohexol are considered reference methods for assessing GFR; however, they are expensive and time-consuming and require radioactive techniques. Given these restrictions, the most commonly used methods to estimate GFR are the measurement of serum creatinine or the mathematical estimation of GFR based on serum creatinine levels.

Observational studies in humans show that higher water intake can possibly have a protective effect on kidney and cardiovascular outcomes. A Canadian cohort of 2148 participants showed that lower urine volume (< 1 L/24 h) at baseline was a predictor of faster decline in estimated glomerular filtration rate (eGFR) when compared to higher daily urinary volumes (> 3 L/24 h) considering a 6-year follow-up. A study for assessing whether increased oral consumption of water can preserve or even improve kidney function in individuals over 65 years of age is thus important and highly justifiable. This intervention is simple and low-cost and, if confirmed, could be implemented at institutions and by family members and health promoters who care for older adults.

OBJECTIVE

The goal of this study is to evaluate the effect of an increase in water intake guided by a mathematical formula (per kg of body weight) on kidney function in older adults.

METHODS

Study design

This will be a randomized, open-label, placebo-controlled clinical trial (Figure 1).

Participants (inclusion and exclusion criteria)

Inclusion criteria for eligible participants will be Internal Medicine and Geriatrics outpatients at our institution, aged 65 years or older, with functional capacity to drink liquids without assistance, and who agreed with the consent form.

Exclusion criteria will comprehend individuals with:
a. New York Heart Association (NYHA) class III or IV heart failure;
b. angina or acute myocardial infarction episodes in the previous 3 months;
c. a pacemaker or defibrillator,
d. chronic kidney disease with eGFR < 30 mL/min/1.73 m²,
e. organic or cognitive impairment that restricted liquid intake,
f. hepatic cirrhosis,
g. hypo or hyperthyroidism;
h. other serious cerebrovascular, cardiac, hepatic, kidney, gastrointestinal, endocrine, or metabolic disorders that deemed them ineligible by the principal investigator.

Randomization
At this stage, participants will be randomly assigned to 1 of 2 groups by stratified permuted block randomization. Assignment factors were sex and kidney function (eGFR ≥ 60 mL/min/1.73 m² and < 60 mL/min/1.73 m²). The random sequence will be created using the https://www.random.org website.

Intervention
Participants in the intervention group will receive verbal and written guidance to drink a calculated amount of water daily — 30 mL/kg, as suggested in the literature, for 14 days. They will receive an acrylic glass with a 200 mL fill line (Figure 2) and are instructed to have the number of glasses of water corresponding to the calculated will volume each day. Participants in the intervention group also receive a leaflet (Figure 3) indicating how many glasses of water they were asked to have per day for 2 weeks. They will be instructed to mark with an “X” the number of glasses of water they actually drank each day during the 2-week period. Participants in the control group will be instructed to maintain their usual water intake. Participants in both groups receive a questionnaire regarding foods and beverages consumed during the day (food diary).

Adherence and safety
Participants will receive a telephone call 1 week after randomization to assess and reinforce adherence and verify the safety and possible complications that may be occurred during the 1-week period. This telephone call is made by one of the researchers from a hospital telephone.
Execution logistics

First visit
Participants are invited to participate in the study and receive an explanation and the consent form. After acceptance, the participant receives guidance for 24-h urine collection and a bioimpedance examination.

Second visit
On this visit, participants undergo a brief consultation with blood pressure and heart rate measurements in addition to a bioimpedance examination.

A researcher picks a brown envelope with the participant’s randomization group from a sequence containing numbers of the randomization process, defined by the https://www.random.org website. Randomization occurs in blocks and is stratified by sex and eGFR (greater or less than 60 mL/min/1.73 m²).

