Effect of Low-Carbohydrate High-Protein Diets on Acid-Base Balance, Stone-Forming Propensity, and Calcium Metabolism

Shalini T. Reddy, MD, Chia-Ying Wang, MD, Khashayar Sakhaee, MD, Linda Brinkley, RD, and Charles Y.C. Pak, MD

• *Background:* Low-carbohydrate high-protein (LCHP) diets are used commonly for weight reduction. This study explores the relationship between such diets and acid-base balance, kidney-stone risk, and calcium and bone metabolism. *Methods:* Ten healthy subjects participated in a metabolic study. Subjects initially consumed their usual non–weight-reducing diet, then a severely carbohydrate-restricted induction diet for 2 weeks, followed by a moderately carbohydrate-restricted maintenance diet for 4 weeks. *Results:* Urine pH decreased from 6.09 (Usual) to 5.56 (Induction; $P < 0.01$) to 5.67 (Maintenance; $P < 0.05$). Net acid excretion increased by 56 mEq/d (Induction; $P < 0.001$) and 51 mEq/d (Maintenance; $P < 0.001$) from a baseline of 61 mEq/d. Urinary citrate levels decreased from 763 mg/d (3.98 mmol/d) to 449 mg/d (2.34 mmol/d; $P < 0.01$) to 581 mg/d (3.03 mmol/d; $P < 0.05$). Urinary saturation of undissociated uric acid increased more than twofold. Urinary calcium levels increased from 160 mg/d (3.99 mmol/d) to 258 mg/d (6.44 mmol/d; $P < 0.001$) to 248 mg/d (6.19 mmol/d; $P < 0.01$). This increase in urinary calcium levels was not compensated by a commensurate increase in fractional intestinal calcium absorption. Therefore, estimated calcium balance decreased by 130 mg/d (3.24 mmol/d; $P < 0.001$) and 90 mg/d (2.25 mmol/d; $P < 0.05$). Urinary deoxypyridinoline and *N*-telopeptide levels trended upward, whereas serum osteocalcin concentrations decreased significantly ($P < 0.01$). *Conclusion:* Consumption of an LCHP diet for 6 weeks delivers a marked acid load to the kidney, increases the risk for stone formation, decreases estimated calcium balance, and may increase the risk for bone loss.

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INDEX WORDS: High-protein diet; low-carbohydrate diet; nephrolithiasis; osteoporosis; calcium.

OBESITY HAS BECOME a problem of epidemic proportions. More than 50% of the US population is either overweight or obese.[1] Despite significant advances in approaches to weight reduction, weight management remains a challenging clinical task. Given the lack of facile weight reduction modalities, patients are turning toward alternative therapies, including various weight-reducing diets. Furthermore, because of cultural pressures of Western society, people of normal body weight also choose these weight-reduction diets.

Current popular diets include those that restrict carbohydrate intake, but allow liberal intakes of protein and fat. One of the most popular of these diets is the Atkins' diet, which imposes a severe restriction on carbohydrate intake to 20 g/d or less for the initial 2 weeks of the diet, with some liberalization of carbohydrate intake afterward.[2] There are no requirements for caloric restriction or adjustments to protein or fat content of this diet. The restriction in carbohydrates leads de facto to an increase in the percentage of protein and fat calories consumed.

There is ample literature on metabolic effects of a high-protein diet alone, without a change in fat or carbohydrate intake. High animal protein intake can confer a marked acid load,[3,4] exaggerate urinary stone risk factors (hypercalciuria, hyperuricosuria, low pH, and hypocitraturia), and enhance the propensity for crystallization of stone-forming salts (calcium oxalate and uric acid).[5,6] High-protein diets also have been associated with negative calcium balance and bone loss.[7-11]

To the best of our knowledge, no study has examined the effects of a low-carbohydrate high-protein (LCHP) diet, such as the Atkins' diet,[2] on risks for stone formation and bone loss. In addition to effects of high-protein diets alone, it is anticipated that a low-carbohydrate diet will provide an exaggerated acid load through incom-

From the Department of Internal Medicine, Section of General Internal Medicine, The University of Chicago, IL; and the Department of Internal Medicine, Division of General Internal Medicine; and the Center for Mineral Metabolism and Clinical Research, The University of Texas Southwestern Medical Center at Dallas, TX.

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Address reprint requests to Shalini T. Reddy, MD, The University of Chicago, Department of Medicine, Section of General Internal Medicine, 5841 S Maryland Ave, MC 3051, Chicago, IL 60637. E-mail: sreddy@medicine.bsd.uchicago.edu

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plete oxidation of fat and resultant ketoanion production. This study is designed to examine the effects of an LCHP diet on acid-base balance, stone-forming propensity, and calcium metabolism.

