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Dietary acid load: A novel nutritional target in chronic kidney disease?

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Abstract

Nonvolatile acid is produced from the metabolism of organic sulfur in dietary protein, and the production of organic anions during the combustion of neutral foods. Organic anion salts that are found primarily in plant foods are directly absorbed in the gastrointestinal tract and yield bicarbonate. The difference between endogenously produced nonvolatile acid and absorbed alkali precursors yields the dietary acid load, technically known as the net endogenous acid production, and must be excreted by the kidney to maintain acid-base balance. Although typically around 1 mEq/kg/day, dietary acid load is lower with greater intake of fruits and vegetables. In the setting of chronic kidney disease, a high dietary acid load invokes adaptive mechanisms to increase acid excretion despite reduced nephron number, such as increased per nephron ammoniagenesis and augmented distal acid excretion mediated by the renin-angiotensin system and endothelin-1. These adaptations may promote renal injury. Additionally, high dietary acid loads produce low-grade, subclinical acidosis that may result in bone and muscle loss. Early studies suggest that lowering the dietary acid load can improve subclinical acidosis, preserve bone and muscle, and slow decline of glomerular filtration rate in animal models and humans. Studies focusing on hard clinical outcomes are needed.

Keywords

chronic kidney disease; nutrition; metabolic acidosis; net endogenous acid production

Introduction

Diet is a major determinant of the acid load that must be excreted by the kidney to maintain acid-base balance (1). Although contemporary diets in industrialized nations are largely acid-inducing, this may not have been the case throughout the vast majority of human evolution, during which more alkalinizing foods were consumed (2-4). As a consequence, humans may be poorly adapted to contemporary acid-inducing diets and this may contribute to the pathogenesis of modern epidemics of chronic disease, including kidney disease (5). A

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modest body of research, including animal studies, observational epidemiology and small clinical trials, has examined the potential role of the dietary acid load in patients with chronic kidney disease (CKD). The evidence largely supports the hypothesis of a direct relationship between higher dietary acid load and CKD progression, bone loss and sarcopenia (6-9). However, due to a wide variety of techniques and terminology used to quantify the dietary acid load, it is not widely appreciated by nephrologists. In this review, we will discuss the dietary determinants of the daily acid load using simplifying terminology, as appropriate, and summarize the published literature on the role of dietary acid load in progression of CKD and CKD-related morbidity.

Net endogenous acid production and relationship to diet

Endogenous acid production

Metabolic processes generate both volatile and nonvolatile acids. Volatile acid is expired through respiration as CO_2, whereas nonvolatile acid (H^+) must be excreted by the kidney in the form of ammonium and titratable acid (10). The amount of nonvolatile acid produced by the body during metabolism is termed the endogenous acid production (11-13). The difference between endogenous acid production and the input of alkali absorbed in the gastrointestinal (GI) tract is the *net* endogenous acid production, and represents the total amount of nonvolatile acid that must be excreted to maintain daily acid-base balance (14). Although the term net endogenous acid production is favored (14), a variety of terms have been used to describe dietary acid load in the literature. A list of terms and definitions used in this review is provided in Table 1.

Endogenous acid is produced when organic sulfur, found in the amino acids methionine and cysteine, is oxidized to inorganic sulfate (11, 15, 16). Additional acid is produced when neutral foods are oxidized to organic anions that are excreted in the urine, including citrate, urate, and oxalate (11, 17). This component, termed the organic anion production, is classically considered diet-independent (11), but may be augmented in response to net alkalinizing diets as a mechanism to increase base excretion (18-21). In addition to these acids that are produced endogenously from neutral foods, exogenous acids and bases are also directly absorbed in the GI tract. In particular, absorbed metabolizable organic anions, such as citrate and malate, are abundant in fruits and vegetables and undergo combustion in the body to yield bicarbonate (12-14, 17, 22). The difference in absorbed, nonmetabolizable cations and anions provides an index of the overall absorption of alkali (i.e. metabolizable organic anions) in the GI tract (13, 23). As a result, the net endogenous acid production is the sum of these biochemical reactions that can either yield or consume protons, and is dependent on diet (1, 13, 14, 17, 22-25).

