

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

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### References

1. van Velden, D.P., et al., *Non-allopathic adjuvant management of osteoarthritis by alkalisation of the diet*. 2015, 2015. **7**(1).
2. Adeva, M.M. and G. Souto, *Diet-induced metabolic acidosis*. Clin Nutr, 2011. **30**(4): p. 416-21.
3. Sebastian, A., et al., *Estimation of the net acid load of the diet of ancestral preagricultural Homo sapiens and their hominid ancestors*. The American journal of clinical nutrition, 2003. **76**: p. 1308-16.
4. Schwalfenberg, G.K., *The alkaline diet: is there evidence that an alkaline pH diet benefits health?* Journal of environmental and public health, 2012. **2012**: p. 727630-727630.
5. Sebastian, A., et al., *Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate*. N Engl J Med, 1994. **330**(25): p. 1776-81.
6. Frassetto, L., 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): p. 200-13.
7. König, D., et al., *Effect of a supplement rich in alkaline minerals on acid-base balance in humans*. Nutrition journal, 2009. **8**: p. 23-23.
8. Maurer, M., 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): p. F32-40.
9. Carnauba, R.A., et al., *Diet-Induced Low-Grade Metabolic Acidosis and Clinical Outcomes: A Review*. Nutrients, 2017. **9**(6): p. 538.
10. Fox, S.I., *Human Physiology*. 8th ed. 2004, New York: McGraw-Hill Publishing.
11. Jehle, S., 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): p. 3213-22.
12. Ilesanmi-Oyelere, B.L., et al., *The Relationship between Nutrient Patterns and Bone Mineral Density in Postmenopausal Women*. Nutrients, 2019. **11**(6): p. 1262.
13. Tucker, K.L., 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): p. 727-36.
14. Welch, A.A., et al., *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): p. 1335-43.
15. Frassetto, L.A., et al., *Estimation of net endogenous noncarbonic acid production in humans from diet potassium and protein contents*. Am J Clin Nutr, 1998. **68**(3): p. 576-83.
16. Frassetto, L., et al., *Acid Balance, Dietary Acid Load, and Bone Effects—A Controversial Subject*. Nutrients, 2018. **10**(4): p. 517.
17. Remer, T. and F. Manz, *Estimation of the renal net acid excretion by adults consuming diets containing variable amounts of protein*. The American Journal of Clinical Nutrition, 1994. **59**(6): p. 1356-1361.
18. Remer, T. and F. Manz, *Potential Renal Acid Load of Foods and its Influence on Urine pH*. Journal of the American Dietetic Association, 1995. **95**(7): p. 791-797.
19. Berardi, J.M., A.C. Logan, and A.V. Rao, *Plant based dietary supplement increases urinary pH*. Journal of the International Society of Sports Nutrition, 2008. **5**(1): p. 20.
20. Lanham-New, S.A., *The balance of bone health: tipping the scales in favor of potassium-rich, bicarbonate-rich foods*. J Nutr, 2008. **138**(1): p. 172s-177s.
21. Passey, C., *Reducing the Dietary Acid Load: How a More Alkaline Diet Benefits Patients With Chronic Kidney Disease*. J Ren Nutr, 2017. **27**(3): p. 151-160.
22. Denton, D.A., *The Hunger for Salt : An Anthropological, Physiological, and Medical Analysis*. 1983, USA: Springer. 650.
23. Konner, M. and S.B. Eaton, *Paleolithic Nutrition*. Nutrition in Clinical Practice, 2010. **25**(6): p. 594-602.
24. Fenton, T.R., 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): p. 1159-66.
25. Bushinsky, D.A., et al., *Chronic acidosis-induced alteration in bone bicarbonate and phosphate*. Am J Physiol Renal Physiol, 2003. **285**(3): p. F532-9.