METHODS

Experimental Subjects

Subjects were recruited by advertisement. Included in the study were men and women with a body mass index (BMI) of 22 kg/m^2 or greater and a desire to lose weight. Exclusion criteria were the presence or history of peptic ulcer disease, intestinal strictures, chronic diarrhea, renal calculi, metabolic acidosis or alkalosis, osteoporosis, gout, hyperuricemia, hyperkalemia, hypokalemia, arrhythmias, hypercalcemia, decreased endogenous creatinine clearance (≤0.6 mL/min/kg [0.0167 mL/s/kg]), and treatment with drugs that affect acid-base balance or potassium metabolism. Subjects also were excluded if they were currently consuming a weight-reducing diet or could not comply with an inpatient metabolic diet required of the trial.

The study was reviewed and approved by the Institutional Review Board of The University of Texas Southwestern Medical Center (Dallas, TX). The study was performed in its entirety at The Center for Mineral Metabolism and Clinical Research, The University of Texas Southwestern Medical Center. Informed consent was obtained from all subjects.

Metabolic Study

All subjects participated in the three stages of the study in the same sequence. Subjects remained on their usual non–weight-reducing diet for the first 2 weeks (usual diet). Subjects then consumed an Atkins'-type induction diet for 2 weeks (induction diet), followed by an Atkins'-type maintenance diet for 4 weeks (maintenance diet).[2] For each subject, the usual, induction, and maintenance diets were calculated to be isocaloric and of similar micronutrient composition. The liberal intake of protein during the induction and maintenance diets precluded the restriction of phosphorus and sulfur intake.

During the last week of each diet, subjects consumed constant metabolic meals. Subjects were provided with frozen meals for the first 3 days when outpatient and freshly prepared meals served in the General Clinical Research Center (GCRC) for the last 4 days when inpatient. Subjects were instructed to consume only the meals and deionized water provided by the metabolic kitchen. Portions of meals not consumed were returned to the GCRC. Total fluid intake was kept constant at 3 L. Perspiration-inducing physical exercise was prohibited.

During the first week of the usual diet, subjects remained on their usual diet at home and kept a diary of food consumed. The dietitian constructed metabolic diets by gathering information from diet diaries and interviews with subjects. During the second week, a constant metabolic diet was provided to subjects as described.

After completing the usual diet, subjects were given a copy of Atkins' diet book.[2] After a personal interview with the dietitian regarding contents and restrictions of the diet, subjects began a weight-reducing diet conforming to the Atkins' induction diet.[2] Subjects ate the induction diet at home, choosing their own food items during the first week. Subjects met with a dietitian during the outpatient diet stage to confirm adherence to the induction diet. Metabolic diets were constructed from a second food diary and another direct interview. Carbohydrate content was adjusted to achieve and maintain positive urine ketones, as directed by Atkins.[2] Atkins recommends using lipolysis-testing strips to measure ketones daily during the induction diet to determine whether lipolysis has commenced. Subjects who have negative ketone test results are advised to progressively reduce carbohydrate consumption until ketone test results become positive.[2]

During the first 3 weeks of the maintenance diet, subjects ate the Atkins' maintenance diet at home while choosing their own food items. Food diaries and direct interviews again were used to construct constant metabolic diets consumed during the last week. Subjects met with a dietician during the outpatient diet stage to confirm adherence to the maintenance diet. Urine ketones were monitored, and carbohydrate content was adjusted to comply with Atkins' recommendations.[2]

Throughout the entire study, all subjects took a daily multivitamin tablet (Mission Pharmacal Co, San Antonio, TX).

Laboratory Tests

Laboratory studies were performed during the last week of each stage. Two 24-hour urine samples were collected days 6 and 7 for the measurement of pH, citrate, ammonium, sulfate, titratable acidity, calcium, uric acid, oxalate, phosphorus, sodium, potassium, magnesium, creatinine, total volume, deoxypyridinoline (DPD), and *N*-telopeptide (NTX). Fasting venous blood samples were obtained on the mornings of days 7 and 8 for sodium, potassium, chloride, total carbon dioxide, blood urea nitrogen, calcium, magnesium, phosphorus, alkaline phosphatase, and creatinine, as well as parathyroid hormone (PTH), 1,25-$(OH)_2$ vitamin D (calcitriol), bone-specific alkaline phosphatase, and osteocalcin. On the morning of day 8, a 2-hour fasting urinary calcium sample was obtained. Fractional intestinal calcium absorption was measured using a dual-tracer stable isotope technique.[12] This technique measures unidirectional flux of calcium across the intestinal lumen. First, calcium 42 (^{42}Ca), 20.0 μg, is administered intravenously. Then oral calcium is administered as ^{46}Ca, 1.0 mg, mixed in 250 mL of a standardized liquid synthetic diet containing 100 mg of elemental calcium as a carrier. The receptacle containing the liquid synthetic diet and ^{46}Ca is rinsed with 50 mL of distilled water that is swallowed by the study subject. Body weight, supine blood pressure, and pulse were measured day 7.

