Chronic Sub-Clinical Systemic Metabolic Acidosis – A Review with Implications for Clinical Practice

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Abstract
When arterial serum pH remains near the lower pH limit of 7.35 for protracted periods of time, a low-grade, sub-clinical form of acidosis results, referred to in this review as chronic, sub-clinical, systemic metabolic acidosis (CSSMA). This narrative review explores the scientific basis for CSSMA, its consequences for health, and potential therapeutic interventions. The major etiology of CSSMA is the shift away from the ancestral, alkaline diet which was rich in fruit and vegetables, toward the contemporary, acidogenic ‘Westernized’ diet characterized by higher animal protein consumption and lack of base forming minerals. Urine pH is reduced with high dietary acid load and may be a convenient marker of CSSMA. Evidence suggests further that CSSMA negatively influences cortisol levels potentially contributing significantly to the pathophysiology thereof. Both CSSMA and high dietary acid load are associated with the risk and prognosis of various chronic diseases. Clinical trials show that CSSMA can be addressed successfully through alkalizing the diet by increasing fruit and vegetable intake and/or supplementing with alkaline minerals. This review confirms the existence of a significant body of evidence regarding this low-grade form of acidosis as well as evidence to support its diverse negative implications for health, and concludes that CSSMA is a condition warranting further research.

Keywords
acidosis, alkaline diet, pH

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Introduction
Self-regulation of blood pH is one of the most carefully controlled homeostatic mechanisms in the human body; it is carefully maintained within a narrow range between pH 7.35 and 7.45 (mean pH 7.4) using various innate buffering systems. An arterial pH of less than 7.35 is regarded as a state of acidosis and greater than 7.45 alkalosis.¹ When arterial serum pH remains near the lower pH limit of 7.35 for protracted periods of time, a low-grade, sub-clinical form of acidosis is established.² This condition is a controversial topic among medical professionals and often misunderstood. Nevertheless, it is well described in the literature but referred to using inconsistent terminology leading to further misunderstanding and ambiguity (Table 1). To avoid confusion, the inclusive and descriptive term chronic, sub-clinical, systemic metabolic acidosis (CSSMA) is proposed in this review and is clearly distinguished from the traditional understanding of ‘acidosis’.

This narrative review explores the scientific basis for CSSMA, its consequences for health, and potential therapeutic interventions, based on the existing scientific literature. The primary objective is to produce a succinct overview of this topic for healthcare providers and summarize the implications for clinical practice (Table 2).

Role of Diet in CSSMA
The major etiology of CSSMA is the shift away from the alkaline human ancestral diet which was rich in fruit and vegetables to that of the contemporary ‘Westernized’ type diet.² The Westernized diet is considered to be ‘acidogenic’ due to high consumption of animal protein,⁴ the lack of

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potassium and bicarbonate rich foods,\textsuperscript{12} and the lack of other base forming minerals such as magnesium and calcium,\textsuperscript{3,4,9,12} all of which are typically found in fruit and vegetables.\textsuperscript{3,4,9,12} A diet with a preponderance of animal food sources (acid precursors) compared to fruit and vegetables (base precursors) results in increased net acid load.\textsuperscript{16}

The influence of dietary elements on net endogenous acid production has been described and calculated in various ways:

- **Net endogenous non-carbonic acid production (NEAP)\textsuperscript{15,17}** (expressed in mEq/Day) is the variation in the quantity of net acid produced by the metabolic system on a daily basis. This quantity is dependent on the difference between dietary acid and base precursors absorbed from the intestine.\textsuperscript{17} Acid precursors are largely derived from protein intake and alkali precursors from organic anions (citrate and acetate) usually bound to cations, most specifically potassium.\textsuperscript{18} Estimated NEAP is typically calculated using one of two algorithms: Frassetto et al\textsuperscript{15} estimate NEAP based on the dietary protein and potassium ratio, whereas Remer et al\textsuperscript{19} estimate NEAP based on average intestinal absorption rates of dietary protein and minerals as well as an estimate of organic acid excretion based on anthropometry.\textsuperscript{20}

- **Renal net acid excretion (NAE).\textsuperscript{19}**

- **The potential renal acid load (PRAL)\textsuperscript{21}** of various food types provides an appropriate prediction of their influence on urine pH.

In summary, dairy, meat and grain products (typically consumed in large quantities in the modern, Westernized diet)

Table 2. Average PRAL of Various Food Categories.\textsuperscript{6,21}

| Food category           | Average PRAL value (mEq)                                      |
|-------------------------|----------------------------------------------------------------|
| Dairy products          | PRAL of $\approx +13.2$ (average of 10 types of dairy products listed, value range $+0.5$ to $+34.2$) |
| Meat                    | PRAL of $\approx +9.5$ (average of 6 types of meat listed, value range $+6.37$ to $+13.2$)          |
| Grain/grain products    | PRAL of $\approx +6.7$ (average of 8 types of grains listed, value range $+1.8$ to $+12.5$)           |
| Vegetables              | PRAL of $\approx -4.61$ (average of 6 vegetables listed, value range $-14.0$ to $-0.8$)              |
| Fruits and fruit juice  | PRAL of $\approx -6.3$ (average of 7 types listed, value range $-21.0$ to $-1.0$)                    |

have significantly higher (i.e. positive) PRAL values (meaning high acid load), in contrast to fruit, fruit juices and vegetables (typically lacking in the Westernized diet) that generally have a lower (i.e. negative) PRAL (meaning an alkalizing action).\textsuperscript{6} The long-term consumption of predominantly acid precursor foods (higher positive PRAL) compared to base precursor foods (lower or negative PRAL) results in a protracted greater endogenous acid load and demand on pH buffering homeostatic mechanisms, resulting in CSSMA.\textsuperscript{2,4} The evolutionary discordance hypothesis suggests that despite 10 000 years of potential opportunity for evolutionary adaptation to this new way of eating, there still exists a genetic mismatch, a discordance between the primary human genome and that of the contemporary diet of modern humans. This hypothesis further proposes that the existence of modern chronic disease is a direct consequence of this genetic mismatch.\textsuperscript{22}

Of interest is the correlation between the PRAL values of foods and inflammation in terms of the dietary inflammatory index (DII), which estimates the inflammatory potential of a diet.\textsuperscript{23,24} As shown in Table 1, dairy products and meat have the highest PRAL values ($\approx +13.2$ mEq and $\approx +9.5$ mEq respectively), while fruit and vegetables have the lowest PRAL values ($\approx -6.3$ mEq and $\approx -4.61$ mEq respectively).\textsuperscript{6,21} Literature confirms an association between the Westernized diet (high in red meat, fat, refined grains) and higher c-reactive protein (CRP), IL-6 and fibrinogen levels,\textsuperscript{23,25,26} suggesting a pro-inflammatory effect, compared to the Mediterranean type diet (high in vegetables, fruit, olive oil, whole grains and fish, with limited red meat) which is linked to lower levels of inflammation.\textsuperscript{23,27} A pro-inflammatory diet as determined by the DII\textsuperscript{24} has been associated with higher levels of inflammatory markers including, TNF-\textalpha, IL-1, IL-2, IFN-\gamma and vascular cell adhesion molecule-1 (VCAM).\textsuperscript{23} A variation of the DII, the empirical dietary inflammatory index (eDII), shows an association between high eDII scores and high inflammatory aging disease (IAD) scores.\textsuperscript{28} Steck et al\textsuperscript{29} confirm that a fast food diet has a significantly higher (pro-inflammatory) DII score than the Mediterranean and macrobiotic diets (DII scores of $+4.07$, $-3.96$ and $-5.54$ respectively), and suggest that a combination of high levels of saturated fat, trans fatty acids together with less fiber, vitamins and flavonoids significantly elevates the DII score. By contrast, higher fruit, vegetable and whole grain intake leads to a much lower DII score and therefore an anti-inflammatory effect.

**Urine pH – A Convenient Predictor of Dietary Acid Load**

Welch et al (2008) investigated the relationship between urine pH and dietary acid-base load (PRAL scores) and found that a low PRAL diet comprising of more fruit and vegetables with less meat resulted in significantly higher urine pH and was readily and conveniently measurable.\textsuperscript{14} Protein content within diet was also shown to directly influence renal NAE, with the renal NAE of a lactovegetarian diet, for example,
being significantly lower than that of moderate and high protein diets, i.e. 3.7 mEq/d versus 62.2 mEq/d and 117 mEq/d respectively. The correlation between NAE and urine pH has also been objectively determined to be significant (r = 0.83; P < .001). As a result of these findings, various subsequent interventional studies applying mineral-based systemic alkalizing agents have measured increases in urine pH as outcomes, confirming their systemic alkalizing action.