26. Frick, K.K. and D.A. Bushinsky, *Effect of metabolic and respiratory acidosis on intracellular calcium in osteoblasts*. Am J Physiol Renal Physiol, 2010. **299**(2): p. F418-25.
27. Yuan, F.-L., et al., *The Roles of Acidosis in Osteoclast Biology*. Frontiers in physiology, 2016. **7**: p. 222-222.
28. Buclin, T., et al., *Diet acids and alkalis influence calcium retention in bone*. Osteoporos Int, 2001. **12**(6): p. 493-9.

29. Jajoo, R., et al., *Dietary acid-base balance, bone resorption, and calcium excretion*. J Am Coll Nutr, 2006. **25**(3): p. 224-30.
30. New, S.A., 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): p. 131-8.
31. Gunn, C.A., et al., *Increased intake of selected vegetables, herbs and fruit may reduce bone turnover in postmenopausal women*. Nutrients, 2015. **7**(4): p. 2499-517.
32. Marangella, M., et al., *Effects of potassium citrate supplementation on bone metabolism*. Calcif Tissue Int, 2004. **74**(4): p. 330-5.
33. Sellmeyer, D.E., M. Schloetter, and A. Sebastian, *Potassium Citrate Prevents Increased Urine Calcium Excretion and Bone Resorption Induced by a High Sodium Chloride Diet*. The Journal of Clinical Endocrinology & Metabolism, 2002. **87**(5): p. 2008-2012.
34. Moseley, K.F., et al., *Potassium citrate supplementation results in sustained improvement in calcium balance in older men and women*. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research, 2013. **28**(3): p. 497-504.
35. Frassetto, L., R.C. Morris, Jr., and A. Sebastian, *Long-term persistence of the urine calcium-lowering effect of potassium bicarbonate in postmenopausal women*. J Clin Endocrinol Metab, 2005. **90**(2): p. 831-4.
36. Dawson-Hughes, B., et al., *Treatment with potassium bicarbonate lowers calcium excretion and bone resorption in older men and women*. J Clin Endocrinol Metab, 2009. **94**(1): p. 96-102.
37. Wesson, D.E., et al., *Dietary protein induces endothelin-mediated kidney injury through enhanced intrinsic acid production*. Kidney International, 2007. **71**(3): p. 210-217.
38. Phisitkul, S., et al., *Dietary protein causes a decline in the glomerular filtration rate of the remnant kidney mediated by metabolic acidosis and endothelin receptors*. Kidney International, 2008. **73**(2): p. 192-199.
39. Wesson, D.E. and J. Simoni, *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): p. 1128-35.
40. Wesson, D.E., *Endogenous endothelins mediate increased acidification in remnant kidneys*. J Am Soc Nephrol, 2001. **12**(9): p. 1826-35.
41. Nath, K.A., M.K. Hostetter, and T.H. Hostetter, *Pathophysiology of chronic tubulo-interstitial disease in rats. Interactions of dietary acid load, ammonia, and complement component C3*. The Journal of Clinical Investigation, 1985. **76**(2): p. 667-675.
42. Raphael, K.L., 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): p. 356-62.
43. Dobre, M., 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): p. 670-8.
44. Kanda, E., et al., *Dietary acid intake and kidney disease progression in the elderly*. Am J Nephrol, 2014. **39**(2): p. 145-52.
45. Scialla, J.J., et al., *Net endogenous acid production is associated with a faster decline in GFR in African Americans*. Kidney International, 2012. **82**(1): p. 106-112.
46. Banerjee, T., et al., *High Dietary Acid Load Predicts ESRD among Adults with CKD*. J Am Soc Nephrol, 2015. **26**(7): p. 1693-700.
47. Rebholz, C.M., et al., *Dietary Acid Load and Incident Chronic Kidney Disease: Results from the ARIC Study*. Am J Nephrol, 2015. **42**(6): p. 427-35.
