Effects of dietary macronutrients on serum urate: results from the OmniHeart trial

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ABSTRACT

Background: Dietary recommendations to prevent gout emphasize a low-purine diet. Recent evidence suggests that the Dietary Approaches to Stop Hypertension (DASH) diet reduces serum urate while also improving blood pressure and lipids.

Objective: To compare the effects of DASH-style diets emphasizing different macronutrient proportions on serum urate reduction.

Methods: We conducted a secondary analysis of the Optimal Macronutrient Intake Trial to Prevent Heart Disease feeding study, a 3-period, crossover design, randomized trial of adults with prehypertension or hypertension. Participants were provided with 3 DASH-style diets in random order, each for 6 wk. Each DASH-style diet emphasized different macronutrient proportions: a carbohydrate-rich (CARB) diet, a protein-rich (PROT) diet, and an unsaturated fat-rich (UNSAT) diet. In the PROT diet, approximately half of the protein came from plant sources. We compared the effects of these diets on serum urate at weeks 4 and 6 of each feeding period.

Results: Of the 163 individuals included in the final analysis, the mean serum urate at baseline was 5.1 mg/dL. Only the PROT diet reduced serum urate from baseline at the end of the 6-wk feeding period (–0.16 mg/dL; 95% CI: –0.28, –0.04; $P = 0.007$). Neither the CARB diet (–0.03 mg/dL; 95% CI: –0.14, 0.09; $P = 0.66$) nor the UNSAT diet (–0.01 mg/dL; 95% CI: –0.12, 0.09; $P = 0.78$) reduced serum urate from baseline. The PROT diet lowered serum urate by 0.12 mg/dL (95% CI: –0.20, –0.03; $P = 0.006$) compared with CARB and by 0.12 mg/dL (95% CI: –0.20, –0.05; $P = 0.002$) compared with UNSAT.

Conclusions: A DASH-style diet emphasizing plant-based protein lowered serum urate compared with those emphasizing carbohydrates or unsaturated fat. Future trials should test the ability of a DASH-style diet emphasizing plant-based protein to lower serum urate and prevent gout flares in patients with gout. This trial was registered at clinicaltrials.gov as NCT00051350. *Am J Clin Nutr* 2021;113:1593–1599.

Keywords: gout, diet, purine, macronutrient, protein, hypertension, lipids

Introduction

Diet has long been considered a significant modifiable factor in the pathogenesis of hyperuricemia and gout (1). Dietary recommendations to prevent gout traditionally emphasize reducing intake of purine-rich foods (e.g., meat, seafood, and purine-rich vegetables) (2), as purines are the precursors to urate via the purine scavenger pathway (3). While purine-restricted diets are often lower in protein, studies have suggested that high total-protein intake is not associated with elevated serum urate and that plant-based protein consumption may be inversely associated with hyperuricemia and gout (4, 5). Furthermore, education on low purine intake has not demonstrated efficacy in reducing serum urate in patients with gout (6), and low-purine diets have unknown effects on cardiovascular disease (CVD) risk factors that often accompany gout, such as hypertension and hyperlipidemia (7). Reduced protein intake may also inadvertently cause increased consumption of refined carbohydrates and saturated fat, thereby exacerbating CVD risk factors (8, 9).

Supported by NIH/National Heart, Lung, and Blood Institute (K23HL135273 and R21HL144876) to SPJ; NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases (P50AR060772 and R01AR065944) to HKC; Mid-Atlantic Nutrition Obesity Research Center (NORC) under NIH award number P30DK072488 to LJA.

Supplemental Tables 1–3, Supplemental Methods 1 and 2, and Supplemental Figure 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: BP, blood pressure; CARB, carbohydrate-rich diet; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GEE, generalized estimated equation; OmniHeart, Optimal Macronutrient Intake Trial to Prevent Heart Disease; PROT, protein-rich diet; SBP, systolic blood pressure; UNSAT, unsaturated fat–rich diet.

