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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'[3,4,6,9,11–15] due to high consumption of animal protein,[4,9,11] the lack of

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potassium and bicarbonate rich foods,[12] and the lack of other base forming minerals such as magnesium and calcium,[9] all of which are typically found in fruit and vegetables.[3,4,9,12–14] A diet with a preponderance of animal food sources (acid precursors) compared to fruit and vegetables (base precursors) results in increased net acid load.[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)*[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.[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.[18] Estimated NEAP is typically calculated using one of two algorithms: Frassetto et al[15] estimate NEAP based on the dietary protein and potassium ratio, whereas Remer et al[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.[20]
- *Renal net acid excretion (NAE)*.[19]
- *The potential renal acid load (PRAL)*[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) 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).[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.[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.[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.[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 (≈ -6.3 mEq and ≈ -4.61 mEq respectively).[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,[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.[23,27] A pro-inflammatory diet as determined by the DII[24] has been associated with higher levels of inflammatory markers including, TNF-α, IL-1, IL-2, IFN-γ and vacular cell adhesion molecule-1 (VCAM).[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.[28] Steck et al[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.

Table 1. Synonymous Terminology for CSSMA in the Published Literature.

Low-grade chronic, compensated metabolic acidosis[3]
Diet-induced metabolic acidosis[4–6]
Low level metabolic acidosis and positive acid balance[7]
Chronic low-grade systemic metabolic acidosis[8]
Subclinical low-grade acidosis[9]
Mild chronic metabolic acidosis[10]
Diet-induced low-grade metabolic acidosis[2]

Table 2. Average PRAL of Various Food Categories.[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 ≈ -4.61 (average of 6 vegetables listed, value range -14.0 to -0.8)
Fruits and fruit juice	PRAL of ≈ -6.3 (average of 7 types listed, value range -21.0 to -1.0)

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.[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.[19] The correlation between NAE and urine pH has also been objectively determined to be significant ($r = 0.83$; $P < .001$).[21] As a result of these findings, various subsequent interventional studies[3,9] 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.[16] 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 demineralization of the skeleton.[30] The skeleton being the largest reservoir of base forming minerals involved in the process of acid-base homeostasis.[6,8] 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.[30] 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.[30] Such a diet significantly increases calcium excretion (74%) and leads to increased levels of bone resorption markers.[34] Furthermore, higher NEAP values have shown a positive association with lower bone mass of the femur, hip and spine in women.[36] 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.[37]

Table 3. Influence of CSSMA on Bone Metabolism.

Influence of CSSMA on bone metabolism
Decrease in osteoblast activity[31,32]
Increase in osteoclast activity[31–33]
Promotion of bone resorption[33,34]
Decrease in gene expression of bone matrix proteins[31,32]
Decrease in alkaline phosphatase activity[31,32]
Increase in urinary calcium excretion[35]
Increase in parathyroid hormone (PTH) levels (associated with NAE)[35]
Increase in N-telopeptide (associated with NAE) which is a marker of bone resorption[35]

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,[38,39] a reduction in bone resorption markers,[38–40] reduced calcium loss,[7,38,39] increased bone mass,[11] and the ability to negate the negative impact of a high NaCl diet on bone health.[40] Similarly, the latter (potassium bicarbonate) reduces calcium excretion,[7,41–43] and favorably influences bone turnover markers i.e. increases serum osteocalcin and lowers urine hydroxyproline[7] and N-telopeptide.[43]

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.[44] 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.[16] 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.[45] 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,[46] 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.[47]

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.[48] 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, alkalinization therapy may be of benefit. These include older persons who have been shown to have higher steady state acid levels,[49] those with compromised kidney function who typically have reduced acid excretory capacity[50,51] or those with both of these scenarios as kidney function typically declines with age.[52,53]

In addition, another important and related pathophysiological 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

considered. The review by Domazetovic et al[54] describes the negative influence of oxidative stress driven by reactive oxygen species (ROS) on bone remodeling and the homeostatic and remedial influence of antioxidants thereon. ROS have been shown to induce apoptosis of osteoblasts and osteocytes, promoting osteoclastogenesis, ultimately leading to decreased bone mineralization and osteogenesis.[54] Antioxidants, on the other hand, promote differentiation of osteoblasts, mineralization and reduce osteoclast action.[54] In osteoporosis, suboptimal antioxidant status and 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.[54–58] Osteoporosis is also linked with reduced absorption of dietary antioxidants in chronic bowel disease.[54,59] A growing body of evidence further supports the positive influence of antioxidants on bone density and prevention of bone loss.[54,60–65]

In terms of bone health, one disadvantage of fruit and vegetables is their phytate content, which can inhibit calcium absorption.[66] The phytate content is not as high as in grains/cereals, legumes and nuts,[66] but does need to be taken into consideration. Nevertheless, on the balance of effect, fruit and vegetables provide more benefit to bone health[67–69] than damage, through the pathways of antioxidants,[54,60–65] ROS,[54–58] and alkalinization.[30]

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.[70]

A high dietary acid load and consequential demand for renal compensation increases production of endothelin-1, angiotensin II[71–73] and aldosterone. These factors are necessary for acid excretion,[74] but can injure the kidneys, leading to renal fibrosis and reduced GFR.[2] 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,[75] 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.[70] 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).[76,77] 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,[70] and preserve GFR and lower urinary angiotensinogen in CKD.[78]

Table 4. Association Between NEAP, DAL and/or NAE and Kidney Function.

