

**Dietary Approaches to Stop Hypertension
(DASH) Diet effects on Serum Uric Acid
(SUA) in adults with hyperuricemia and
gout.**

DIGO

THE DIET GOUT TRIAL

STATISTICAL ANALYSIS PLAN

VERSION 1.0

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1 Introduction

DIGO is an individual level, crossover, randomized trial to determine the effect of 4-weeks of DASH groceries' on serum uric acid in 40 adults with self-reported gout and hyperuricemia and not on urate lowering therapy. Participants are randomly assigned to 1 of 2 sequences: (1) the DASH grocery intervention followed by the self-directed diet or (2) the self-directed diet followed by DASH groceries.

The **primary outcome** is the difference in mean uric acid measured in serum after each feeding period.

1.1 Primary aim

To determine the effect of the DASH Diet on serum uric acid among adults with self-reported gout and hyperuricemia. In this crossover, randomized controlled trial (RCT) of 40 patients with hyperuricemia (SUA level $\geq 7\text{mg/dL}$), we will compare a DASH diet grocery intervention vs. a self-directed control diet over 4 weeks to determine the effect of the DASH diet on uric acid.

1.2 Other aims

To estimate the effects of the DASH diet on the following outcomes:

- A. Clinic blood pressure
- B. Orthostatic hypotension
- C. Timed Up and Go
- D. Body mass index
- E. Urinary sodium, potassium, and creatinine excretion
- F. Self-reported fruit, vegetable, and fat consumption
- G. Gout severity and flares
- H. Global physical function
- I. Joint pain
- J. Fasted LDL cholesterol
- K. Fasting blood sugar
- L. Urine pH and uric acid level

2 Data Source

Data will be entered by clinic staff into a REDCap dataset. Grocery nutrient information will be derived from the ESHA platform. Backup files of the database will be generated and stored at regular intervals in a secure, off-site location, to permit regeneration of the database in the event that it is destroyed.

3 Primary Outcome: Serum Uric Acid

3.1 Randomization and primary analysis

Participants will be randomized using a computer-generated randomization scheme with varying sized blocks to 1 of 2 sequences in a 1:1 ratio such that approximately half of participants will undergo the DASH grocery intervention first followed by the self-directed phase while the other half will undergo the self-directed (reference) phase first, followed by the DASH grocery intervention. There is no washout period.

We will first confirm that the residuals of uric acid are normally distributed (if not these values will be log-transformed). We will then assess for carryover effects by: (1) examining a period variable in relation to uric acid (temporal effects) and (2) an intervention-by-period interaction term. If this is significant, we will conduct a period 1 only analysis (treating the trial as a parallel design), comparing the unpaired effects of 4-week DASH groceries on uric acid compared to 4 weeks of the self-directed group. This will be performed with linear regression adjusted for baseline uric acid values.

If there is not sufficient evidence of a carryover effect, we will compare serum uric acid measurements from both periods within person using the trial's crossover design. These comparisons will be performed with generalized estimated equations (normal distribution, identity function) with an exchangeable working matrix and robust variance estimator. These analyses will be adjusted for baseline uric acid measurements.¹

We will use an intent-to-treat approach for either of the two scenarios above.

Our hypothesis is that 4-weeks of the DASH grocery intervention will lower serum uric acid compared to 4-weeks of the self-directed diet. The null hypothesis is that there will be no difference in uric acid between either phases of the study.

3.2 Power and sample size

Based on a cross-over trial design, using a variance of 1.71 at an alpha level of 0.05 using a twosided paired means test with a power of 0.8, we estimated that we would need 41 participants to detect a 4-week difference of -0.75 mg/dL between interventions.² In two prior studies we had observed reductions of -1.3 and -1 mg/dL among subpopulations with a uric acid above 7 mg/dL.^{3,4}

3.3 Secondary Contrast

We will compare end of period uric acid with baseline values to determine baseline change in uric acid over each study period.