The Mini Nutritional Assessment (MNA) and Mini Mental State Examination (MMSE) questionnaires are also applied at this moment, and participants in the intervention group receive verbal instruction to increase water intake in a proper amount, an acrylic glass, and a structured form for recording the number of glasses of water ingested. All participants receive a food diary to fill with food and beverages taken for 4 days out of the 2-week intervention. The 24-h urine sample is delivered to the laboratory, and the participant goes through serum sample and urine collection for osmolality analyses.

Telephone call
One week after the second visit, participants receive a telephone call to reinforce adherence and assess safety and possible questions. This call also verifies the occurrence of clinical complications unrelated to the study which may require discontinuation of the intervention.

Third visit
It takes place 14 days after the intervention. Participants undergo a consultation with blood pressure and heart rate measurements and a new bioimpedance examination. The MNA and MMSE questionnaires are applied once again and the food diary and structured form are collected. A new 24-h urine sample is delivered to the laboratory and the same laboratory tests from the second visit are collected.

Measurement tools

Laboratory tests
Laboratory tests are collected at both the second and third visits (Figure 1). Sample collection takes place after each appointment by a trained professional at our institution's

![Water ingestion record](https://www.ggaging.com)

FIGURE 3. Structured form for recording how many cups of water were ingested.
Clinical Research Center. The participant brings the 24-h urine sample, as previously instructed. Another urine sample is collected at each appointment for dosing urine osmolality.

Blood and urine samples are collected at the second visit (beginning of the intervention) and at the third visit (at the end of the intervention). Blood samples are drawn after each research visit by a trained professional at the Clinical Research Center.

Blood tests: creatinine, cystatin C, copeptin, urea, sodium, glucose, uric acid, and osmolality; 24-h urine tests: sodium, urea, creatinine, and 24-h volume. The analyses are performed at the Clinical Pathology Laboratory of Hospital de Clínicas de Porto Alegre.

Kidney function is assessed through GFR equations that use creatinine and/or cystatin C. The selected equations are CKD-EPI, CKD-EPI Cys, MDRD, BIS-1, and BIS-2 (Cys). Inulin clearance, iohexol, and 51Cr-EDTA are considered reference methods to assess GFR, but are costly, time-consuming, and not widely available.

Anthropometric measures
Height is measured with a wall-mounted standardized stadiometer (model E150A, Tonelli®) at the first visit by a trained researcher. Weight is measured by a trained researcher using electrical bioimpedance InBody 370® equipment. To properly perform the bioimpedance examination, participants receive detailed instructions as to fast for 4 h; not ingest foods or drinks containing caffeine or alcohol 24 h before the examination; avoid medications with caffeine during this period; not practice physical activity 12 h before the examination; take diuretic drugs (if currently in use) only after the examination (scheduled for 7:30 am to avoid medication interference), have no fever or other acute condition, and urinate 30 minutes before the examination. The main role of bioimpedance in this work is to demonstrate total body water, the percentage of body water, and free-fat mass.

Vital signs
Blood pressure — blood pressure is measured with an aneroid analogue sphygmomanometer (Premium®), according to the standard non-invasive blood pressure measurement technique. Measurements are performed twice at each visit, with the patient seated, after at least 10 minutes of rest.

Heart rate — measurements are performed during cardiac auscultation with a Littmann® Classic 2 stethoscope by directly counting the number of beats/min.

Measurements are performed by the researchers (all properly trained) at the second visit and after 14 days.

Nutritional assessment
MNA is a nutritional assessment tool that allows the identification of malnourished older adults and those at risk of malnutrition, being validated to the Brazilian population.3 In this protocol, this tool is applied to participants at the second and third visits.

Food diary — Patients are verbally advised to keep a food diary for 4 of the 14 days of the study. The food diary is a way to estimate the amount of liquid ingested daily by the patients, especially in the control group, where no other record of liquid intake is present.

Cognitive assessment
The MMSE is a screening examination of cognitive function. It has a maximum score of 30 points, assessing different domains: orientation to time and place, registration, attention and calculation, recall, and language. The MMSE version used in this study has been translated and validated to Brazilian Portuguese32,33 and is applied by the researchers at the second and third visits.

