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Review

Diet-induced metabolic acidosis

María M. Adeva^{b,*}, Gema Souto^a^a Clinical Center of the National Institutes of Health, Washington DC, USA^b Hospital General Juan Cardona, c/ Pardo Bazán s/n 15406 Ferrol, La Coruña, Spain

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SUMMARY

The modern Western-type diet is deficient in fruits and vegetables and contains excessive animal products, generating the accumulation of non-metabolizable anions and a lifespan state of overlooked metabolic acidosis, whose magnitude increases progressively with aging due to the physiological decline in kidney function. In response to this state of diet-derived metabolic acidosis, the kidney implements compensating mechanisms aimed to restore the acid-base balance, such as the removal of the non-metabolizable anions, the conservation of citrate, and the enhancement of kidney ammoniogenesis and urinary excretion of ammonium ions. These adaptive processes lower the urine pH and induce an extensive change in urine composition, including hypocitraturia, hypercalciuria, and nitrogen and phosphate wasting. Low urine pH predisposes to uric acid stone formation. Hypocitraturia and hypercalciuria are risk factors for calcium stone disease. Even a very mild degree of metabolic acidosis induces skeletal muscle resistance to the insulin action and dietary acid load may be an important variable in predicting the metabolic abnormalities and the cardiovascular risk of the general population, the overweight and obese persons, and other patient populations including diabetes and chronic kidney failure. High dietary acid load is more likely to result in diabetes and systemic hypertension and may increase the cardiovascular risk. Results of recent observational studies confirm an association between insulin resistance and metabolic acidosis markers, including low serum bicarbonate, high serum anion gap, hypocitraturia, and low urine pH.

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Contemporary human diet in industrialized countries is deficient in fruits and vegetables and contains excessive animal products and sodium chloride. Fruits and vegetables are abundant in potassium salts of metabolizable anions, including citrate and malate, which consume hydrogen ions when metabolized, having an alkalinizing effect. Moreover, plant proteins are usually richer than animal proteins in glutamate, an anionic amino acid whose metabolism also consumes hydrogen ions to become neutral. Animal proteins and cereal grains contain sulfur-containing amino acids (methionine, homocysteine and cysteine) whose oxidation generates sulfate, a non-metabolizable anion that constitutes a major determinant of the daily acid load. The content of these amino acids is from 2- to 5-fold higher in meat and eggs than in grains and legumes. The accompanying anions for potassium are

chiefly phosphate and chloride in animal products and cereals, making these nutrients more acidogenic than fruits and vegetables.^{1–5} The modern Western diet based on animal products generates an acid load not compensated by the shortage of fruit and vegetables causing a lifespan state of unnoticed and growing metabolic acidosis,^{6,7} which has been recently associated with increased cardiovascular risk (Fig. 2).

The net endogenous acid production (NEAP) is the diet-dependent net acid load produced by the excessive dietary content of acid precursors relative to alkali precursors and it can be approximately estimated from the renal net acid excretion (RNAE), defined as: [titratable acid (TA)] + [ammonium (NH₄⁺)] – [bicarbonate (HCO₃⁻)] in 24-h urine (in mEq/day).⁸

$$\text{RNAE (mEq/day)} = [\text{TA}] + [\text{NH}_4^+] - [\text{HCO}_3^-] \approx \text{Estimated NEAP (mEq/day)}$$

The kidney net acid excretion rate varies inversely with the urinary potassium (K⁺) excretion (an index of fruits and vegetables consumption) and directly with the urinary urea excretion rate, which is an indicator of dietary protein intake. The urinary net acid

Abbreviations: DASH, dietary approaches to stop hypertension; NEAP, net endogenous acid production; RNAE, renal net acid excretion; TA, titratable acid; HOMA-IR, homeostasis model assessment–insulin resistance; NHANES, national health and nutrition examination surveys.

* Corresponding author. Tel.: +34 664 527 257; fax: +34 981 17 81 59.