Analytical Procedures

Serum electrolytes, blood urea nitrogen, calcium, magnesium, phosphorus, alkaline phosphatase, and creatinine were analyzed as part of a sequential multiple analyzer-20 (SMA-20). Serum osteocalcin level was determined using immuno-

radiometric assay (IRMA) Kit (Immutropics, San Clemente, CA). Intact PTH was measured using a radioimmunoassay kit (Nichols' Institute, San Juan Capistrano, CA). Serum calcitriol was measured using a competitive radioactive ligand-binding assay, and bone-specific alkaline phosphatase was determined using an enzyme-linked immunosorbent assay (ELISA; Metra Biosystems Inc, Mountain View, CA).

Urinary calcium and magnesium were analyzed by atomic absorption spectrophotometry; sodium and potassium, by flame photometry; and sulfate and oxalate, by ion chromatography. An autoanalyzer was used to determine urinary creatinine, phosphorus, uric acid, ammonium, citrate, and sulfate levels. Urine bicarbonate concentration was calculated using the Henderson-Hasselbalch equation. The urinary concentration of titratable acidity was measured directly by titrating undiluted urine collected for 24 hours under mineral oil to 7.40 by using an automated burette end-point titration system (Radiometer; Hatch Co, Loveland, CO). Net acid excretion was calculated as the sum of urinary titratable acidity and ammonium minus the calculated urinary bicarbonate.

Urinary DPD was analyzed by the Pyrilinks-D ELISA (Metra Biosystems Inc). NTX was determined by the Osteomark ELISA (Ostex, Seattle, WA). Values for DPD and NTX were not corrected for creatinine excretion because urinary creatinine levels could be elevated secondary to increased consumption of meat.

Relative saturation ratios (RSRs) of calcium oxalate, brushite ($CaHPO_4 \cdot 2H_2O$), and monosodium urate were calculated by dividing the ionic activity product in actual urine samples by the respective thermodynamic solubility product,[13] using the EQUIL2 computer program of Finlayson (Gainesville, FL).[14] A value of 1 represents saturation; greater than 1, supersaturation; and less than 1, undersaturation. Estimated calcium balance was calculated as the difference between estimated total calcium absorbed (product of dietary calcium and fractional intestinal calcium absorption) and urinary calcium loss.[15]

Statistical Analysis

Repeated-measures analysis of variance was performed to assess differences in calcium balance and serum and urine biochemistry results among the three dietary stages. When analysis of variance was significant ($P < 0.05$) or showed a trend, paired *t*-tests were used to compare induction and maintenance diets with the usual diet. Statistical analyses were performed using SAS version 8.0 (SAS Institute, Cary, NC). Results are expressed as mean ± SD unless otherwise stated.

RESULTS

Baseline Demography

Eighty volunteers were screened for the study. Ten healthy subjects (seven women, three men; age, 21 to 52 years; mean, 38.4 years) participated in the study. Three subjects were Latin American, and seven subjects were white. At entry, subjects had a mean height of 166 cm (range, 152 to 189 cm), mean weight of 81.4 kg (range, 56.7 to 109.9 kg), and mean BMI of 29.4 kg/cm^2 (range, 22.0 to 38.3 kg/cm^2).

Composition of Metabolic Diets

The composition of each subject's three different metabolic diets was estimated by using US Department of Agriculture food tables[16] and a database generated by our GCRC of analyzed contents of individual food components used in the metabolic diets. The amount consumed was determined by subtracting the amount of unconsumed returned food from the food provided (Table 1). Compared with the usual diet, induction and maintenance diets had nearly twofold greater protein and fat contents and significantly lower carbohydrate content. Amounts of calcium, magnesium, sodium, potassium, and chloride did not differ significantly among the diets. The induction and maintenance diets had significantly greater contents of phosphorus, sulfur, and acid ash compared with the usual diet. Protein was primarily derived from meat. The oxalate content of the induction and maintenance diets was lower than that of the usual diet, reaching statistical significance for the induction diet.