	Association with kidney function
Serum bicarbonate levels	↑ Within normal range = better renal outcome and survival in CKD[79]
	↓ = Independent risk factor for CKD progression[80]
NEAP	↑ Independently associated with CKD progression[81]
	↑ Associated with faster decline in GFR[18]
	↓ May be effective kidney protective therapy[81]
DAL	↑ In patients with CKD is independently associated with ESRD[82]
	↑ PRAL associated with higher risk of incident CKD[83]
	↑ PRAL = risk of CKD 42% higher than with ↓PRAL diet[84]
NAE	↑ Associated with greater odds of albuminuria and higher risk of lower eGFR[85]

DAL = dietary acid load; GFR = glomerular filtration rate; ESRD = end stage renal disease (renal failure).

Renal Nephrolithiasis

When compensating for CSSMA, calcium and oxalate excretion and concentration in urine increase[2,4] and citrate levels decrease.[86] The presence of citrate in urine usually prevents formation of calcium oxalate crystals and stones[4,86]; 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.[87]

A meta-analysis confirms that supplemental potassium citrate significantly protects against recurrence of nephrolithiasis during the year after extracorporeal shock wave lithotripsy.[88] Similary, 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.[89] Frassetto and Kholstadt (2011) also confirm that in order to prevent calcium oxalate, cystine and uric acid stones, urine should be alkalinized by eating a diet high in fruit and vegetables, taking supplemental or prescription citrate (calcium, magnesium or potassium citrate), or drinking alkaline mineral waters.[90]

Gout and Uric Acid Nephrolithiasis

Gout sufferers often have low urine pH[91,92] which is also a major risk factor for the development of uric acid stones.[93,94] There is evidence to support systemic alkalization 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.[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.[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.[2] Studies confirm high PRAL and NEAP scores to be positively associated with development of type 2 diabetes[98] and risk thereof,[99] as well as higher HOMA-IR scores (insulin resistance).[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.[101] A less well known feature of metabolic syndrome is uric acid nephrolithiasis[94] and a significantly lower 24 h urine pH. A decreasing urine pH is associated with worsening of the syndrome.[102] Takahashi et al[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.[103] In addition, NAFLD has been positively associated with low urine pH in a review of over 2 000 cases.[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 ratios [A:P] $P < .001$).[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.[106] Thirdly, these increases lead to increased urinary calcium excretion (a consequence of CSSMA) which leads to increased blood pressure.[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.[109]

Both high PRAL and NEAP have been shown to have a positive association with raised diastolic pressure[110,111] and systolic pressure.[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.[112]