Received August 13, 2020. Accepted for publication December 14, 2020.

First published online March 1, 2021; doi: https://doi.org/10.1093/ajcn/nqaa424.

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Recent studies suggest that the Dietary Approaches to Stop Hypertension (DASH) diet—a carbohydrate-rich diet emphasizing fruit, vegetables, and low-fat dairy (10)—reduces serum urate in addition to its established effects on blood pressure (BP) and lipids (11, 12). Moreover, a large prospective observational study found that the DASH diet may decrease the risk of developing gout (13). The Optimal Macronutrient Intake Trial to Prevent Heart Disease (OmniHeart) was a 3-period, crossover design, feeding study conducted to evaluate whether the DASH diet's beneficial effects on CVD risk factors may be improved by partial replacement of carbohydrates with either protein or unsaturated fat (14). In the trial, adults with elevated BP or hypertension were assigned to each of 3 healthy DASH-style diets that emphasized different proportions of macronutrients (carbohydrate, protein, or unsaturated fat). The OmniHeart trial demonstrated that partial substitution of carbohydrates with either protein or monounsaturated fat enhances the beneficial effects of the DASH diet on systolic BP (SBP), lipid concentrations, and 10-year risk of CVD based on the Framingham risk equation. However, the impact of each respective diet on serum urate was not studied.

In this post hoc analysis, we measured serum urate in stored specimens from the OmniHeart trial to determine the effects of 3 DASH-style diets that emphasized different macronutrient proportions on serum urate. We hypothesized that all 3 of the DASH-style diets would lower serum urate and that the diet emphasizing carbohydrates (i.e., lower protein and fat) would have the greatest effect based on our prior work (15).

Methods

The investigator-initiated OmniHeart trial was a multicenter, randomized, 3-period crossover design, feeding study funded by the National Heart, Lung, and Blood Institute that investigated the effects of 3 healthy diets with different macronutrient compositions on CVD risk factors. The rationale, design, and primary results have been previously reported (14, 16). The primary outcomes for the original OmniHeart Trial were BP and lipids, and the results have previously been published (14). The original study protocol was approved by the institutional review boards at Johns Hopkins University, Brigham and Women's Hospital, and the Harvard School of Public Health.

Participant recruitment

The OmniHeart trial included men and women ≥30 y of age with elevated BP or hypertension [defined at the time of the trial as SBP 120–159 mm Hg or diastolic BP (DBP) 80–99 mm Hg] but who were otherwise healthy. Participants were enrolled in the protocol between April 2003 and June 2005 and were recruited from areas around Boston, Massachusetts, and Baltimore, Maryland. Exclusion criteria included a diagnosis of diabetes, kidney disease [estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2], history of CVD, weight more than 350 lbs (158.75 kg), >2 alcoholic drinks per day for men or >1 alcoholic drink per day for women, or those on pharmacotherapy for hypertension or hyperlipidemia. Further details on exclusion and inclusion criteria can be found in the original OmniHeart report (14) and in the participant flowchart (**Supplemental Figure 1**).

Dietary interventions

Study diets consisted of 3 healthy variations of the DASH diet that were distinguished primarily by macronutrient composition: *1*) a carbohydrate-rich diet (CARB), *2*) a protein-rich diet (PROT), and *3*) an unsaturated fat-rich diet (UNSAT). Aside from the differences in macronutrients, the 3 diets had similar features, consistent with the DASH diet; all diets emphasized fruit, vegetables, and fiber while limiting saturated fat, cholesterol, and sodium (<2300 mg/d). Protein sources across each diet included lean beef, fish, poultry, dairy, and egg product substitutes. Each diet limited energy from saturated fat to 6% of the total daily kcal.