Adherence to the diet is reflected in the statistically significant weight loss (usual diet, 81.3 ± 18.5 kg; induction, 78.4 ± 18.1 kg; $P < 0.001$; maintenance, 77.2 ± 17.5 kg; $P < 0.001$) and significant increase in blood urea nitrogen levels (Table 2). In addition, seven subjects had positive urine ketones during the induction diet. The remaining three subjects were persistently negative for urine ketones despite reductions in carbohydrate intake to 15 to 20 g/d or 3% to 4% of total daily caloric intake during the inpatient supervised metabolic diets.

Effects on Acid-Base Balance

Serum sodium levels were slightly but significantly lower during the induction and maintenance diets compared with the usual diet (Table 2). None of the subjects developed a clinically detectable metabolic acidosis. Serum, potassium, chloride, carbon dioxide, calcium, and phosphorus levels remained unchanged.

Urinary pH and citrate values decreased significantly in the induction and maintenance diets compared with the usual diet (Figs 1 and 2).

Table 1. Macronutrient and Micronutrient Composition of Diets

	Phase			
	Usual	Induction	Maintenance	ANOVA *P*
Kilocalorie/d	2,314 ± 409	1,930 ± 503*	2034 ± 464†	0.0008
Protein (g/d)	91 ± 19	164 ± 49‡	170 ± 47‡	<0.0001
Fat (g/d)	90 ± 17	133 ± 34*	136 ± 32‡	<0.0001
Carbohydrate (g/d)	285 ± 57	19 ± 4‡	33 ± 16‡	<0.0001
Calcium (mg/d)	889 ± 312	805 ± 359	826 ± 352	0.02
Magnesium (mg/d)	300 ± 51	261 ± 129	243 ± 58	0.35
Phosphorus (mg/d)	1,381 ± 305	1,948 ± 659*	2,020 ± 667*	0.0006
Oxalate (mg/d)	160 ± 47	130 ± 34†	140 ± 42	0.04
Sodium (mEq/d)	144 ± 36	140 ± 61	147 ± 59	0.68
Potassium (mEq/d)	81 ± 12	74 ± 18	82 ± 23	0.08
Chloride (mEq/d)	130 ± 48	129 ± 63	128 ± 64	0.98
Sulfur (mmol/d)	34 ± 6	62 ± 20‡	66 ± 19‡	<0.0001
Acid ash (mEq/d)	3 ± 27	106 ± 56‡	114 ± 57‡	<0.0001

NOTE. Quantities actually consumed by subjects are shown. Results expressed as mean ± SD. Conversion factors to SI units are as follows: calcium, mg/d × 0.025 = calcium, mmol/d; magnesium, mg/d × 0.0411 = magnesium, mmol/d; phosphorus, mg/d × 0.03229 = phosphorus, mmol/d; oxalate, mg/d × 11.11 = oxalate μmol/d; sodium, mEq/d × 1 = sodium, mmol/d; potassium, mEq/d × 1 = potassium, mmol/d; chloride, mEq/L × 1 = chloride, mmol/L.

Abbreviation: ANOVA, analysis of variance.

*$P < 0.01$ from the usual diet.

†$P < 0.05$ from the usual diet.

‡$P < 0.001$ from the usual diet.

Urinary ammonium, titratable acidity, net acid excretion, and sulfate values increased almost twofold.

Effects on Urinary Saturation of Stone-Forming Salts

Compared with the usual diet, urinary calcium and phosphorus levels increased substantially by approximately 90 mg/d (2.25 mmol/d) and 500 mg/d (12.48 mmol/d) during the LCHP diets, respectively (Tables 3 and 4). Urinary uric acid, oxalate, sodium, potassium, and total volume did not differ significantly among the three diets. Urinary magnesium level decreased during both LCHP diets.

Urinary content of undissociated uric acid

Table 2. Serum Biochemistry

	Phase			
	Usual	Induction	Maintenance	ANOVA *P*
Sodium (mEq/L)	139 ± 1	137 ± 2*	137 ± 1†	0.009
Potassium (mEq/L)	4.2 ± 0.2	4.1 ± 0.3	4.1 ± 0.3	0.67
Chloride (mEq/L)	106 ± 3	105 ± 2	105 ± 2	0.72
Total carbon dioxide (mEq/L)	28 ± 2	27 ± 2	27 ± 2	0.06
Creatinine (mg/dL)	0.9 ± 0.2	0.9 ± 0.1	0.9 ± 0.2	0.21
Blood urea nitrogen (mg/dL)	11 ± 2	20 ± 4‡	20 ± 4‡	<0.0001

NOTE. Results expressed as mean ± SD. Conversion factors to SI units are as follows: sodium, mEq/L × 1 = sodium, mmol/L; potassium, mEq/L × 1 = potassium, mmol/L; chloride, mEq/L × 1 = chloride, mmol/L; total carbon dioxide, mEq/L × 1 = total carbon dioxide, mmol/L; creatinine, mg/dL × 88.4 = creatinine, μmol/L; blood urea nitrogen, mg/dL × 0.357 = blood urea nitrogen, mmol/L.

