Chronic sub-clinical systemic metabolic acidosis (CSSMA) – fact or fiction?

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Introduction

Self-regulation of blood pH is one of the most carefully controlled homeostatic mechanisms in the human body; blood pH is carefully maintained with a narrow margin of pH 7.35 and 7.45 (mean pH 7.4) using various innate buffering systems with an arterial pH of less than 7.35 considered *acidosis* and greater than 7.45 considered *alkalosis*. [10] To avoid confusion, CSSMA should be clearly distinguished from the traditional understanding of 'acidosis', CSSMA rather occurring when despite compensatory buffering action, arterial serum pH remains near the lower pH limit of 7.35 for protracted periods of time (but still within 'normal' range).[9]

Dietary aetiology of CSSMA

The major aetiology of CSSMA is the shift away from the alkaline human ancestral diet which was rich in fruits and vegetables to that of the contemporary 'Westernised' type diet [9] which is widely considered to be 'acidogenic' [1, 2, 4, 7, 11-15] due to high consumption of animal protein [2, 7, 11] and compounded by the lack of potassium and bicarbonate rich foods[12] as well as a lack of other base forming minerals such as magnesium and calcium [7] which are typically found in fruit and vegetables. [1, 2, 7, 12-14] A diet with preponderance toward animal food sources (acid precursors) compared to fruit and vegetables (base precursors) results in increased net acid load. [16]

The influence of diet on net endogenous acid production has been described and quantified using various methods:

- *Net Endogenous Non-carbonic Acid Production* (NEAP) [15] (expressed in mEq/Day) considers two variables i.e. the acidifying effect of protein and the alkalising effect of potassium as a means to accurately quantify the impact of diet on endogenous acid production.
- *Renal Net Acid Excretion* (NAE) [17]
- *Potential Renal Acid Load* (PRAL) [18] of various food types provides an appropriate prediction of their influence on urine pH.

Food category	Average PRAL value
Dairy products	PRAL of ≈ +13.2 (average of 10 types of dairy products listed)
Meat	PRAL of ≈ +9.5 (average of 6 types of meat listed)
Grain/grain products	PRAL of ≈ +6.7 (average of 8 types of grains listed)
Vegetables	PRAL of ≈ -4.61 (average of 6 vegetables listed)
Fruits and fruit juice	PRAL of ≈ -6.3 (average of 7 types listed)

Table 1 – average PRAL of various food categories [4,18]

In summary, dairy, meat and grain products (typically consumed in large quantities in the 'modern, Westernised diet') have significantly higher (positive) PRAL values (high acid load), in contrast to fruits, fruit juices and vegetables (typically lacking in the 'Westernised diet') that generally have a negative PRAL (alkalising action).[4] Thus the long-term consumption of predominantly acid precursor foods (those with higher positive PRAL) and limited base precursor foods (those with lower or negative PRAL) results in a protracted greater endogenous acid load and demand on pH buffering homeostatic mechanisms, resulting in CSSMA. [2, 9] '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 man.' It proposes further that the existence of modern chronic disease is a direct consequence of this genetic mismatch. [23]

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), a low PRAL diet comprising more fruit and vegetables with less meat results in significantly higher urine pH and is readily and conveniently measurable.[14] Protein content within diet was also shown to directly influence renal net acid excretion, for example renal NAE of the lactovegetarian diet was confirmed to be significantly lower

than that of moderate and high protein diets, i.e. 3.7 mEq/d versus 62.2 and 117 mEq/d respectively [17] and correlation (r=.83; P<0.001) between NAE and urine pH has also been objectively determined.[18] As a result of these findings, various subsequent interventional studies [1, 7] applying mineral based systemic alkalising agents measure subsequent increases in urine pH as outcomes confirming their systemic alkalising action.

Potential Consequences of CSSMA

1. Bone health

The *acid-ash diet hypothesis of osteoporosis* states that CSSMA induced by the contemporary 'Westernised' diet leads to chronic demineralisation of the skeleton[24] as the largest reservoir of base forming minerals as a means of implementing acid-base homeostasis[4, 6]. A large body of evidence now supports the adverse effects of CSSMA on bone metabolism, suggesting it as a primary risk factor for bone health. [24] **Table 2** summarises the some of the published *in vitro* data in this regard.