Measuring dietary acid load

Several groups have derived methods to estimate the dietary acid load from measures of dietary intake (2, 14, 23-25). The most widely used methods calculate either the net endogenous acid production, or the more classically diet-dependent portion of net acid excretion, known as the potential renal acid load (Table 2) (22-24). Net endogenous acid production can be estimated either indirectly, based on the ratio of protein to potassium intake in the diet (25), or directly, using the sulfur content of foods, body weight or diet-based estimates of organic anion production and the calculated GI alkali absorption (2). Each of these intake-based estimates are limited by imprecision in the measurement of dietary intake as a result of inaccurate reporting and variation over time. Additionally, absorption of nutrients in the GI tract and the actual nutrient composition of specific foods can vary considerably across individuals and methods of preparation, but this is not accounted for by these equations (Table 2).

To surmount challenges inherent in dietary intake assessment, net endogenous acid production can be most accurately assessed as the steady-state net acid excretion measured in a 24 hour urine collection (Table 2) (14). In addition to error related to under and over-collection, in some circumstances evaluation of urinary acidification may require collection under oil, making this more difficult to perform clinically (26, 27). Furthermore, estimating dietary acid load in this way assumes acid-base equilibrium and that short term dietary intake is similar to habitual intake, which can be more directly ascertained by a food frequency questionnaire (28). Urine pH has also been proposed as a cost-effective, simple tool to monitor net endogenous acid production and may be appropriate for use in large population based studies (29). However, the relationship between net acid excretion and urine pH may not be reliable in populations with CKD, age-related renal function decline, or in those with renal tubular acidosis where distal acidification of the urine is compromised (30-33).

Foods and dietary acid load

The potential renal acid load of selected common foods using the equation develop by Remer has been reported previously (Figure 1) (22). This equation does not account for differences in the sulfur content of proteins from different sources (3, 34, 35). Other estimates that directly account for sulfur, as well as the impact of dietary alkali on organic anion production, yield essentially neutral estimates for nuts and legumes (2, 5). In general, common foods that impart a high dietary acid load include cheese, meat, eggs and grains, whereas fruits and vegetables provide alkali (22, 36-39). The average American diet delivers approximately 15-17% of its energy as protein, predominantly from animal sources (40). In addition, it is low in potassium-rich fruit and vegetables (41) resulting in an average dietary acid load of approximately 1 mEq/kg/day (17). This is consistent with median estimates of dietary acid load of approximately 50-75 mEq/day reported in several general population cohorts and nearly neutral acid load in populations consuming a vegan diet (8, 24, 35-39, 42-44).

To demonstrate the net endogenous acid production of diets that are relatively enriched with plant foods (fruits, vegetables, nuts and legumes) but not vegan, we calculated the dietary acid load of three diets prescribed in the Dietary Approaches to Stop Hypertension (DASH) trial (45). The DASH study included a control diet with macronutrient and mineral content similar to average US consumption; a fruit and vegetable diet in which servings of sweets and grains were replaced with fruits and vegetables; and a combination diet that was enriched in fruits, vegetables and low fat dairy with reductions in fats, oils and meats (45). The fruit and vegetable diet yields a substantially reduced dietary acid load compared to control (net endogenous acid production of 31 versus 78 mEq/d), despite comparable protein intake (Table 3). The combination diet included a higher intake of protein than control, but also resulted in a lower dietary acid load due to more servings of fruits and vegetables (45). Recently, a small trial of patients with early CKD confirmed that augmentation of fruit and vegetable intake can lower net acid excretion by approximately a third and was comparable to administration of 0.5 mEq/kg/day of sodium bicarbonate (7). Overall these findings suggest that replacing nutrient poor, energy dense foods that are common in contemporary diets, with greater intake of fruits and vegetables could substantially lower net endogenous acid production without requiring excessive protein restriction (46, 47).

Acid excretion and development of acidosis in CKD

Metabolic acidosis is a common complication of moderate to severe CKD that results from impaired renal acid excretion (48-51). Although overt metabolic acidosis is a late complication of CKD, low-grade, subclinical metabolic acidosis likely begins early in CKD, but may be hidden by intracellular and bone buffering (52-56). In rat models of early CKD,

acid loading resulted in decline of renal cortical and intramuscular pH with little change in overt measures of systemic acidosis, such as serum bicarbonate and blood pH (57). This finding suggests that the subtle differences in serum bicarbonate concentrations that result from differences in dietary acid load (44), may indicate a significant degree of underlying subclinical acidosis that could be mitigated by greater intake of base (58).

