



Diet-Induced Cellular Acidosis

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AARM

Association for the Advancement
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- Academic
 - Founding president of Bastyr University, first accredited, natural medicine university
 - Editor-in-Chief: *Integrative Medicine: A Clinician's Journal*
 - *Textbook of Natural Medicine*, 4th edition 2012
 - *Clinical Pathophysiology, A Functional Perspective*, 2012
- Policy
 - Member Medicare Coverage Advisory Committee, 2003-2005
 - Member White House Commission on CAM Policy, 2000-2002
- Public
 - *Encyclopedia of Natural Medicine*, 3rd Ed 2012 (2,000,000 copies in 6 languages)
 - *Encyclopedia of Healing Foods*, 2005
- Example Awards and Recognitions
 - Clinician of the Year, Natural Products Association, 2012
 - Juror for Roger's Prize, 2009, 2011, 2013
 - Institute for Functional Medicine, Linus Pauling Award, 2004
 - American Holistic Medical Association: *Pioneer in Holistic Medicine*, 2003
 - *Natural Health Magazine: Leading health educator in the past 30 years*. 2001
 - *Alternative Healthcare Management: 1 of the 4 most influential CAM leaders*, 2000



Overview

- Introduction to Diet-Induced Acidosis
- Acid/Base Physiology & Contributing Factors
- Clinical Relevance
 - Renal
 - Bone
 - Glutathione
 - Inflammation
 - Metabolic Syndrome
 - Muscle Mass and Exercise Performance
 - Renal Stones
- Assessment
- Treatment & Prevention



pH

“The pH of body fluids is one the most important key factors regulating various cell function(s) such as enzyme activity and protein-protein interaction(s) via modification of...binding affinity. Therefore, to keep cell function normal, the pH of body fluids is maintained constant by various systems.”

~Yoshinori Marunaka



What is Acidosis?

- Acidosis refers to a process, **not acidemia**, or a trend toward acidemia, without necessarily reaching a blood pH of less than 7.35, or actual acidemia
- Acidosis only becomes **acidemia** when compensatory measures to correct it fail, particularly respiratory or renal function
- Western diet is associated with low-grade, chronic, metabolic acidosis, not frank acidemia
- A blood pH constantly at the lower end of the normal range has also been termed latent acidosis



Affects of Significant Acidemia
Serious

Symptoms of Acidemia

Central

- Headache
- Sleepiness
- Confusion
- Loss of consciousness
- Coma

Respiratory

- Shortness of breath
- Coughing

Heart

- Arrhythmia
- Increased heart rate

Muscular

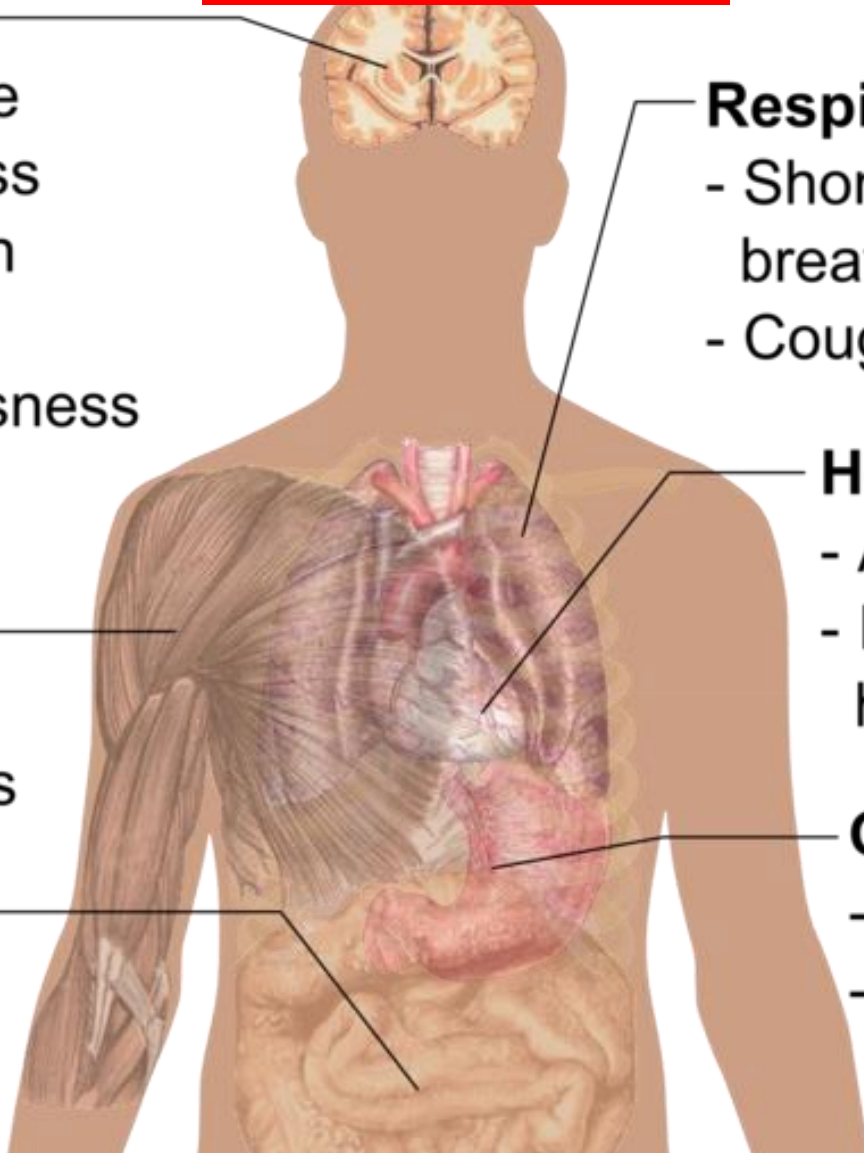
- Seizures
- Weakness

Gastric

- Nausea
- Vomiting

Intestinal

- Diarrhea





pH has a Logarithmic Association with the Concentration of H⁺

TABLE 1. Hydrogen ion concentrations in different pH values

| pH | H ⁺ concentration (nEq/L) | Acid-base status |
|------|--------------------------------------|------------------|
| 7.50 | 32 | Alkalemia |
| 7.40 | 40 | Normal |
| 7.30 | 50 | Acidemia |
| 7.20 | 63 | Acidemia |
| 7.10 | 80 | Acidemia |
| 7.00 | 100 | Acidemia |
| 6.90 | 125 | Acidemia |

Kalantar-Zadeh K, Mehrotra R, Fouque D, *et al.* (2004) Metabolic acidosis and malnutrition-inflammation complex syndrome in chronic renal failure. *Semin Dial* **17**, 455-65.



Physiological Effects of pH

- Even small fluctuations in H^+ concentration affect activity of cellular enzymes
- Varies considerably in each organ/tissue

pH influences:

- Structure & function of proteins
- Permeability of cell membranes
- Distribution of electrolytes
- Structure of connective tissue

| Organ, Fluid or Membrane | pH | Purpose of pH |
|--------------------------|---------|--------------------------------------|
| Skin | 4.0-6.5 | Barrier protection |
| Urine | 4.6-8.0 | Limit microbe growth |
| Stomach | 1.3-3.5 | Begin digestion |
| Bile | 7.6-8.8 | Neutralize stomach acid |
| Pancreatic fluid | 8.8 | Neutralize stomach acid |
| Vaginal fluid | <4.7 | Limit growth of organisms |
| Intracellular | 6.0-7.2 | From acid production of cells |



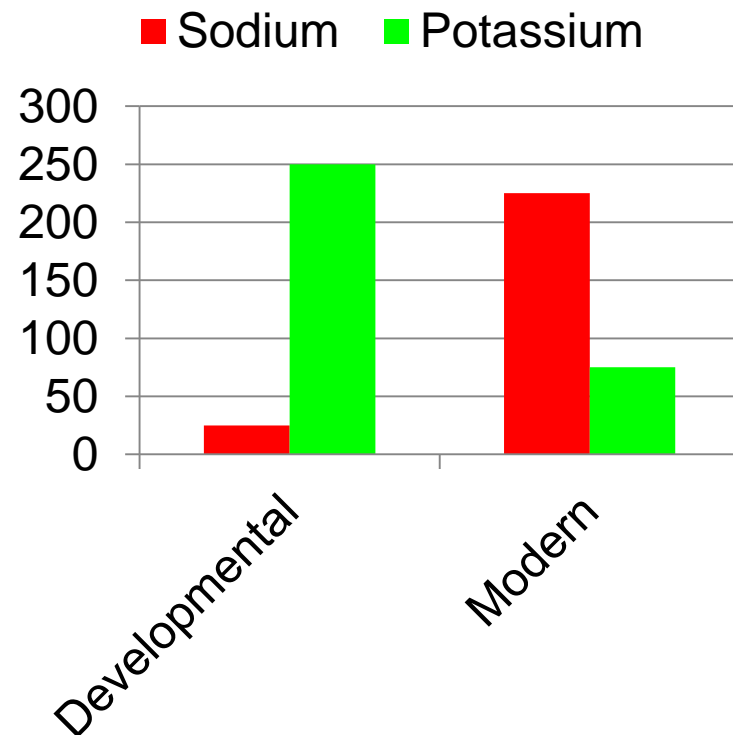
Role of Diet in Acidosis

- Nutrition has long been known to strongly influence acid–base balance in human subjects
- Contemporary **Western diets** contain acid precursors in excess of base precursors, yielding a daily systemic net acid load of varying amounts
- “**Adaptations of the skeleton, skeletal muscle, kidney and endocrine systems that serve to mitigate** the degree of that perturbation [caused by diet-induced acidosis] impose a cost in cumulative organ damage that the body pays out over decades of adult life”



Mismatch of Genes & Modern Diet

- Diet today significantly different than during millions of years of hominid evolution
- “From an evolutionary nutritional perspective, **contemporary humans are Stone Agers** habitually ingesting a diet discordant with their genetically determined metabolic machinery and integrated organ physiology”
- Ex: In modern diet, the K/Na ratio is reversed, from 1:10, to >3:1.





Modern Diet & Acid Load

- 87% of 159 **pre-agricultural diets** were estimated to be **base-producing**, with an mean NEAP of **negative 88 mEq/d**
- In comparison, NHANES III found the average **American diet to be acid producing**, with an NEAP (net endogenous acid production) of **positive 48 mEq/d**
- Equivalent of 4.9g HCl every day
- → 3 g of bone to neutralize 1 g of acid
- < 1% of hominid evolutionary time for this transition



Terminology

- NEAP (Net Endogenous Acid Production)
 - NEAP represents the amount of net acid produced by the metabolic system every day; a combination of cellular metabolism and exogenous acid and base loads from the diet).
 - It can be calculated (and most often is) based upon dietary constituents (estimated), or measured directly using diet/stool/urine samples
- NEA (Net Acid Excretion)
 - NEA, the net acid excretion by the kidneys, often very close in value to NEAP, and usually considered equivalent
 - Can be measured directly, includes urinary excretion of ammonium, titratable acids and bicarbonate
- PRAL (Potential Renal Acid load)
 - Calculated estimate of NEAP, based upon protein & mineral intake of diet, but also dependent on body surface area



How Diet Influences Systemic pH

- Food contributes a net acid or base effect due to a balance between the acid & base forming constituents
 - Acid forming example: **sulfuric acid produced from the catabolism of methionine and cystine in dietary proteins**
 - Base-forming example: bicarbonate produced from the metabolism of the K salts of organic anions in plant food
- **Independently of dietary net acid load, sodium chloride intake** influences systemic acid-base status:
 - Mechanism not clear, perhaps by affecting renal excretion of $\text{Cl}^-/\text{NH}_4^+$
 - 7.7g of NaCl = 132 mEq

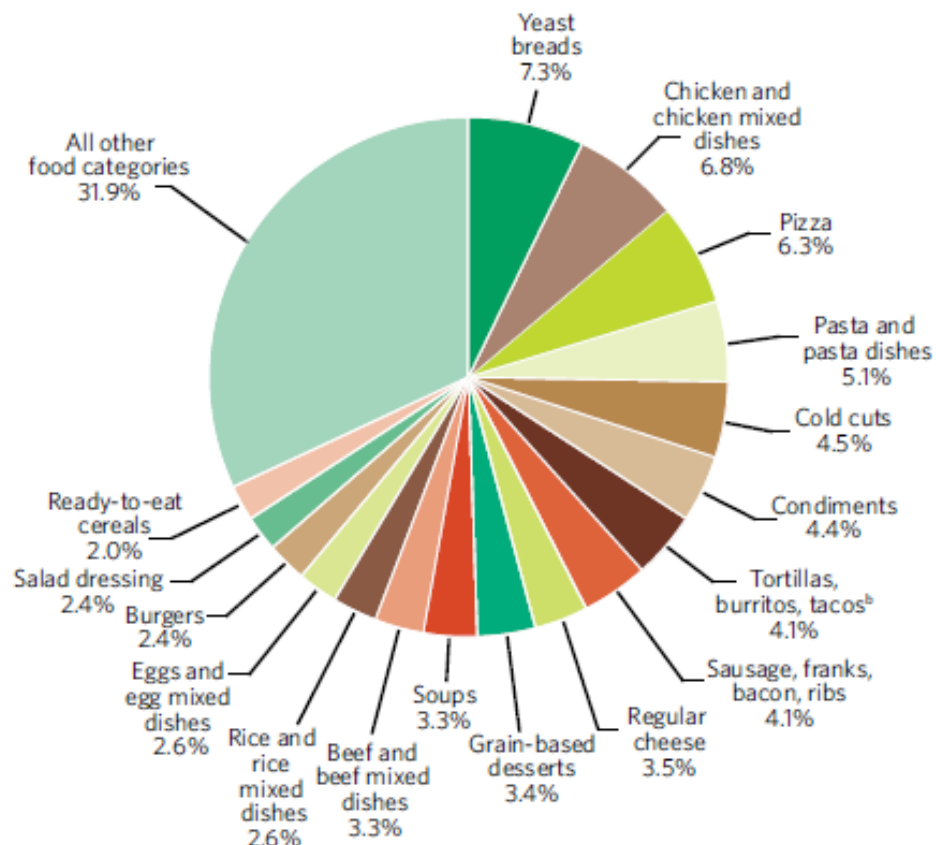


Sodium Chloride Influence on Acidosis

- 77 healthy volunteer subjects
- Each subject ingested one of 12 diets that yielded renal constant net acid excretion rate, varied urine excretion rates of chloride (Cl^-)
- Urine chloride excretion and diet net acid load independently predict systemic acid-base status
- **NaCl load causes 50-100%** of the acidosis-producing effect of the diet net acid load