The CARB diet most closely resembled the macronutrient proportions of the original DASH diet, except for a slight increase in carbohydrates (58% compared with 55% of kcal) and a slight decrease in protein (15% compared with 18% of kcal). The total protein in the CARB diet was reduced to 15% of kcal to achieve a 10% of kcal contrast with the PROT diet (25% of kcal). The PROT diet and UNSAT diet each replaced 10% of kcal from carbohydrates with protein or unsaturated fat, respectively (**Supplemental Table 1**). The additional unsaturated fat in the UNSAT diet was primarily monounsaturated (e.g., olive, canola, and safflower oils, as well as nuts and seeds). Approximately half of the additional protein in the PROT diet came from plant sources (e.g., legumes, grains, nuts, and seeds). The average daily contribution of each of these plant-based protein sources was as follows: legumes (85 g/d), soy (35 g/d), whole grains (33 g/d), nuts and seeds (30 g/d), wheat gluten (22 g/d), and peanuts/peanut butter (16 g/d) (17). The remainder of the additional protein came from nonplant sources, including lean beef, poultry, fish (tuna or scrod), egg product substitutes, and dairy.

After collecting baseline data and completing a run-in period, participants were randomly assigned to each diet for a 6-wk feeding period in 1 of 6 dietary sequences. The feeding periods were separated by a washout period of 2 to 4 wk, during which participants ate their own food. Individuals were advised to continue their usual amount of physical activity and alcohol consumption throughout the study period. Calorie targets for each participant (based on body size, sex, and physical activity) were developed to maintain weight within 2% of baseline and were adjusted as needed to achieve this goal. There was minimal deviation from the study protocol regarding nonstudy food consumption (i.e., participants were adherent to the study protocol for >95% of trial person-days). Adherence was assessed through self-report and objective measurements, including 24-h urinary collections obtained at baseline and once during the last 2 wk of each feeding period. Mean urine urea nitrogen was highest on the protein diet, reflecting greater protein intake (**Supplemental Table 2**).

Of the 191 participants randomly assigned to a dietary sequence, 160 completed all 3 feeding periods. Following the analytic methods used in the main results paper of the OmniHeart trial (14), the 163 participants who completed at least 2 feeding periods were included in the final analyses.

Measurement of serum urate

Fasting blood samples were collected at baseline and weeks 4 and 6 of each feeding period. After collection, blood samples

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were allowed to clot at room temperature for 15 min and then centrifuged in a serum-separating tube at 1500 RPM for 15 min at 4°C. The resulting serum was stored in aliquots at –70 °C. Serum urate was measured via a uricase reaction using a standard assay at the University of Maryland (Baltimore). This assay has a within-laboratory CV of 1% at a mean of 6.6 mg/dL (**Supplemental Methods 1**).

Other measurements and covariates

Additional information regarding age, sex, race (white, African American, or other), ethnicity (Hispanic or non-Hispanic), current smoking status, and education was collected by questionnaire. Baseline height and weight measurements were used to determine BMI (in kg/m^2). Baseline SBP and DBP were calculated based on an average of 3 BP readings over 3 screening visits at least 1 wk apart. Hypertension in our analysis was defined as an average baseline SBP ≥130 mm Hg or DBP ≥80 mm Hg. Laboratory data included LDL cholesterol, HDL cholesterol, and triglycerides. Traditional enzymatic assays were used to obtain total triglycerides, whereas LDL cholesterol was estimated (18).

Statistical analysis

Study population characteristics were described using means (SDs) and proportions. The main outcome of interest in our ancillary study was end-of-period serum urate concentration. The main comparison was end-of-period mean difference (95% CI) in serum urate between diets using the following contrasts: PROT compared with CARB, PROT compared with UNSAT, and CARB compared with UNSAT. The analyses were performed using generalized estimated equations (GEEs) that included robust standard errors and an exchangeable covariance matrix to account for correlated measures. Note that the robust variance estimator allows the model to produce valid standard errors even if the correlation structure is not as specified.