### Potential Clinical Consequences of CSSMA

#### Bone Health

The literature is divided on the potential influence of the acidogenic diet and CSSMA on bone mineral density with proponents for and opponents against the potential benefit of alkalinization in the prevention of osteoporosis. The disagreement is centred around the degree to which alkaline calcium salts derived from bone reserves are mobilized to combat net acid load and whether or not this could realistically lead to osteoporosis. Given this discordance, the literature needs to be interpreted and applied with discretion.

Proponents thereof generally support the acid-ash diet hypothesis of osteoporosis which states that CSSMA induced by the contemporary ‘Westernized’ diet leads to chronic den minimization of the skeleton. The skeleton being the largest reservoir of base forming minerals involved in the process of acid-base homeostasis. Supporters of this hypothesis refer to a body of evidence which points to the adverse effects of CSSMA on bone metabolism, suggesting that it is a primary risk factor for bone health. Table 3 summarizes some of the published in vitro data in this regard.

A meta-analysis of 25 studies confirms the detrimental effect of the acidogenic diet on bone mineral density. Such a diet significantly increases calcium excretion (74%) and leads to increased levels of bone resorption markers. Furthermore, higher NEAP values have shown a positive association with lower bone mass of the femur, hip and spine in women. Conversely, a low PRAL (> 9 servings of fruit and vegetables daily) diet has been shown to increase urine pH, reduce calcium excretion, and positively influence bone turnover markers.

Various research studies have demonstrated the bone preservation effects of supplemental potassium citrate or potassium bicarbonate as a result of their systemic alkalizing action. The former leads to lower net acid excretion, a reduction in bone resorption markers, reduced calcium loss, increased bone mass, and the ability to negate the negative impact of a high NaCl diet on bone health. Similarly, the latter (potassium bicarbonate) reduces calcium excretion and favorably influences bone turnover markers i.e. increases serum osteocalcin and lowers urine hydroxyproline and N-telopeptide.

According to Frassetto et al (2018) however, opponents argue that if bone mineral reserves were the major origin for neutralization of dietary acid load, that the skeletal structure would be fully compromised in a relatively short period of time. This has been quantified by Oh (1991) to be likely exhausted within 4 years. Further it cannot be presumed that calcium loss which occurs in CSSMA originates from and significantly depletes the minerals necessary for bone strength. Opponents also question the reliability in the measures of acid excretion used in supporting studies and the validity of using short term studies on bone resorption markers to assume changes in bone density. In addition, there is literature contrary to the proposed association of CSSMA and bone metabolism; in two of the longest randomized, controlled trials, Macdonald et al (2008) found that neither potassium citrate supplementation nor additional fruit and vegetables for 2 years reduced bone turnover or increased bone density in 276 postmenopausal women. Similarly, Frassetto et al (2012) found there to be no positive effect of two years of dietary alkali therapy on bone mineral density or bone resorption, and Fenton et al (2010) found no association between urine pH and acid excretion with fracture incidence or changes in bone mineral density over five years.

In an attempt to bridge the polarized literature, Frassetto et al (2018) suggests that bone mineral reserves alone are insufficient to maintain pH homeostasis and that the effect of the acidogenic diet as a risk factor for osteoporosis is rather relatively small compared to other established risk factors like age, gender, weight, diet and smoking. It has also been suggested that endogenous acid production can be altered according to need as a means to support blood pH homeostasis. Frassetto et al (2018) in their review conclude that for the majority of persons with normal kidney function and acid excretory capacity, a Westernized type diet would not significantly contribute to decline in bone mineral density. However, in certain exceptions, alkalization therapy may be of benefit. These include older persons who have been shown to have higher steady state acid levels, those with compromised kidney function who typically have reduced acid excretory capacity or those with both of these scenarios as kidney function typically declines with age.

In addition, another important and related pathophysiologicaal process and independent contributing factor which could also be compounded by the Westernized diet which is typically low in antioxidants and fruit and vegetables should be

| Table 3. Influence of CSSMA on Bone Metabolism. |
|-----------------------------------------------|
| Influence of CSSMA on bone metabolism          |
| Decrease in osteoblast activity                |
| Increase in osteoclast activity                |
| Promotion of bone resorption                  |
| Decrease in gene expression of bone matrix proteins |
| Decrease in alkaline phosphatase activity     |
| Increase in urinary calcium excretion         |
| Increase in parathyroid hormone (PTH) levels (associated with NAE) |
| Increase in N-telopeptide (associated with NAE) which is a marker of bone resorption |
considered. The review by Domazetovic et al describes the negative influence of oxidative stress driven by reactive oxygen species (ROS) on bone remodeling and the homeostatic and remedial influence of antioxidants therein. ROS have been shown to induce apoptosis of osteoblasts and osteocytes, promoting osteoclastogenesis, ultimately leading to decreased bone mineralization and osteogenesis. Antioxidants, on the other hand, promote differentiation of osteoblasts, mineralization and reduce osteoclast action. In osteoporosis, suboptimal antioxidants promote differentiation of osteoblasts, mineralization and osteogenesis. Antioxidants, on the other hand, promote differentiation of osteoblasts, mineralization and reduce osteoclast action. In osteoporosis, suboptimal antioxidants, high levels of oxidative stress as a result of sex hormone deficiency is well described and linked with reduced production of endogenous antioxidant enzymes and glutathione. Osteoporosis is also linked with reduced absorption of dietary antioxidants in chronic bowel disease. A growing body of evidence further supports the positive influence of antioxidants on bone density and prevention of bone loss.

In terms of bone health, one disadvantage of fruit and vegetables is their phytate content, which can inhibit calcium absorption.

Kidney Function and Prognosis in CKD

The kidneys play a major role in the maintenance of acid base homeostasis via three mechanisms, namely: excretion of acid (utilizing phosphate in the monohydrate format); neutralization of acid (through metabolism of glutamine); and, the excretion of anions (citrate, oxalate and urate). As kidney function fails (as evidenced by a reduction in estimated glomerular filtration rate [eGFR]), so do the compensatory mechanisms of acid excretion and neutralization.

A high dietary acid load and consequential demand for renal compensation increases production of endothelin-1, angiotensin II and aldosterone. These factors are necessary for acid excretion, but can injure the kidneys, leading to renal fibrosis and reduced GFR. Ammonia, a by-product of acid neutralization in the kidneys, also increases in the proximal renal tubules as H+ load increases. Increased levels of this toxin lead to tubular toxicity and further renal injury, which may ultimately lead to the onset of chronic kidney disease (CKD). Several publications explore the link between increased dietary acid load (DAL) and risk of or prognosis in CKD (Table 4).

Addressing DAL with alkaline supplements has been shown to reduce markers of kidney injury and reduce the progression of CKD. Bicarbonate supplementation slows the decline in creatinine clearance and the progression of CKD, as well as reduces the risk of end stage renal disease (ESRD). Similarly, alkalizing the diet by increasing fruit and vegetables in addition to lowering animal protein intake has been shown to lead to an increase in serum bicarbonate and stabilization or improvement in renal function, and preserve GFR and lower urinary angiotensinogen in CKD.

Renal Nephrolithiasis

When compensating for CSSMA, calcium and oxalate excretion and concentration in urine increase and citrate levels decrease. The presence of citrate in urine usually prevents formation of calcium oxalate crystals and stones; its absence in the presence of increased calcium and oxalate leads to stone formation. The association between an acidogenic diet and nephrolithiasis has been investigated: animal protein to potassium ratio (estimate of net acid load) increases the risk of nephrolithiasis (P < .004), while potassium consumption decreases the risk thereof (P < .001) and a high PRAL increases the risk of stones by 2.5 times, a risk mitigated by increasing fruit and vegetable intake.

A meta-analysis confirms that supplemental potassium citrate significantly protects against recurrence of nephrolithiasis during the year after extracorporeal shock wave lithotripsy. Similarly, a Cochrane report states that potassium citrate salts significantly reduce stone size and prevent stone formation as well as reduce the need for retreatment or stone removal. Frassetto and Kholstadt (2011) also confirm that in order to prevent calcium oxalate, cystine and uric acid stones, urine should be alkalized by eating a diet high in fruit and vegetables, taking supplemental or prescription citrate (calcium, magnesium or potassium citrate), or drinking alkaline mineral waters.