E-mail address: madevaa@yahoo.com (M.M. Adeva).

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Table 1
Kidney adaptations to acidogenic diet.

1. Increased urinary elimination of sulfate, phosphate, urate, and chloride.
2. Increased elimination of calcium
3. Decreased urinary excretion of citrate
4. Increased urinary excretion of ammonium ions
5. Kidney vasodilatation and increased glomerular filtration rate

excretion falls as the ratio of urinary K^+ /urea increases. Conversely, as urinary urea rises and the ratio of urinary K^+ /urea declines, the kidney net acid excretion increases. Quantitatively, dietary protein intake of 75 g/day produces urinary urea excretion rate of about 400 mmol/day (11 g of urea nitrogen) and net acid excretion of 50 mEq/day. The urinary net acid excretion increases by 0.10–0.15 mEq/mmol urinary urea. A ratio of urinary K^+ /urea of about 0.25 mmol/mmol is associated with urinary net acid excretion rates of 50 mEq/day.⁹

Persons consuming a diet based on animal protein have higher kidney net acid excretion and more acidic urinary pH than persons on a plant-based diet. The urinary excretion of sulfate, phosphate, and uric acid is also higher in persons on the animal protein diet, compared with the vegetarian diet.²

Dietary sodium chloride also influences systemic acid-base status, being an independent negative predictor of plasma bicarbonate. Excessive consumption of animal proteins and sodium chloride with insufficient ingestion of plant-based foods increase the body acid load and induce metabolic acidosis by accumulation of non-metabolizable anions, predominantly sulfate and chloride.^{9–11}

The magnitude of the lifespan diet-induced metabolic acidosis escalates progressively with advancing age probably due to the decline in kidney function occurring with aging. There is a gradual increase in blood hydrogen ions concentration in healthy humans from youth to old.^{7,12}

In response to the metabolic acidosis imposed by the acidogenic diet, the kidney implements adaptive processes aimed to restore the acid-base balance, including the amplification of the urinary excretion of non-metabolizable anions, such as chloride, phosphate and sulfate, the conservation of metabolizable anions, such as citrate, and the activation of the urinary excretion of ammonium ions to expand both hydrogen ions and anions elimination (Table 1 and Table 2).

Diet-dependent accumulation of non-metabolizable (end-product) anions triggers a widespread change in the urine ionic composition in order to eliminate the negative charge while maintaining urine electrically neutral, which demands simultaneous elimination of cations. In response to the diet-induced metabolic acidosis, the urinary excretion of anions such as sulfate, chloride, and phosphate increases and there is also urinary loss of calcium.

The urinary excretion of sulfate correlates strongly and directly with animal protein content, being higher in individuals consuming animal protein-based diets than in subjects on vegetarian diets.^{2,7,9} Urinary sulfate excretion is inversely correlated with urine pH and has been found significantly greater in insulin resistant subjects compared to persons with normal insulin sensitivity in univariate analysis of a cross-sectional study of healthy subjects, suggesting a link between animal dietary protein, endogenous acid production and insulin resistance.^{13,14}

Table 2
Clinical consequences of diet-induced metabolic acidosis.

1. Kidney stone disease.
2. Nitrogen wasting
3. Insulin resistance

Metabolic acidosis promotes chloride (and sodium) urinary loss, inducing negative sodium chloride balance, with secondary activation of the renin-angiotensin-aldosterone system and subsequent rise in plasma and urine aldosterone concentration.¹⁵ The blood hydrogen ions concentration correlates positively with net acid excretion and with the urinary excretion of chloride in cross-sectional analysis of healthy subjects.¹¹

Metabolic acidosis results in decreased renal tubular phosphate reabsorption and negative phosphorus balance, with subsequent increase in 1,25(OH)₂ vitamin D production rate and decreased serum concentration of intact parathyroid hormone in healthy individuals.¹⁶ Administration of potassium bicarbonate corrects the renal phosphate wasting associated with metabolic acidosis.¹⁷