FIGURE 3-2. Sources of Sodium in the Diets of the U.S. Population Ages 2 Years and Older, NHANES 2005-2006^a



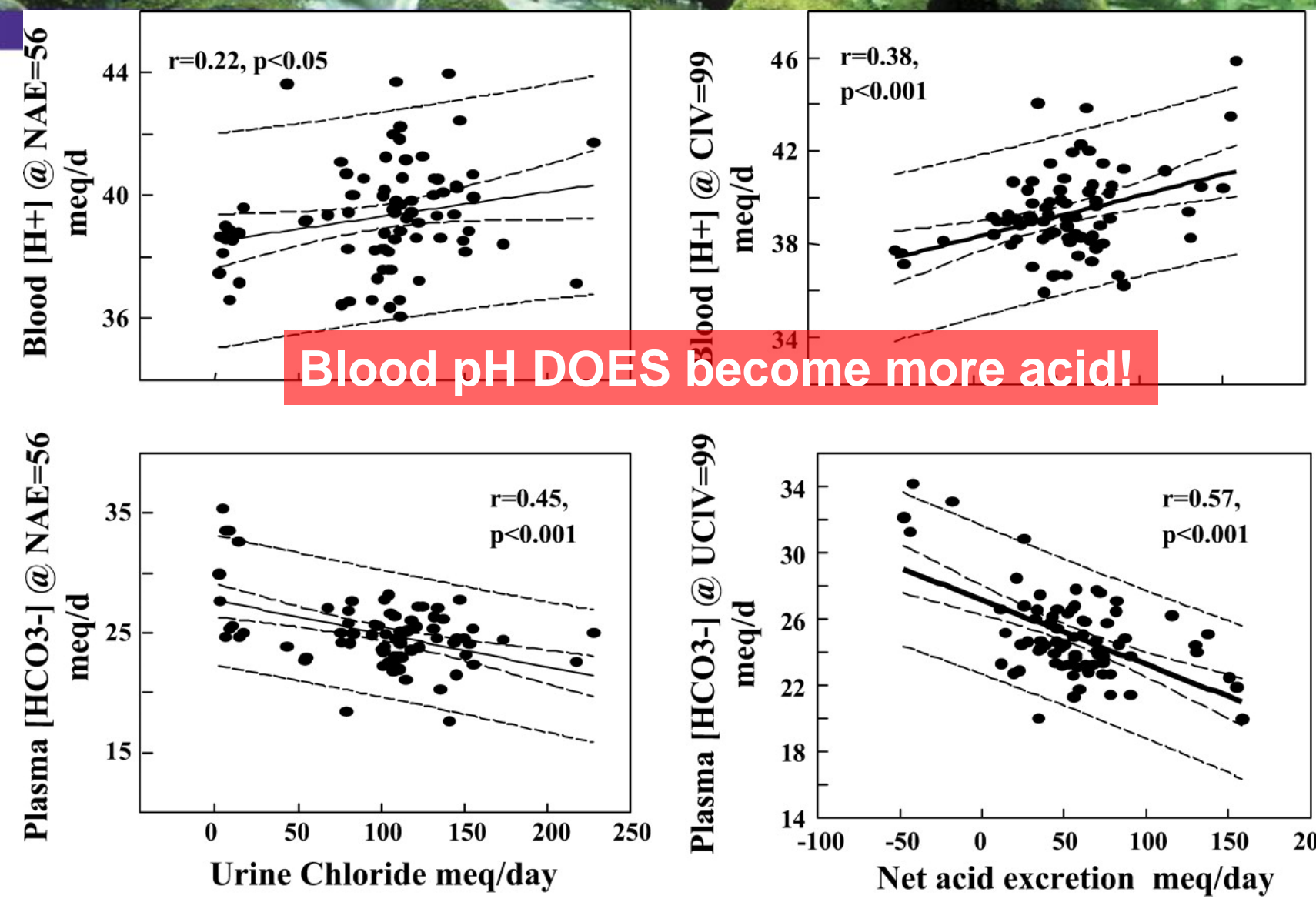
a. Data are drawn from analyses of usual dietary intake conducted by the National Cancer Institute. Foods and beverages consumed were divided into 97 categories and ranked according to sodium contribution to the diet. "All other food categories" represents food categories that each contributes less than 2% of the total intake of sodium from foods.

b. Also includes nachos, quesadillas, and other Mexican mixed dishes.

Source: National Cancer Institute. Sources of Sodium in the Diets of the U.S. Population Ages 2 Years and Older, NHANES 2005-2006. Risk Factor Monitoring and Methods, Cancer Control and Population Sciences. <http://riskfactor.cancer.gov/diet/foodsources/sodium/table1a.html>. Accessed August 11, 2010.



Diet-Induced Acidosis: Small Changes But Still in “Normal Range”



Blood pH DOES become more acid!

Adapted from Frassetto LA, et al. (2007) 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 293, F521–F525 (figure used with permission).



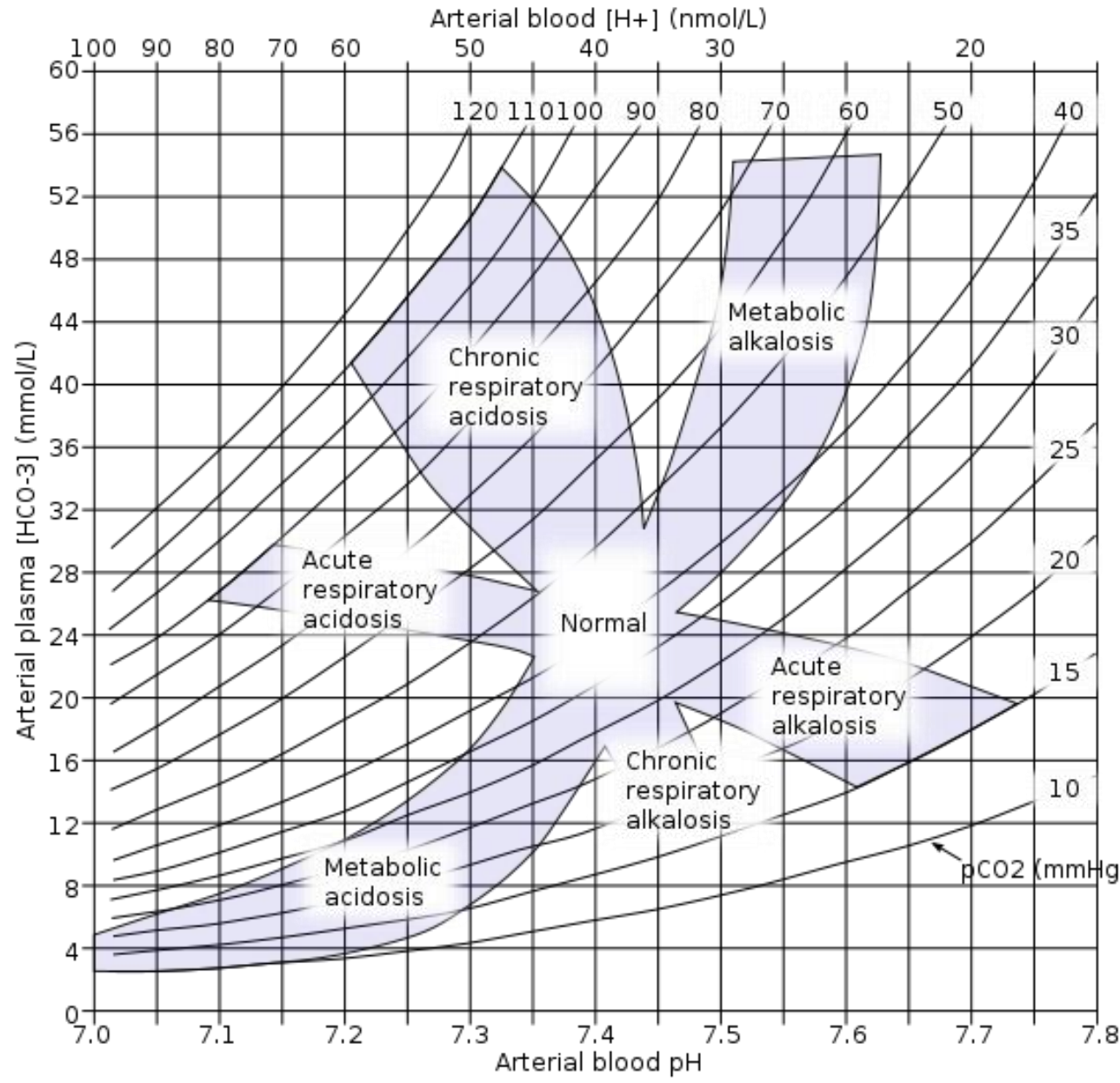
Other Causes of Acidosis - 1

- These cause a range of mild to severe acidosis
- Pharmacological examples:
 - **Impair renal H⁺ excretion** of dietary acid load: NSAIDs, beta-blockers, ACE inhibitors and angiotensin II type 1 receptor antagonists, K⁺-sparing diuretics - such as amiloride and triamterene, antibacterials (trimethoprim -commonly administered in combination with sulfamethoxazole as cotrimoxazole)
 - Many **other drugs**/mechanisms
 - **Diseases**: renal disease, diabetes, diarrhea, pancreatic drainage and biliary fistula, Sjogren's syndrome, SLE, urinary tract obstruction, fever, aldosterone deficiency, androgen deficiency
 - **Anaerobic exercise**
 - Phosphoric acid-containing **soft drinks**



Adaptive Responses to Acidosis

- Blood pH controlled by extracellular and intracellular buffers, together with respiratory and renal regulatory mechanisms.

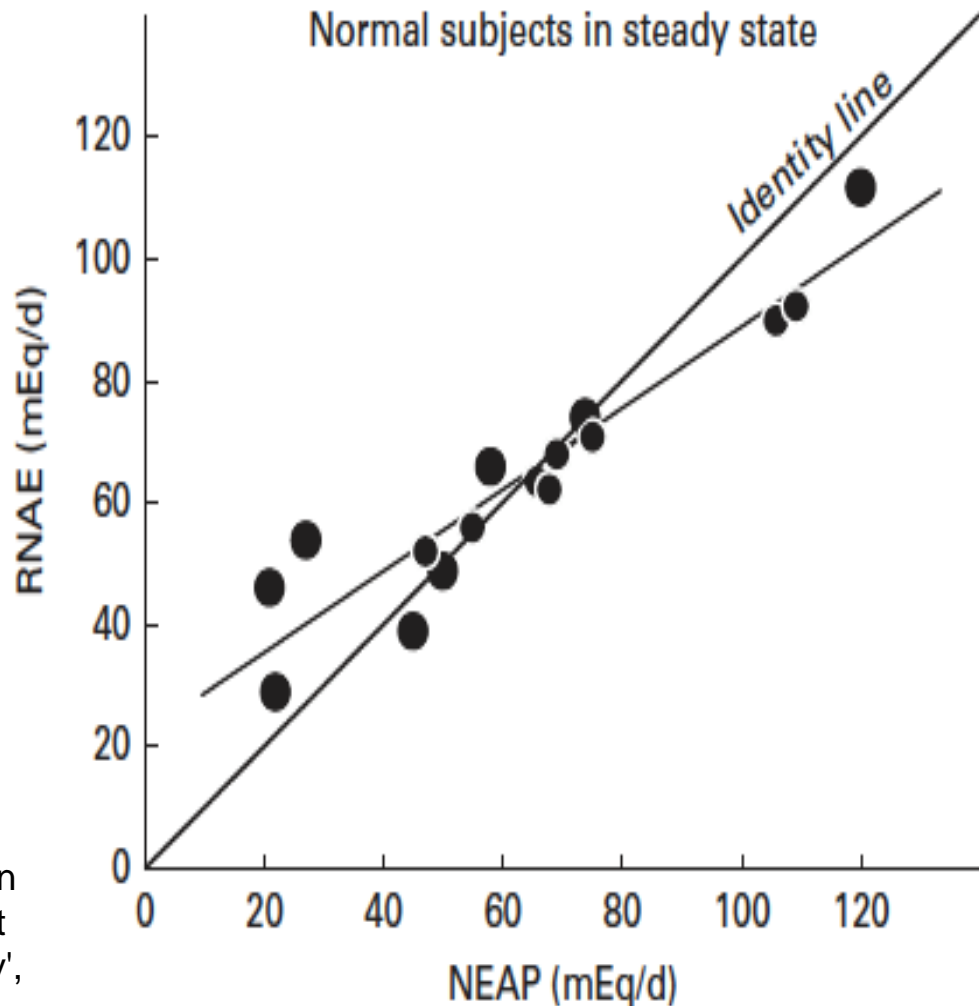


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Influence of Acid Intake on Acid Excretion

- Under **high acid loads**, the Net Acid Excretion is insufficient to accommodate Net Endogenous Acid Production leading to **acid accumulation**
- Under **low acid loads**, RNAE exceeds NEAP implying that there is **endogenous neoacid generation** taking place



Frassetto LA & Sebastian A (2013) Commentary to accompany the paper entitled 'nutritional disturbance in acid-base balance and osteoporosis: a hypothesis that disregards the essential homeostatic role of the kidney', by Jean-Philippe Bonjour. *Br J Nutr* **110**, 1935-7.