Gout and Uric Acid Nephrolithiasis

Gout sufferers often have low urine pH which is also a major risk factor for the development of uric acid stones. There is evidence to support systemic alkanization and
subsequently increase in urine pH as a means of addressing gout as well as uric acid kidney stones, with more alkaline urine being conducive to uric acid elimination and prevention of uric acid stones.\textsuperscript{95,96} Ferrari and Bonny (2004) report that the most important risk factor for the development of uric acid stones is low urine pH (less than 5.5 pH) and suggest increasing (alkalizing) urine pH to between 6.2 and 6.8 as a therapeutic intervention using potassium citrate (or sodium bicarbonate). This approach is an effective method for dissolution of existing stones as well as being the treatment of choice in preventing recurrence.\textsuperscript{97}

**Insulin Resistance and Type 2 Diabetes**

A blood pH of close to the lower pH limit on an ongoing basis may lead to decreased glucose uptake by muscle, negatively impacting the binding of insulin to receptors or disrupting insulin signaling pathways. This typically leads to insulin resistance which is known to be a core contributing factor to development of type 2 diabetes mellitus.\textsuperscript{2} Studies confirm high PRAL and NEAP to be positively associated with development of type 2 diabetes\textsuperscript{98} and risk thereof,\textsuperscript{99} as well as higher HOMA-IR scores (insulin resistance).\textsuperscript{100}

**Metabolic Syndrome**

Metabolic syndrome has evolved into a global health problem, largely as a result of a Western lifestyle characterized by lack of exercise and a low fiber, high calorie, refined food diet.\textsuperscript{101} A less well known feature of metabolic syndrome is uric acid nephrolithiasis\textsuperscript{94} and a significantly lower 24 h urine pH. A decreasing urine pH is associated with worsening of the syndrome.\textsuperscript{102} Takahashi et al\textsuperscript{91} in their study confirmed the association between insulin resistance (a cardinal feature of metabolic syndrome), low urine pH and gout.

Non-alcoholic fatty liver disease (NAFLD), an additional feature of metabolic syndrome, has been found to be positively associated with dietary acid load; for every 20 mEq/day increase in NEAP score, the odds thereof have been shown to increase by 1.32.\textsuperscript{103} In addition, NAFLD has been positively associated with low urine pH in a review of over 2,000 cases.\textsuperscript{104} From a cohort of 3,882 participants, 1,337 cases with NAFLD were identified and confirmed to have significantly higher dietary acid loads (confirmed using PRAL, NEAP and animal protein: potassium ratio ⟨A:P⟩ \( P < .001 \)).\textsuperscript{105}

**Hypertension**

The association of CSSMA with hypertension involves a three-step process. Firstly, CSSMA activates the pituitary gland and, secondly, releases adrenocorticotropic hormone (ACTH) leading to increased cortisol and aldosterone production.\textsuperscript{106} Thirdly, these increases lead to increased urinary calcium excretion (a consequence of CSSMA) which leads to increased blood pressure.\textsuperscript{107,108} Sodium chloride consumption is also a well-known etiology of hypertension and is also reported to be an independent predictor of acid-base status with CSSMA advancing with increased consumption thereof.\textsuperscript{109}

Both high PRAL and NEAP have been shown to have a positive association with raised diastolic pressure\textsuperscript{110,111} and systolic pressure.\textsuperscript{111} Data from 87,393 women after a 14 year follow up period confirmed that NEAP and animal protein: potassium ratio are positively associated with hypertension risk i.e. those with higher NEAP scores had a 23% increased risk of hypertension compared to those with low scores.\textsuperscript{112}

**Arthritis and Back Pain**

Acidosis is harmful to human osteoarthritis chondrocytes.\textsuperscript{113} Acidosis of synovial fluid has been shown to correlate with features of radiological joint destruction and granulocyte concentration in knee rheumatoid arthritis (\( P < .002 \)).\textsuperscript{114} with acidosis being a feature of chronic inflammatory arthritis. Van Velden et al (2015) postulate that an acidic extra cellular environment in the arthritic joint may subsequently result in increased intracellular acid load in chondrocytes, potentially driving disease progression.\textsuperscript{7} Wu et al (2007) determined that even a minor alteration in extracellular pH may have significant impact on metabolism and the biosynthetic ability of chondrocytes with a maximum glycosaminoglycan synthesis occurring at a pH of 7.2.\textsuperscript{115} Research studies have shown that chronic low back pain,\textsuperscript{116} rheumatoid arthritis\textsuperscript{117} and osteoarthritis of the hands\textsuperscript{3} respond favorably to alkaline mineral supplementation (discussed below).

**Loss of Muscle Mass**

Loss of muscle mass is a known consequence of severe chronic metabolic acidosis. This phenomenon has been described in studies on patients with advanced renal failure experiencing renal induced metabolic acidosis.\textsuperscript{118,119} CSSMA, although a significantly less aggressive form of acidosis, if protracted, may also contribute to loss of muscle mass, particularly in older patients. In a three-year observational study of 384 subjects 65 years or older, researchers concluded that higher consumption of potassium rich foods such as fruit and vegetables was associated with significant preservation of muscle mass.\textsuperscript{42} Large observational cohort studies also confirm the positive association between NEAP scores and appendicular muscle mass in older patients\textsuperscript{120} and low PRAL with the maintenance of muscle mass.\textsuperscript{121} Maintenance of muscle mass is particularly important in older patients with possible concurrent low bone density to prevent falls and osteoporotic fractures.\textsuperscript{121}

**Digestive Health – Pancreatic and Biliary Function**

Melamed and Melamed (2014) propose CSSMA as an important aetiological factor in the rapidly increasing prevalence of indigestion in the developing world.\textsuperscript{122} They argue that since both bile and pancreatic juice are highly alkaline and contain high levels of bicarbonate, the presence of CSSMA may negatively impact on their respective functions. Furthermore, since
Table 5. Supplementary Data - Summary of Trials Applying Alkalizing Minerals in the Context of CSSMA.

| Author | Intervention                                                                 | Context                                                                 |
|--------|------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| **Bone health** |                                                                 |                                                                 |
| Sellmeyer et al 2002 | Potassium citrate 90 mmol/day (9270 mg/day) Potassium citrate 0.08 g/kg to 0.1 g/kg body weight daily (≈5000 mg for 50 kg adult) | Postmenopausal women with low bone density Postmenopausal women with osteopenia |
| Marangella et al 2004 | Sodium bicarbonate 60 mmol/day (6 480 mg or 9 720 mg)                          | Older men and women                                                      |
| Jehle et al 2006 | Potassium citrate 30 mEq/day (1 240 mg/day) Potassium citrate 0.55 mmol/kg Potassium bicarbonate 0.55 mmol/kg | Postmenopausal women Healthy subjects                                    |
| Moseley et al 2013 | Potassium citrate 30 mEq/day, 60 mEq/kg/day Potassium bicarbonate 1 mEq/kg/day | Postmenopausal women                                                     |
| Sebastian et al 1994 | Sodium bicarbonate 0.5 mEq/kg lean body weight (≈ 35 mEq for 70 kg)              | CKD stage 2                                                              |
| Maurer et al 2003 | Potassium citrate 30 mmol/d, 60 mmol/d, 90 mmol/d | Postmenopausal women                                                     |
| Frassetto et al 2005 | Potassium bicarbonate 60 mmol/d, 60 mmol/d, 90 mmol/d | Postmenopausal women                                                     |
| Dawson-Hughes et al 2009 | Potassium bicarbonate 67.5 mmol/day Potassium bicarbonate 60 mmol/d | Older men and women                                                      |
| De Brito-Ashurst et al 2009 | Sodium bicarbonate 1.82 g/day Potassium bicarbonate 0.5 mEq/kg lean body weight (≈ 35 mEq for 70 kg) Potassium bicarbonate 0.55 mmol/kg | CKD patients CKD stage 4 patients                                         |
| Mahajan et al 2010 | Sodium bicarbonate 0.5 mEq/kg lean body weight (≈ 35 mEq for 70 kg)             | CKD stage 2                                                              |
| Goraya et al 2013 | Sodium bicarbonate 1 mEq/kg/d Potassium citrate 60 mmol/d | Calcium oxalate urolithiasis patients post shockwave lithotripsy Children on ketogenic diet (at risk of urolithiasis) Prevention of stone recurrence after lithotripsy (metanalysis) |
| **Urolithiasis** |                                                                 |                                                                 |
| Soygür et al 2004 | Potassium citrate 60 mmol/d Potassium citrate 0.25 g/kg daily Potassium bicarbonate 0.5 mEq/kg daily Potassium bicarbonate 0.55 mmol/kg | Postmenopausal women                                                     |
| McNally et al 2009 | Potassium citrate 2 mEq/kg daily                                               | Postmenopausal women                                                     |
| Carvalho et al 2017 | Potassium citrate 55 mEq/day (mean dosage of 4 trials) | Rheumatoid arthritis                                                    |
| **Arthritis** |                                                                 |                                                                 |
| Cseuz et al 2008 | Calcium citrate 400 mg Potassium citrate 250 mg Sodium citrate 20 mg | Rheumatoid arthritis                                                    |
| Vormann et al 2001 | Calcium citrate 405 mg Potassium citrate 291 mg Sodium citrate 375 mg Magnesium citrate 20.4 mg Trace amounts of: Fe, Sr, Mn, Cu, V, Co, Ni, Rb, Cr, Ti, Te, Bi, Sn, W, Mo as lactate. | Rheumatoid arthritis                                                    |
| Van Velden et al 2015 | Magnesium hydrogen phosphate 488 mg Calcium citrate 290 mg Potassium bicarbonate 1.566 mg Magnesium citrate 630 mg Potassium citrate 1.740 mg Di-calciumphosphate 2 hydrate 1.946 mg Organic plant calcium Acerola and mannitol | Osteoarthritis of the hands                                               |
| **Physical performance and recovery** |                                                                 |                                                                 |
| McNaughton et al 1999 | Sodium bicarbonate 0.5 g/kg body mass Potassium citrate 0.2 g/kg Sodium bicarbonate 0.5 g/kg | Impact on high intensity physical performance Impact on recovery kinetics of pH Performance and recovery from exercise in heat conditions |
| Robers et al 2005 | Sodium bicarbonate 0.5 g/kg Potassium citrate 0.2 g/kg | Postmenopausal women                                                     |
| Mündel (2018) | Sodium bicarbonate 0.5 g/kg body mass Potassium citrate 0.2 g/kg | Postmenopausal women                                                     |
pancreatic enzymes require an alkaline milieu for optimal function, lowering pH disables the action of pancreatic digestive enzymes, potentially leading to indigestion and possibly dysbiosis as acidified pancreatic juice loses its antimicrobial action. Acidification of pancreatic juice and bile leads to premature activation of pancreatic protease within the pancreas, causing pancreatitis. Acidification of bile causes precipitation of bile acids irritating the biliary tract and possibly leading to stone formation. A combination of these pathological phenomena may lead to irregular contraction of the duodenum with the possibility of biliary reflux into the stomach or esophagus.\textsuperscript{122}