Arthritis and Back Pain

Acidosis is harmful to human osteoarthritis chondrocytes.[113] Acidosis of synovial fluid has been shown to correlate with features of radiological joint destruction and granulocyte concentration in knee rheumatoid arthritis ($P < .002$),[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.[3] 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.[115] Research studies have shown that chronic low back pain,[116] rheumatoid arthritis[117] and osteoarthritis of the hands[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.[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.[42] Large observational cohort studies also confirm the positive association between NEAP scores and appendicular muscle mass in older patients[120] and low PRAL with the maintenance of muscle mass.[121] Maintenance of muscle mass is particularly important in older patients with possible concurrent low bone density to prevent falls and osteoporotic fractures.[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.[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.[40]	Potassium citrate 90 mmol/day (9270 mg/day)	Postmenopausal women
Marangella et al 2004[38]	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
Jehle et al 2006.[11]	Potassium citrate 30 mEq/day (3 240 mg/day)	Postmenopausal women with osteopenia
Moseley et al 2013[39]	Potassium citrate 60 mmol or 90 mmol/day (6 480 mg or 9 720 mg)	Older men and women
Sebastian et al 1994[7]	Potassium bicarbonate 60 mmol/day to 120 mmol/day	Postmenopausal women
Maurer et al 2003[10]	Sodium bicarbonate 0.55 mmol/kg + Potassium bicarbonate 0.55 mmol/kg	Healthy subjects
Frassetto et al 2005[41]	Potassium bicarbonate 30 mmol/d, 60 mmol/d, 90 mmol/d	Postmenopausal women
Dawson-Hughes et al 2009[43]	Potassium bicarbonate 67.5 mmol/day	Older men and women
CKD		
De Brito-Ashurst et al 2009[76]	Sodium bicarbonate 1.82 g/day	CKD patients
Mahajan et al 2010[77]	Sodium bicarbonate 0.5 mEq/kg lean body weight (≈ 35 mEq for 70 kg)	CKD stage 2
Goraya et al 2013[144]	Sodium bicarbonate 1 mEq/kg/day	CKD stage 4 patients
Urolithiasis		
Soygür et al 2004[143]	Potassium citrate 60 mEq/day	Calcium oxalate urolithiasis patients post shockwave lithotripsy
McNally et al 2009[142]	Potassium citrate 2 mEq/kg daily	Children on ketogenic diet (at risk of urolithiasis)
Carvalho et al 2017[88]	Potassium citrate 55 mEq/day (mean dosage of 4 trials)	Prevention of stone recurrence after lithotripsy (metanalysis)
Arthritis		
Cseuz et al 2008[117]	Calcium citrate 400 mg Potassium citrate 250 mg Sodium citrate 250 mg Magnesium citrate 100 mg Ferrous citrate 5 mg Cupric citrate 1 mg Zinc gluconate 5 mg Potassium iodide 0.1 mg Sodium molybdate 0.08 mg Chromium chloride 0.06 mg Sodium selenite 0.03 mg	Rheumatoid arthritis
Vormann et al 2001.[116]	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.	Chronic low back pain
Van Velden et al 2015.[3]	Magnesium hydrogenium phosphate 488 mg Calcium citrate 290 mg Potassium bicarbonate 1 566 mg Magnesium citrate 630 mg Potassium citrate 1740 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. [145]	Sodium bicarbonate 0.5 g/kg^{-1} body mass	Impact on high intensity physical performance
Robergs et al 2005.[126]	Sodium bicarbonate 0.2 g/kg Sodium citrate 0.2 g/kg	Impact on recovery kinetics of pH
Mündel (2018).[129]	Sodium bicarbonate 0.5 g/kg^{-1} body mass	Performance and recovery from exercise in heat conditions

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.[122]

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.[123,124] Athletes are also known to follow higher protein diets which further increases urine acidity and calcium loss in the urine.[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,[123,126] suggesting that CSSMA caused by diet may compound the additional acidogenic burden induced by exercise which may compromise performance and recovery time.[123] Systemic alkalization during high intensity exercise may delay the onset of fatigue,[127,128] with supplemental bicarbonate shown to improve performance and recovery and improve repeated exercise performance.[129,130]

Upregulation of Cortisol – A Major Contribution to Pathogenesis of CSSMA

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

One of the major consequences of upregulated glucocorticoid production is metabolic syndrome.[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,[135] and some of the cardinal features thereof such as cardiometabolic risk,[136] increased cardiovascular risk in terms of the Framingham Cardiovascular Risk Score,[137] dysglycaemia, insulin resistance, modified adiposity and higher odds of type 2 diabetes,[138] and obesity.[139] In addition, uric acid nephrolithiasis,[94] acidic urine,[102] NAFLD,[103–105,140] and hypertension[110–112] are conditions strongly associated with CSSMA and also features of metabolic syndrome.

Clinical Interventions to Address CSSMA

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.[5] PRAL charts are useful reference tools in differentiating acidogenic from alkalizing 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[2,4,5,13,14,16,37,78,96] to > 9 servings daily[37,141] or consult PRAL charts to reduce the total PRAL by 50% daily.[18]
2. Reduce animal protein intake[70,96] by decreasing high biological value protein (HBV) (animal protein and soya) and increasing low biological protein (LBP) sources.[96]
3. Reduce NaCl intake.[70,109] Passey (2017) recommends a 'no added salt' approach. The impact of NaCl is confirmed by Frassetto et al[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)[70] recommends the removal of such from the diet in CKD and replacement with alkaline water (pH 7.4).

Supplementation with Alkaline Minerals

Studies addressing CSSMA and its consequences through supplementation generally apply one or a combination of alkalizing 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[3,11,38–40,88,116,117,142,143]
- Potassium bicarbonate[3,7,10,41,43]
- Sodium bicarbonate[10,76,77,116,117,126,129,144,145]

- Calcium citrate[3,116,117]
- Magnesium citrate[3,116,117]
- Other citrate salts[116,117]

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),[3] chronic low back pain (Vorman et al 2001),[116] and rheumatoid arthritis (Cseuz et al 2008).[117] 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 alkalizing 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.[9] 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. Alkalizing 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 alkalization 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 alkalization on bone and skeletal health, kidney function, and aspects of metabolic and cardiovascular health.

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Author Contributions

DF Naude[1] 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 distributer of health supplements and complementary medicines in South Africa.

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