Influence of CSSMA on bone metabolism
Osteoblast activity decreased[25, 26]
Osteoclast activity increased[25-27]
Promotion of bone resorption[27, 28]
Decreased gene expression of bone matrix proteins[25, 26]
Decreased alkaline phosphatase activity[25, 26]
Increased urinary calcium excretion [29]
Increased parathyroid hormone (PTH) levels (associated with NAE)[29]
Increased N-telopeptide (associated with NAE) – marker of bone resorption[29]

Table 2 – Influence of CSSMA on bone metabolism

A meta-analysis of 25 studies confirms the detrimental effect of the *acidogenic diet* on bone mineral density[24]; an acidogenic diet significantly increasing calcium excretion (74%) and leading to increased levels of bone resorption markers, [28] and higher NEAP values have also shown positive association with lower bone mass of the femur, hip and spine in women. [30] Conversely, a low PRAL (>9 servings of fruit and vegetables daily) diet has been shown to lead to increased urine pH, less calcium excretion and positively influence bone turnover markers. [31]

Various trials also demonstrate the bone preservation effects of supplemental *potassium citrate* or *potassium bicarbonate* through their systemic alkalising action. The former leads to lower net acid excretion [32,34], a reduction in bone resorption markers [32-34], reduced calcium loss, [5,33,34] and increased bone mass [11] and the ability to negate the negative impact of high NaCl diet on bone health. [33] Similarly, the latter (*potassium bicarbonate)* reduces calcium excretion [5,35,36] and favourably influences bone turnover markers i.e. increases serum osteocalcin, lowers urine hydroxyproline [5] and N-telopeptide. [36]

2. 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 (utilising phosphate in the monohydrate format), neutralisation of acid (through metabolism of glutamine) and the excretion of anions (citrate, oxalate and urate). As kidney function fails, (reduction in eGFR) so the compensatory mechanisms of acid excretion and neutralisation are compromised. [21]

A high dietary acid load and consequential demand for renal compensation directly leads to kidney injury by increasing production of endothelin-1, angiotensin II [37-39] and aldosterone, factors which although necessary for acid excretion [40] can lead to reduced GFR and renal fibrosis [9] [9]. Ammonia, a by-product of acid neutralisation in the kidneys, also increases in proximal renal tubules as H^+ load increases; increased levels of this toxin lead to tubular toxicity and further renal injury, [41] which may ultimately lead to the onset of chronic kidney disease (CKD). Several publications explore the link between increased dietary acid load and risk of or prognosis in CKD, **Table 3** summarises these below.

Addressing DAL with *supplemental alkali* is shown to reduce markers of kidney injury and the progression of CKD [21]. Bicarbonate supplementation is shown to slow decline in creatinine clearance, progression of CKD and reduce the risk of ESRD [50,51]. Similarly, *alkalising the diet* by increasing fruit and vegetables in addition to lowering animal protein intake has been shown to lead to increase serum bicarbonate and stabilise or improve renal function [21], and in another trial preserve GFR and lower urinary angiotensinogen in CKD. [53]

Serum bicarbonate levels	↑ Within normal range = better renal outcome and survival in CKD [42] ↓ = Independent risk factor for CKD progression [43]
NEAP	↑Independently associated with CKD progression [44] ↑Associated with faster decline in GFR [45] ↓May be effective kidney protective therapy [44]
DAL	↑ In patients with CKD is independently associated with ESRD [46] ↑(PRAL) associated with higher risk of incident CKD [47] ↑(PRAL) = risk of CKD 42% higher than with ↓PRAL diet [48]
NAE	↑Associated with greater odds of albuminuria and higher risk of lower eGFR[49]
DAL = dietary acid load; GFR = glomerular filtration rate; ESRD = end stage renal disease (renal failure)	

Table 3 –Summary of publications of association between DAL and/or NAE and kidney function