Increased rates of endogenous acid production are also associated with reduced kidney tubule calcium reabsorption, resulting in hypercalciuria and negative calcium balance. Quantitatively, the urinary calcium excretion varies directly with the net acid excretion by 0.035 mmol/mEq. The urinary excretion of calcium is enhanced even with mild reductions of arterial pH to values still within the normal range.^{3,9} The relationship between hypercalciuria and metabolic acidosis is further confirmed by population studies, in which urinary calcium excretion is lower when the urine is more alkaline, whereas more acidic urine is associated with higher urinary calcium.¹⁸

Urinary calcium excretion rate is higher in persons ingesting an animal protein diet compared to a vegetarian diet, being directly correlated with net acid excretion.² As animal protein intake increases, the urinary excretion of calcium rises and the calcium balance becomes progressively more negative. Quantitatively, urinary calcium increases by about 0.04 mmol/g dietary protein. On average, for every 50 g increase in dietary animal protein, there is approximately a 1.6–2 mmol increase in 24-h urinary calcium excretion.^{3,9,19} Conversely, urinary calcium excretion falls as fruits and vegetables ingestion rises. The consumption of plant-based foods has a calcium-retaining effect and is a predictor of greater bone density in postmenopausal women²⁰ and healthy children.²¹ Dietary depletion of fruits and vegetables induces hypercalciuria.²²

In addition to the urinary excretion of non-metabolizable anions, the kidney induces an avid conservation of metabolizable anions such as citrate in response to metabolic acidosis. Citrate metabolism permits hydrogen ions consumption having an alkalinizing effect on this account. Furthermore, the reduction of urinary citrate facilitates the excretion of end-product anions, assisting in the elimination of negative charge. Kidney citrate reabsorption is primarily determined by the proximal tubule cell pH. In response to metabolic acidosis, there is an avid increase in the kidney tubule reabsorption of citrate with subsequent hypocitraturia. Conversely, urinary citrate excretion increases during metabolic alkalosis. Urinary citrate excretion is a highly sensitive indicator of whether the body is responding to an increased acid load and even slight reductions of arterial pH to values still within the normal range induce a reduction in urinary citrate.²³ Accordingly, the administration of potassium citrate or potassium bicarbonate results in greater increase in urinary citrate excretion than the administration of potassium chloride.^{5,8} The urinary excretion of citrate declines as the ingestion of animal protein increases, being higher in persons consuming vegetarian diets compared with animal-based diets.^{2,9}

A major homeostatic adaptation to metabolic acidosis is the enhancement of ammonium ions (NH_4^+) excretion by the kidney to allow the simultaneous elimination of hydrogen ions and anions. Urinary ammonium excretion is primarily determined by the acid-base balance. In healthy subjects under normal acid-base balance conditions, total kidney ammonia production is approximately half released to the kidney venous blood and half excreted by urine.

Chronic metabolic acidosis prompts an increase in total kidney ammonia production and urinary ammonium excretion. Glutamine is a major precursor of kidney ammoniogenesis in normal conditions and chronic metabolic acidosis, but other amino acids such as glycine and ornithine may also be used to produce ammonia by the human kidney.^{24,25} Urinary excretion of ammonium varies directly with dietary animal protein content. Animal protein-based diets are accompanied by increased acid excretion with a corresponding rise in urinary ammonium, compared with vegetarian diets.^{2,10}