\textbf{Physical Performance and Exercise Recovery}

There has been extensive research into supporting endogenous acid buffering mechanisms as a means of enhancing physical performance and recovery. Exercise induces a state of relative metabolic acidosis, resulting in increased demand on the body’s buffering mechanisms leading to disturbance in mineral balance and increased calcium excretion in the urine.\textsuperscript{123,124} Athletes are also known to follow higher protein diets which further increases urine acidity and calcium loss in the urine.\textsuperscript{123,125} Pre-exercise systemic pH and blood pH buffering capacity has been shown to impact significantly on recovery kinetics and endurance capacity in recurrent exercise,\textsuperscript{123,126} suggesting that CSSMA caused by diet may compound the additional acidogenic burden induced by exercise which may compromise performance and recovery time.\textsuperscript{123} Systemic alkalization during high intensity exercise may delay the onset of fatigue,\textsuperscript{127,128} with supplemental bicarbonate shown to improve performance and recovery and improve repeated exercise performance.\textsuperscript{129,130}

\textbf{Upregulation of Cortisol – A Major Contribution to Pathogenesis of CSSMA}

Pathophysiologically studies in humans and animals show that induced metabolic acidosis results in increased circulating glucocorticoids.\textsuperscript{131–133} This occurrence is necessary in order to facilitate renal elimination of H\textsuperscript{+}.\textsuperscript{132} Data now confirms that even insidious forms thereof such as CSSMA can also upregulate glucocorticoid production.\textsuperscript{10,106,134} However, when the acidogenic diet is neutralized, plasma cortisol levels reduce significantly with a simultaneous increase in calcium retention.\textsuperscript{10} Even a short-term switch to a lactovegetarian diet with low PRAL leads to a significant decrease in urinary free cortisol.\textsuperscript{134}

One of the major consequences of upregulated glucocorticoid production is metabolic syndrome.\textsuperscript{135} The association between CSSMA and upregulated glucocorticoids is interesting because it is evident from the literature presented thus far in this review that CSSMA shares a number of consequences that are similar to upregulated cortisol levels, particularly metabolic syndrome. Several studies confirm the link between raised cortisol and metabolic syndrome in general,\textsuperscript{135} and some of the cardinal features thereof such as cardiometabolic risk,\textsuperscript{136} increased cardiovascular risk in terms of the Framingham Cardiovascular Risk Score,\textsuperscript{137} dysglycaemia, insulin resistance, modified adiposity and higher odds of type 2 diabetes,\textsuperscript{138} and obesity.\textsuperscript{139} In addition, uric acid nephrolithiases,\textsuperscript{94} acidic urine,\textsuperscript{102} NAFLD,\textsuperscript{103–105,140} and hypertension\textsuperscript{110–112} are conditions strongly associated with CSSMA and also features of metabolic syndrome.

\textbf{Clinical Interventions to Address CSSMA}

\textbf{Dietary Interventions}

Clinicians’ primary aim should be to reinstate high bicarbonate plant foods, i.e. root vegetables, tubers, leafy greens and fruit to offset the net acid producing food groups such as dairy products, meat and eggs which feature too strongly in the contemporary Western diet.\textsuperscript{5} PRAL charts are useful reference tools in differentiating acidogenic from alkalinizing foods and can be useful guides for consumers when making food choices.

Most references to the ‘alkaline diet’ in the published literature recommend the following principles:

1. Increase the consumption of fruit and vegetables\textsuperscript{2,4,5,13,14,16,37,78,96} to > 9 servings daily\textsuperscript{37,141} or consult PRAL charts to reduce the total PRAL by 50% daily.\textsuperscript{18}
2. Reduce animal protein intake\textsuperscript{70,96} by decreasing high biological value protein (HBV) (animal protein and soya) and increasing low biological protein (LBP) sources.\textsuperscript{96}
3. Reduce NaCl intake.\textsuperscript{70,109} Passey (2017) recommends a ‘no added salt’ approach. The impact of NaCl is confirmed by Frassetto et al\textsuperscript{109} who report that NaCl has approximately 50% to 100% of the acidosis-producing effect of the dietary net acid load in healthy subjects consuming an acidogenic diet.
4. Reduce carbonated drinks. Fizzy drinks contain carbonic acid and as a result have a low pH. Cola drinks containing phosphoric acid are considered to be significantly acidogenic. Passey (2017)\textsuperscript{70} recommends the removal of such from the diet in CKD and replacement with alkaline water (pH 7.4).

\textbf{Supplementation with Alkaline Minerals}

Studies addressing CSSMA and its consequences through supplementation generally apply one or a combination of alkalinizing minerals as interventions (see supplementary data – Table 5). The most frequently applied alkaline minerals in the clinical trials include bicarbonate and the citrate salts:

- Potassium citrate\textsuperscript{3,11,38–40,88,116,117,142,143}
- Potassium bicarbonate\textsuperscript{3,7,10,41,43}
- Sodium bicarbonate\textsuperscript{10,76,77,116,117,126,129,144,145}
Three trials applying combinations of alkaline minerals in the management of CSSMA were applied specifically in the following clinical contexts: osteoarthritis of the hands (Van Velden et al 2015), chronic low back pain (Vorman et al 2001), and rheumatoid arthritis (Cseuz et al 2008). All three trials achieved significant improvement in their respective assessments of pain compared to controls, and Van Velden et al and Cseuz et al reported a subsequent reduction in the need for analgesic and anti-inflammatory medication. Van Velden et al and Vormann et al also reported significant systemic alkalinizing actions in response to their alkaline mineral interventions, i.e., increased urine pH and blood pH respectively. A fourth trial supplied a combination of citrate salts and trace elements to healthy subjects and demonstrated small but significant increases in both urine and blood pH. Of the four trials identified, the most frequently used citrate salts were potassium citrate (4/4), magnesium citrate (4/4), calcium citrate (4/4), sodium citrate (3/4), ferrous citrate (1/4) and cupric citrate (1/4). Only one formulation (Van Velden et al) included both citrate salts and a bicarbonate, namely, potassium bicarbonate.

Conclusion
Being knowledgeable about CSSMA, and not just frank acidosis, can strengthen clinical practice. There is a growing body of evidence linking CSSMA with various forms of chronic disease. Alkalinizing the diet, or supplementing the diet with alkaline minerals, are two measures which have demonstrated positive outcomes in clinical trials addressing CSSMA and related conditions. Given the progressive, worldwide dietary shift toward an acidogenic, Westernized diet, and the potential consequences of CSSMA for health, further research on this condition and the role of alkalinization is warranted. Prospective, long-term trials, for example, could accurately ascertain the impact of alkalinization. Based on the available evidence, key areas of investigation should include the impact of alkalinization on bone and skeletal health, kidney function, and aspects of metabolic and cardiovascular health.

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Author Contributions
DF Naude was responsible for the conceptualization, visualization, investigation, data curation, writing- original draft, writing – review and editing of this review, final editing performed by Mrs Monique du Randt & Dr Richard Steele.

Declaration of Conflict of Interest
DF Naude is a consultant employed by the Irma Schutte Foundation a non-profit organization (NPO) which is affiliated with S.A Natural Products (Pty) Ltd; a distributor of health supplements and complimentary medicines in South Africa.