Abbreviation: ANOVA, analysis of variance.

*$P < 0.05$ from the usual diet.

†$P < 0.01$ from the usual diet.

‡$P < 0.001$ from the usual diet.

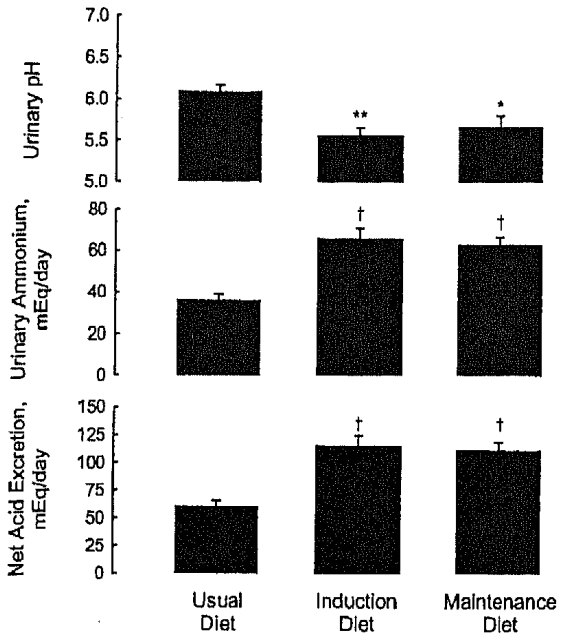

Fig 1. Effect on acid-base balance. Vertical bars indicate mean + SEM. *$P < 0.05$. **$P < 0.01$. †$P < 0.001$ from the usual diet.

doubled from 105 ± 76 mg/d (0.625 ± 0.45 mmol/d) during the usual diet to 249 ± 98 mg/d (1.48 ± 0.58 mmol/d; $P = 0.009$) during the induction diet and to 226 ± 85 mg/d (1.34 ± 0.51 mmol/d; $P = 0.002$) during the maintenance diet (Fig 2). RSRs of brushite, calcium oxalate, and sodium urate did not differ significantly among diets.

Baseline weight correlated with baseline daily caloric intake ($r = 0.76$; $P = 0.01$). Baseline caloric intake also correlated with the incremental increase in urinary sulfate excretion from the usual to the induction diet ($r = 0.72$; $P = 0.02$).

Effect on Calcium Metabolism

Whereas dietary calcium intake remained unchanged or modestly decreased (Table 1), urinary calcium excretion increased significantly during both LCHP diets compared with the usual diet (Table 3). Fractional intestinal calcium absorption was unchanged. Estimated calcium balances decreased during the induction and maintenance diets by 130 mg/d (3.24 mmol/d) and 90 mg/d (2.25 mmol/d) from the usual diet, respectively (Fig 3). Fasting urinary calcium levels were significantly greater during LCHP diets from the usual diet.

Serum calcium and phosphorus levels did not differ significantly among the three diets (Table 3). Total serum alkaline phosphatase levels decreased significantly during LCHP diets from the usual diet, but bone-specific alkaline phosphatase levels did not differ. Serum osteocalcin levels were significantly lower during LCHP diets. Although not statistically significant, there was an upward trend in urinary DPD and NTX levels (Table 3). There was no significant difference in serum PTH and calcitriol levels among the three diets (Table 3). Compared with the usual diet, endogenous creatinine clearance was significantly higher during both LCHP diets (Table 4).

DISCUSSION

The objective of this study is to examine the effects of LCHP weight-reducing diets on acid-base balance, stone-forming propensity, and calcium metabolism in healthy individuals. Our data show that such a diet provides an exaggerated acid load, increasing risks for renal calculi formation and bone loss.

The increased acid load delivered by an LCHP diet was reflected in the increased urinary titratable acidity and urinary ammonium excretion.