In response to metabolic acidosis significant functional changes take place in the kidney, including an increase in renal plasma flow (RPF) and glomerular filtration rate (GFR), which probably serve to remove the excess acid load.^{15,26,27} Metabolic acidosis also produces kidney hypertrophy presumably due to the increase in kidney ammoniogenesis.²⁸ Clinical situations in which the kidney is required to excrete a high acid load display similar renal hemodynamic changes and kidney hypertrophy. Among these conditions are high animal protein consumption, obesity, and diabetes. High dietary protein intake is associated with an increase in RPF and GFR. The effect on kidney hemodynamics is different according to the source of proteins. Unlike animal proteins, vegetable proteins do not induce renal vasodilatation or glomerular hyperfiltration. In healthy subjects, the ingestion of animal protein induce kidney vasodilation and an increase in RPF and GFR, which is reversed by the sequential consumption of vegetable protein by the same individuals, who display a consistent rise in kidney vascular resistance during vegetable protein intake compared to animal protein ingestion.^{2,29,30} After a meat load, healthy persons maintain acid-base parameters in the normal range, while patients with chronic kidney failure disclose a slight metabolic acidosis, indicating that the acid load imposed to the kidney by the meat ingested exceeds its excretory capacity.³¹

Excess body weight induces kidney functional changes similar to those related to high animal protein intake and weight loss is associated with an improvement of these hemodynamic alterations.^{32,33} Protein intake (assessed from urinary excretion of urea) is higher in overweight than in lean subjects and the GFR is positively correlated with the urinary excretion of urea, suggesting that the excessive animal dietary protein consumption is the initiating event causing the functional changes in the kidney.³²

Similar hemodynamic adaptations than those associated with animal protein ingestion and excess body weight are observed in type 1 and type 2 diabetes. Elevated RPF, GFR, and kidney size are noted in diabetic patients early in the course of the disease compared with nondiabetic individuals.^{34,35} Both the consumption of vegetable proteins and the careful metabolic control of the

disease contribute to ameliorate these functional kidney modifications, presumably via improvement of the acidotic state associated with high animal protein dietary intake and uncontrolled diabetes.^{36,37} The differing effect of vegetable and animal proteins on kidney hemodynamics observed in healthy subjects is also apparent in diabetic patients, which show lower GFR and RPF during the consumption of vegetable protein diets compared to animal protein diets.³⁷ Additionally, vegetarian diets reduce the urinary albumin excretion rate in healthy individuals, patients with chronic kidney disease, and diabetic patients compared with animal protein diets.^{30–32,37,38}

The adaptive mechanisms imposed by the diet-derived metabolic acidosis elicit tradeoff deleterious consequences, including predisposition to kidney stone disease, nitrogen wasting, and resistance to the insulin action on skeletal muscle (Fig. 1).

Diet-induced metabolic acidosis promotes low urine pH, hypercalciuria, and hypocitraturia, predisposing to uric acid and calcium kidney stone formation. Low urine pH is a major risk factor for uric acid stone formation whereas hypocitraturia and hypercalciuria are predisposing factors for calcium nephrolithiasis. Calcium associates with citrate in the urine to form water soluble complexes, so low amounts of citrate in urine allow calcium to form less soluble complexes. Prospective and epidemiological studies reveal a robust association between dietary components and nephrolithiasis. Plant-based food rich in dietary magnesium and potassium strongly decrease the risk of nephrolithiasis, while animal protein ingestion is associated with increased frequency of kidney stones.^{2,39,40} Urinary potassium correlates with potassium intake from fruits and vegetables and the occurrence of kidney stones is highly correlated to the urinary Na^+/K^+ ratio.²¹

The activation of kidney ammoniogenesis and intensification of urinary excretion of ammonium ions imposed by metabolic acidosis requires amino acids catabolism and promotes loss of skeletal muscle and negative nitrogen balance.^{8,41} Quantitatively, one Kg of lean body mass is equivalent to 32 gr nitrogen. Correction of the acidosis with potassium bicarbonate reduces urinary ammonia and urea nitrogen and reverses the muscle protein breakdown in postmenopausal women.⁴² Urinary potassium excretion is positively correlated with the percentage of lean body mass in healthy elderly persons.⁴³ Maintaining muscle mass while aging is important to prevent falls and fractures and the diet-dependent and age-amplifying chronic metabolic acidosis contributes to the decline in skeletal muscle mass occurring with aging.^{42,43}

In healthy individuals even a slight degree of metabolic acidosis results in decreased sensitivity to insulin and subsequent impairment of glucose tolerance.⁴⁴ Other situations leading to metabolic