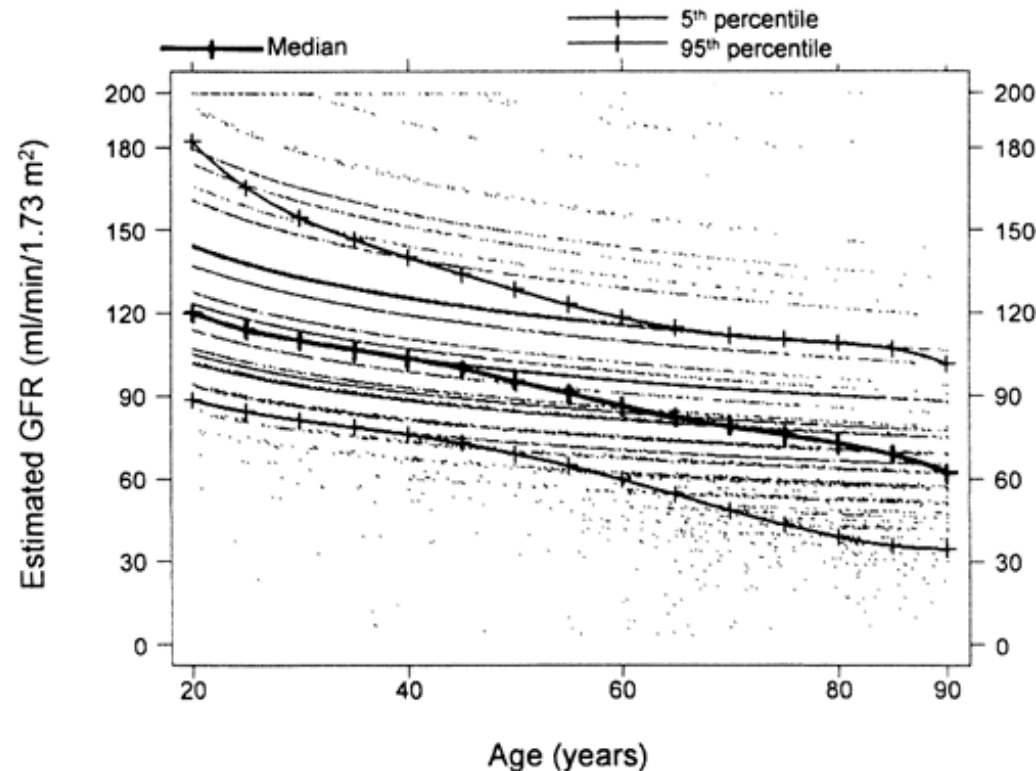
Renal Adaptations

- The **kidney mitigates, but does not eliminate**, the severity of diet-induced acidemia and hypobicarbonatemia by the following:
 - **Increased** urinary **excretion of sulfate, phosphate, urate, and chloride.**
 - **Increased** urinary **excretion of calcium and ammonium ions**
 - **Decreased** urinary **excretion of citrate**
 - Kidney vasodilatation and increased glomerular filtration rate
- **Wears out the kidney over time and likely primary cause of loss of function with aging**



Influence of Age on Renal Function

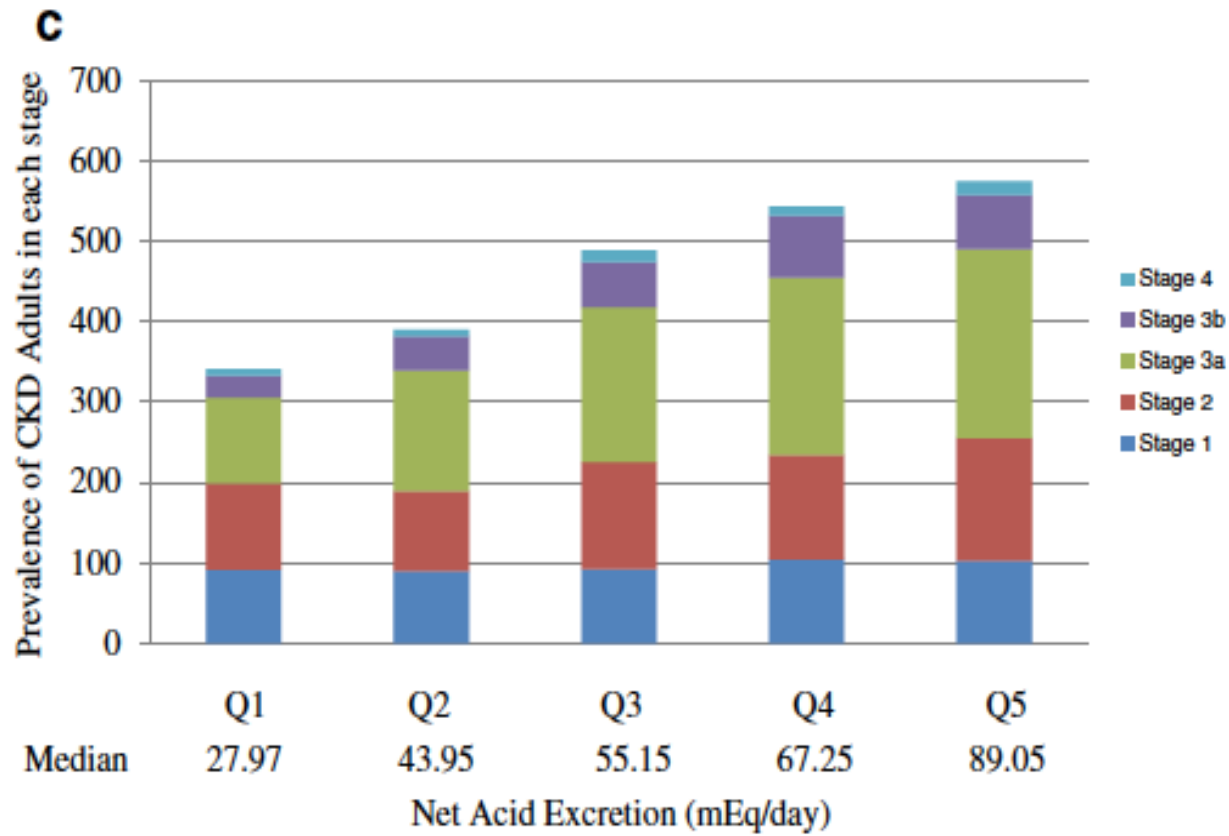
- NHANES shows loss of kidney function with age
- Study:
 - 64 apparently healthy adults age 17-74
 - Develop progressive, low-grade, chronic metabolic acidosis with age, not accounted for by change in diet acid load
- **Progressive loss of renal competence may be due to chronic dietary acidosis**



(NHANES III)

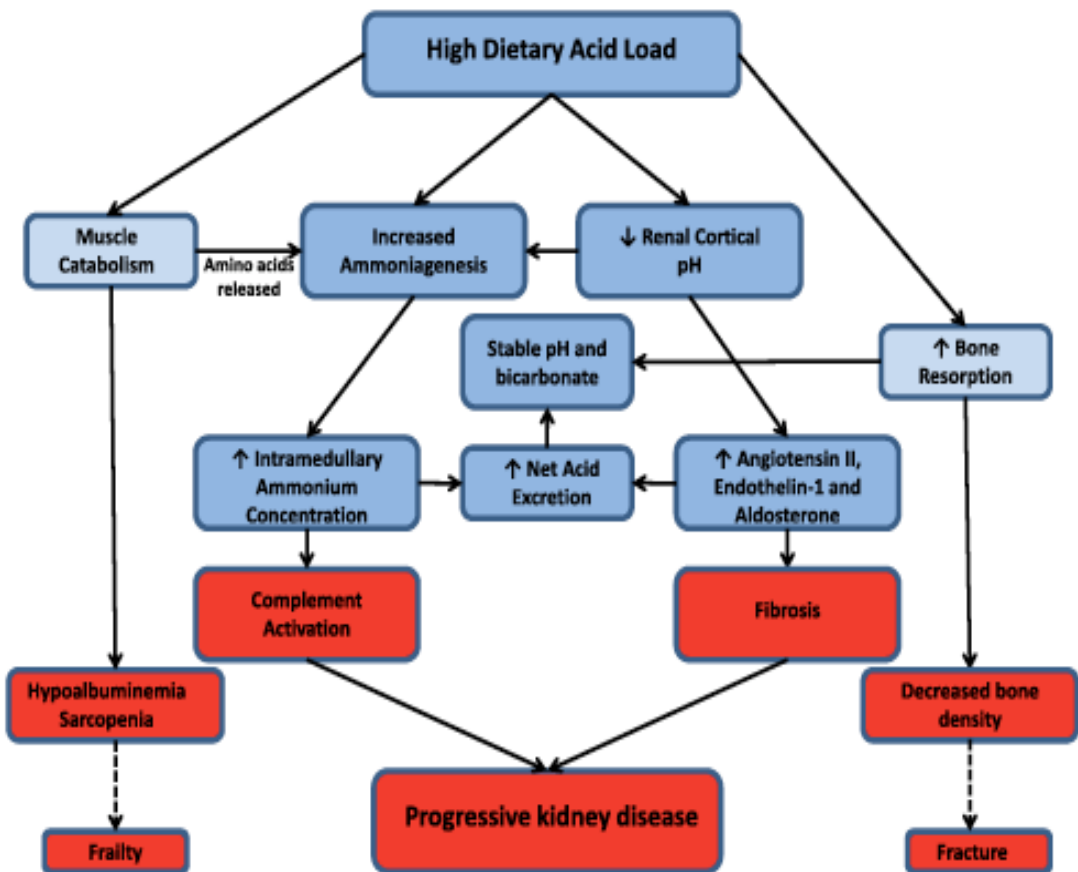


Acid Load Correlated with Worse CKD



Banerjee T, Crews DC, Wesson DE, *et al.* (2014) Dietary acid load and chronic kidney disease among adults in the United States. *BMC Nephrol* **15**, 137.

Proposed Physiologic Adaptations to Acidosis and Their Consequences in CKD



- Blue Boxes – Physiologic Responses
- Red Boxes – Potential Adverse Effects
- Dashed Lines – Projected Clinical Sequelae based on Indirect Evidence



Sodium Bicarbonate Supplementation Slows Functional Decline in ESRD

- 134 adult patients with CKD and serum bicarbonate 16-20 mmol/L
- Supplemented with NaHCO_3 or given standard care for 2 years

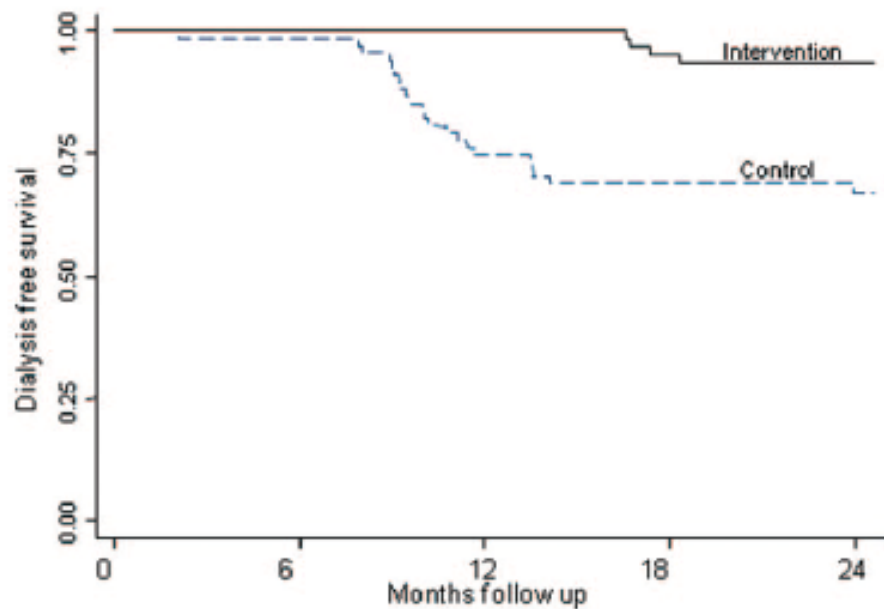
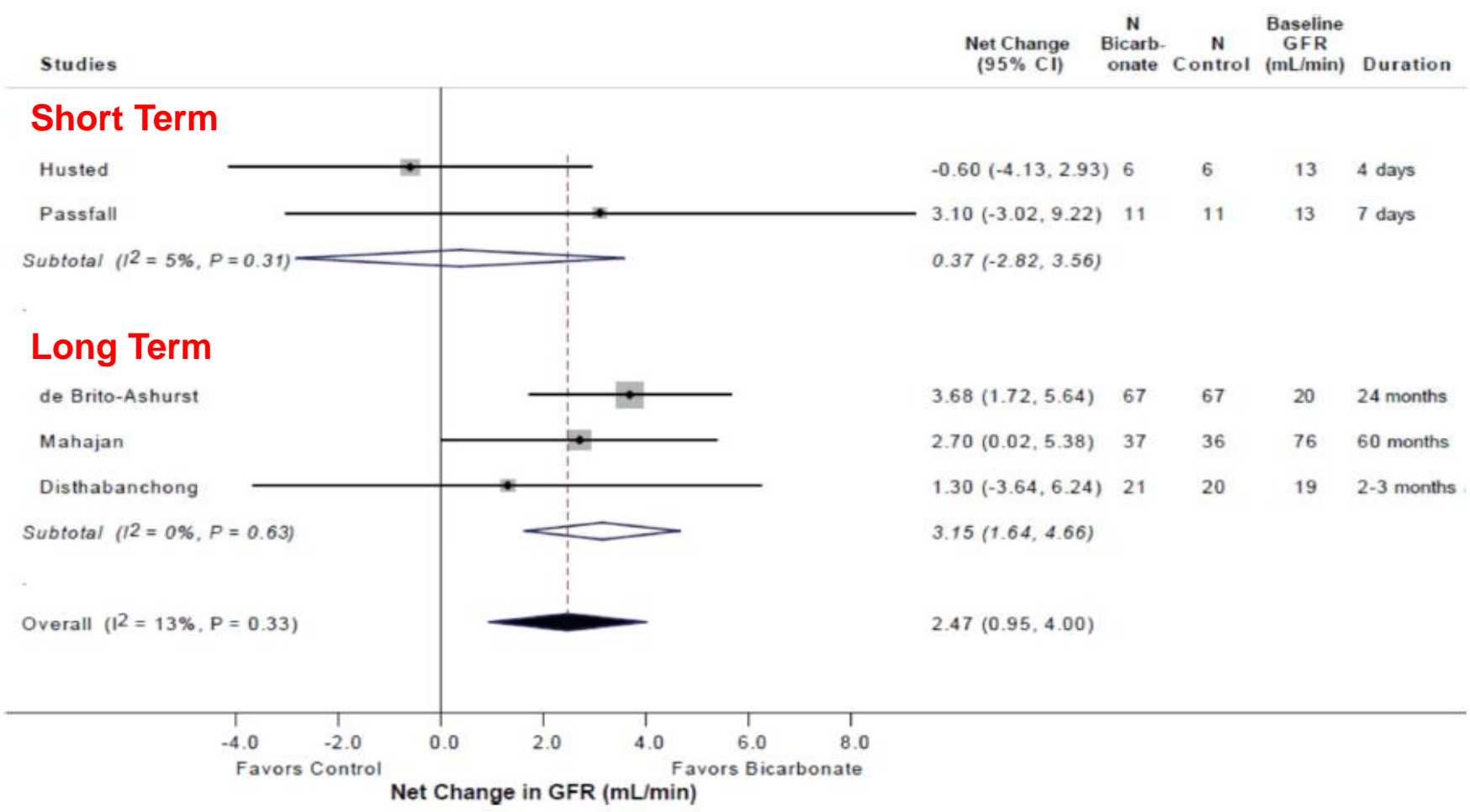


Figure 3. Kaplan-Meier analysis to assess the probability of reaching ESRD for the two groups.

de Brito-Ashurst I, Varaganam M, Raftery MJ, *et al.* (2009) Bicarbonate supplementation slows progression of CKD and improves nutritional status. *J Am Soc Nephrol* **20**, 2075-84.