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References
1. Fox SI. Human physiology. 8th ed. McGraw-Hill Publishing; 2004.

2. Carnauba RA, Baptistella AB, Paschoal V, Hübscher GH. Diet-induced low-grade metabolic acidosis and clinical outcomes: A review. Nutrients. 2017;9(6):538. doi:10.3390/nu9060538

3. Van Velden DP, Reuter H, Kidd M, Müller FO. Non-allopathic adjuvant management of osteoarthritis by alkalinisation of the diet. Afr J Prim Health Care Fam Med. 2015;7(1). doi:10.4102/phchm.v7i1.780

4. Adeva MM, Souto G. Diet-induced metabolic acidosis. Clin Nutr. 2011;30(4):416-421. doi:10.1016/j.clnu.2011.03.008

5. Sebastian A, Frassetto L, Sellmeyer D, et al. Estimation of the net acid load of the diet of ancestral preagricultural homo sapiens and their hominid ancestors. Am J Clin Nutr. 2002(76):1308-1316. doi:10.1093/ajcn/76.6.1308

6. Schwalfenberg GK. The alkaline diet: Is there evidence that an alkaline pH diet benefits health? Environ Public Health. 2012;2012:1-17. doi:10.1155/2012/727630

7. Sebastian A, Harris ST, Ottaway JH, et al. Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. N Engl J Med. 1994;330(25):1776-1781. doi:10.1056/nejm199406233302502

8. Frassetto L, Morris RCJr, Sellmeyer DE, et al. Diet, evolution and aging--the pathophysiologic effects of the post-agricultural inversion of the potassium-to-sodium and base-to-chloride ratios in the human diet. Eur J Nutr. 2001;40(5):200-213. doi:10.1007/s00394-001-8347-4

9. König D, Muser K, Dickhuth H-H, et al. Effect of a supplement rich in alkaline minerals on acid-base balance in humans. Nutr J. 2009;8:23-23. doi:10.1186/1475-2891-8-23

10. Maurer M, Riesen W, Muser J, et al. Neutralization of Western diet inhibits bone resorption independently of K intake and reduces cortisol secretion in humans. Am J Physiol Renal Physiol. 2003;284(1):F32-F40. doi:10.1152/ajprenal.00212.2002
11. Jehle S, Zanetti A, Muser J, et al. Partial neutralization of the acidogenic Western diet with potassium citrate increases bone mass in postmenopausal women with osteopenia. *J Am Soc Nephrol.* 2006;17(11):3213-3222. doi:10.1681/asn.2006030233

12. Ilesanmi-Oyelere BL, Brough L, Coad J, et al. The relationship between nutrient patterns and bone mineral density in postmenopausal women. *Nutrients.* 2019;11(6):1262.

13. Tucker KL, Hannan MT, Chen H, et al. Potassium, magnesium, and fruit and vegetable intakes are associated with greater bone mineral density in elderly men and women. *Am J Clin Nutr.* 1999;69(4):727-736. doi:10.1093/ajcn/69.4.727

14. Welch AA, Mulligan A, Bingham SA, Khaw KT. Urine pH is an indicator of dietary acid-base load, fruit and vegetables and meat intakes: Results from the European prospective investigation into cancer and nutrition (EPIC)-norfolk population study. *Br J Nutr.* 2008;99(6):1335-1343. doi:10.1017/s0007114507862350

15. Frassetto LA, Todd KM, Morris RC Jr., Sebastian A. Estimation of net endogenous noncarboxylic acid production in humans from diet potassium and protein content. *Am J Clin Nutr.* 1998;68(3):576-583. doi:10.1093/ajcn/68.3.576

16. Frassetto L, Banerjee T, Powe N, Sebastian A. Acid balance, dietary acid load, and bone effects—A controversial subject. *Nutrients.* 2018;10(4):517.

17. Frassetto LA, Hanam–New SA, MacDonald HM, et al. Standardizing terminology for estimating the diet-dependent net acid load to the metabolic system. *J Nutr.* 2007;137(6):1491-1492. doi:10.1093/jn/jut149

18. Scialla JJ, Appel LJ, Astor BC, et al. Net endogenous acid production is associated with a faster decline in GFR in African Americans. *Kidney Int.* 2012;82(1):106-112. https://doi.org/10.1038/ki.2012.82

19. Remer T, Manz F. Estimation of the renal net acid excretion by adults consuming diets containing variable amounts of protein. *Am J Clin Nutr.* 1994;59(6):1356-1361. doi:10.1093/ajcn/59.6.1356

20. Chan R JL, Woo J. Estimated net endogenous acid production and risk of prevalent and incident hypertension in community-dwelling older people. *World J Hypertens.* 2015;5(4):129-136. doi:10.5494/wjh.v5.i4.129

21. Remer T, Manz F. Potential renal acid load of foods and its influence on urine pH. *J Am Diet Assoc.* 1995;95(7):791-797. https://doi.org/10.1016/S0002-8223(95)00219-7

22. Konner M, Eaton SB. Paleolithic nutrition. *Nutr Clin Pract.* 2010;25(6):594-602. doi:10.1177/0884533610385702

23. Shivappa N, Hebert JR, Marcos A, et al. Association between dietary inflammatory index and inflammatory markers in the HELENA study. *Mol Nutr Food Res.* 2017;61(6). doi:10.1002/mnfr.201600707

24. Shivappa N, Steck SE, Hurley TG, et al. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr.* 2014;17(8):1689-1696. doi:10.1017/s1368980013002115

25. Johansson-Persson A, Ulmius M, Cloatens L, et al. A high intake of dietary fiber influences C-reactive protein and fibrinogen, but not glucose and lipid metabolism, in mildly hypercholesterolemic subjects. *European Nutr.* 2014;53(1):39-48. doi:10.1007/s00394-013-0496-8

26. King DE, Egan BM, Geesey ME. Relation of dietary fat and fiber to elevation of C-reactive protein. *Am J Cardiol.* 2003;92(11):1335-1339. doi:10.1016/j.amjcard.2003.08.020

27. Estruch R, Martinez-González MA, Corella D, et al. Effects of a Mediterranean-style diet on cardiovascular risk factors: A randomized trial. *Ann Intern Med.* 2006;145(1):1-11. doi:10.7326/0003-4819-145-1-200607040-00004

28. Kanauchi M, Shibata I, Iwamura M. A novel dietary inflammatory index reflecting for inflammatory ageing: Technical note. *Ann Med Surg.* 2019;47:44-46. https://doi.org/10.1016/j.amsu.2019.09.012

29. Steck S, Shivappa N, Tabung F, et al. The dietary inflammatory Index: A new tool for assessing diet quality based on inflammatory potential. *The Digest.* 2014;49:1-9.

30. Fenton TR, Eliaziw M, Lyon AW, et al. Meta-analysis of the quantity of calcium excretion associated with the net acid excretion of the modern diet under the acid-ash diet hypothesis. *Am J Clin Nutr.* 2008;88(4):1159-1166. doi:10.1093/ajcn/88.4.1159

31. Bushinsky DA, Smith SB, Gavrilov KL, et al. Chronic acidosis-induced alteration in bone bicarbonate and phosphate. *Am J Physiol Renal Physiol.* 2003;285(3):F532-F539. doi:10.1152/ajprenal.00128.2003

32. Frick KK, Bushinsky DA. Effect of metabolic and respiratory acidosis on intracellular calcium in osteoblasts. *Am J Physiol Renal Physiol.* 2010;299(2):F418-F425. doi:10.1152/ajprenal.00136.2010

33. Yuan F-L, Xu M-H, Li X, et al. The roles of acidosis in osteoclast biology. *Front Physiol.* 2016;7:222-222. doi:10.3389/physiol.2016.00222

34. Buclin T, Cosma M, Appenzeller M, et al. Diet acids and alkalosis influence calcium retention in bone. *Osteoporos Int.* 2001;12(6):493-499. doi:10.1007/s001980170095

35. Jajoo R, Song L, Rasmussen H, et al. Dietary acid-base balance, bone resorption, and calcium excretion. *J Am Coll Nutr.* 2006;25(3):224-230. doi:10.1080/07315724.2006.10719536

36. New SA, MacDonald HM, Campbell MK, et al. Lower estimates of net endogenous non-carbonic acid production are positively associated with indexes of bone health in premenopausal and perimenopausal women. *Am J Clin Nutr.* 2004;79(1):131-138. doi:10.1093/ajcn/79.1.131

37. Gunn CA, Weber JL, McGill AT, Kruger MC. Increased intake of selected vegetables, herbs and fruit may reduce bone turnover in post-menopausal women. *Nutrients.* 2015;7(4):2499-2517. doi:10.3390/nu7042499

38. Marangella M, Di Stefano M, Casalis S, et al. Effects of potassium citrate supplementation on bone metabolism. *Calcif Tissue Int.* 2004;74(4):330-335. doi:10.1007/s00223-003-0091-8