3.4 Pre-specified Stratified Analysis

We will repeat the primary analysis in subpopulations based on the following criteria:

1. Race (black vs white)
2. Stage II hypertension (>140/>90)
3. Obesity (BMI > 30 kg/m²)
4. Estimated glomerular filtration rate < 60 ml/min per 1.73 m²
5. Estimated Calorie intake (> vs ≤ median value)
6. Baseline uric acid 7-<8, 8-<9, 9-<10, ≥10 mg/dL (note categories may be combined to ensure a reasonable number in each group, given our small overall sample size)
7. Gout severity (based on number of flares at baseline, stratified by median value)

Interaction terms will be used to assess for effect modification by baseline characteristic. Note these analyses are contingent of the distribution of baseline characteristics.

Other stratified analyses based on baseline characteristics may be performed for hypothesis generation beyond the main study.

3.4 Sensitivity analyses

1. Models will be run with no adjustment for baseline uric acid
2. We will perform an on-treatment analysis: (i) persons who ate 25% or less of non-study foods during the DASH grocery intervention, (ii) persons whose estimated Calorie intake was met or exceeded by the food provided through the DASH grocery intervention, and (iii) persons who did not change antihypertensive medications or urate lowering therapies during the post-randomization study period
3. We will perform an analysis excluding women
4. Depending on whether there were carryover effects, we will perform the parallel (period 1 only) or crossover analysis as a sensitivity analysis.

4 Other outcomes

3.5 Secondary Endpoints

We will examine the effect of the diets on the following additional outcomes, testing the null hypothesis that there is no difference in the following outcomes between the self-directed (reference) and DASH diet intervention phases of the study. All these outcomes will be evaluated using generalized estimated equations to compare change between the 2 trial phases adjusted for baseline. We will examine the distribution of all variables. Model function will be based on the variable distribution whereby we will use linear regression for normally distributed outcomes and logistic regression for binomial outcomes. Continuous variables with non-normal residuals will be log-transformed with effects reported as a % change.

- A. Clinic blood pressure
 - Continuous variable, normal distribution
- B. Orthostatic hypotension
 - Binary variable, binomial distribution
- C. Timed Up and Go Test
 - Continuous variable, normal distribution
- D. Body mass index
 - Continuous variable, normal distribution
- E. Urinary sodium, potassium, and creatinine excretion
 - These may require log-transformation; anticipate continuous variables, normal distribution
- F. Self-reported fruit, vegetable, and fat consumption
 - These may require log-transformation; anticipate continuous variables, normal distribution
- G. Gout severity
 - Binary variables (severe vs not), binomial distribution
- H. Global physical function
 - Continuous variable, normal distribution
- I. Joint pain
 - Anticipate skewed scale that may require log-transformation
- J. Fasted LDL cholesterol

- Continuous variable, normal distribution

K. Fasting blood sugar

- Continuous variable, normal distribution

L. Urine pH and uric acid level

- Continuous variable, normal distribution

5 Missing data

We will employ a number of recommended strategies to prevent missing data:⁵⁻⁸

- A simplified data collection schedule that minimizes participant burden;
- Intention-to-treat analysis that includes following participants according to the data collection schedule regardless of compliance with the study intervention;
- Frequent engagement with the participants through visit reminder calls or notes;
- A 24-hour phone number that participants can contact for questions and support; □
 - Contiguous windows of time during which specific follow-up visits are allowed; □
 - Monetary incentives to encourage enrollment and continued participation;
- Rigorous training of clinic staff emphasizing the importance of:
 - Positive and warm interpersonal relationships between the participants and study staff
 - Study commitment during the consent process to ensure that potential participants understand the importance of completing the study
 - Addressing participant concerns to minimize dissatisfaction
 - Collecting data even if a participant discontinues the study treatment

Reasons for any drop-outs will be documented. If a drop-out occurs for reasons related to the study, i.e., informative censoring, we will perform sensitivity analyses using established methods for addressing informative censoring, namely, imputation techniques for missing data, best and worst-case scenarios, and use of the drop out event as a study end-point.⁹ We will review these approaches to minimize bias. Further, we will compare the baseline characteristics of participants with missing measures between the two assignments.

6 Safety outcomes

We will compare the rate of gout flares by assignment group using Poisson regression. We will also compare self-reported symptoms that are thought to potentially arise from the diets.

7 References

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