Meta-Analysis of Bicarbonate Therapy in CKD



Susantitaphong P, Sewaralthahab K, Balk EM, *et al.* (2012) Short- and long-term effects of alkali therapy in chronic kidney disease: a systematic review. *Am J Nephrol* **35**, 540-7



Age – Other Findings

- Severity of age-related metabolic acidosis parallels and is largely accounted for by the normally occurring age-related decline in renal function
- Age had ~1.6 times greater effect on blood $[H^+]$ and plasma $[HCO_3^-]$ than diet net acid load.
- Increasing age therefore substantially amplifies the chronic low-grade metabolic acidosis induced by diet
- Renal insufficiency contributes to a metabolic acidosis by reducing conservation of filtered bicarbonate and excretion of acid.



Increased Buffering – Bone Health

- Our **major reservoir of base is the skeleton** (in the form of alkaline salts of calcium) which provides the buffer needed to maintain blood pH and plasma bicarbonate concentrations.
- To some degree, **skeletal muscle also acts as a buffer**
- **Acid-promoting diets are associated with both increased calcium and bone-matrix protein excretion**
- **Neutralizing acid intake with diet or bicarbonate supplements decreases urine Ca and bone matrix protein excretion**

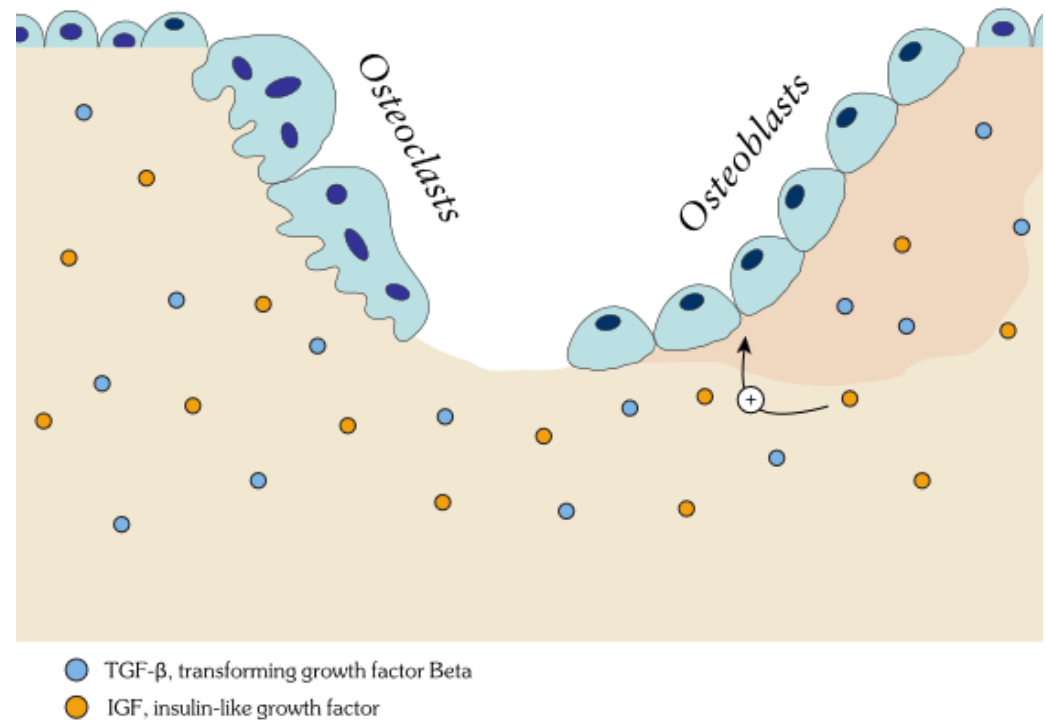
Bailey JL, et al. (1996) Influence of acid loading, extracellular pH and uremia on intracellular pH in muscle. *Miner Electrolyte Metab* 22, 66–68.

Buclin T, et al. (2001) Diet acids and alkalis influence calcium retention in bone. *Osteoporos Int* 12, 493–499.



Acidosis Inhibits Bone Mineralization

- Bone health best documented clinical consequence of diet-induced acidosis
- Not a “passive process” as previously thought
- Rather, **active resorption by osteoclasts**; H^+ is the trigger
- Acidosis also **inhibits mineral deposition by osteoblasts**



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Osteoclast Activation

- Extracellular H^+ appears to be the 'long-sought osteoclast activation factor'
- In-vitro experiments show osteoclasts to be almost inactive at a pH above 7.4
- pH reductions of \leq to 0.1 are sufficient to cause a doubling of resorption pit formation, removing both mineral and organic components of bone
- Ovarian cancer G protein-coupled receptor-1 (OGR1) is the proton-sensing receptor on the osteoblast that leads to osteoclast activation

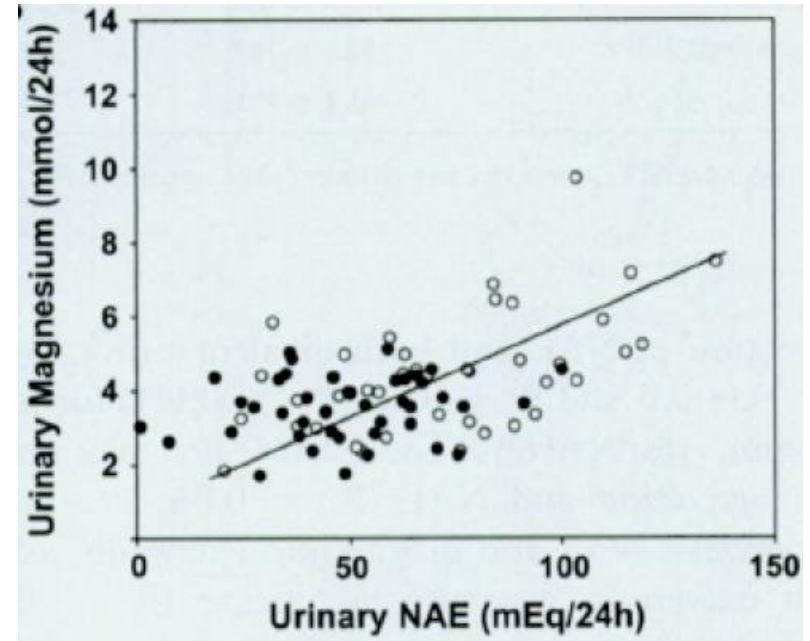
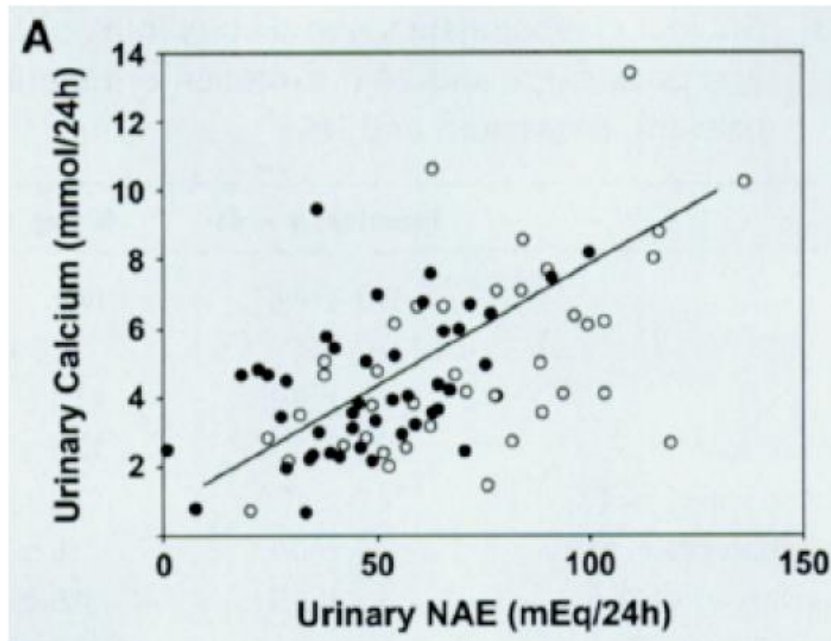
Arnett TR. Extracellular pH regulates bone cell function. J Nutr. 2008 Feb;138(2):415S-418S

Frick KK, et al. (2009) Metabolic acidosis increases intracellular calcium in bone cells through activation of the proton receptor OGR1. J Bone Miner Res 24, 305–313.



Mineral Loss Observed in Urine

- 85 healthy adults
- Loss of Mg remains significant when adjusting for potassium



Rylander R, Remer T, Berkemeyer S, *et al.* (2006) Acid-base status affects renal magnesium losses in healthy, elderly persons. *J Nutr* **136**, 2374-7.



Bone – Clinical Data

- 1,000 women (ages 45-54)
 - Found a **lower dietary intake of acid-producing foods correlated with greater spine and hip bone mineral density**, as well as greater forearm bone mass, after adjusting for age, weight, height and menstrual status
- 1,000 women (age 65+)
 - Study of Osteoporotic Fractures Research cohort – prospective
 - Those with a **high dietary ratio of animal to vegetable protein intake (a marker for a greater NEAP)** were found to have **more rapid femoral neck bone loss** and a greater risk of hip fracture than did those with a low ratio

New SA, et al. (2004) 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* 79, 131–138.

Sellmeyer DE, Stone KL, Sebastian A, et al. (2001) A high ratio of dietary animal to vegetable protein increases the rate of bone loss and the risk of fracture in postmenopausal women. Study of Osteoporotic Fractures Research Group. *Am J Clin Nutr* 73, 118–122.



PRAL Diet Predicts Bone Mass/Size In Children

- Subgroup of participants of the Dortmund Nutritional and Anthropometric Longitudinally Designed (DONALD) Study – 197 children age 6-18
- Prospective longitudinal analysis
- Found anabolic influences of higher protein intake and lower dietary acid load (via PRAL)



High PRAL & High Urinary Ca⁺ Also Predict Poorer Bone Status In Children

- Subgroup of DONALD study – 154 children
- Calcium excretion was negatively associated with vBMD, cortical BMC, and cortical CSA in those children with higher uPRALs, but not in those with low uPRALs
- Conclusion: Long-term higher calciuria within the physiological range predicted lower diaphyseal bone mass and bone density only in those healthy children and adolescents with long-term higher potential renal acid load



Bone – Metabolic Acidosis Compounded by Low Vitamin D

- Lower vitamin D levels associated with reduced calcium absorption from GI tract
- 2 small studies of 34 postmenopausal women
- Ca absorption was 65% higher at serum 25(OH)D levels averaging 86.5 nmol/L than at levels averaging 50 nmol/L
- Recent study found 70%-97% of Canadians demonstrate vitamin D insufficiency (25(OH)D level < 75-80nmol/l)

Heaney RP, et al. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. J Am Coll Nutr. 2003 Apr;22(2):142-6.

Schwalfenberg GK, et al. Addressing vitamin D deficiency in Canada: a public health innovation whose time has come. Public Health. 2010 Jun;124(6):350-9.



Vitamin D & Acidosis

- Small study of children presenting with type 1 diabetes
- Eighty-five percent of children with a low 25(OH)-vitamin D3 level at diagnosis had a bicarbonate less than 18 mmol/L
- Resolution of acidosis was associated with normalization of the vitamin D level in 10 of the 11 children who had both acidosis and a low vitamin D level at presentation
- Causality not shown, but suggests relationship between acidosis & vitamin D



Bone & Sodium Chloride

- Postmenopausal women – given high/low salt intake & high/low calcium intake
- With a low calcium intake, bone calcium balance was negative on both high and low salt diets
- **Moderately high salt intake (11.2 g/d) caused a significant increase in urinary calcium excretion** with the high calcium diet (changed bone calcium balance from positive to negative)



Potassium Citrate Improves Calcium Balance

- RCT x 6 mo, 52 men and women, mean age 65, Kcit 60 or 90 mmol/d vs. placebo
- 1st evidence that oral Kcit had “long-term, positive effect on calcium balance by reducing urine calcium and having a neutral effect on gastrointestinal absorption of calcium.”
- Net acid excretion significantly lower in both groups vs. placebo and negative, indicating subjects' dietary acid completely neutralized
- Kcit 90 mmol/d: Net calcium balance was significantly improved, and intact parathyroid hormone decreased
- Serum C-telopeptide decreased significantly in both Kcit groups
- Kcit “positively and definitively benefits the calcium economy”



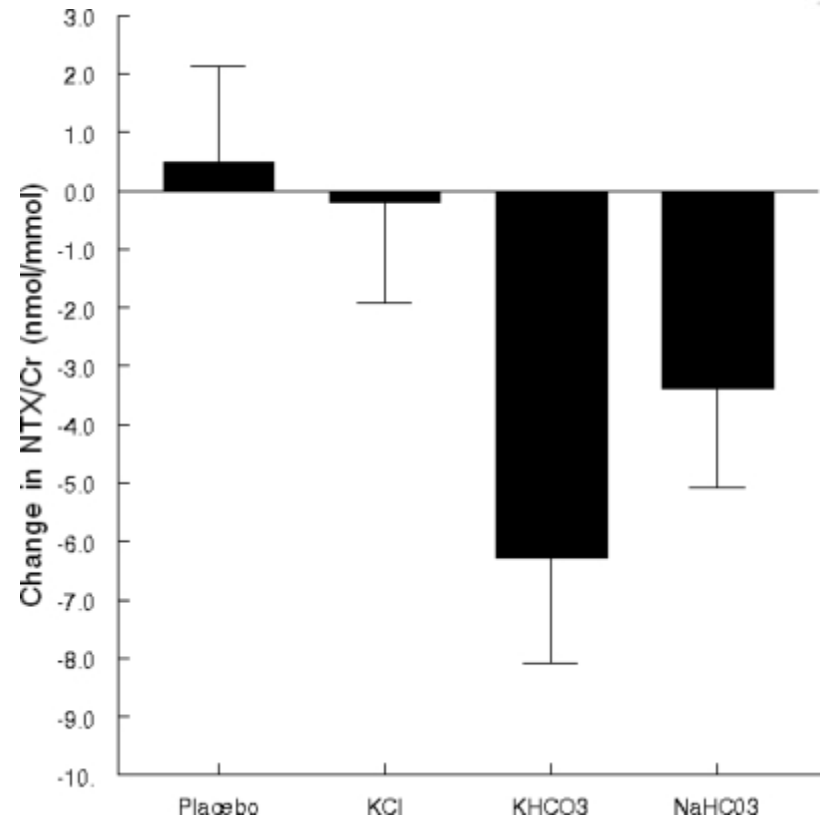
Bicarbonate Water

- 30 female dieticians aged 26.3 yrs
- Randomized into two groups, followed an identical weighed, balanced diet (965 mg Ca) and drank 1.5 l/d of
 - per litre: 520 mg Ca, 291 mg HCO_3^- , 1160 mg SO_4^- , Potential Renal Acid load (PRAL)= + 9.2 mEq
 - OR per litre: 547 mg Ca, 2172 mg HCO_3^- , 9 mg SO_4^- , PRAL= - 11.2 mEq
- Alkaline water (rich in bicarbonate) led to a significant decrease of PTH and of S-CTX
- Acid calcium-rich water had no effect on bone resorption



Potassium or Sodium?