We also performed analyses to elucidate possible mechanisms of action by which diet affected serum urate. We examined the change in serum urate from baseline for each diet and adjusted for concurrent changes in SBP, DBP, LDL cholesterol, and serum creatinine from baseline to determine if changes in serum urate were independent of these factors. The change in serum urate from baseline was also compared with change in SBP, DBP, LDL cholesterol, and serum creatinine from baseline using GEEs with adjustments for age, sex, and race (African American, non-African American).

To assess whether dietary assignment had different effects on serum urate in specific subgroups, we repeated the between-diet contrasts (PROT compared with CARB, PROT compared with UNSAT, and CARB compared with UNSAT) in strata of age (<60 y compared with ≥60 y), baseline serum urate (<6 mg/dL compared with ≥6 mg/dL), sex, race (African American, non-African American), baseline hypertension (SBP ≥130 or DBP ≥80 mm Hg), obesity (BMI ≥30), and current alcohol use (yes, no). Interaction terms were used to compare effects across subgroups. All analyses were performed using Stata version 15.1 (StataCorp).

TABLE 1 Baseline characteristics of OmniHeart trial participants[1]

Characteristic	Overall (n = 164)
Age, mean (SD), y	53.5 (10.8)
Women, No. (%)	73 (45)
Race, No. (%)	
African American	90 (55)
Non-Hispanic white	65 (40)
Other	9 (5)
BMI, mean (SD), kg/m^2	30.2 (6.1)
Baseline hypertension,[2] No. (%)	
No	73 (45)
Yes	91 (55)
HOMA-IR index, geometric mean (SD)[3]	1.79 (2.17)
Smoking status, No. (%)	
Current	18 (11)
Former and never	146 (89)
Triglycerides, geometric mean (SD),[3] mg/dL	109.1 (1.76)
HDL cholesterol, mean (SD), mg/dL	50.0 (16.1)
LDL cholesterol, mean (SD), mg/dL	129.2 (32.4)
Serum urate (SD), mean, mg/dL	5.1 (1.2)
Education, No. (%)	
≤ High school diploma	33 (20.1)
≥ Some college education	131 (79.9)

[1]Counts do not always equal total numbers due to missing data. DBP, diastolic blood pressure; SBP, systolic blood pressure.
[2]Hypertension defined by SBP ≥130 or DBP ≥80 mm Hg.
[3]Calculated geometric means due to skewed data distribution.

Results

Baseline characteristics

Baseline characteristics of trial participants are summarized in **Table 1**. The mean (SD) age was 53.5 (10.8) y, 45% were women, and 55% were African American. The mean (SD) BMI was 30.2 (6.1), 11% were current smokers, and 55% of participants had hypertension. At baseline, mean serum urate was 5.1 (95% CI: 4.9, 5.3) mg/dL.

Change in serum urate from baseline and between-diet comparisons

Only the PROT diet reduced serum urate from baseline at the end of the 6-wk feeding period (–0.16 mg/dL; 95% CI: –0.28, –0.04; P = 0.007) (**Figure 1**, **Table 2**). Compared with the CARB and UNSAT diets, the PROT diet lowered serum urate by 0.12 mg/dL (95% CI: –0.20, –0.03; P = 0.006) and 0.12 mg/dL (95% CI: –0.20, –0.05; P = 0.002), respectively (**Table 3**).

Among adults with a baseline serum urate ≥6 mg/dL (n = 29), serum urate lowered from baseline regardless of diet (–0.39 to –0.52 mg/dL), and differences between diets were not significant (Table 3).