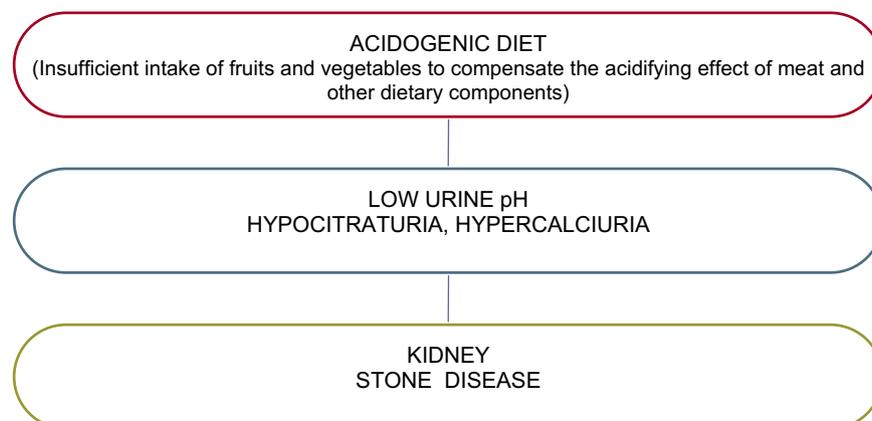


Fig. 1. Acidogenic diet and kidney stone disease.

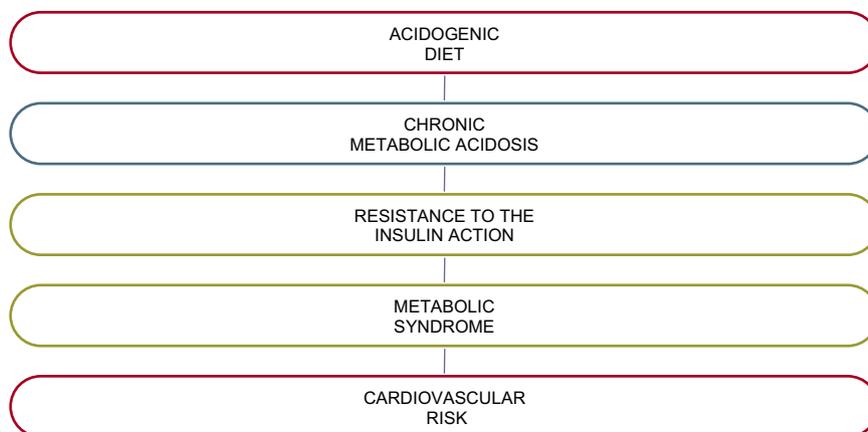


Fig. 2. Acidogenic diet and cardiovascular risk.

acidosis, such as elevations of basal lactate in healthy persons, the presence of ketone bodies in diabetic subjects, and chronic kidney disease-related metabolic acidosis are associated with the development of insulin resistance as well.^{45–48} Metabolic acidosis induces skeletal muscle resistance to the insulin action to permit protein degradation, a process required in order to provide amino acids for ammonium generation.⁴⁴ Metabolic acidosis enhances glucocorticoid secretion and increases plasma and urine cortisol concentrations. Excess cortisol may contribute to insulin resistance, proteolysis and increased urinary ammonium excretion in metabolic acidosis.^{3,41,49} Modern acidogenic diet is associated with cortisol excess and bicarbonate administration decreases significantly plasma cortisol concentration and urinary excretion of free cortisol and tetrahydrocortisol.³