48. Mirmiran, P., 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): p. 119-25.
49. Banerjee, T., et al., *Dietary acid load and chronic kidney disease among adults in the United States*. BMC Nephrol, 2014. **15**: p. 137.
50. de Brito-Ashurst, I., et al., *Bicarbonate Supplementation Slows Progression of CKD and Improves Nutritional Status*. Journal of the American Society of Nephrology, 2009. **20**(9): p. 2075-2084.
51. Mahajan, A., et al., *Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy*. Kidney International, 2010. **78**(3): p. 303-309.
52. Goraya, N., et al., *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): p. 371-81.
53. Goraya, N., et al., *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): p. 1031-8.
54. Dunkler, D., et al., *Diet and kidney disease in high-risk individuals with type 2 diabetes mellitus*. JAMA Intern Med, 2013. **173**(18): p. 1682-92.
55. Trinchieri, A., et al., *Effect of potential renal acid load of foods on urinary citrate excretion in calcium renal stone formers*. Urol Res, 2006. **34**(1): p. 1-7.
56. Trinchieri, A., et al., *Potential renal acid load and the risk of renal stone formation in a case-control study*. Eur J Clin Nutr, 2013. **67**(10): p. 1077-80.
57. Carvalho, M., et al., *Effect of potassium citrate supplement on stone recurrence before or after lithotripsy: systematic review and meta-analysis*. Urolithiasis, 2017. **45**(5): p. 449-455.

58. Phillips, R., et al., *Citrate salts for preventing and treating calcium containing kidney stones in adults*. Cochrane Database Syst Rev, 2015(10): p. Cd010057.
59. Frassetto, L. and I. Kohlstadt, *Treatment and prevention of kidney stones: an update*. Am Fam Physician, 2011. **84**(11): p. 1234-42.
60. McNally, M.A., et al., *Empiric Use of Potassium Citrate Reduces Kidney-Stone Incidence With the Ketogenic Diet*. Pediatrics, 2009. **124**(2): p. e300-e304.
61. Soygur, T., A. Akbay, and S. Kupeli, *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): p. 149-52.
62. Takahashi, S., 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): p. 511-4.
63. Pakpoy, R.K., *URINARY PH IN GOUT*. Australas Ann Med, 1965. **14**: p. 35-9.
64. Alvarez-Nemegyei, J., et al., *Prevalence and risk factors for urolithiasis in primary gout: is a reappraisal needed?* J Rheumatol, 2005. **32**(11): p. 2189-91.
65. Abate, N., et al., *The metabolic syndrome and uric acid nephrolithiasis: novel features of renal manifestation of insulin resistance*. Kidney Int, 2004. **65**(2): p. 386-92.
66. Kanbara, A., M. Hakoda, and I. Seyama, *Urine alkalization facilitates uric acid excretion*. Nutr J, 2010. **9**: p. 45.
67. Kanbara, A., et al., *Effect of urine pH changed by dietary intervention on uric acid clearance mechanism of pH-dependent excretion of urinary uric acid*. Nutrition Journal, 2012. **11**(1): p. 39.
68. Teixeira, F., et al., *AB0631 Efficacy and safety of urine alkalization for patients with uric acid nephrolithiasis with or without gout arthritis: a systematic review*. Annals of the Rheumatic Diseases, 2013. **72**(Suppl 3): p. A982-A982.
69. Ferrari, P. and O. Bonny, *[Diagnosis and prevention of uric acid stones]*. Ther Umsch, 2004. **61**(9): p. 571-4.
70. Gluszek, J., *The effect of glucose intake on urine saturation with calcium oxalate, calcium phosphate, uric acid and sodium urate*. International Urology and Nephrology, 1988. **20**(6): p. 657-663.
71. Mandel, E.I., et al., *Plasma bicarbonate and risk of type 2 diabetes mellitus*. Cmaj, 2012. **184**(13): p. E719-25.