The presence of subclinical acidosis in patients with CKD is supported indirectly by a recent study in which the kidney's response to a bolus of intravenous serum bicarbonate was evaluated in patients with stage 2 versus stage 1 CKD in the setting of a constant diet (56). Despite equivalent serum bicarbonate concentrations, the decline in renal acid excretion was blunted in participants with stage 2 versus stage 1 CKD, suggesting a total body deficit of buffer stores early in CKD that was otherwise unapparent. Administration of alkali supplements to both groups for 30 days decreased the difference between groups (56). Similar physiology is observed in older adults and closely linked to age-related renal function decline (30, 59). In older populations, reduction of the net endogenous acid production to near neutral results in small, but measurable, increases in serum bicarbonate and pH (8). Overall, the current body of literature suggests that modern dietary patterns result in low grade, subclinical metabolic acidosis in the setting of CKD and age-related renal function decline that may be "hidden" by a normal serum bicarbonate concentration.

Relationship of acidosis and dietary acid load to CKD progression

Metabolic acidosis and CKD progression

Several observational studies have demonstrated that metabolic acidosis is associated with progression of kidney disease (60-62). Consistent with these observational findings, a single-center randomized study demonstrated that amelioration of metabolic acidosis with exogenous alkali supplements slowed progression of patients with late stage CKD to dialysis dependence (63). Importantly, lower serum bicarbonate levels, even within the normal range, are also associated with faster disease progression (61), suggesting that differences in dietary acid load may underlie this observation (44).

Dietary acid load and CKD progression

In a small clinical trial of 120 patients with stage 2 hypertensive CKD and normal serum bicarbonate, the addition of sodium bicarbonate at a dose of 0.5 mEq/kg/day, resulted in a slower rate of decline in both creatinine-based and cystatin C-based estimates of glomerular filtration rate (GFR) compared to placebo over 5 years of follow-up (64). Notably, achieved serum bicarbonate levels in the treatment arm were not significantly different from placebo, but daily net acid excretion was lowered by about 15 mEq/day, reflecting the fall in net endogenous acid production. Subsequently, a similar finding was observed in participants with moderate to severe hypertensive CKD from the African American Study of Kidney Disease and Hypertension (AASK) who were consuming their free-living diets (6). In this observational study, higher estimated net endogenous acid production, based solely on diet (i.e. without the use of exogenous alkali supplements), was associated with a faster rate of decline in directly measured I^{125}iothalamate GFR (6). This finding was present even after adjustment for serum bicarbonate and among the subset with normal serum bicarbonate concentrations. It is important to note that dietary acid load is related to protein intake, a risk factor for CKD progression that has been widely studied (65-68).

Two proposed mechanisms may underlie the associations between dietary acid load and progressive CKD, including tubular toxicity of elevated ammonium concentrations and activation of the renin-angiotensin system (56, 58, 69). With increased dietary acid load, production of ammonia is increased in the proximal tubule and H^+ excretion is increased distally to augment overall acid excretion (10, 70, 71). In the setting of a reduced number of

functioning nephrons in CKD, the per nephron demand for acid excretion rises dramatically, resulting in a markedly elevated rate of per nephron ammonia generation (71-73), rising intramedullary ammonium gradient (74), and increases in angiotensin II, aldosterone and endothelin-1 that promote H^+ excretion (Figure 2) (70, 75-79).

In animal models, both acid loading and potassium deficiency augmented ammoniagenesis and resulted in activation of the alternative complement cascade (69, 80). In a rat model of early CKD, Wesson and colleagues demonstrated that acid loading increased, and base-loading decreased, angiotensin II, endothelin-1 and aldosterone-mediated renal injury (75, 81, 82). Additionally, base administration better preserved GFR and reduced kidney injury compared to acid-loaded or control animals in these and other models of CKD (58, 69, 82, 83). Subsequently, small translational studies in patients with early CKD demonstrated that lowering dietary acid load either with supplements or fruits and vegetables decreased urinary endothelin-1, aldosterone and markers of tubulointersitial injury in addition to slowing GFR decline (7, 64, 84).It is not yet known how these therapies may interact with other renoprotective strategies, such as renin-angiotensin system antagonism.

Relationship of acidosis and dietary acid load to morbidity in CKD

Metabolic acidosis and morbidity in CKD

To increase the availability of amino acid substrates for ammoniagenesis (72), metabolic acidosis stimulates muscle catabolism and inhibits albumin production through activation of the ATP-dependent ubiquitin-proteolytic pathway (85-89). Additionally, overt metabolic acidosis induces calciuria due to a combination of physiochemical effects on bone mineral and activation of osteoclastic bone resorption (90, 91). As a result of this physiology, chronic metabolic acidosis is associated with bone and muscle loss and growth restriction in children, each of which can be corrected by base administration (63, 92-97).