3. Renal nephrolithiasis (kidney stones)

When compensating for CSSMA, calcium and oxalate excretion and concentration in urine increases [2,9] and citrate levels decrease. [55] The presence of citrate in urine usually prevents formation of calcium oxalate crystals and stones, [2,55] its absence in the presence of increased calcium and oxalate leads to stone formation. The risk posed by the acidogenic diet is well reported; animal protein to potassium ratio (estimate of net acid load) was associated with higher risk of kidney stones ($p<0.004$) and that potassium consumption associated with decreased risk thereof ($p<0.001$), similarly, a high PRAL increases the risk of stones by 2.5 times, a risk mitigated by increasing fruit and vegetable intake. [56]

A meta-analysis confirms that supplemental *potassium citrate* significantly protects against recurrence of nephrolithiasis during the year after extracorporeal shock wave lithotripsy. [57] Similary, a Cochrane report states that citrate salts significantly reduce stone size and prevent stone formation as well as reduce the need for retreatment or stone removal.[58] Frassetto & Kholstadt (2011) also confirm that in order to prevent calcium oxalate, cystine and uric acid stones, urine should be alkalinised by eating a diet high in fruits and vegetables, taking supplemental or prescription citrate (calcium, magnesium or potassium citrate) or drinking alkaline mineral waters.

4. *Gout and uric acid nephrolithiasis*

It has been determined that gout sufferers often have low urine pH [62, 63] which is also a major risk factor for the development of uric acid stones.[64, 65] There is evidence to support systemic alkalisation and subsequently increasing urine pH as a means to address gout as well as uric acid kidney stones, with more alkaline urine being more conducive for uric acid eliminaiton and less likely to lead to the formation of uric acid stones. [66,67] 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 (alkalising) urine to pH 6.2 - 6.8 as a therapeutic intervention with potassium citrate (or sodium bicarbonate) which is also an effective method of dissolution of existing stones with potassium citrate being the treatment of choice in preventing recurrence. [69]

5. Insulin resistance and type 2 diabetes

CSSMA with a blood pH close to the lower pH limit on an ongoing basis may lead to decreased glucose uptake by muscle, negatively impact the binding of insulin to receptors or disrupt insulin signalling pathways. The occurrence of such typically leads to insulin resistance which is known to be a core contributing factor in type 2 diabetes mellitus.[9] This is supported by studies which confirm high PRAL and NEAP scores to be positively associated with development of incident type 2 diabetes [72] and risk thereof ,[74] as well as HOMA-IR scores (insulin resistance).[73]

6. Metabolic syndrome

Largely, as a result of the Western lifestyle characterised by lack of exercise and a low fibre, high calorie, refined food diet, metabolic syndrome has evolved into a global health problem. [75] A less well known, yet scientifically proven feature of metabolic syndrome and considered a renal manifestation thereof, is uric acid nephrolithiasis [65] as is the fact that those with metabolic syndrome have significantly lower 24 hour urine pH, with evidence to support that decreasing urine pH is associated with further advancing of the syndrome. [76] Takahashi *et al.* [62] have also 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, was found also to be positively associated with dietary acid load; for every 20mEq/day increase in NEAP score the odds thereof have been shown to increase by 1.32. [77] In addition, NAFLD was also positively associated with low urine pH in a review of over 2000 cases.[79] From a cohort of 3882 participants, 1337 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] $p<0.001$).[80]

7. Hypertension

The association of CSSMA with hypertension comprises a three step process; firstly, CSSMA activates the pituitary gland and secondly, the release ACTH finally leading to increased cortisol and aldosterone production.[81] Increased urinary calcium excretion (a consequence of CSSMA) is known to lead to increased blood pressure [82, 83] and sodium chloride consumption, is also a well-known aetiology of hypertension and is also reported to be an independent predictor of acid-base status with CSSMA advancing with increased consumption thereof. [84]

Both high PRAL and NEAP have been shown to have a positive association with raised diastolic pressure [85, 86] and systolic pressure, [86] and data from 87393 women after 14 year follow up 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 than those with low scores. [87]