- Double-blind, controlled trial, 171 men and women age 50 and older
- Randomized to receive placebo or 67.5 mmol/d of potassium bicarbonate, sodium bicarbonate, or potassium chloride for 3 months
- Bicarbonate favorably affected the study outcomes (24-hour urinary N-telopeptide and calcium), whereas potassium did not, but **potassium 2x better than sodium bicarbonate**



NCBI Public Domain



Potassium Citrate Counteracts Salt

- Postmenopausal women (n = 60) adapted to a low-salt diet for 3 wk, then randomized to a high-salt diet plus potassium citrate or a high-salt diet plus placebo for 4 wk
- The **addition of oral potassium citrate to a high-salt diet prevented the increased excretion of urine calcium** and the bone resorption markers caused by a high salt intake
- Roughly equivalent to 7-8 servings fruit/veg per day



Mineral Citrates

- Potassium magnesium citrate counters renal stone formation associated with immobilization
- Supplementation associated with a significant increase in urinary pH, in urinary citrate and pCO₂, and significant decreases in urinary NH₄⁺ and total titratable acidity
- Significantly retarded crystallization of calcium oxalate vs. placebo
- (Bed rest 5 weeks, 2 weeks recovery)



Kcit Improves BMD & Microarchitecture

- RCT x 2 years, 200 men & women age 65+
- **Kcit @ 60 mEq qd significantly increased lumbar spine areal bone mineral density (aBMD)** by $1.7 \pm 1.5\%$ [95% confidence interval (CI) = 1.0–2.3, $P < 0.001$] net of placebo
- Increased trabecular density at several sites (tibia, radius) – measured by HR-pQCT
- Decreased fracture prediction score by FRAX significantly in both sexes.
- In 1 yr RCT, Kcit also improved metabolic acidosis, bone surface, connectivity density, cortical thickness, and cortical porosity better than KCl among renal transplant patients

Jehle S, et al. Effect of potassium citrate on bone density, microarchitecture, and fracture risk in healthy older adults without osteoporosis: a randomized controlled trial. *J Clin Endocrinol Metab.* 2013 Jan;98(1):207-17.
Starke A, et al. Correction of metabolic acidosis with potassium citrate in renal transplant patients and its effect on bone quality. *Clin J Am Soc Nephrol.* 2012 Sep;7(9):1461-72



Bone – Intervention Research

- Trials documenting bone loss reversal by using base (NOT calcium)
 - 170 postmenopausal women
 - **Potassium bicarbonate** (KBC) - randomized to KBC 30, 60, or 90 mmol/d, or placebo, for up to 36 months (30 nmol = 3g)
 - Reduced daily urinary Ca excretion
 - Could predict which women would benefit most – those with the greatest urinary Ca loss



Bone - KBC

- 18 postmenopausal women given KBC for 18 days (60 to 120 mmol per day)
- Calcium and phosphorus balance became less negative or more positive
- Serum osteocalcin concentrations increased & urinary hydroxyproline excretion decreased
- Supplementation “..reduces the rate of bone resorption, increases the rate of bone formation, and attenuates or reverses the loss of bone in defense of systemic acid-base homeostasis”



Bone – Combined Base Therapies

- Postmenopausal women – crossover trial
- Given potassium citrate, calcium citrate, both, or placebo
- Potassium citrate alone conferred an alkali load, reducing urinary calcium and potentially causing calcium retention.
- Calcium citrate alone probably suppressed parathyroid function, conferred a mild alkali load, and reduced bone resorption
- Combined treatment reduced bone resorption by dual effects of alkali load from potassium citrate and of absorbed calcium from calcium citrate



Bone – Prospective Trials

- Randomized, prospective, controlled, double-blind trial
- 161 postmenopausal women (age 58.6 +/- 4.8 yr), received 30 mEq of oral potassium citrate (Kcitrate—9g) or 30 mEq of K chloride (KCl) daily.
- Compared with the women who received KCl, women who received Kcitrate exhibited an intergroup increase in BMD of $1.87 \pm 0.50\%$ at L2 through L4 ($P < 0.001$), of $1.39 \pm 0.48\%$ ($P < 0.001$) at femoral neck, and of $1.98 \pm 0.51\%$ ($P < 0.001$) at total hip
- “Magnitude of the effect is large, and the safety profile was found to be excellent”
- Conclusion: “Bone mass can be increased significantly in postmenopausal women with osteopenia by increasing their daily alkali intake as Kcitrate and that this effect is independent of reported in vitro skeletal effects of co-administered K”



Acidosis & Metabolism

- The regulation of intra & extracellular pH is essential for enzyme-mediated metabolic processes
- **Acidosis has been shown to reduce insulin sensitivity**
- pH also influences endocrine function
 - Experimentally induced metabolic acidosis increases circulating glucocorticoids
 - Serum IGF-1 concentrations are also decreased, with peripheral insensitivity to GH action likely

Remer T, et al. Renal Net Acid Excretion and Plasma Leptin Are Associated with Potentially Bioactive Free Glucocorticoids in Healthy Lean Women. *J Nutr.* 2008 Feb;138(2):426S-430S.

Souto G, et al. Metabolic acidosis-induced insulin resistance and cardiovascular risk. *Metab Syndr Relat Disord.* 2011 Aug;9(4):247-53.



pH and Cellular Function

- Acidification increases cellular calcium levels, **encourages tumor cell growth**
- An acidic pH affects immune cells, impairing lymphocyte proliferation and cytotoxicity
- Acidic pH also impairs mitochondrial function, reducing cellular energy production
- A **low pH activates osteoclasts**, increasing the rate of bone resorption, and inhibiting matrix mineralization



Acidosis & Hypoxia

- Hypoxia stimulates osteoclast formation from mononuclear precursors
- Hypoxia blocks osteoblast growth and differentiation – and thus bone formation.
- Hypoxia is usually accompanied by acidosis due to reduced vascular perfusion and increased glycolytic metabolism
- Disruption of the blood supply can have multiple negative consequences for the skeleton via direct actions of hypoxia and acidosis on bone cells



Acidosis and Brain Function

- Multiple mechanisms
 - Acid Sensitive Ion Channel Activation
 - Interactions with other chemical signals
 - Cytosolic Effects
 - Membrane Potential Changes
 - Hormonal Dysregulation



Brain Effects from Acidosis

- Neuron death associated with cerebral ischemia
 - Acidic shift ~> full activation of ASIC1a
 - pH may fall to 6.0 or lower
 - ASIC1a ~> influx of Ca^{+2}
 - Calcium overload = final common pathway ~> Damage
 - Blockade of ASIC protects neurons
- Traumatic brain injury

Xiong ZG, Chu XP & Simon RP (2007) Acid sensing ion channels--novel therapeutic targets for ischemic brain injury. *Front. Biosci* 12, 1376-86.

Pignataro G, Simon RP & Xiong ZG (2007) Prolonged activation of ASIC1a and the time window for neuroprotection in cerebral ischaemia. *Brain* 130,151-8.

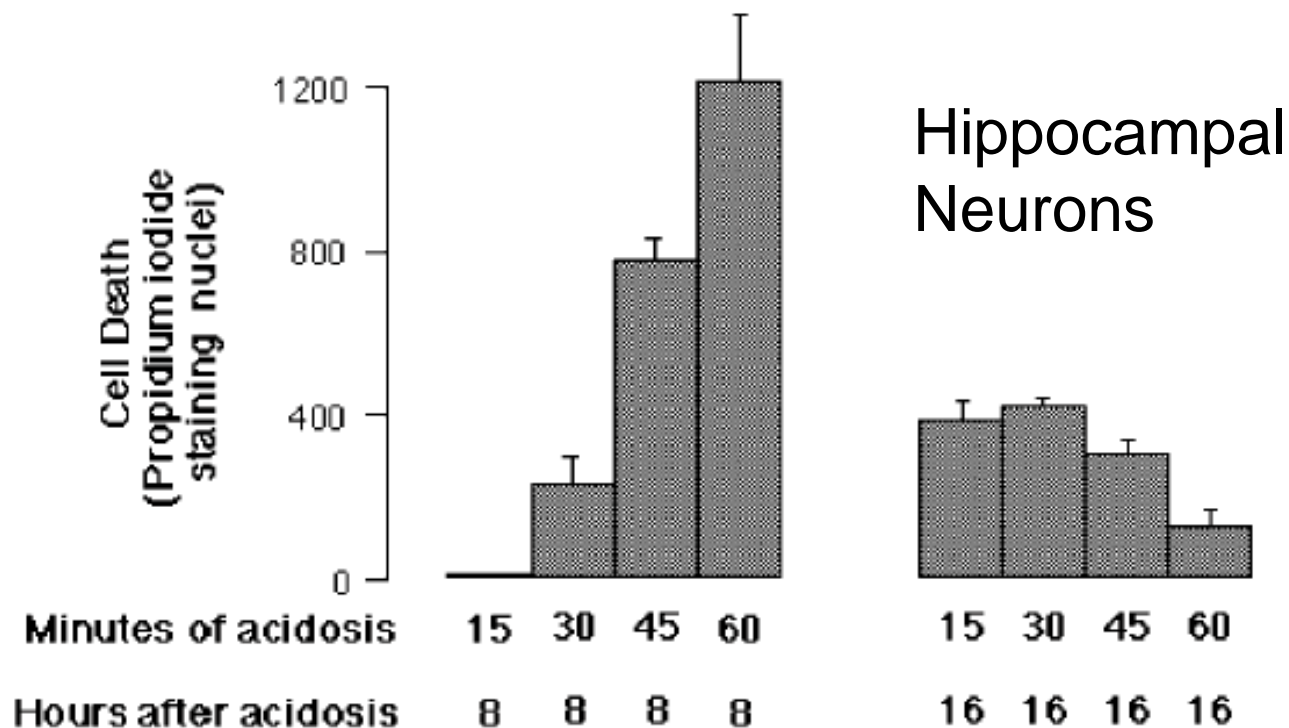
Yao H, Haddad GG (2004) Calcium and pH homeostasis in neurons during hypoxia and ischemia. *Cell Calcium* 36, 247–255.

Zygun DA, Steiner LA, Johnston AJ, et al. (2004) Hyperglycemia and brain tissue pH after traumatic brain injury. *Neurosurgery* 55, 877-82.

Nedergaard M, Kraig RP, Tanabe J, et al. (1991) Dynamics of interstitial and intracellular pH in evolving brain infarct. *Am J Physiol* 260, R581–8.



Cell Death Following Acidosis to pH 6.5



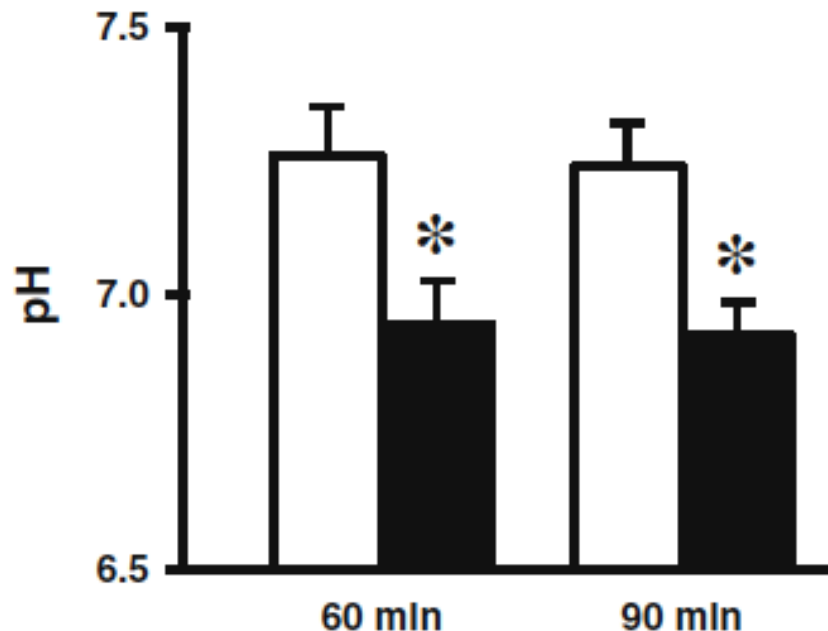
Ding D, Moskowitz SI, Li R, *et al.* (2000) Acidosis induces necrosis and apoptosis of cultured hippocampal neurons. *Exp Neurol* **162**, 1-12.