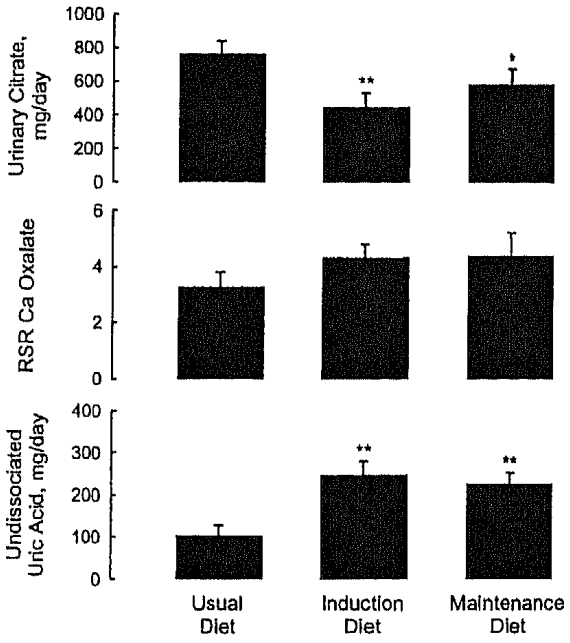

Fig 2. Effect on stone-forming propensity. Vertical bars indicate mean + SEM. For calcium oxalate RSR, analysis of variance P was 0.12; P was 0.03 between the usual and induction diets. *$P < 0.05$, **$P < 0.01$, †$P < 0.001$ from the usual diet.

Table 3. Calcium Metabolism

	Phase			
	Usual	Induction	Maintenance	ANOVA *P*
Serum				
Calcium (mg/dL)	9.2 ± 0.2	9.3 ± 0.3	9.2 ± 0.2	0.21
Phosphorus (mg/dL)	3.3 ± 0.4	3.4 ± 0.4	3.4 ± 0.3	0.79
Calcitriol (pg/mL)	32 ± 14	32 ± 11	30 ± 13	0.74
PTH (pg/mL)	34 ± 11	33 ± 8	36 ± 11	0.49
Alkaline phosphatase (U/L)	56 ± 14	49 ± 12*	50 ± 15*	<0.0001
Bone-specific alkaline phosphatase (U/L)	19 ± 8	18 ± 7	18 ± 7	0.45
Osteocalcin (ng/mL)	5.7 ± 2.2	4.8 ± 1.6†	5.0 ± 1.1	0.03
Urine				
Calcium (mg/d)	160 ± 75	258 ± 88*	248 ± 106†	<0.0001
Fasting calcium (mg/dL GF)	0.05 ± 0.03	0.08 ± 0.03†	0.08 ± 0.04†	0.01
DPD (nmol/d)	43 ± 10	48 ± 12	52 ± 20	0.26
NTX (nmol BCE/d)	452 ± 142	448 ± 155	487 ± 211	0.59
Fractional intestinal calcium absorption (%)	46.8 ± 9.3	50.0 ± 11.4	51.5 ± 8.6	0.17

NOTE. Results expressed as mean ± SD. Conversion factors to SI units are as follows: serum calcium, mg/dL × 0.2495 = serum calcium, mmol/L; phosphorus, mg/dL × 0.3229 = phosphorus, mmol/L, calcitriol, pg/ml × 2.4 = calcitriol, pmol/L; alkaline phosphatase, U/L × 0.01667 = alkaline phosphatase, ukat/L; urinary calcium, mg/d × 0.02495 = urinary calcium, mmol/d.

Abbreviations: GF = glomerular filtrate; BCE, bone collagen equivalents; ANOVA, analysis of variance.

*$P < 0.001$ from the usual diet.

†$P < 0.01$ from the usual diet.

These diets were associated with a striking increase in net acid excretion by approximately 50 mEq/d, presumably derived from the combined effects of a high-protein and low-carbohydrate diet. Other changes in urinary biochemistry results related to the acid load were also detected, including decreased urinary pH and citrate values and increased urinary calcium levels. Acid load was adequately compensated because systemic metabolic acidosis did not develop.

The source of the increased acid load from an LCHP diet is likely twofold. LCHP diets tend to be high in animal proteins that are rich in sulfur-containing amino acids. Oxidation of sulfur to sulfate generates protons.[17] In this study, LCHP diets had a much greater content of sulfur and acid ash than the usual diet. A severe restriction of carbohydrates may also cause production of keto-acids.[18] Our data are consistent with previous reports showing that high-protein diets deliver an exaggerated acid load.[3,19,20]

The changes in urinary biochemistry cited enhance the propensity for the formation of uric acid and calcium stones. At a urine pH of 5.35, the pKa of uric acid, uric acid is sparingly soluble in the urinary environment and may precipitate and form uric acid stones and/or induce heterogeneous nucleation of calcium oxalate crystals, thus promoting the formation of calcium oxalate stones.[21] Urinary pH decreased from approximately 6.0 during the usual diet to 5.5 during LCHP diets, reducing the pH closer to the dissociation constant of uric acid. The mean concentration of undissociated uric acid increased to more than twice the previously reported solubility of uric acid.[22] The RSR of calcium oxalate was not increased, likely because of the small study size and in part because of urine dilution by the imposition of a high-fluid intake. However, LCHP diets increased urinary calcium by approximately 60% and significantly decreased urinary citrate, an inhibitor of calcium stone formation.[23] These results confirm previous reports noting a positive correlation between animal protein consumption and risk for kidney stone disease.[7,24-26]