Concurrent change analysis

The reduction in serum urate from the PROT diet in comparison with the CARB diet was attenuated after adjustment for change in DBP, LDL cholesterol, and serum creatinine from baseline, whereas adjustment for change in SBP from baseline had minimal effects (**Table 4**). Of these, the attenuation was greatest when adjusted for change in serum creatinine. When comparing the PROT with UNSAT diets, only serum creatinine

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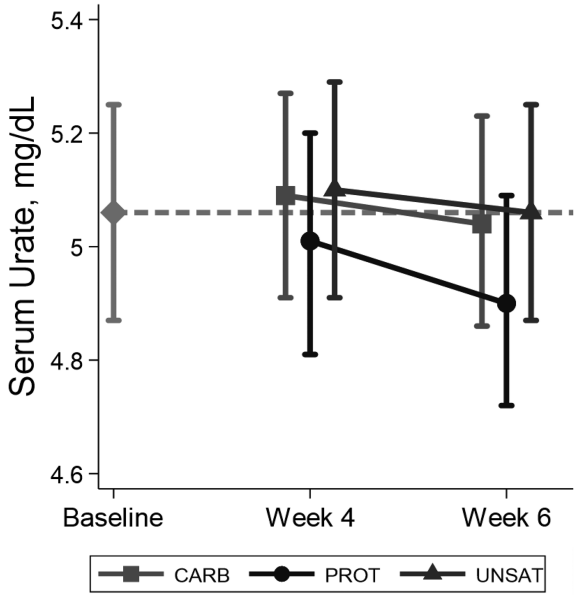

FIGURE 1 Mean serum urate concentration at baseline and by study week according to diet (n = 162 at baseline; n = 161/158/160 for CARB/PROT/UNSAT at 4 wk; n = 161/160/159 for CARB/PROT/UNSAT at 6 wk). The dashed line represents mean serum urate at baseline. Point estimates and corresponding 95% CIs are in Table 2. CARB, carbohydrate-rich diet; PROT, protein-rich diet; UNSAT, unsaturated fat-rich diet.

attenuated the results. There was no difference between CARB and UNSAT diets regardless of adjustment.

Change in serum urate from baseline was strongly associated with change in LDL cholesterol (0.01 mg/dL per 1-mg/dL change in LDL cholesterol; 95% CI: 0.00, 0.01; P = 0.004) and serum creatinine (0.99 mg/dL per 1-mg/dL change in creatinine; 95% CI: 0.14, 1.85; P = 0.023) from baseline (**Table 5**). Change in SBP or DBP was not associated with change in serum urate.

Stratified analysis of other baseline participant characteristics

The effects of the PROT compared with CARB or UNSAT diets on serum urate were consistent across strata of age, sex, race, hypertension, obesity, and current alcohol use (**Supplemental Table 3**). However, there was evidence of a greater decrease in serum urate from PROT compared with UNSAT in men than women (P-interaction = 0.04).

Discussion

In this secondary analysis of overweight or obese individuals with elevated BP or hypertension, a DASH-style diet emphasizing plant-based protein reduced serum urate compared with diets emphasizing either carbohydrates or unsaturated fat. Changes in serum urate were correlated with dietary effects on serum lipids and renal clearance. Overall, contrary to our hypothesis and common teaching regarding purine metabolism, our findings suggest that a DASH-style diet emphasizing plant-based protein has the potential to lower serum urate while also improving BP and lipids.

Dietary recommendations to reduce serum urate emphasize a low-purine diet (2); however, a purine-restricted diet is difficult to sustain due to limited palatability and is ineffective in managing hyperuricemia and gout (6). In OmniHeart, the protein-enhanced diet substituted 10% of kcal from carbohydrates with mainly plant-based protein (approximately half), which increased daily protein intake to 25% of total kcal. Comparatively, the amount of protein in the average American diet is estimated to be 14–16% of total kcal (19). Our results expand on prior observations regarding the effects of dietary protein on serum urate. Evidence from observational studies suggests that high total-protein intake is not associated with higher concentrations of serum urate and that plant-based protein may be inversely associated with serum urate and gout (4, 5). Furthermore, an open-label trial found that a diet high in protein and low in carbohydrates and unsaturated fat decreased mean serum urate and the frequency of monthly gout attacks (8).