39. Moseley KF, Weaver CM, Appel L, et al. Potassium citrate supplementation results in sustained improvement in calcium balance in older men and women. *J Bone Miner Res.* 2013;28(3):497-504. doi:10.1002/jbmr.1764

40. Sellmeyer DE, Schloetter M, Sebastian A. Potassium citrate prevents increased urine calcium excretion and bone resorption.
induced by a high sodium chloride diet. J Clin Endocrinol Metab. 2002;87(5):2008-2012. doi:10.1210/jcem.87.5.8470

41. Frassetto L, Morris RCJr, , Sebastian A. Long-term persistence of the urine calcium-lowering effect of potassium bicarbonate in postmenopausal women. J Clin Endocrinol Metab. 2005;90(2):831-834. doi:10.1210/jc.2004-1350

42. Dawson-Hughes B, Harris SS, Ceglia L. Alkaline diets favor lean tissue mass in older adults. Am J Clin Nutr. 2008;87(3):662-665. doi:10.1093/ajcn/87.3.662

43. Dawson-Hughes B, Harris SS, Palermo NJ, et al. Treatment with potassium bicarbonate lowers calcium excretion and bone resorption in older men and women. J Clin Endocrinol Metab. 2009;94(1):96-102. doi:10.1210/jc.2008-1662

44. Oh MS. Irrelevance of bone buffering to acid-base homeostasis. Am J Physiol Renal Physiol. 2005;288(6):F826-F834. doi:10.1152/ajprenal.00587.2010

45. Macdonald HM, Black AJ, Aucott L, et al. Effect of potassium citrate supplementation or increased fruit and vegetable intake on bone metabolism in healthy postmenopausal women: A randomized controlled trial. Am J Clin Nutr. 2008;88(2):465-474. doi:10.1093/ajcn/88.2.465

46. Frassetto LA, Hardcastle AC, Sebastian A, et al. No evidence that the skeletal non-response to potassium alkali supplements in healthy postmenopausal women depends on blood pressure or sodium chloride intake. Eur J Clin Nutr. 2012;66(12):1315-1322. doi:10.1038/ejcn.2012.151

47. Fenton TR, Eliasziw M, Tough SC, et al. Low urine pH and acid excretion do not predict bone fractures or the loss of bone mineral density: A prospective cohort study. BMC Musculoskelet Disord. 2010;11:88. doi:10.1186/1471-2474-11-88

48. Hood VL, Tannen RL. Protection of acid-base balance by pH regulation of acid production. N Engl J Med. 1998;339(12):819-826. doi:10.1056/nejm199809173391207

49. Frassetto L, Sebastian A. Age and systemic acid-base equilibrium: Analysis of published data. J Gerontol A Biol Sci Med Sci. 1996;51A(1):B91-B99. doi:10.1093/gerona/51a.1.b91

50. Wesson DE, Simoni J, Broglio K, Sheather S. Acidity concentration accompanies reduced GFR in humans and increases plasma levels of endothelin and aldosterone. Am J Physiol Renal Physiol. 2011;300(4):F830-F837. doi:10.1152/ajprenal.00587.2010

51. Goraya N, Simoni J, Sager LN, et al. Urine citrate excretion as a marker of acid retention in patients with chronic kidney disease without overt metabolic acidosis. Kidney Int. 2019;95(5):1190-1196. doi:10.1016/j.kint.2018.11.033

52. Rowe JW, Andres R, Tobin JD, et al. The effect of age on creatinine clearance in men: A cross-sectional and longitudinal study. J Gerontol. 1976;31(2):155-163. doi:10.1093/geronj/31.2.155

53. Lu JL, Molnar MZ, Naseer A, et al. Association of age and BMI with kidney function and mortality: A cohort study. The Lancet Diabetes & Endocrinology. 2015;3(9):704-714. https://doi.org/10.1016/S2213-8587(15)00128-X

54. Domazetovic V, Marcucci G, Iantomasi T, et al. Oxidative stress in bone remodeling: Role of antioxidants. Clin Cases Miner Bone Metab. 2017;14(2):209-216. doi:10.11138/ccmb/2017.14.1.209

55. Sendur OF, Turan Y, Tastaban E, Serter M. Antioxidant status in patients with osteoporosis: A controlled study. Joint Bone Spine. 2009;76(5):514-518. https://doi.org/10.1016/j.jbspin.2009.02.005

56. Lean JM, Jagger CJ, Kirstein B, et al. Hydrogen peroxide is essential for estrogen-deficiency bone loss and osteoclast formation. Endocrinology. 2005;146(2):728-735. doi:10.1210/en.2004-1021

57. Bellanti F, Matteo M, Rollo T, et al. Sex hormones modulate circulating antioxidant enzymes: Impact of estrogen therapy. Redox Biol. 2013;1(1):340-346. https://doi.org/10.1016/j.redox.2013.05.003

58. Sumi D, Hayashi T, Matsui-Hirai H, et al. 17beta-estradiol Inhibits NADPH oxidase activity through the regulation of p47phox mRNA and protein expression in THP-1 cells. Biochim Biophys Acta. 2003;1640:113-118.

59. Tilg H, Moschen AR, Kaser A, et al. Gut, inflammation and osteoporosis: Basic and clinical concepts. Gut. 2008;57(5):684-694. doi:10.1136/gut.2006.117382

60. Ormstrup MJ, Harslof T, Kjaer TN, et al. Resveratrol increases bone mineral density and bone alkaline phosphatase in obese men: A randomized placebo-controlled trial. J Clin Endocrinol Metab. 2014;99(12):4720-4729. doi:10.1210/jc.2014-2799

61. Shen C-L, Yeh JK, Cao JJ, et al. Green tea polyphenols mitigate bone loss of female rats in a chronic inflammation-induced bone loss model. J Nutr Biochem. 2010;21(10):968-974.

62. Shen CL, Chyu MC, Wang JS. Tea and bone health: Steps forward in translational nutrition. Am J Clin Nutr. 2013;98(6 Suppl):1694s-1699s. doi:10.3945/ajcn.113.058255

63. Devine A, Hodgson JM, Dick IM, Prince RL. Tea drinking is associated with benefits on bone density in older women. Am J Clin Nutr. 2007;86(4):1243-1247. doi:10.1093/ajcn/86.4.1243

64. Zhang J, Lazarenko OP, Blackburn ML, et al. Blueberry consumption prevents loss of collagen in bone matrix and inhibits senescence pathways in osteoblastic cells. Age (Dordr). 2013;35(3):807-820. doi:10.1007/s11357-012-9412-z

65. Tou JC. Evaluating resveratrol as a therapeutic bone agent: Preclinical evidence from rat models of osteoporosis. Ann N Y Acad Sci. 2015;1348(1):75-85. doi:10.1111/nyas.12840

66. Schlemmer U, Frolich W, Prieto RM, Grases F. Phytate in foods and significance for humans: Food sources, intake, processing, bioavailability, protective role and analysis. Mol Nutr Food Res. 2009;53(S2):S330-S375. https://doi.org/10.1002/mnfr.200900999

67. Lanham-New SA. Fruit and vegetables: The unexpected natural answer to the question of osteoporosis prevention? Am J Clin Nutr. 2006;83(6):1254-1255. doi:10.1093/ajcn/83.6.1254

68. Qiu R, Cao WT, Tian HY, et al. Greater intake of fruit and vegetables is associated with greater bone mineral density and lower osteoporosis risk in middle-aged and elderly adults. PLoS One. 2017;12(1):e0168906. doi:10.1371/journal.pone.0168906

69. Chen Y-M, Ho SC, Woo JLF. Greater fruit and vegetable intake is associated with increased bone mass among postmenopausal Chinese women. British J Nutr. 2006;96(4):745-751. doi:10.1079/BJN20061883
70. Passey C. Reducing the dietary acid load: How a more alkaline diet benefits patients with chronic kidney disease. *J Ren Nutr.* 2017;27(3):151-160. doi:10.1053/j.jrn.2016.11.006

71. Wesson DE, Nathan T, Rose T, et al. Dietary protein induces endothelin-mediated kidney injury through enhanced intrinsic acid production. *Kidney Int.* 2007;71(3):210-217. https://doi.org/10.1038/sj.ki.5002036

72. Phisitkul S, Hacker C, Simoni J, et al. Dietary protein causes a decline in the glomerular filtration rate of the remnant kidney mediated by metabolic acidosis and endothelin receptors. *Kidney Int.* 2008;73(2):192-199. https://doi.org/10.1038/sj.ki.5002647

73. Wesson DE, Simoni J. Acid retention during kidney failure induces endothelin and aldosterone production which lead to progressive GFR decline, a situation ameliorated by alkali diet. *Kidney Int.* 2010;78(11):1128-1135. doi:10.1038/ki.2010.348

74. Wesson DE. Endogenous endothelins mediate increased acidification in remnant kidneys. *J Am Soc Nephrol.* 2001;12(9):1826-1835.