Findings of this study may underestimate changes in stone risk factors for overweight individuals consuming an LCHP diet. Lemann et al[27] showed that for a given amount of oxalate intake, urine oxalate excretion correlated positively with body weight. In our study, baseline body weight did not correlate with any incremental increases in stone risk factors for the induc-

Table 4. Urinary Biochemistry and Acid Excretion

	Phase			
	Usual	Induction	Maintenance	ANOVA *P*
Total volume (L/d)	2.44 ± 0.30	2.44 ± 0.17	2.64 ± 0.45	0.23
pH	6.09 ± 0.24	5.56 ± 0.33*	5.67 ± 0.40†	0.0004
Sodium (mEq/d)	104 ± 28	107 ± 52	127 ± 63	0.22
Potassium (mEq/d)	60 ± 9	54 ± 14	62 ± 15	0.11
Magnesium (mg/d)	116 ± 37	96 ± 26†	101 ± 29†	0.02
Phosphorus (mg/d)	828 ± 244	1,347 ± 415‡	1,452 ± 350‡	<0.0001
Uric acid (mg/d)	566 ± 112	675 ± 264	694 ± 228	0.17
Oxalate (mg/d)	28 ± 6	26 ± 7	30 ± 17	0.61
Citrate (mg/d)	763 ± 241	449 ± 257*	581 ± 296†	0.004
Sulfate (mmol/d)	22 ± 5	39 ± 14*	40 ± 11‡	0.0001
Ammonium (nEq/d)	36 ± 10	66 ± 17‡	63 ± 12‡	<0.0001
Titratable acidity (mEq/d)	26 ± 9	50 ± 15‡	49 ± 10‡	<0.0001
Calculated bicarbonate (mEq/d)	1.3 ± 0.6	0.4 ± 0.3*	0.6 ± 0.4†	0.0005
Net acid excretion (mEq/d)	61 ± 17	116 ± 29‡	112 ± 21‡	<0.0001
Endogenous creatinine clearance (mL/min)	121 ± 28	130 ± 29	144 ± 37*	0.004
Urinary saturations				
RSR brushite	0.78 ± 0.43	0.94 ± 0.59	1.20 ± 1.03	0.17
RSR sodium urate	1.04 ± 0.38	1.06 ± 1.04	1.39 ± 1.32	0.45
RSR ammonium urate	2.61 ± 0.79	4.42 ± 3.18	4.59 ± 2.77†	0.04

NOTE. Results expressed as mean ± SD. Conversion factors to SI units are as follows: sodium, mEq/d × 1 = sodium, mmol/d; potassium, mEq/d × 1 = potassium, mmol/d; magnesium, mg/day × 0.0411 = magnesium, mmol/d; phosphorus, mg/d × 0.03229 = phosphorus, mmol/d; Uric Acid, mg/d × 0.00595 = uric acid, mmol/d; oxalate, mg/d × 11.11 = oxalate μmol/d; citrate, mg/d × 0.00521 = citrate, mmol/d; ammonium, mEq/d × 1 = ammonium, mmol/d; calculated bicarbonate, mEq/d × 1 = calculated bicarbonate, mmol/d; endogenous creatinine clearance, mL/min × 0.01667 = endogenous creatinine clearance, mL/s.

Abbreviation: ANOVA, analysis of variance.

*$P < 0.01$ from the usual diet.

†$P < 0.05$ from the usual diet.

‡$P < 0.001$ from the usual diet.

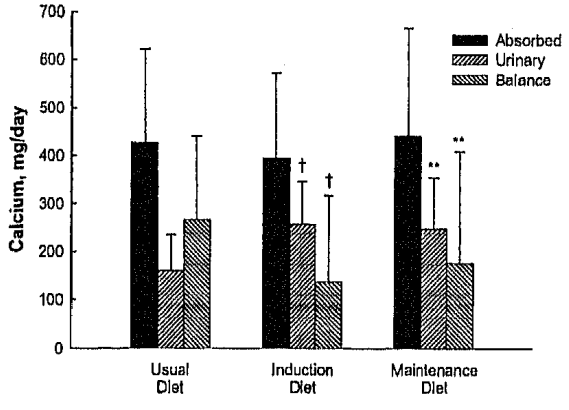

Fig 3. Estimated calcium balance; estimated total calcium absorbed was calculated as dietary calcium consumed multiplied by the fractional intestinal calcium absorption. Urinary calcium losses were subtracted from the estimated calcium absorption to yield the estimated calcium balance. **$P < 0.01$ from usual diet. †$P < 0.001$ from usual diet.