The DASH-style diet emphasizing plant-based protein may lower serum urate through several mechanisms. First, human physiologic studies suggest that reductions in serum urate observed with higher protein intake may be mediated through increased urate excretion (20–22) and direct uricosuric effects (9, 23, 24). Second, although the total purine content in plant-based foods varies, the proportion of more "uricogenic" purines (e.g., hypoxanthine) is generally lower in plant-based

TABLE 2 Baseline change in serum urate, mg/dL (n = 163)

Characteristic	Mean (95% CI)	Mean change from baseline (95% CI)	P value
Baseline	5.1 (4.9, 5.3)	—	—
Carbohydrate diet			
4-wk	5.1 (4.9, 5.3)	0.02 (–0.09, 0.13)	0.71
6-wk	5.0 (4.9, 5.2)	– 0.03 (–0.14, 0.09)	0.66
Combined 4-wk and 6-wk measures	5.1 (4.9, 5.2)	– 0.00 (–0.10, 0.10)	0.95
Protein diet			
4-wk	5.0 (4.8, 5.2)	– 0.08 (–0.19, 0.03)	0.17
6-wk	4.9 (4.7, 5.1)	–0.16 (–0.28, –0.04)	0.007
Combined 4-wk and 6-wk measures	4.9 (4.8, 5.1)	–0.12 (–0.23, –0.01)	0.028
Unsaturated fat diet			
4-wk	5.1 (4.9, 5.3)	0.01 (–0.09, 0.12)	0.79
6-wk	5.0 (4.9, 5.2)	– 0.01 (–0.12, 0.09)	0.78
Combined 4-wk and 6-wk measures	5.1 (4.9, 5.2)	– 0.00 (–0.10, 0.10)	1.00

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TABLE 3 Mean difference between diets (overall, baseline SU <6 and baseline SU ≥6)[1]

Characteristic	Overall, $n = 163$		Baseline SU <6 mg/dL, $n = 134$		Baseline SU ≥6 mg/dL, $n = 29$		
	Mean difference (95% CI)	*P* value	Mean difference (95% CI)	*P* value	Mean difference (95% CI)	*P* value	*P*-interaction
CARB vs. baseline	0.00 (–0.10, 0.10)	0.95	0.08 (–0.02, 0.18)	0.111	–0.39 (–0.68, –0.10)	0.01	0.002
PROT vs. baseline	–0.12 (–0.23, –0.01)	0.03	– 0.03 (–0.14, 0.08)	0.555	–0.52 (–0.79, –0.24)	<0.001	0.001
UNSAT vs. baseline	0.00 (–0.10, 0.10)	1.00	0.09 (–0.01, 0.19)	0.087	–0.40 (–0.63, –0.17)	0.001	<0.001
PROT vs. CARB	–0.12 (–0.20, –0.03)	0.006	–0.12 (–0.20, –0.03)	0.008	– 0.13 (–0.38, 0.13)	0.33	0.93
PROT vs. UNSAT	–0.12 (–0.20, –0.05)	0.002	–0.12 (–0.20, –0.05)	0.002	– 0.12 (–0.35, 0.12)	0.33	0.96
CARB vs. UNSAT	0.00 (–0.07, 0.07)	0.93	– 0.01 (–0.07, 0.06)	0.85	0.01 (–0.22, 0.25)	0.92	0.88

[1]Mean difference between diets compared using combined 4-wk and 6-wk serum urate measures. CARB, carbohydrate-rich diet; PROT, protein-rich diet; UNSAT, unsaturated fat–rich diet; SU, serum urate.

protein than in animal protein (25–27). Third, insulin resistance and compensatory hyperinsulinemia have been postulated to lower renal clearance of urate (8, 28, 29). Replacing part of a carbohydrate-rich diet with plant-based protein may reduce insulin secretion (30), thereby increasing renal clearance of serum urate. Finally, the PROT diet included ∼22 g/d of wheat gluten, which has been shown to lower serum urate independently of changes in renal urate clearance or alterations in insulin secretion (31). Of note, in a secondary analysis of a related trial (OmniCarb) (32), which investigated the effects of modifying the glycemic index and proportion of carbohydrates of a DASH-style diet on CVD risk factors, we found that reducing the proportion of carbohydrates by increasing protein and unsaturated fat increased serum urate (15). However, in OmniCarb, the additional protein was mainly from animal sources (32).