Dietary acid load and morbidity in CKD

These adverse physiologic consequences of overt metabolic acidosis may be present to a lesser degree in states of low grade, subclinical acidosis, such as early CKD and aging. Several studies suggest that these adverse effects may be mitigated by a reduction in the dietary acid load, although this area remains controversial (98, 99). In interventional studies, markers of bone resorption are reduced by potassium bicarbonate supplementation or consumption of the DASH diet (9, 100, 101). Observational studies have also documented an association between lower dietary acid load and improved bone density (102, 103), as well as lower rates of hip fracture in elderly women (103, 104). Importantly, adequate protein intake is important for bone health, therefore lowering acid load through greater intake of fruits and vegetables is likely to have a larger effect than protein restriction alone, but further work is needed in this area (105, 106). Finally, administration of alkali supplements to neutralize the daily acid load improves nitrogen balance in healthy elderly patients without overt metabolic acidosis (8). Most of this work has been performed in aging populations in which low grade metabolic acidosis may be present due to age-related renal function decline. It is possible that similar mechanisms underlie the elevated risk of fracture and frailty observed in CKD (107-111), but this hypothesis requires further testing.

Implications for care and research

Nutritional recommendations in CKD have focused on restriction of individual nutrients, such as dietary protein, potassium, phosphate and sodium (112). While the restriction of some nutrients, such as protein, has modest benefits in CKD (66-68), little guidance is provided regarding the intake of foods. From an acid-base perspective, a foods-based approach that considers the balance of acid-inducing and base-inducing dietary inputs is

more logical and reflects consumption patterns. Greater intake of fruits and vegetables and lower intake of cereal grains, can lower dietary acid load without the need for excessive protein restriction or a large pill burden. This foods-based approach has theoretical benefits over supplement-based approaches, due to more favorable effects on blood pressure (7, 39, 43, 45) and other health benefits of fruits and vegetables (113). Risk of hyperkalemia may be greater in patients with moderate to severe CKD consuming diets high in fruits and vegetables and is an important area for future studies. Risk of hyperkalemia did not differ by dietary acid load in the AASK study (114), however, AASK only included participants with hypertensive kidney disease and these risks may be higher in diabetic patients.

CKD is a condition in which case detection and awareness are low (115). Public health strategies focusing on improving diet quality on a population level have the potential to improve CKD outcomes even in the large population of patients with early to moderate CKD who are undiagnosed or unaware. The benefits and harms of lowering dietary acid load for secondary prevention in early to moderate CKD should be rigorously tested.

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Clinical Summary

- The dietary acid load is determined by the balance of acid-inducing foods, such as meats, eggs, cheese and cereal grains, and base-inducing foods, such as fruits and vegetables.
- In the setting of chronic kidney disease and aging, higher dietary acid load may result in low-grade, subclinical acidosis despite a normal serum bicarbonate concentration.
- Adaptations to maintain stable blood pH and augment per nephron acid excretion in the setting of chronic kidney disease may promote bone and muscle loss and further decline in glomerular filtration rate, but can be mitigated by alkali.
- Studies with hard outcomes are needed to determine the safety and benefits of a foods-based approach to reducing the dietary acid load in patients with early to moderate chronic kidney disease.

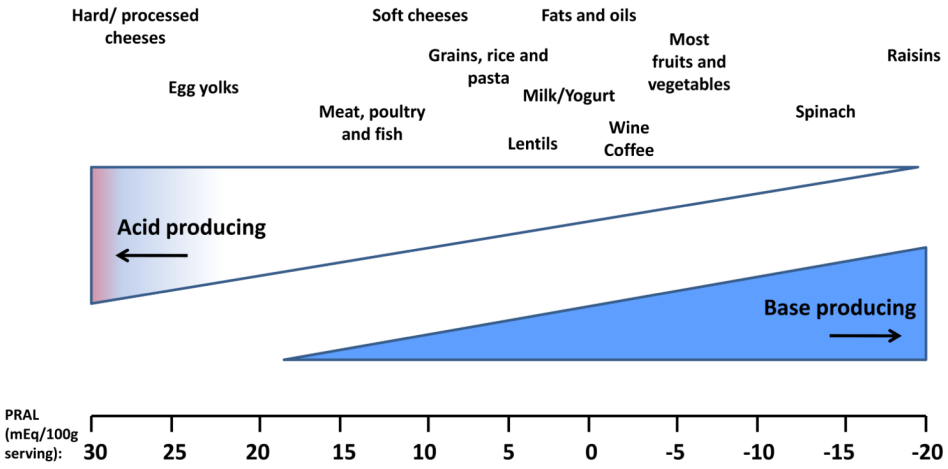

Figure 1.