Systemic Inflammatory Diseases can cause Acidosis of Brain Tissue

- pH electrodes inserted into the brains of diabetic rat positioned in the hippocampal interstitial space

White Bars – Control Rats
Black Bars – Diabetic Rats

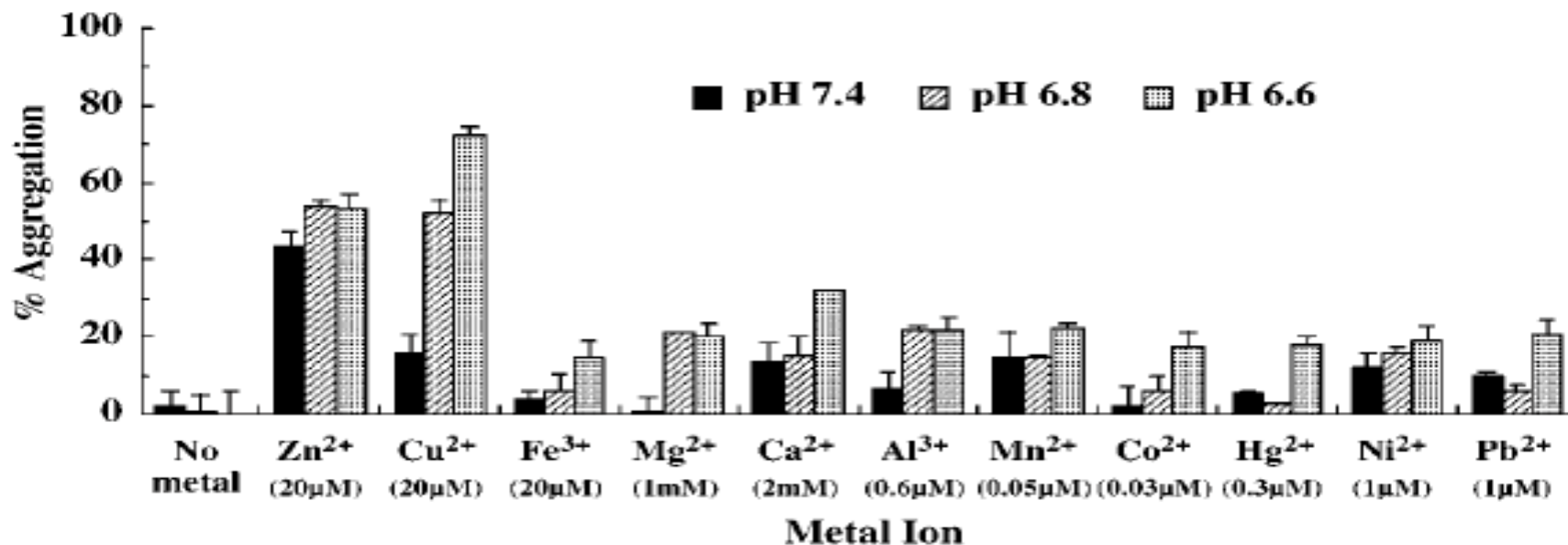


Marunaka Y, Yoshimoto K, Aoi W, *et al.* (2014) Low pH of interstitial fluid around hippocampus of the brain in diabetic OLETF rats. *Mol Cell Ther* 2, 6.



Acidic Environment Promotes Amyloid-Beta Aggregation

- Metal-mediated effect
- Trend holds for most metals tested

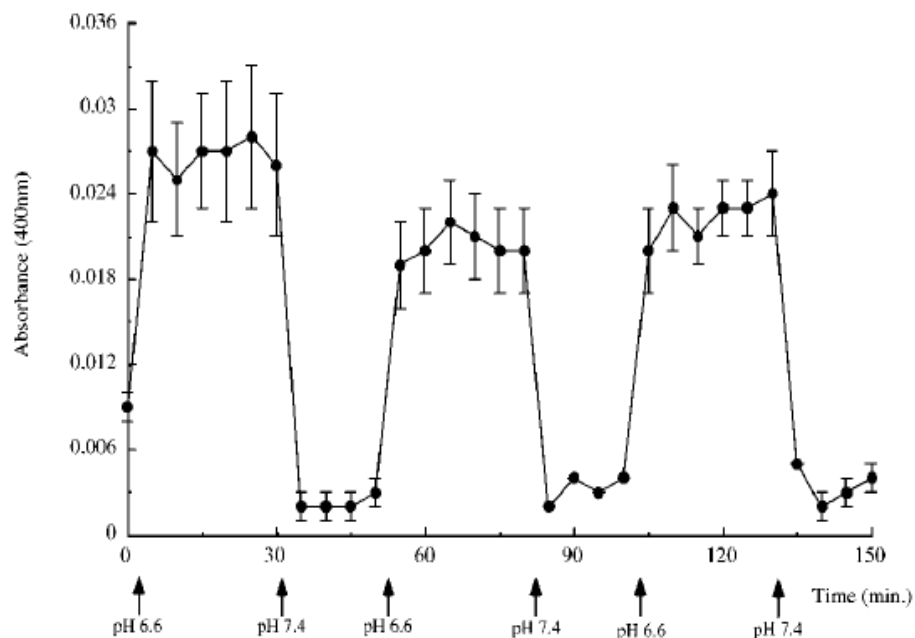
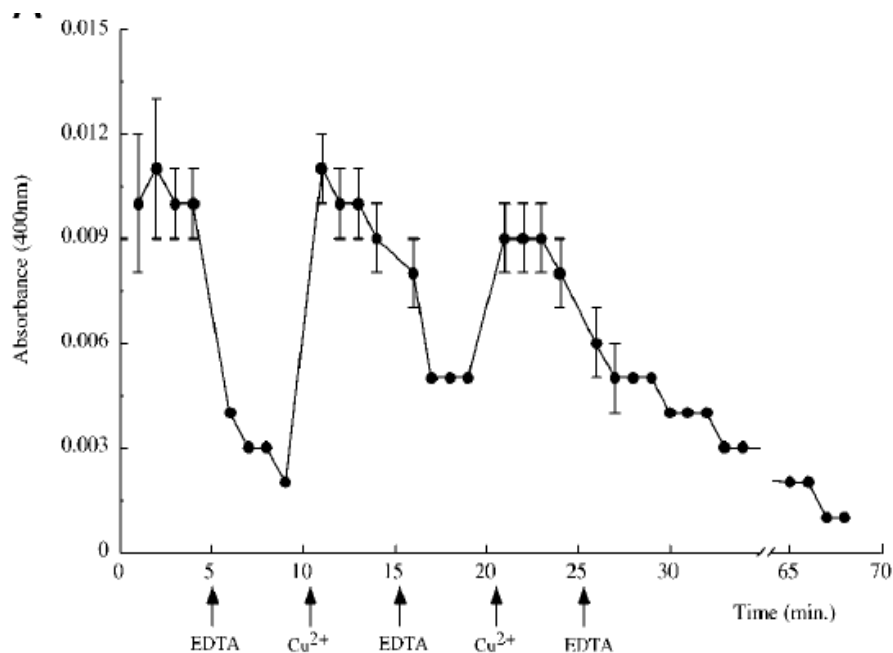


Atwood CS, Moir RD, Huang X, *et al.* (1998) Dramatic aggregation of Alzheimer A β by Cu(II) is induced by conditions representing physiological acidosis. *J Biol Chem* **273**, 12817–12826.



Metal-Induced Aggregation is Reversible

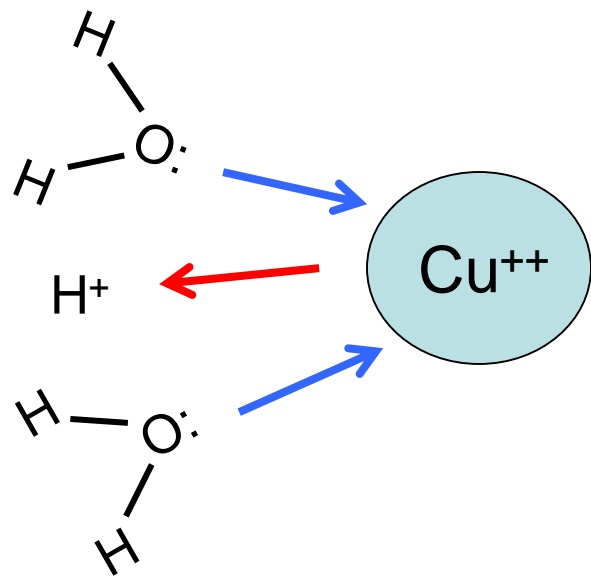
- Effect can be reversed with chelation of the metal or increase in pH



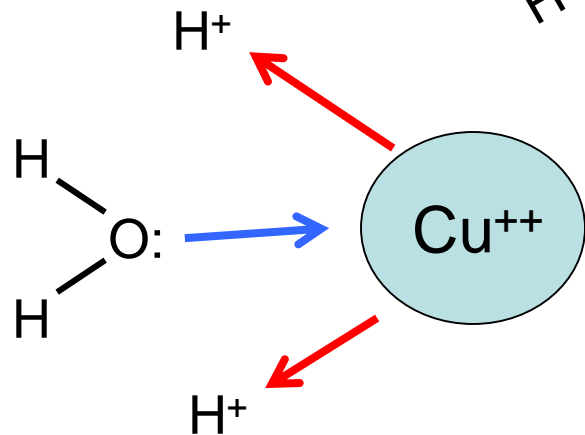
Atwood CS, Moir RD, Huang X, *et al.* (1998) Dramatic aggregation of Alzheimer A β by Cu(II) is induced by conditions representing physiological acidosis. *J Biol Chem* **273**, 12817–12826



Mechanism? Change in Chemical Potential



Alkaline pH: Electron donation from water stabilizes cationic metal centers



Acidotic pH: Acidic environment withdraws electrons from metal center increasing its reactivity



In the Words of Another Scientist

“Further, the acidic environment occurring in the brain would be related to diminution of neuronal function and onset of Alzheimer’s disease.”

“...we suggest that maintenance of the interstitial fluid pH at the normal level or the recovery of the “interstitial” pH to normal from lowered levels would be a key factor in developing molecular and cellular therapies for metabolic brain disorders including Alzheimer’s disease.”



Does Acidosis Promote Parkinson's Disease?

- PD is characterized by the loss of dopaminergic neurons in the substantia nigra (SN)
- The SN is located in the striatum
- The “**striatum** is one of the brain regions [that is] the **most sensitive** to the effects of hypoxia/ischemia, not only because it lies deeper and is **subject to greater acidification**, but also because it is rich in (dopaminergic signaling)”

Barrier L, Barc S, Fauconneau B, *et al.* (2003) Evidence that acidosis alters the high-affinity dopamine uptake in rat striatal slices and synaptosomes by different mechanisms partially related to oxidative damage. *Neurochem Int* **42**, 37-44.

Smith ML, Aue RN & Siesjö BK (1984) The density and distribution of ischemic injury in the rat following 2–10 min of ischemia. *Acta Neuropathol* **64**, 319–332.



Cerebral Lactic Acidosis Induces PD

- PD is associated with cerebral lactic acidosis
- MPTP is a neurotoxin used in mouse model of PD
- Amiloride (Am) is a diuretic that blocks ASIC
 - Found to be protective in cerebral ischemia
- **Am reduces losses of:**
 - Tyrosine hydroxylase
 - Dopamine transporter
 - Dopaminergic cell bodies in the substantia nigra

Arias RL, Sung ML, Vasylyev D, *et al.* (2008) Amiloride is neuroprotective in an MPTP model of Parkinson's disease. *Neurobiol Dis* **31**, 334-41.

Bowen BC, Block RE, Sanchez-Ramos J, *et al.* (1995) Proton MR spectroscopy of the brain in 14 patients with Parkinson disease. *AJNR Am J Neuroradiol* **16**, 61-8.



Acidosis Inhibits Dopamine Reuptake

- Using rat striatal slices at pH 5.5
- Dopamine reuptake slowed by 60-70%
- Partially due to **ROS generation**
- Both Dopamine transporter and Na/K-ATPase affected
- Authors suggest effect maybe due to **changes in membrane integrity**
- (Possible reduction in uptake of GABA, serotonin, norepinephrine as well)

Barrier L, Barc S, Fauconneau B, *et al.* (2003) Evidence that acidosis alters the high-affinity dopamine uptake in rat striatal slices and synaptosomes by different mechanisms partially related to oxidative damage. *Neurochem Int* **42**, 37-44.



What About Motor Neurons? ALS

- Mitochondrial dysfunction, Ca^{+2} overloading, local hypoxia/ischemia all implicated in ALS
- Strong increase in ASIC2 in ALS progression
- Motor neurons susceptible to acidotox *in vitro*
- Inhibition of ASIC channels with a lipophilic AM derivative “**potently protected motoneurons against acidotoxicity, and, given post-symptom onset, significantly improved lifespan, motor performance and motoneuron survival in (ALS) mice.**”



Acidosis & Glutathione

- Cell-based study
- Acidosis inhibits glutathione synthesis on multiple levels
- **Inhibits cysteine import (rate limiting step in production of GSH)**
- **Inhibits GSH synthesis downstream of cystine,** by impairing GCL (has pH optimum of 8.2–8.6)
- NAC improves GSH recovery
- Gamma-glutamylcysteine ethyl ester (GCEE) looks promising for acidosis



Acidosis & GSH

- Perhaps just as importantly, **acidosis also impairs glutathione conjugation**, i.e. binding of GSH to various organic substrates, and via the non-enzymatic coupling of GSH to organic molecules
- Acidosis may exacerbate GSH depletion during cell stress, depending on several factors, including depending on the relative rates of de novo-synthesis, recycling, export and consumption of GSH
- Thus, **acidosis impairs both synthesis & utilization of GSH!**



IR, Glutathione Depletion, & POP Exposure

- If acidosis contributes to decrease in GSH synthesis and inhibits GSH conjugation, could also **exacerbate environmental toxin exposure**
- Glutathione conjugation is the main route of POP detox
- Cellular GGT metabolizes extracellular GSH, allowing precursor amino acids to be reutilized for intracellular GSH.
- Exposure to POPs induces GGT as a defensive mechanism
- **GGT in normal range** closely associated with insulin resistance

Bianchi C, et al. Serum gamma-glutamyltransferase levels are related to insulin sensitivity and secretion in subjects with abnormal glucose regulation. *Diabetes Metab Res Rev.* 2010 Mar;26(3):181-6.

Lee DH, et al. Serum gamma-glutamyltransferase: new insights about an old enzyme. *J Epidemiol Community Health.* 2009 Nov;63(11):884-6.



Clinical Effects of Acidosis

- Dietary acidosis increases **bone loss, osteoporosis, fractures, hypertension, renal stone formation, insulin resistance, neuron damage.**
- Diet high in acid-producing foods causes **bone loss.**
- Acid load of the diet found to be the strongest predictor of **renal stone formation**
- Data from Nurses' Health Study II (87,000 women) found increased incidence of **hypertension** with higher acid diet.
- Acidic urine also is correlated to the **metabolic syndrome** and the degree of insulin resistance
- Acidification of cellular environment cause **neuron damage**

New SA, 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 Jan;79(1):131-8.

Trinchieri A, et al. Effect of potential renal acid load of foods on urinary citrate excretion in calcium renal stone formers. *Urol Res.* 2006 Feb;34(1):1-7.