Statistical analysis
Sample size calculation
The sample size was calculated using PSS® software. A significance level of 0.05%, a power of 90%, and a standard deviation of eGFR (CKD-EPI and MDRD in healthy adults)22,34 of 15 mL/min/1.73 m² were used to detect differences of 20 mL/min/1.73m² in eGFR. Therefore, 12 patients would be necessary in each group. Considering an estimated loss of 20%, 15 patients will be included per group.

The analysis of results will be performed using SPSS, version 22.0, with a 95% significance level for type I error (p < 0.05).

Continuous variables with normal distribution will be described as means and standard deviations. Variables without normal distributions will be described as medians and interquartile ranges and will be analyzed after logarithmic transformation.

Categorical variables will be described as numbers of cases (%) and compared by the χ² test, and continuous variables will be analyzed with Student’s t-test for analyses related to baseline measurements. To evaluate differences over time and between groups, the Generalized Estimating Equations (GEE) test will be performed. A Bland-Altman analysis will be used to assess the concordance of eGFR calculated using creatinine and cystatin C levels between different equations.

Ethical approval
The study project was registered and accepted in Plataforma Brasil and has been approved by our institution’s Research Ethics Committee and Research and Graduate Group (GPPG) under No. 16-0153.

Trial registration — ClinicalTrials.gov NCT03002415. Trial status — patient recruitment and data analysis.
EXPECTED RESULTS AND RELEVANCE
Situations that lead to chronic dehydration states in older people can be quite frequent, and still, they are little studied. Metabolic changes in body water homeostasis can influence and cause chronic dehydration states, contributing to a loss of GFR.14

We believe that water intake based on body weight may represent a safe and promising intervention to prevent chronic dehydration in older individuals without decompensated comorbidity. In addition, it may dilute waste products, protecting the kidneys. We expect that our intervention results in an improvement in eGFR in older adults assessed by the formulas that use creatinine and cystatin-C.

A few studies have randomized patients to increased water intake and compared this intervention with placebo; however, none of them focused on the older population. Clark et al.35 published a randomized controlled trial in 2018 with a coaching method to increase water intake in patients of any age with chronic kidney disease compared with those who maintained their water intake; this intervention did not significantly slow the decline in kidney function after 1 year.

Nakamura et al.36 also performed a similar study using orientation to increase water intake in healthy adults in Japan as intervention, and although eGFR was not improved, this study showed that an increase in water intake could represent a safe intervention with the potential for lowering blood pressure in healthy adults.

An advantage of our study is the fact that it considers older adults as the object of study. Therefore, the use of specific formulas that are more sensitive to changes in eGFR in the older population (such as BIS1 and BIS2) could suggest that increased water intake brings benefits to kidney function in this unique group of people. Our study could also show whether a shorter intervention could bring short-term changes in patients’ kidney function and eGFR.

The main limitation of this study is the short duration of the intervention. This study is relevant because, in case of positive results, it might suggest that even short-term interventions with guidance on water intake can have a positive effect in this population. Guided water intake could thus bring several health benefits.

ACKNOWLEDGMENTS
We thank the Event and Research Incentive Fund (Fundo de Incentivo à Pesquisa e Eventos, FIPE) and the National Council for Scientific and Technological Development (Conselho Nacional de Desenvolvimento Científico e Tecnológico, CNPq) for supporting this project.

Conflicts of interest
None of the authors have conflicts of interest to declare.

Funding
This work is supported by FIPE, grant number 16-0153, 2016; and CNPq, grant number 16-0153.

Authors’ contributions
MRRF: Conceptualization, writing – original draft. ACB: Conceptualization, writing – review & editing. GBMR: Project administration. LRD: Project administration. MPM: Writing – original draft. AKB: Writing – original draft. RPB: Writing – original draft.

REFERENCES