Estimated acid-producing potential of selected foods. Potential renal acid load (PRAL) of selected food items (per 100g serving) is adapted from estimates performed by Remer (22), and calculated as: PRAL (mEq/d) = 0.49 × protein (g/d) + 0.037 × P (mg/d) − 0.021 × K (mg/d) − 0.026 × Mg (mg/d) − 0.013 × Ca (mg/d).

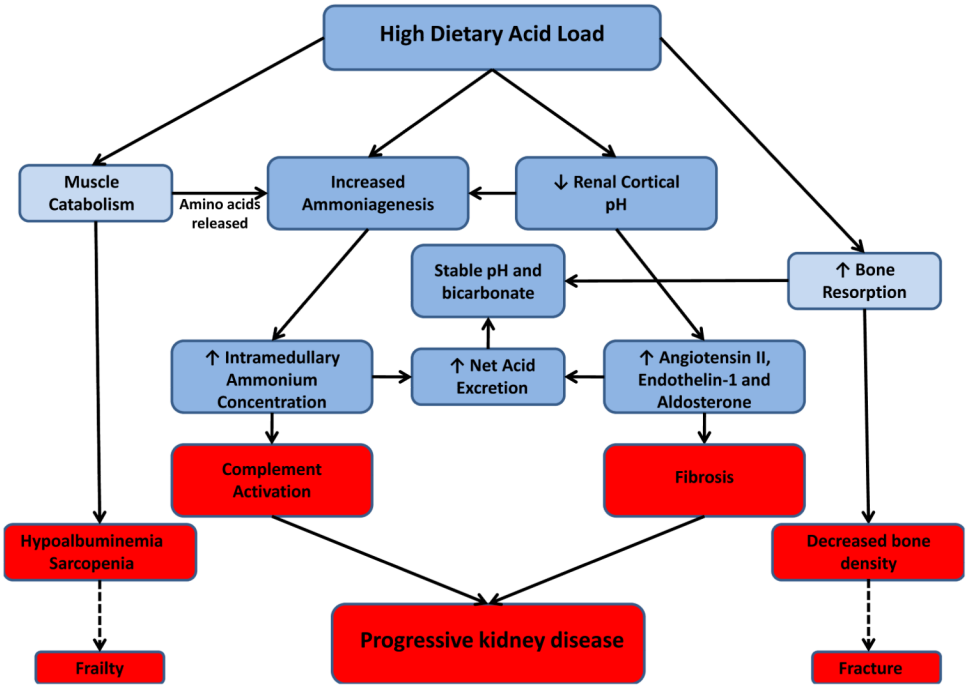

Figure 2.

Proposed physiologic adaptations and consequences resulting from a high dietary acid load in the setting of chronic kidney disease. Blue boxes represent physiologic responses and red boxes their potential adverse effects. Dashed lines represent projected clinical sequelae for which current evidence is indirect.

Table 1

Definitions and relationships between terminology used in prior literature

Term	Definition	Relationship to other terms†
Endogenous acid production (EAP)	The sum of acid produced during oxidation of sulfur-containing protein and the generation of organic anions (OA) from neutral foods	EAP = NEAP + GI alkali absorption
Gastrointestinal (GI) alkali absorption	The net addition of alkali as the result of nutrients absorbed in the GI tract.	GI alkali absorption = EAP − NEAP
Net endogenous acid production (NEAP)	The total load of nonvolatile acid added to the body as a result of endogenous acid production and GI absorption.	NEAP = EAP − GI alkali absorption NEAP = PRAL + OA production‡
Potential renal acid load (PRAL)	The contribution of a food or dietary pattern to net endogenous acid production.	PRAL ≈ NEAP − OA production‡
Net acid excretion (NAE)	The total amount of acid excreted by the kidney daily	NAE ≈ NEAP NAE ≈ PRAL + OA production‡