75. Nath KA, Hostetter MK, Hostetter TH. Pathophysiology of chronic tubulo-interstitial disease in rats. Interactions of dietary acid load, ammonia, and complement component C3. *J Clin Invest.* 1985;76(2):667-675. doi:10.1172/JCI112020

76. De Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. *J Am Soc Nephrol.* 2009;20(9):2075-2084. doi:10.1681/asn.2008111205

77. Mahajan A, Simoni J, Sheather SJ, et al. Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. *Kidney Int.* 2010;78(3):303-309. https://doi.org/10.1038/ki.2010.129

78. Goraya N, Simoni J, Jo CH, Wesson DE. Treatment of metabolic acidosis in patients with stage 3 chronic kidney disease with fruits and vegetables or oral bicarbonate reduces urine angiotensinogen and preserves glomerular filtration rate. *Kidney Int.* 2014;86(5):1031-1038. doi:10.1038/ki.2014.83

79. Raphael KL, Wei G, Baird BC, et al. Higher serum bicarbonate levels within the normal range are associated with better survival and renal outcomes in African Americans. *Kidney Int.* 2011;79(3):356-362. doi:10.1038/ki.2010.388

80. Dobre M, Yang W, Chen J, et al. Association of serum bicarbonate with risk of renal and cardiovascular outcomes in CKD: A report from the chronic renal insufficiency cohort (CRIC) study. *Am J Kidney Dis.* 2013;62(4):670-678. doi:10.1053/j.ajkd.2013.01.017

81. Kanda E, Ai M, Kuriyama R, et al. Dietary acid intake and kidney disease progression in the elderly. *Am J Nephrol.* 2014;39(2):145-152. doi:10.1159/000358262

82. Banerjee T, Crews DC, Wesson DE, et al. High dietary acid load predicts ESRD among adults with CKD. *Am J Nephrol.* 2015;42(7):1693-1700. doi:10.1586/asn.201404332

83. Rehbolz CM, Coresh J, Grams ME, et al. Dietary acid load and incident chronic kidney disease: Results from the ARIC study. *Am J Nephrol.* 2015;42(6):427-435. doi:10.1159/000443746

84. Mirmiran P, Yuzbashian E, Bahadoran Z, et al. Dietary acid-base load and risk of chronic kidney disease in adults: Tehran lipid and glucose study. *Iran J Kidney Dis.* 2016;10(3):119-125.

85. Banerjee T, Crews DC, Wesson DE, et al. Dietary acid load and chronic kidney disease among adults in the United States. *BMC Nephrol.* 2014;15(137). doi:10.1186/1471-2296-15-137

86. Trinchieri A, Lizzano R, Marchesotti F, Zanetti G. Effect of potential renal acid load of foods on urinary citrate excretion in calcium renal stone formers. *Urol Res.* 2006;34(1):1-7. doi:10.1007/s00240-005-0001-9

87. Trinchieri A, Maletta A, Lizzano R, Marchesotti F. Potential renal acid load and the risk of renal stone formation in a case-control study. *Eur J Clin Nutr.* 2013;67(10):1077-1080. doi:10.1038/ejcn.2013.155

88. Carvalho M, Erbano BO, Kuwaki EY, et al. Effect of potassium citrate supplement on stone recurrence before or after lithotripsy: Systematic review and meta-analysis. *Urolithiasis.* 2017;45(5):449-455. doi:10.1007/s00240-016-0950-1

89. Phillips R, Hancharale VS, Myatt A, et al. Citrate salts for preventing and treating calcium containing kidney stones in adults. *Cochrane Database Syst Rev.* 2015;(10):Cd010057. doi:10.1002/14651858.CD010057.pub2

90. Frassetto L, Kohlstadt I. Treatment and prevention of kidney stones: An update. *Am Fam Physician.* 2011;84(11):1234-1242.

91. Takahashi S, Inokuchi T, Kobayashi T, et al. Relationship between insulin resistance and low urinary pH in patients with gout, and effects of PPARalpha agonists on urine pH. *Horm Metab Res.* 2007;39(7):511-514. doi:10.1055/s-2007-982517

92. Pakpoy RK. Urinary PH in gout. *Australas Ann Med.* 1965;14:35-39.

93. Alvarez-Nemegyey J, Medina-Escobedo M, Villanueva-Jorge S, Vazquez-Mellado J. Prevalence and risk factors for urolithiasis in primary gout: Is a reappraisal needed? *J Rheumatol.* 2005;32(11):2189-2191.

94. Abate N, Chandalia M, Cabo-Chan AV Jr., et al. The metabolic syndrome and uric acid nephrolithiasis: Novel features of renal manifestation of insulin resistance. *Kidney Int.* 2004;65(2):386-392. doi:10.1111/j.1523-1755.2004.00386.x

95. Kanbara A, Hakoda M, Seyama I. Urine alkalinization facilitates uric acid excretion. *Nutr J.* 2010;9(45). doi:10.1186/1475-2891-9-45

96. Kanbara A, Miura Y, Hyogo H, et al. Effect of urine pH changed by dietary intervention on uric acid clearance mechanism of pH-dependent excretion of urine uric acid. *Nutr J.* 2012;11(1):39. doi:10.1186/1475-2891-11-39

97. Ferrari P, Bonny O. [Diagnosis and prevention of uric acid stones]. *Ther Umsch.* 2004;61(9):571-574. Diagnostik und Pravention des Hamsauresteins. doi:10.1024/0040-5930.61.9.571

98. Fagherazzi G, Vilier A, Bonnet F, et al. Dietary acid load and risk of type 2 diabetes: The E3N-EPIC cohort study. *Diabetologia.* 2014;57(2):313-320. doi:10.1007/s00125-013-3100-0

99. Akter S, Kurotani K, Kashino I, et al. High dietary acid load score is associated with increased risk of type 2 diabetes in Japanese men: The Japan public health center-based prospective study. *J Nutr.* 2016;146(5):1076-1083. doi:10.3945/jn.115.225177

100. Akter S, Eguchi M, Kuwahara K, et al. High dietary acid load is associated with insulin resistance: The furukawa nutrition and health study. *Clin Nutr.* 2016;35(2):453-459. https://doi.org/10.1016/j.clinu.2015.03.008
101. Saklayen MG. The global epidemic of the metabolic syndrome. *Curr Hypertens Rep*. 2018;20(12).

102. Maalouf NM, Cameron MA, Moe OW, et al. Low urine pH: A novel feature of the metabolic syndrome. *Clin J A Soc Nephrol*. 2007;2(5):883-888. doi:10.2215/cjn.06070207

103. Chan R, Wong VW, Chu WC, et al. Higher estimated net endogenous acid production may be associated with increased prevalence of nonalcoholic fatty liver disease in Chinese adults in Hong Kong. *PLoS One*. 2015;10(4):e0122406. doi:10.1371/journal.pone.0122406

104. Okamura T, Hashimoto Y, Hamaguchi M, et al. Low urine pH is a risk for non-alcoholic fatty liver disease: A population-based longitudinal study. *Clin Res Hepatol Gastroenterol*. 2018;42(6):570-576. doi:10.1016/j.clinre.2018.06.005

105. Alferink LJ, Kiefte-de Jong JC, Erler NS, et al. Diet-Dependent acid load-the missing link between an animal protein-rich diet and nonalcoholic fatty liver disease? *J Clin Endocrinol Metab*. 2019;104(12):6325-6337. doi:10.1210/jc.2018-02792

106. Esche J, Shi L, Sánchez-Guijo A, et al. Higher diet-dependent renal acid load associates with higher glucocorticoid secretion and potentially bioactive free glucocorticoids in healthy children. *Kidney Int*. 2016;90(2):325-333. doi:10.1016/j.kint.2016.02.033

107. Kesteloot H, Tzoulaki I, Brown IJ, et al. Relation of urinary calcium and magnesium excretion to blood pressure: The international study of macro- and micro-nutrients and blood pressure and the international cooperative study on salt, other factors, and blood pressure. *Am J Epidemiol*. 2011;174(1):44-51. doi:10.1093/aje/kwr049

108. Nielsen TF, Rylander R. Urinary calcium and magnesium excretion relates to increase in blood pressure during pregnancy. *Arch Gynecol Obstet*. 2011;283(3):443-447. doi:10.1007/s00404-010-1371-y

109. Frassetto LA, Morris RC Jr. Sebastian A. Dietary sodium chloride intake independently predicts the degree of hyperchloremic metabolic acidosis in healthy humans consuming a net acid-producing diet. *Am J Physiol Renal Physiol*. 2007;293(2):F521-F525. doi:10.1152/ajprenal.00048.2007

110. Luis D, Huang X, Riserus U, et al. Estimated dietary acid load is not associated with blood pressure or hypertension incidence in men who are approximately 70 years old. *J Nutr*. 2015;145(2):315-321. doi:10.3945/jn.114.197020

111. Murakami K, Sasaki T, Takahashi Y, Uenishi K. Association between dietary acid-base load and cardiometabolic risk factors in young Japanese women. *Br J Nutr*. 2008;100(3):642-651. doi:10.1017/S0007114508091288

112. Zhang L, Curhan GC, Forman JP. Diet-dependent net acid load and risk of incident hypertension in United States women. *Hypertension (Dallas, Tex : 1979)*. 2009;54(4):751-755. doi:10.1161/HYPERTENSIONAHA.109.135582

113. Collins JA, Moos RJ, Winstanley R, et al. Oxygen and pH-sensitivity of human osteoarthritic chondrocytes in 3-D alginate bead culture system. *Osteoarthritis Cartilage*. 2013;21(11):1790-1798. doi:10.1016/j.joca.2013.06.028

114. Geborek P, Saxne T, Pettersson H, Wollheim FA. Synovial fluid acidosis correlates with radiological joint destruction in rheumatoid arthritis knee joints. *J Rheumatol*. 1989;16(4):468-472.