Recent observational studies confirm an association between insulin resistance and indicators of metabolic acidosis, such as low serum bicarbonate, high serum anion gap, hypocitraturia, and low urine pH. In participants in the 1999–2000 and 2001–2002 National Health and Nutrition Examination Surveys (NHANES). Both lower bicarbonate and higher anion gap are independently associated with insulin resistance.⁵⁰ In nondiabetic patients with calcium nephrolithiasis, there is a negative correlation between insulin resistance estimated by the homeostasis model assessment (HOMA-IR) and the urinary citrate excretion.⁵¹ A significant inverse relationship between urine pH and the degree of insulin resistance has been found in several population groups, including healthy volunteers, uric acid stone formers, and in patients with gout.^{14,52,53} The incidence of diabetes mellitus and glucose intolerance is much higher in persons with a lower urinary pH than in normal volunteers.⁵⁴ As mentioned before, the urinary sulfate excretion is inversely correlated with urine pH and is greater in insulin resistant subjects than in persons with normal insulin sensitivity.^{13,14}

Metabolic acidosis is also linked to systemic hypertension, which usually is a component of the metabolic syndrome associated with insulin resistance. In participants of the 1999–2000 and 2001–2002 NHANES a direct correlation between the anion gap and systolic blood pressure has been shown and plasma bicarbonate is inversely related to blood pressure.⁵⁵ A cross-sectional direct association between the serum anion gap and blood pressure is also present among nondiabetic patients, in whom is estimated that every 1 mEq/L higher serum anion gap is associated with a 0.27 mm Hg higher systolic and 0.20 mm Hg higher diastolic arterial blood pressure.⁵⁶ In healthy participants in the Nurses Health Studies I and II and the Health Professionals Follow-up Study, lower urinary citrate excretion is independently associated with prevalent hypertension.⁵⁷

The increase in fruits and vegetables dietary consumption improves insulin sensitivity and blood pressure control mediating a definite beneficial effect upon the metabolic syndrome and systemic hypertension. Plant-based diets are abundant in soluble fiber and carbohydrates with low glycemic index (legumes, whole grain products such as oats and barley, fruits and vegetables), which are characterized by a slow intestinal absorption and minimal postprandial insulin secretion, preventing hyperinsulinemia and insulin resistance. In healthy subjects with normal weight, it has been shown that animal protein ingestion is associated with insulin resistance. Glucose, insulin, and HOMA-IR values were significantly lower in vegetarians than in subjects on a Western-type diet. There is a significant increase of HOMA-IR values in non-vegetarians already in the age decade 31–40 years, whereas vegetarian subjects maintain a HOMA-IR of approximately 1 in all age decades. The occurrence of HOMA-IR values greater than 3.8 was found in 6% of the healthy normal weight population ingesting animal protein but in no vegetarian.⁵⁸ Plant-based diets have also shown favorable metabolic effects in other populations. In nondiabetic overweight women, a vegan diet is associated with increased insulin sensitivity (and reduced body weight).⁵⁹ Vegan diets improve glycemic and lipid control in type 2 diabetic patients.³⁸ Furthermore, high potassium intake has been associated with lower risk of developing type 2 diabetes.^{4,60}

The blood pressure lowering effect associated with potassium ingestion and the protective role of fruits and vegetables against systemic hypertension and stroke have been known for years.^{4,8}

The dietary (and urinary) Na^+/K^+ ratio associates positively with blood pressure.²⁹

The administration of potassium salts results in a large reduction in blood pressure and improves essential hypertension control.⁵ Dietary potassium has been long known to have a robust natriuretic and diuretic action and even minimal dietary potassium deficiency evokes an impaired renal capacity to excrete sodium chloride and generates sodium retention.^{5,21,61}

The Dietary Approaches to Stop Hypertension (DASH) consist of a diet high in fruits and vegetables and low in animal protein but with plant protein from legumes and nuts.²⁰ The DASH diet substantially reduces blood pressure and is usually recommended for the prevention and treatment of systemic hypertension. Adherence to the DASH diet also reduces the blood concentration of low-density lipoproteins cholesterol and is associated with a lower risk of coronary heart disease and stroke in prospective studies.⁶²

Conflicts of interest

There are no conflicts of interest.

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MA conceived the study and drafted the manuscript. GS participated in its design and helped to revise it. All authors read and approved the final manuscript.

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