Maalouf NM, et al. Low urine pH: a novel feature of the metabolic syndrome. *Clin J Am Soc Nephrol.* 2007;2(5):883-8.

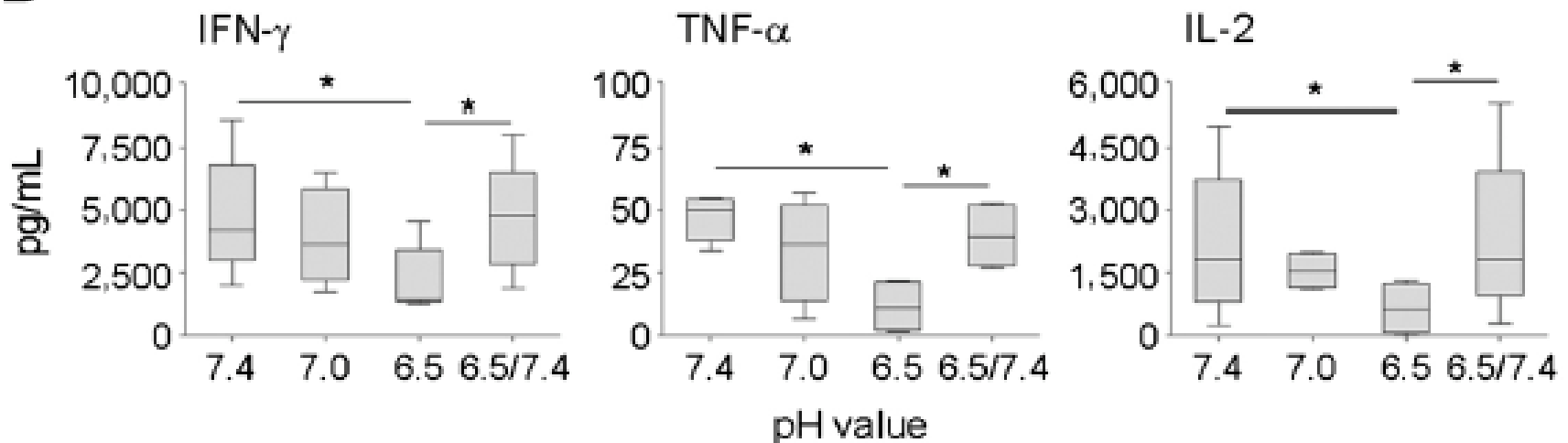
Zhang L, Diet-dependent net acid load and risk of incident hypertension in United States women. *Hypertension.* 2009 Oct;54(4):751-5.



pH Reduction Induces Anergy in Lymphocytes

- Study looked at tumor-infiltrating lymphocytes
- Reduction of cytokines in response to pH reduction
- **Cytokine response is restored by pH normalization**
- Fewer cells produced cytokines rather than an overall diminished cellular response

B

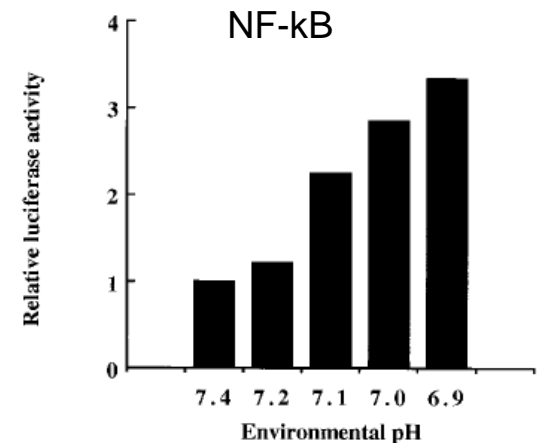
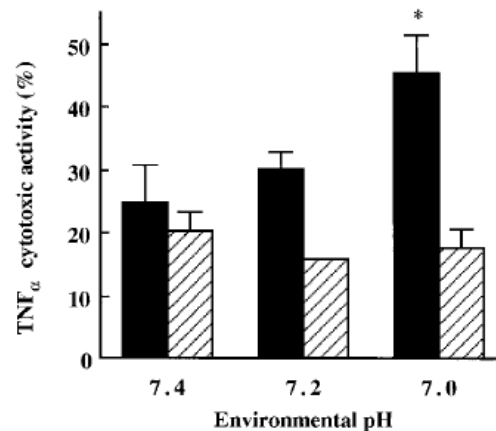
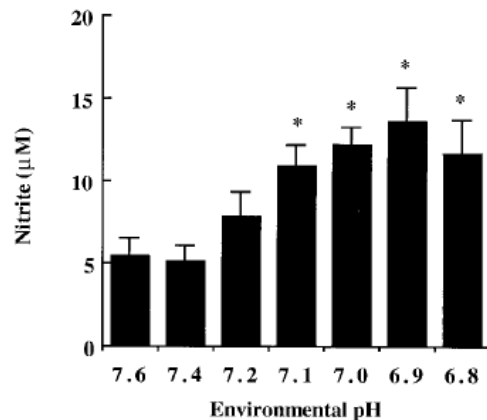


Calcinotto A, Filipazzi P, Grioni M, *et al.* (2012) Modulation of microenvironment acidity reverses anergy in human and murine tumor-infiltrating T lymphocytes. *Cancer Res* **72**, 2746-56.



pH Reduction Increases Cytokine Expression In Macrophages

- Similar study to the last slide only showing macrophages instead of lymphocytes
- Increased cytokine production with more acidic environment
- Blockade of NFkB abolished this activity



Bellocq A, Suberville S, Philippe C, *et al.* (1998) Low environmental pH is responsible for the induction of nitric-oxide synthase in macrophages. Evidence for involvement of nuclear factor-kappaB activation. *J Biol Chem* **273**, 5086-92



Acidosis Induces Inflammation

- 4525 healthy adults excluding those with chronic disease, recent infection, or reduced kidney function
- Those in the upper quartile of **anion gap** had a **$1.0 \times 10^9/L$ increase in leukocytes count** and a **10.9 nmol/L increase in CRP** (vs. the lowest quartile, adjusted for multiple variables)
- Those in the lowest quartile of **serum bicarbonate** had a **$0.7 \times 10^9/L$ increase in leukocyte count** and a **4.0 nmol/L increase in CRP** (vs. the lowest quartile, adjusted for multiple variables)



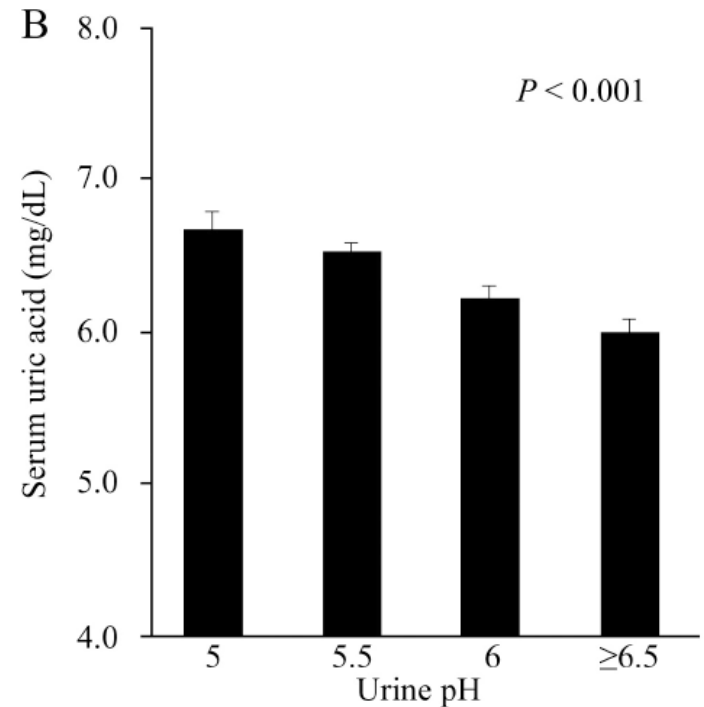
Acidosis & Insulin Resistance (IR)

- In healthy individuals **even a slight degree of metabolic acidosis results in decreased sensitivity to insulin and subsequent impairment of glucose tolerance**
- Elevations of basal lactate in healthy persons, the presence of ketone bodies in diabetic subjects, and chronic kidney disease-related metabolic acidosis are also associated with the development of IR



Acidosis & Met-S

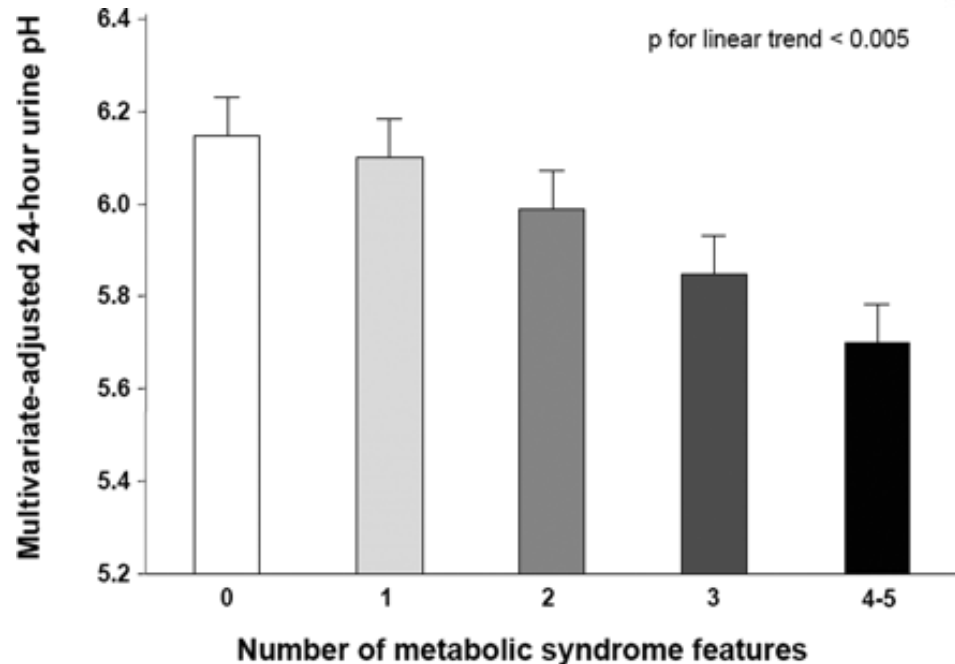
- 1,051 male Japanese subjects
- Excluded history of hypertension, dyslipidemia, diabetes mellitus, and hyperuricemia and past history of chronic liver disease, chronic kidney disease and cancer
- Lower urine pH was associated with higher serum urea nitrogen, an increase in waist circumference, HOMA-R, fasting plasma glucose, HbA1c, serum triglyceride, serum uric acid and a decrease in HDL



Otsuki 2011

Acidosis & Met-S

- Evaluation of 148 adults with no kidney stones
- Participants with the **metabolic syndrome had a significantly lower 24 h urine pH** than those without, with an incremental reduction in pH associated with the number of metabolic abnormalities present



Maalouf 2007

Maalouf NM, et al. (2007) Low urine pH: a novel feature of the metabolic syndrome. Clin J Am Soc Nephrol 2, 883–888.

Abate N, et al. (2004) The metabolic syndrome and uric acid nephrolithiasis: novel features of renal manifestation of insulin resistance. Kidney Int 65, 386–392.





Acidosis and Cardiometabolic Risk

- 1136 female Japanese dietetic students aged 18-22
- After adjustments for confounding factors –
 - Higher PRAL and Protein:Potassium ratio were associated with **higher systolic and diastolic blood pressure**
 - (P for trend.0.028 and 0.035 for PRAL and 0.012 and 0.009 for Pro:K, respectively)
 - PRAL was associated with **total cholesterol and LDL**
 - (n 1121; P for trend.0.042 and 0.021, respectively)
 - Pro:K was associated with **BMI and waist circumference**
 - (P for trend.0.024 and 0.012, respectively)



Lipid Metabolism

- 20 healthy female volunteers, 7-day course of NH_4Cl to induce acidosis
- Adiponectin decreased from 10,623pg/mL to 9723pg/mL ($P < 0.005$)
- Adiponectin enhances insulin sensitivity along with possessing anti-atherogenic and anti-inflammatory properties. It is inversely correlated with cardiovascular events.



IR, Acidosis, & Diabetes Risk

- Increased cortisol may mediate the relation between metabolic acidosis and reduced insulin sensitivity
- Potassium intake is a major determinant of dietary base, may help explain the **inverse associations between potassium or potassium-rich foods and the risk of incident Type 2 diabetes**

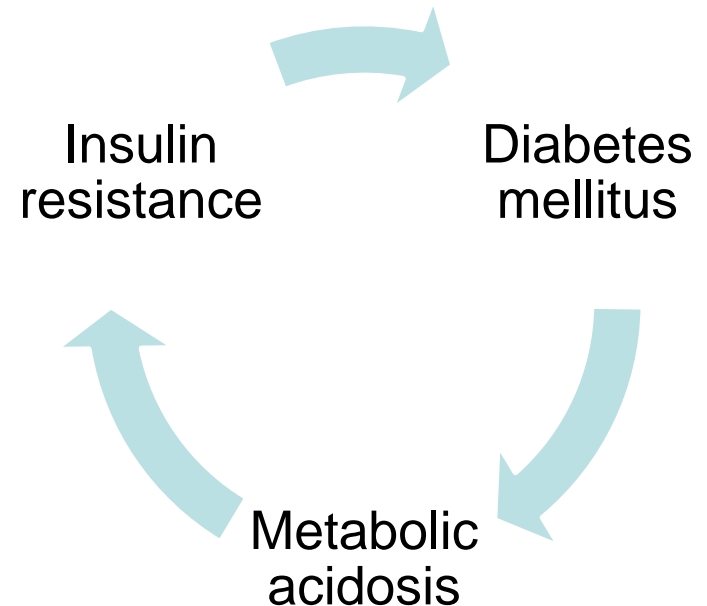
McCarty MF. Acid-base balance may influence risk for insulin resistance syndrome by modulating cortisol output. *Med Hypotheses*. 2005;64(2):380-4.

Farwell WR et al. Serum bicarbonate, anion gap and insulin resistance in the National Health and Nutrition Examination Survey. *Diabet Med*. 2008 Jul;25(7):798-804.



Acidosis & Diabetes: Vicious Cycle

- Diabetics prone also because diets restricted in carbohydrates and fat are often abundant in animal protein
- If poorly controlled, the **formation of ketone bodies intensifies the baseline acidotic state and generates a vicious circle by inducing resistance to the insulin action**, either exogenous or endogenous





Diabetes & Fracture Risk – A Link?