Our findings are also consistent with recent studies that suggest the DASH diet may be more effective in lowering serum urate among adults with hyperuricemia (11, 12). Among participants with higher baseline concentrations of serum urate, all DASH-style diets lowered serum urate, and there were no significant between-diet differences. Although the absolute reduction in serum urate was modest in this cohort of persons without hyperuricemia, we suspect that the urate-lowering effects of any of the 3 DASH-style diets examined in OmniHeart may be clinically relevant in individuals with hyperuricemia if adherence to the diet is sustained longer term (33) or if the diet is contrasted with a typical, less healthy American diet (11). Although mechanisms by which DASH lowers urate are unclear, we speculate that the balance of emphasizing dietary characteristics known to lower serum urate [e.g., higher vitamin C from fruit (34, 35), low-fat dairy (4, 5)] while restricting foods associated with higher serum urate (sweets, red meat), may be synergistic in reducing serum urate regardless of macronutrient profile. However, the observed changes in serum urate from baseline in OmniHeart may be affected by regression to the mean and should be interpreted cautiously.

An analysis to elucidate possible mechanisms of action by which diet affected serum urate found that the changes in serum urate were related to dietary effects on lipids and renal clearance. Several observational studies suggest a relationship between hyperlipidemia and elevated serum urate (7, 36, 37). The overlap in the pathogenesis of hyperlipidemia and hyperuricemia requires further study but may be mechanistically related to both synthesis and renal clearance of urate (37–39). Furthermore, our results suggest that the enhanced reduction in serum urate from the protein diet may have been partly mediated by an increase in eGFR. A previous analysis of the OmniHeart trial demonstrated that a high-protein diet increases eGFR (40). Whether the increased eGFR observed on a high-protein diet reflects a maladaptive response to a higher protein load that may ultimately lead to the development of chronic kidney disease requires further study (40–42).

There are limitations to our study. First, most participants had baseline serum urate concentrations <6 mg/dL, which limited

TABLE 4 Effects of diet on serum urate adjusted for change in SBP, DBP, LDL cholesterol, and Cr[1]

Characteristic	Baseline *n*	PROT vs. CARB Mean difference (95% CI)	*P* value	PROT vs. UNSAT Mean difference (95% CI)	*P* value	CARB vs. UNSAT Mean difference (95% CI)	*P* value
Unadjusted	163	– 0.14 (–0.24, –0.03)	0.009	– 0.15 (–0.25, –0.06)	0.002	– 0.01 (–0.10, 0.08)	0.81
Adjusted for Δ SBP	163	– 0.14 (–0.24, –0.03)	0.011	– 0.15 (–0.25, –0.05)	0.002	– 0.01 (–0.11, 0.08)	0.80
Adjusted for Δ DBP	163	– 0.13 (–0.24, –0.02)	0.016	– 0.15 (–0.24, –0.05)	0.003	– 0.02 (–0.11, 0.08)	0.71
Adjusted for Δ LDL cholesterol	162	– 0.13 (–0.24, –0.02)	0.019	– 0.15 (–0.24, –0.06)	0.002	– 0.02 (–0.11, 0.07)	0.67
Adjusted for Δ Cr	163	– 0.10 (–0.21, –0.00)	0.047	– 0.12 (–0.21, –0.02)	0.013	– 0.01 (–0.10, 0.08)	0.81
Adjusted for Δ all	162	– 0.08 (–0.19, 0.02)	0.120	– 0.11 (–0.20, –0.02)	0.021	– 0.02 (–0.11, 0.07)	0.62

[1]Comparisons based on end of 6-wk feeding period changes. CARB, carbohydrate-rich diet; Cr, creatinine; DBP, diastolic blood pressure; PROT, protein-rich diet; SBP, systolic blood pressure; UNSAT, unsaturated fat-rich diet.