115. Wu MH, Urban JP, Cui ZF, et al. Effect of extracellular pH on matrix synthesis by chondrocytes in 3D agarose gel. *Biotechnol Prog*. 2007;23(2):430-434. doi:10.1021/bp060024v

116. Vormann J, Worlitschek M, Goedecke T, Silver B. Supplementation with alkaline minerals reduces symptoms in patients with chronic low back pain. *J Trace Elem Med Biol*. 2001;15(2–3):179-183. doi:10.1016/s0946-672x(01)80064-x

117. Csezó RM, Barna I, Bender T, Vormann J. Alkaline mineral supplementation decreases pain in rheumatoid arthritis patients: A pilot study. *Open Nutr J*. 2009;2:100-105. doi:10.2174/18742880902010100

118. Obi Y, Qader H, Kovesdy CP, Kalantar-Zadeh K. Latest consensus and update on protein-energy wasting in chronic kidney disease. *Curr Opin Clin Nutr Metab Care*. 2015;18(3):254-262. doi:10.1097/MCO.0000000000000171

119. Garibotto G, Verzola D. Studying muscle protein turnover in CKD. *Clin J Am Soc Nephrol*. 2016;11(7):1131-1132. doi:10.2215/cjn.04790516

120. Chan R, Leung J, Woo J. Association between estimated net endogenous acid production and subsequent decline in muscle mass over four years in ambulatory older Chinese people in Hong Kong: A prospective cohort study. *J Gerontol A Biol Sci Med Sci*. 2015;70(7):905-911. doi:10.1093/gerona/glu215

121. Welch AA, MacGregor AJ, Skinner J, et al. A higher alkaline dietary load is associated with greater indexes of skeletal muscle mass in women. *Osteoporos Int*. 2013;24(6):1899-1908. doi:10.1007/s00198-012-2203-7

122. Melamed P, Melamed F. Chronic metabolic acidosis destroys pancreas. *Jop*. 2008;24;15(6):552-560. doi:10.6092/1590-8577/2854

123. Berardi JM, Logan AC, Rao AV. Plant based dietary supplement increases urinary pH. *J Int Soc Sports Nutr*. 2008;5(1):20. doi:10.1186/1550-2783-5-20

124. Ashizawa N, Ouchi G, Fujimura R, et al. Effects of a single bout of resistance exercise on calcium and bone metabolism in untrained young males. *Calcif Tissue Int*. 2005;77(5):347. doi:10.1007/s00223990090402

125. Cardinale M, Leiper J, Farajian P, Heer M. Whole-body vibration can reduce calcium induced by high protein intakes and may counteract bone resorption: A preliminary study. *J Sports Sci*. 2007;25(1):111-119. doi:10.1080/02604140600717816

126. Robergs R, Hutchinson K, Hendee S, et al. Influence of pre-exercise acidosis and alkalosis on the kinetics of acid-base recovery following intense exercise. *Int J Sport Nutr Exerc Metab*. 2005;15(1):59-74. doi:10.1123/ijsnem.15.1.59

127. Seebohar B. Aerobic endurance supplements. In: Campbell B, Spano MA, eds. *NSCA’s guide to sport and exercise nutrition*. Human Kinetics Publishers; 2011, pp.141-147.

128. Requena B, Zabala M, Padial P, Feriche B. Sodium bicarbonate and sodium citrate: Ergogenic aids? *J Strength Cond Res*. 2005;19(1):213-224. doi:10.1519/13733.1

129. Mündel T. Sodium bicarbonate ingestion improves repeated high-intensity cycling performance in the heat. *Temperature (Austin)*. 2018;5(4):343-347. doi:10.1080/23232890.2018.1436393

130. Hadzic M, Eckstein ML, Sehugardt M. The impact of sodium bicarbonate on performance in response to exercise duration in athletes: A systematic review. *J Sports Sci Med*. 2019;18(2):271-281.
131. Remer T, Dimitriou T, Maser-Gluth C. Renal net acid excretion and plasma leptin are associated with potentially bioactive free glucocorticoids in healthy lean women. *J Nutr.* 2008;138(2):426S-430S. doi:10.1093/jn/138.2.426S

132. Lee Hamm L. Role of glucocorticoids in acidosis. *Am J Kidney Dis.* 1999;34(5):960-965.

133. Espino L, Suarez ML, Santamarina G, et al. Effects of dietary cation-anion difference on blood cortisol and ACTH levels in reproducing ewes. *J Vet Med A Physiol Pathol Clin Med.* 2005;52(1):8-12. doi:10.1111/j.1439-0442.2004.00677.x

134. Remer T, Pietrzik K, Manz F. Short-term impact of a lactovegetarian diet on adrenocortical activity and adrenal androgens. *J Clin Endocrinol Metab.* 1998;83(6):2132-2137. doi:10.1210/jcem.83.6.4883

135. Anagnostis P, Athyros VG, Tziomalos K, et al. The pathogenetic role of cortisol in the metabolic syndrome: A hypothesis. *J Clin Endocrinol Metab.* 2009;94(8):2692-2701. doi:10.1210/jc.2009-0370

136. Cozma S, Dima-Cozma LC, Ghiciuc CM, et al. Salivary cortisol and α-amylase: subclinical indicators of stress as cardiometabolic risk. *Brazil J Med Biol Res.* 2017;50(2):e5577.

137. Haas AV, Hopkins PN, Brown NJ, et al. Higher urinary cortisol levels associate with increased cardiovascular risk. *Endocr Connect.* 2019;8(6):634. doi:10.1530/ec-19-0182

138. Ortiz R, Kluwe B, Odei JB, et al. The association of morning serum cortisol with glucose metabolism and diabetes: The Jackson heart study. *Psychoneuroendocrinology.* 2019;103:25-32. https://doi.org/10.1016/j.psyneuen.2018.12.237

139. Noppe G, van den Akker ELT, de Rijke YB, et al. Long-term glucocorticoid concentrations as a risk factor for childhood obesity and adverse body-fat distribution. *Int J Obes.* 2016;40(10):1503-1509. doi:10.1038/ijo.2016.113

140. Krupp D, Johner SA, Kalthoff H, et al. Long-term dietary potential renal acid load during adolescence is prospectively associated with indices of nonalcoholic fatty liver disease in young women. *J Nutr.* 2012;142(2):313-319. doi:10.3945/jn.111.150540

141. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH collaborative research group. *N Engl J Med.* 1997;336(16):1117-1124. doi:10.1056/nejm199704173361601

142. McNally MA, Pyzik PL, Rubenstein JE, et al. Empiric use of potassium citrate reduces kidney-stone incidence with the ketogenic diet. *Pediatrics.* 2009;124(2):e300-e304. doi:10.1542/peds.2009-0217

143. Soygur T, Akbay A, Kupeli S. Effect of potassium citrate therapy on stone recurrence and residual fragments after shockwave lithotripsy in lower caliceal calcium oxalate urolithiasis: A randomized controlled trial. *J Endourol.* 2002;16(3):149-152. doi:10.1089/089277902753716098

144. Goraya N, Simoni J, Jo CH, Wesson DE. A comparison of treating metabolic acidosis in CKD stage 4 hypertensive kidney disease with fruits and vegetables or sodium bicarbonate. *Clin J Am Soc Nephrol.* 2013;8(3):371-381. doi:10.2215/cjn.02430312

145. McNaughton L, Backx K, Palmer G, Strange N. Effects of chronic bicarbonate ingestion on the performance of high-intensity work. *Eur J Appl Physiol Occup Physiol.* 1999;80(4):333-336. doi:10.1007/s004210050600