8. Arthritis and back pain

Acidosis is harmful to human osteoarthritis chondrocytes [88] as is acidosis of synovial fluid, shown to correlate with features of radiological joint destruction and granulocyte concentration in knee rheumatoid arthritis ($p<0.002$) [89] with acidosis being a feature of chronic inflammatory arthritis. Van Velden *et al.* (2015) postulates that an acidic extra cellular environment in the arthritic joint may subsequently result in increased intracellular acid load in chondrocytes, potentially driving disease progression. [1]Wu *et al.* (2007) determined that even minor alteration in extracellular pH may have significant impact on metabolism and biosynthetic ability of chondrocytes with a maximum glycosaminoglycan synthesis occurring at a pH of 7.2.[90]

Three clinical trials addressing arthritis by targeting CSSMA were identified. Chronic low back pain [91], rheumatoid arthritis [92] and osteoarthritis of the hands [1] responded favourably to alkaline mineral supplementation. Two of the trials also reporting concomitant increase in serum [91] and urine pH, [1] confirming concurrent systemic alkalising action and two trials reporting a reduction in need for NSAIDs and/or analgesic medication. [1,92]

9. Preservation 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.[93, 94] CSSMA, although a significantly less aggressive form of acidosis, if protracted, may too contribute to loss of muscle mass, particularly in older patients. In a 3-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. [95] Large observational cohort studies also confirm the positive association between NEAP scores and appendicular muscle mass in older patients [96] and PRAL (more alkaline diet with higher levels of potassium and magnesium) with the maintenance of muscle mass, [97] which is particularly important in older patients with possible concurrent low bone density as the maintenance of muscle mass is necessary for the prevention of falls and osteoporotic fractures.[97]

10. Digestive health – pancreatic and biliary function

Melamed & Melamed (2014) propose CSSMA as an important aetiological factor in the rapidly increasing prevalence of indigestion in the developing world. [98] 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 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 whilst still within the pancreas causing pancreatitis and bile, when acidified, results in 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 oesophagus. [98]

11. Physical performance and exercise recovery

Although not considered 'pathology' per se, 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. [19, 101] Athletes are also known to follow higher protein diets which further increases urine acidity and calcium loss in the urine.[19, 102] Pre-exercise systemic pH and blood pH buffering capacity was shown to impact significantly on recovery kinetics and endurance capacity in recurrent exercise, [19, 103] suggesting that CSSMA caused by diet may compound the additional acidogenic burden induced by exercise which may compromise performance and recovery time.[19] Systemic alkalisation during high intensity exercise may delay the onset of fatigue [100, 104] with supplemental bicarbonate shown to improve recovery and repeated exercise performance,[105] and a recent meta-analysis confirming its performance enhancing action. [106]

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. [107-109] This occurrence is actually necessary to facilitate renal elimination of H^+.[108] Data now confirms that even insidious forms thereof such as CSSMA may too upregulate glucocorticoid production,[8,79,108] for example when the acidogenic diet is neutralised, plasma cortisol levels reduce significantly with simultaneous increase in calcium retention.[8] Even a short-term switch to a lactovegetarian diet with low PRAL led to a significant decrease in urinary free cortisol. [108]

This association between CSSMA and upregulated glucocorticoids is interesting since from the literature presented thus far in this review, we also begin to see that CSSMA shares a number of additional potential consequences with that of upregulated cortisol levels, particularly the shared consequence of metabolic syndrome. Extensive literature confirms links between raised cortisol and metabolic syndrome in general [109] or some of the cardinal features thereof, such as cardiometabolic risk [112], Framingham Cardiovascular Risk Score [113], dysglycaemia, insulin resistance, modified adiposity and a higher odds of type 2 diabetes [114] and obesity.[115] In addition, uric acid nephrolithiasis [65], acidic urine [76], NAFLD [77-80] and hypertension [85-87] conditions strongly associated with CSSMA are also features of metabolic syndrome.