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TABLE 5 Association of changes in CVD risk factors from baseline with change in serum urate from baseline

			Difference in SU, mg/dL	
Δ from baseline in CVD risk factor	No. of participants	No. of assessments	Mean difference (95% CI)	*P* value
Systolic blood pressure per 1 mm Hg	163	480	− 0.00 (–0.01, 0.01)	0.851
Diastolic blood pressure per 1 mm Hg	163	480	− 0.01 (–0.02, 0.01)	0.396
LDL cholesterol per 1 mg/dL	160	471	0.01 (0.00, 0.01)	0.004
Serum creatinine per 1 mg/dL	163	480	0.99 (0.14, 1.85)	0.023

CVD, cardiovascular disease; SU, serum urate.

our ability to assess the effects of the DASH-style diets on serum urate in individuals with hyperuricemia (i.e., >7 mg/dL). Second, individuals with moderate to severe chronic kidney disease, diabetes, CVD, or hyperlipidemia were excluded from the trial, which may limit generalizability. Third, the dietary interventions were of short duration. Therefore, we were unable to assess whether sustained adherence to the diets results in more profound reductions in serum urate. Fourth, the interventions were dietary patterns that differed primarily in macronutrients. Hence, by design, it is uncertain which aspect of the PROT diet is responsible for the enhanced reduction of serum urate. Fifth, urine urate was not measured in 24-h urine assessments, so we cannot distinguish distinct mechanisms by which the protein diet reduced serum urate. Finally, our study is one of several ancillary analyses that have been conducted using stored samples from the original OmniHeart trial. Nevertheless, the serum urate endpoint in this trial was hypothesis driven, as a specific aim of an NIH R01 grant (R01AR065944) (**Supplemental Methods 2**). The intent to publish was made prior to examination of the serum urate data, and the present findings reflect the efforts to test our a priori hypotheses. Still, our results should be interpreted as exploratory analyses and our conclusions tested in confirmatory trials.

This study has several health implications. Hyperuricemia is an established risk factor for the development of gout (43), is strongly related to hypertension (44), and may be a risk factor for CVD (45). The original OmniHeart trial demonstrated that a DASH-style diet that partially replaced carbohydrates with protein (approximately half from plant sources) further reduced BP, LDL cholesterol, and triglycerides (14). These findings suggest that a DASH-style diet emphasizing plant-based protein may be an effective strategy to optimize CVD risk factors, such as hypertension and hyperlipidemia, while at the same time reducing serum urate.

In conclusion, a DASH-style diet emphasizing a higher proportion of plant-based protein in comparison to carbohydrates or unsaturated fat lowered serum urate among obese or overweight adults with prehypertension or stage 1 hypertension. The protein-rich version of the DASH diet may be an optimal dietary approach to lower serum urate in adults with gout while also improving BP and lipids. Trials that test the ability of a DASH-style diet emphasizing plant-based protein to lower serum urate and prevent gout flares in patients with gout are warranted.

We are indebted to the original participants in the OmniHeart trial.

The authors' responsibilities were as follows—MJB and SPJ: wrote the first draft of the manuscript and had primary responsibility for the final content; SPJ: performed all statistical analyses; LJA, FMS, and ERM: were responsible for the original OmniHeart trial concept and study design; all authors: read and approved the final manuscript.

Author disclosures: The authors report no conflicts of interest.

Data Availability

Data described in the article, code book, and analytic code will be made available upon request pending application and approval.

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