72. Fagherazzi, G., et al., *Dietary acid load and risk of type 2 diabetes: the E3N-EPIC cohort study*. Diabetologia, 2014. **57**(2): p. 313-20.
73. Akter, S., et al., *High dietary acid load is associated with insulin resistance: The Furukawa Nutrition and Health Study*. Clinical Nutrition, 2016. **35**(2): p. 453-459.
74. Akter, S., 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): p. 1076-83.
75. Saklayen, M.G., *The Global Epidemic of the Metabolic Syndrome*. Current Hypertension Reports, 2018. **20**(12).
76. Maalouf, N.M., et al., *Low Urine pH: A Novel Feature of the Metabolic Syndrome*. Clinical Journal of the American Society of Nephrology, 2007. **2**(5): p. 883-888.
77. Chan, R., 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): p. e0122406.
78. Krupp, D., 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): p. 313-9.
79. Okamura, T., 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): p. 570-576.
80. Alferink, L.J.M., 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): p. 6325-6337.
81. Esche, J., et al., *Higher diet-dependent renal acid load associates with higher glucocorticoid secretion and potentially bioactive free glucocorticoids in healthy children*. Kidney International, 2016. **90**(2): p. 325-333.
82. Kesteloot†, H., 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*. American Journal of Epidemiology, 2011. **174**(1): p. 44-51.
83. Nielsen, T.F. and R. Rylander, *Urinary calcium and magnesium excretion relates to increase in blood pressure during pregnancy*. Arch Gynecol Obstet, 2011. **283**(3): p. 443-7.
84. Frassetto, L.A., R.C. Morris, Jr., and A. Sebastian, *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): p. F521-5.
85. Luis, D., et al., *Estimated Dietary Acid Load Is Not Associated with Blood Pressure or Hypertension Incidence in Men Who Are Approximately 70 Years Old*. The Journal of Nutrition, 2014. **145**(2): p. 315-321.
86. Murakami, K., et al., *Association between dietary acid-base load and cardiometabolic risk factors in young Japanese women*. Br J Nutr, 2008. **100**(3): p. 642-51.
87. Zhang, L., G.C. Curhan, and J.P. Forman, *Diet-dependent net acid load and risk of incident hypertension in United States women*. Hypertension (Dallas, Tex. : 1979), 2009. **54**(4): p. 751-755.
88. Collins, J.A., et al., *Oxygen and pH-sensitivity of human osteoarthritic chondrocytes in 3-D alginate bead culture system*. Osteoarthritis and cartilage, 2013. **21**(11): p. 1790-1798.
89. Geborek, P., et al., *Synovial fluid acidosis correlates with radiological joint destruction in rheumatoid arthritis knee joints*. J Rheumatol, 1989. **16**(4): p. 468-72.

90. Wu, M.H., et al., *Effect of extracellular pH on matrix synthesis by chondrocytes in 3D agarose gel*. Biotechnol Prog, 2007. **23**(2): p. 430-4.
91. Vormann, J., et al., *Supplementation with alkaline minerals reduces symptoms in patients with chronic low back pain*. J Trace Elem Med Biol, 2001. **15**(2-3): p. 179-83.
92. Cseuz, R.M., et al., *Alkaline Mineral Supplementation Decreases Pain in Rheumatoid Arthritis Patients: A Pilot Study*. The Open Nutrition Journal, 2008. **2**: p. 100-105.
93. Obi, Y., et al., *Latest consensus and update on protein-energy wasting in chronic kidney disease*. Current opinion in clinical nutrition and metabolic care, 2015. **18**(3): p. 254-262.
94. Garibotto, G. and D. Verzola, *Studying Muscle Protein Turnover in CKD*. Clinical journal of the American Society of Nephrology : CJASN, 2016. **11**(7): p. 1131-1132.
95. Dawson-Hughes, B., S.S. Harris, and L. Ceglia, *Alkaline diets favor lean tissue mass in older adults*. Am J Clin Nutr, 2008. **87**(3): p. 662-5.