† all terms represented in mEq

‡ Results from endogenous production of organic anions from neutral foods and is classicially considered diet-independent

Table 2

Measurements used in literature in estimation dietary acid load

Method	Data Needed	Calculation	Strengths	Limitations
Endogenous Acid Production (EAP)	Dietary intake or 24 hour urine collection	Diet: EAP (mEq/d) = 0.75 × dietary sulfur (mEq/d) + organic anion (OA) production[§] Urine: EAP (mEq/d) = urinary sulfate (mEq/d) + OA production[§]	• Easily measured • Accounts for differences in sulfur content of different protein sources • Can reflect long term intake	• Ignores the effect of dietary alkali • OA production is variable
Gastrointestinal (GI) alkali absorption	Dietary intake	Diet[†]: GI alkali absorption (mEq/d)= 0.95 × Na + 0.8 × K + 0.25 × Ca + 0.32 × Mg − 0.95 × Cl − 0.63 × P	• Can reflect long term intake	• Dependent on accurate nutrient composition databases • Assumes average rates of nutrient absorption
Net Endogenous Acid Production (NEAP)	Dietary intake	Direct: NEAP (mEq/d)= EAP − GI alkali absorption Indirect: NEAP (mEq/d) = 54.5 [protein (g/day)/K (mEq/d)] − 10.2	• Direct method accounts for all relevant dietary factors • Indirect method requires only limited dietary intake data • Both can reflect long term intake	• Dependent on accurate nutrient composition databases • Direct method assumes average rates of nutrient absorption • Indirect method assumes sulfur content of all proteins is similar • Indirect method assumes mineral cations other than K are negligible
Potential Renal Acid Load (PRAL)	Dietary intake	PRAL (mEq/d) = 0.49 × protein (g/d) + 0.037 × P (mg/d) − 0.021 × K (mg/d) − 0.026 × Mg (mg/d) − 0.013 × Ca (mg/d)[‡]	• Can reflect long term intake	• Dependent on accurate nutrient composition databases • Assumes sulfur content of all proteins is similar • Assumes average rates of nutrient absorption
Net Acid Excretion (NAE)	24 hour urine collection	Direct[†]: NAE (mEq/d) = NH_4^+ + TA − HCO_3^- Indirect[†]: NAE (mEq/d) = (Cl + P + SO_4 + OA[§]) − (Na + K + Ca + Mg)	• Most direct measurement • Makes no assumptions about composition of foods, nutrient absorption and sulfur content of proteins	• Assumes acid-base equilibrium • Reflects short term dietary intake • Cumbersome to perform

OA, organic anions; Na, sodium; K, potassium; Ca, calcium; Mg, magnesium; Cl, chloride; P, phosphate; NH_4^+, ammonium; TA, titratable acidity; HCO_3^-, bicarbonate; SO_4, sulfate

[†]All ions expressed as mEq/d; valence of phosphate is assumed to be 1.8

[‡] Some investigators include sodium and chloride in this calculation, but here it is ignored because they are generally balanced in the diet. Calcium is sometimes ignored due to variable GI absorption across individuals. Note dietary input variables here are expressed in different units than GI alkali absorption to be consistent with reporting in the literature.

[§] Organic anions can be estimated from body surface area if assumed to be diet independent: OA (mEq/d)=body surface area × 41/1.73; or based on the GI alkali absorption to account for partial diet-dependence: OA (mEq/d)=32.9 + 0.15 × GI alkali absorption(2).

Table 3

Estimated net endogenous acid production of diets in the Dietary Approaches to Stop Hypertension Trial scaled to 2100 kilocalories

	Control diet	Fruits and vegetable diet	Combination diet
Net endogenous acid production- Indirect (mEq/day)[†]	78.0	30.7	35.2
Potential renal acid load (mEq/day)[‡]	31.8	−23.7	−25.4
Protein (% kilocalories)	13.8	15.1	17.9
Servings of fruits and vegetables (number/day)	3.6	8.5	9.6

[†]Estimated NEAP (mEq/d) = 54.5 [protein (g/day)/K (mEq/d)] − 10.2(25)

[‡]Estimated PRAL (mEq/d) = 0.49 × protein (g/d) + 0.037 × P (mg/d) − 0.021 × K (mg/d) − 0.026 × Mg (mg/d) − 0.013 × Ca (mg/d)(22).

Phosphate (P) intake was not provided for diets and was estimated from 24 hour urinary phosphate assuming average intestinal absorption of 63%(2)