tion or maintenance diets. However, the study size may have been too small to detect these relationships. In addition, the wide range of body sizes among participants could have masked positive findings in larger individuals. In our study, 2 of the 10 subjects had a BMI less than 25 kg/m^2. The criterion to include subjects with a BMI of 22 kg/m^2 or greater was chosen to include normal body mass because some individuals in the general public may choose this diet to lose weight despite having a normal BMI. Had there been more subjects of larger body size, a more striking increase in urinary oxalate levels between the baseline and LCHP diets might have been apparent.

In our study, fluid intake was fixed to eliminate urine volume as a confounding factor in urinary stone risk. The purpose of this study is to evaluate effects of an LCHP diet, not to reassess known effects of varying urine volumes on the

risk for stone formation.[28] Three liters of fluid per day was selected for all three dietary stages of this study; 1 L for insensible fluid losses, and the remaining 2 L to prevent spontaneous precipitation of calcium-containing stones under conditions of normal urinary calcium excretion (100 to 200 mg/d; 2.50 to 4.99 mmol/d). Three liters of fluid intake is greater than the intake previously reported among healthy subjects consuming a self-selected diet.[27] Ad lib fluid intake may have resulted in a greater increase in risk for stone formation. Therefore, it appears reasonable to suggest that individuals consuming an Atkins'-type diet should maintain a high fluid intake to help decrease the propensity for stone formation.

Hypercalciuria detected during LCHP diets most likely resulted from the acid load. Previous studies have shown that urinary calcium levels vary directly with net acid excretion, reviewed by Lemann.[4] Enhanced hyperfiltration of calcium from an increased glomerular filtration rate, impaired renal tubular calcium reabsorption, and cation trapping by sulfate and phosphate may contribute to enhanced renal calcium excretion.[29-31]

Fractional intestinal calcium absorption did not significantly change during LCHP diets. Our data are consistent with past reports showing that a high-protein diet produces no significant change in fractional intestinal calcium absorption and therefore predisposes to negative calcium balance.[10,32]

It is not possible to ascertain from this study whether bone turnover was affected directly by LCHP diets. Although not statistically significant, urinary DPD and NTX levels, markers of bone resorption, trended upward during the maintenance diet. Serum osteocalcin levels declined significantly. Results of this study are supportive of previous in vitro experiments showing chronic metabolic acidosis enhances bone resorption and diminishes bone formation.[33] The lack of a significant change in bone resorption markers is not surprising because of the small sample size, short study duration, and large coefficient of variation inherent in assays. A review of the literature shows conflicting effects of a high animal protein diet on bone turnover. Short-term controlled dietary studies[34-36] and a cross-sectional[37] survey suggest high-protein diets are associated with increased bone turnover. Two studies evaluating hip fracture incidence suggest that lower protein intake is associated with increased hip fractures.[38,39] Other studies suggest bone mineral density is better maintained with high-protein diets,[40] although perhaps only in premenopausal women.[41] The source of protein may influence the effects seen.[42] A detailed metabolic study of normal postmenopausal women suggested that acid retention from relative animal protein excess could impair bone formation and stimulate bone resorption.[35]

Our study represents a metabolic study of short duration in a limited number of subjects. However, acid excess will be sustained as long as carbohydrate restriction and high-protein intake are maintained. Thus, the increased risk for stone formation might be expected during the entire duration of such a diet.

Implications from this study on long-term effects on stone-forming propensity and bone metabolism must be explored in a prospective long-term trial. Nevertheless, this short-term metabolic study stresses that an LCHP weight-reducing diet may enhance the risk for stone formation and bone loss. Because these potential complications probably are produced by the exaggerated acid load, preliminary studies showing the potential value of alkali therapy should be expanded.[35,43] Further examination of chronic effects on bone is warranted. Patients who choose to pursue weight reduction through carbohydrate-restricted diets should be made aware of a potential increase in risk for kidney stone formation and the unknown long-term risk to bone health.

In conclusion, low-carbohydrate diets are popular and are consumed by many people in an attempt to reduce their weight. Our study shows that such a diet delivers an exaggerated acid load. Clinical implications of this enhanced acid load include an increase in kidney stone risk, decrease in estimated calcium balance, and potential increase in risk for bone loss.

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