96. Chan, R., J. Leung, and J. Woo, *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): p. 905-11.
97. Welch, A.A., et al., *A higher alkaline dietary load is associated with greater indexes of skeletal muscle mass in women*. Osteoporos Int, 2013. **24**(6): p. 1899-908.
98. Melamed, P. and F. Melamed, *Chronic metabolic acidosis destroys pancreas*. Jop, 2014. **15**(6): p. 552-60.
99. Hawley, J.A. and T. Reilly, *Fatigue revisited*. J Sports Sci, 1997. **15**(3): p. 245-6.
100. Seebohar, B., *Aerobic Endurance Supplements*. NSCA's Guide to Sport and Exercise Nutrition, 2011: p. 141-147.
101. Ashizawa, N., et al., *Effects of a Single Bout of Resistance Exercise on Calcium and Bone Metabolism in Untrained Young Males*. Calcified Tissue International, 1998. **62**(2): p. 104-108.
102. Cardinale, M., et al., *Whole-body vibration can reduce calciuria induced by high protein intakes and may counteract bone resorption: A preliminary study*. J Sports Sci, 2007. **25**(1): p. 111-9.
103. Robergs, R., 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): p. 59-74.
104. Requena, B., et al., *Sodium bicarbonate and sodium citrate: ergogenic aids?* J Strength Cond Res, 2005. **19**(1): p. 213-24.
105. Mündel, T., *Sodium bicarbonate ingestion improves repeated high-intensity cycling performance in the heat*. Temperature (Austin), 2018. **5**(4): p. 343-347.
106. Hadzic, M., M.L. Eckstein, and M. Schugardt, *The Impact of Sodium Bicarbonate on Performance in Response to Exercise Duration in Athletes: A Systematic Review*. J Sports Sci Med, 2019. **18**(2): p. 271-281.
107. Remer, T., T. Dimitriou, and C. Maser-Gluth, *Renal Net Acid Excretion and Plasma Leptin Are Associated with Potentially Bioactive Free Glucocorticoids in Healthy Lean Women*. The Journal of Nutrition, 2008. **138**(2): p. 426S-430S.
108. Lee Hamm, L., *Role of Glucocorticoids in Acidosis*. American Journal of Kidney Disease, 1999. **34**(5): p. 960-965.
109. Espino, L., 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): p. 8-12.
110. Remer, T., K. Pietrzik, and F. Manz, *Short-term impact of a lactovegetarian diet on adrenocortical activity and adrenal androgens*. J Clin Endocrinol Metab, 1998. **83**(6): p. 2132-7.
111. Anagnostis, P., et al., *The Pathogenetic Role of Cortisol in the Metabolic Syndrome: A Hypothesis*. The Journal of Clinical Endocrinology & Metabolism, 2009. **94**(8): p. 2692-2701.
112. Cozma, S., et al., *Salivary cortisol and  $\pm$ -amylase: subclinical indicators of stress as cardiometabolic risk*. Brazilian Journal of Medical and Biological Research, 2017. **50**.
113. Haas, A.V., et al., *Higher urinary cortisol levels associate with increased cardiovascular risk*. 2019. **8**(6): p. 634.
114. Ortiz, R., et al., *The association of morning serum cortisol with glucose metabolism and diabetes: The Jackson Heart Study*. Psychoneuroendocrinology, 2019. **103**: p. 25-32.
115. Noppe, G., et al., *Long-term glucocorticoid concentrations as a risk factor for childhood obesity and adverse body-fat distribution*. International Journal of Obesity, 2016. **40**(10): p. 1503-1509.
116. Appel, L.J., 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): p. 1117-24.
117. McNaughton, L., et al., *Effects of chronic bicarbonate ingestion on the performance of high-intensity work*. Eur J Appl Physiol Occup Physiol, 1999. **80**(4): p. 333-6.