Clinical interventions to address CSSMA

1. Dietary interventions

When making strategic dietary interventions for CSSMA, clinicians should primarily aim 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.[3] PRAL charts are also useful reference tools in determining acidogenic from alkalising foods and can be useful guides for consumers when making food choices.
Most reference to the 'alkaline diet' in the published literature recommend the following principles:

1. *Increasing the consumption of fruit and vegetables* [2, 3, 9, 13, 14, 16, 31, 53, 67] to > 9 servings daily [31,116] or by consulting PRAL charts to reduce the total PRAL by 50% daily. [18]

2. *Reducing animal protein intake* [21, 67] by decreasing high biological value protein (HBV) (animal protein and soya) and increasing low biological protein (LBP) sources. [67]

3. *Reducing NaCl intake.* [21, 84] Passey (2017) recommends a 'no added salt.' The impact of NaCL is confirmed by Frassetto *et al.* reporting that NaCl has approximately 50-100% of the acidosis-producing effect of the diet net acid load in healthy subjects consuming an acidogenic diet.

4. *Reducing 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) [21] recommends the removal of such from the diet in CKD and replacement with alkaline water (pH 7.4).

2. Supplementation with alkaline minerals

Intervention studies addressing CSSMA consequences or aspects thereof with supplementation generally apply one or a combination of alkalising minerals as interventions. The most frequently applied alkaline minerals in the clinical trials include bicarbonate and the citrate salts:

Potassium citrate [1, 11, 32-34, 57, 60, 61, 91, 92] Potassium bicarbonate [1, 5, 8, 35, 36]
Sodium bicarbonate [8, 50-52, 91, 92, 103, 105, 117] Calcium citrate [1, 91, 92]
Magnesium citrate [1, 91, 92] Other citrate salts [91, 92]

An in-depth literature review also revealed four trials applying combinations of alkaline minerals designed to address CSSMA in general but applied specifically in the following clinical contexts: osteoarthritis of the hands (Van Velden *et al.* 2015)[1], chronic low back pain (Vorman *et al.* 2001)[91] and rheumatoid arthritis (Cseuz *et al.* 2008).[92] All three trials achieved significant improvement in their respective assessments of pain compared to controls and both Van Velden *et al.* and Cseuz *et al.* reported a subsequent reduction in need for analgesic and anti-inflammatory medication. Van Velden *et al.* and Vormann *et al.* also reported significant systemic alkalising actions in response to their respective alkaline mineral interventions, i.e. increased urine pH and blood pH respectively. The fourth trial identified applied a combination of citrate salts and trace elements to healthy subjects and demonstrated small but significant increases in both urine and blood pH. [7] Of the four trials identified, the most frequently incorporated alkalising citrate salts included 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 however (Van Velden *et al.*) included both citrate salts and bicarbonate, i.e. potassium bicarbonate.

Conclusion

Conceptually, clinicians should clearly distinguish between CSSMA and the traditional understanding of frank 'acidosis,' and use clear terminology when referring to this phenomenon which is supported by a significant, growing body of evidence. The major contributing factor to CSSMA is the shift from the ancestral, alkaline diet toward the contemporary, acidogenic 'Westernised' diet comprising of increasing proportions of animal protein, grains, salt and other EDNP foods to the detriment of bicarbonate and potassium rich food such as fruit and vegetables. Evolutionary discordance hypothesis describes how this dietary shift has occurred at a rate too rapid for genetic adaptation, leading to the development of conditions associated with CSSMA. There is a growing body of evidence linking CSSMA and various forms of chronic disease including loss of bone mineral density, compromised kidney function, urolithiasis, gout, metabolic syndrome and arthritis, with some evidence suggesting one of the underlying mechanisms to be the consequent upregulation of cortisol. Clinical trials where CSSMA is addressed through alkalising the diet and or supplementing with alkaline minerals such as citrate salts and bicarbonate report positive outcomes in terms of bone mineral density, kidney function, urolithiasis, gout and arthritis as well as improvement in physical performance and exercise recovery. CSSMA is a condition deserving of more attention and formal recognition and should be considered as an aetiological factor by clinicians when addressing these respective chronic diseases either by making dietary adjustments or supplementing with alkalising minerals.