- Higher fracture risk in diabetics
 - T2D: ~1.4–1.7-fold risk relative to non-diabetic controls for hip fracture
 - T1DM: ~6.9–7.1-fold risk relative to non-diabetic controls
- Recent hypothesis: **diabetes leads to cellular acidotic and oxidative stress**, either of which alone impair bone, with a feed-forward mechanism that mutually intensifies acidotic and oxidative stress
 - Acidosis can increase ROS formation in part as a consequence of pH-dependent decoupling of iron from its binding sites
 - Acidosis can lead to oxidative stress by other mechanisms including **decreased intracellular levels of glutathione** (thus increasing toxicity from POPs and metals), a decrease achieved through multiple pH-related mechanisms



IR, Acidosis, & Fitness

- NHANES 1999-2002
 - 1,496 adults without diabetes or other chronic disease
 - Lower levels of serum bicarbonate and higher levels of serum anion gap were associated with higher levels of fasting insulin and lower insulin sensitivity
 - Independent of age, gender, race, BMI, blood pressure and serum albumin
 - The magnitudes of the associations were greater in overweight and obese individuals
 - **Lower bicarbonate & higher anion gap associated with reduced cardiorespiratory fitness** in adults aged 20–49 years in the general US population

Farwell WR et al. Serum bicarbonate, anion gap and insulin resistance in the National Health and Nutrition Examination Survey. *Diabet Med.* 2008 Jul;25(7):798-804.

Abramowitz et al. Lower serum bicarbonate and a higher anion gap are associated with lower cardiorespiratory fitness in young adults. *Kidney Int.* 2012 May;81(10):1033-42.



Does Acid Neutralization Improve Exercise?

- Short-term intake of sodium bicarbonate
 - Reduced the exercise-related drop in pH, & improved anaerobic performance in a dose-dependent manner
 - Improved intermittent sprint performance(81) and was of
 - Had **ergogenic benefits** in the performance of short-term, high intensity work

Douroudos F et al. (2006) Dose related effects of prolonged NaHCO₃ ingestion during high-intensity exercise. *Med Sci Sports Exerc* 38, 1746–1753.

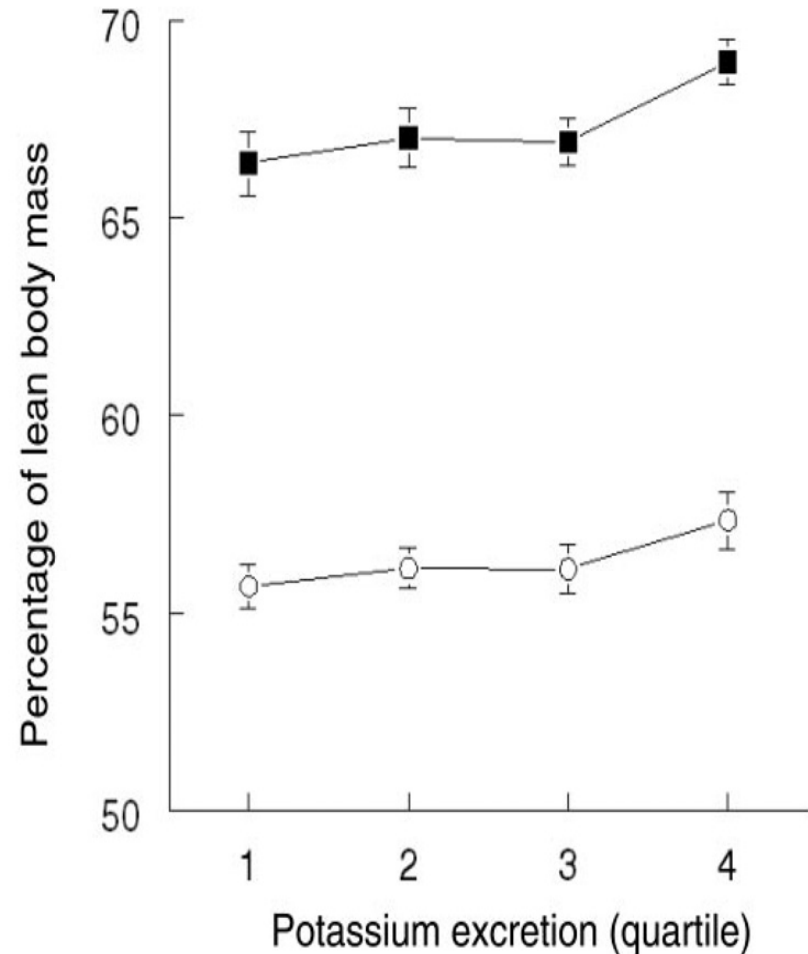
Bishop D et al. (2005) Effects of induced metabolic alkalosis on prolonged intermittent-sprint performance. *Med Sci Sports Exerc* 37, 759–767.

McNaughton et al. (1999) Effects of chronic bicarbonate ingestion on the performance of high intensity work. *Eur J Appl Physiol Occup Physiol* 80, 333–336.



Preserving Muscle Mass

- Subjects were 384 men and women ≥ 65 y old who participated in a 3-y trial comparing calcium and vitamin D with placebo
- Urinary potassium was significantly positively associated with %LBM at baseline
- Conclusion: **“Higher intake of foods rich in potassium, such as fruit and vegetables, may favor the preservation of muscle mass in older men and women”**

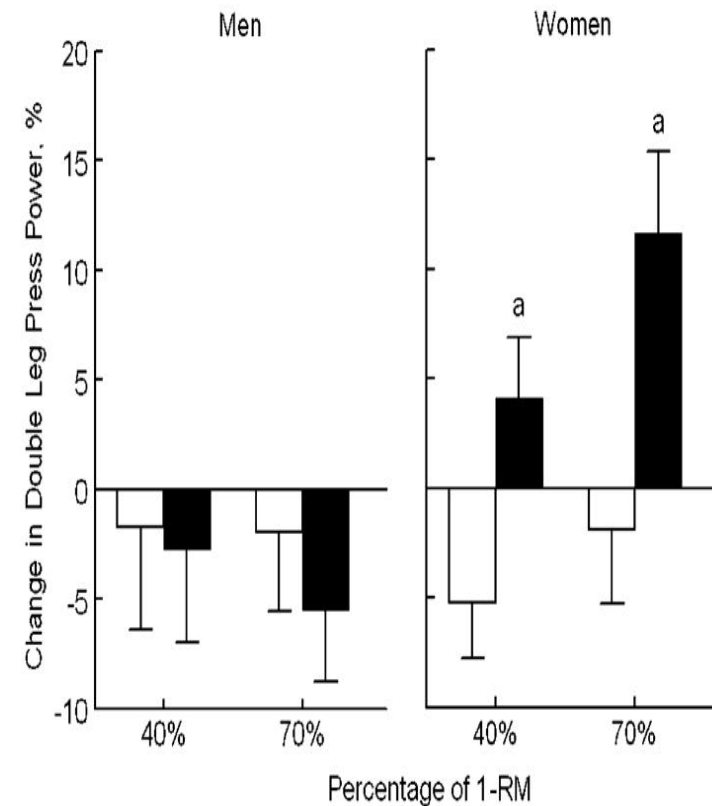


NCBI Public Access



Leg Press Power with Bicarbonate – Women Improved

- The women treated with bicarbonate had **significantly improved lower-extremity power** vs. control, as indicated by greater changes in the double leg press power output at both 40% and 70% of 1-RM ($P=0.006$ and $P=0.003$, respectively)
- The women in the bicarbonate group also had more favorable adjusted mean changes in peak knee extension power at 70% 1-RM ($P=0.014$) and in isokinetic knee extension endurance at $240^\circ /s$ ($P=0.047$) than the women in the control group



NCBI Public Access



Potassium Bicarbonate May Prevent Muscle Loss

- Potassium bicarbonate has been shown to neutralize the metabolic acidosis, and reduce urinary N-wasting in postmenopausal women
- N-sparing may prevent loss of muscle mass, and may even restore past deficits
- Animal-based study suggests acidosis stimulates muscle degradation, by activating the ATP-ubiquitin-proteasome-dependent, proteolytic pathway

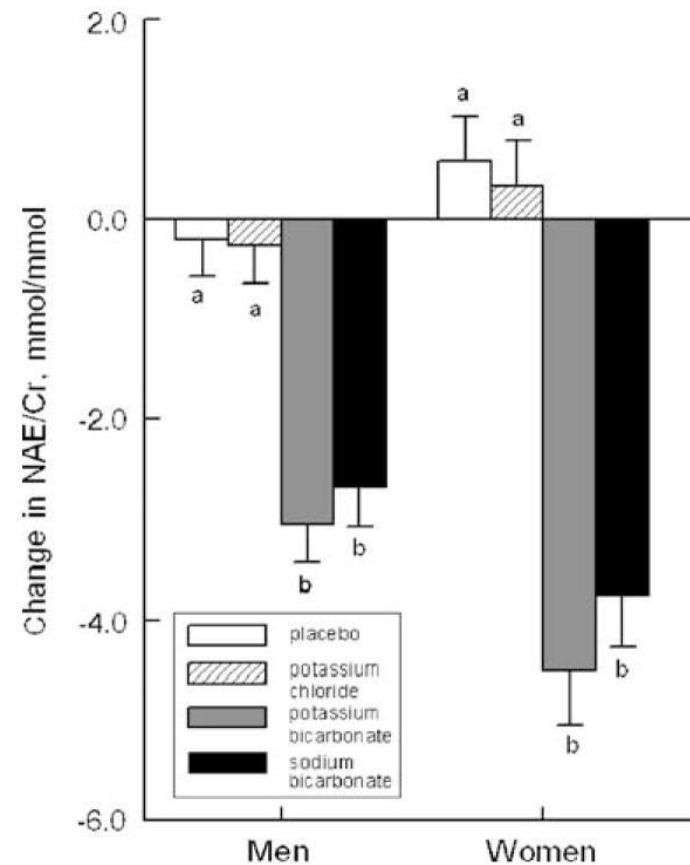
Frassetto L, et al. (1997) Potassium bicarbonate reduces urinary nitrogen excretion in postmenopausal women. *J Clin Endocrinol Metab* 82, 254–259.

Mitch WE, et al. (1994) Metabolic acidosis stimulates muscle protein degradation by activating the adenosine triphosphate-dependent pathway involving ubiquitin and proteasomes. *J Clin Invest* 93, 2127–2133.



Bicarbonate & Muscle Performance in Older Adults

- Healthy subjects age 50+
- Randomized to 67.5 mmol of bicarbonate or to no bicarbonate daily for 3 months
- Groups receiving bicarbonate salts had similar and significant decreases in NAE/Cr whereas the other two groups did not
- In women, **bicarbonate increased double leg press power at 70% one repetition maximum by 13%** ($P=0.003$) compared with no bicarbonate
- No change in men



NCBI Public Access



Acidosis & Cancer

- Lower pH levels in the extracellular space promote the invasive and metastatic potential of cancer cells
- Acidification increases cellular calcium levels and induces pathways that lead to cell growth in tumor cells
- No direct evidence yet, but related pathways involved (adrenal glucocorticoid, insulin growth factor (IGF-1), and adipocyte cytokine signaling)

Robey IF. Examining the relationship between diet-induced acidosis and cancer. *Nutr Metab (Lond)*. 2012 Aug 1;9(1):72

Huang WC, et al. Extracellular acidification elicits spatially and temporally distinct Ca²⁺ signals. *Curr Biol*. 2008 May 20;18(10):781-5.



IR, pH, & Hypocitraturia

- Insulin resistance has been associated with a lower urinary citrate excretion
 - Hypocitraturic patients show greater insulin resistance than normocitraturic Ca stone-formers
- A significant **inverse relationship between urine pH and the degree of insulin resistance** has been found in several population groups, including healthy volunteers, uric acid stone formers, and in patients with gout.
- T2D increases the risk of uric acid stone formation, because it causes a lower urinary pH (due to impaired kidney ammoniogenesis)

Cupisti A, et al. (2007) Insulin resistance and low urinary citrate excretion in calcium stone formers. *Biomed Pharmacother* 61, 86–90.

Adeva MM, et al. Diet-induced metabolic acidosis. *Clin Nutr*. 2011 Aug;30(4):416-21.

Daudon M, et al. (2006) Type 2 diabetes increases the risk for uric acid stones. *J Am Soc Nephrol* 17, 2026–2033.



Hypocitraturia & Stone Formation

- Hypocitraturia has been associated with a low urinary K level and a more acidic urinary pH, both of which can be predicted by dietary intake
- **Dietary acid load is a better predictor of urinary citrate than the intake of most individual nutrients, including dietary K**
 - Trial of 187 patients with renal Ca stone disease: inverse correlation (-0.18) was found between daily PRAL and daily urinary citrate (P 0.01)

Domrongkitchaiporn S, et al. (2006) Causes of hypocitraturia in recurrent calcium stone formers: focusing on urinary potassium excretion. *Am J Kidney Dis* 48, 546–554.

Borghi L, et al. (2002) Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. *N Engl J Med* 346, 77–84.

Trinchieri A, Lizzano R, Marchesotti F, et al. (2006) Effect of potential renal acid load of foods on urinary citrate excretion in calcium renal stone formers. *Urol Res* 34, 1–7



Renal Stone Formation

- Diet-induced metabolic acidosis promotes low urine pH, hypercalciuria, and hypocitraturia, predisposing to uric acid and calcium kidney stone formation.
- Low urine pH is a major risk factor for **uric acid stone formation** whereas hypocitraturia and hypercalciuria are predisposing factors for **calcium nephrolithiasis**



Stone Formation – Biggest Risk Factor?

- In a study of nearly 200 renal stone-formers designed to identify the greatest risk factors for nephrolithiasis: the potential **acid load of the diet had the strongest association with stone risk**
- “a diet with a very low potential acid load should be encouraged in renal stone patients for the prevention of recurrent stones. This result can be obtained by the restriction of animal proteins but also by abundant supplementation with vegetables and fruits”



Renal Stones – Combination Therapy

- Magnesium, increasing pH, and citrate supplementation all associated with benefit, may be complementary
- KNaCitrate & MgO more effective together
 - 25 male volunteers aged 21-42 years without a history of urinary stones and 14 with recurrent CaOx stones
 - Given either KNa-Cit or MgO, or both
 - In both groups, the ion activity product index of CaOx decreased significantly more after administration of the combination than with either compound alone

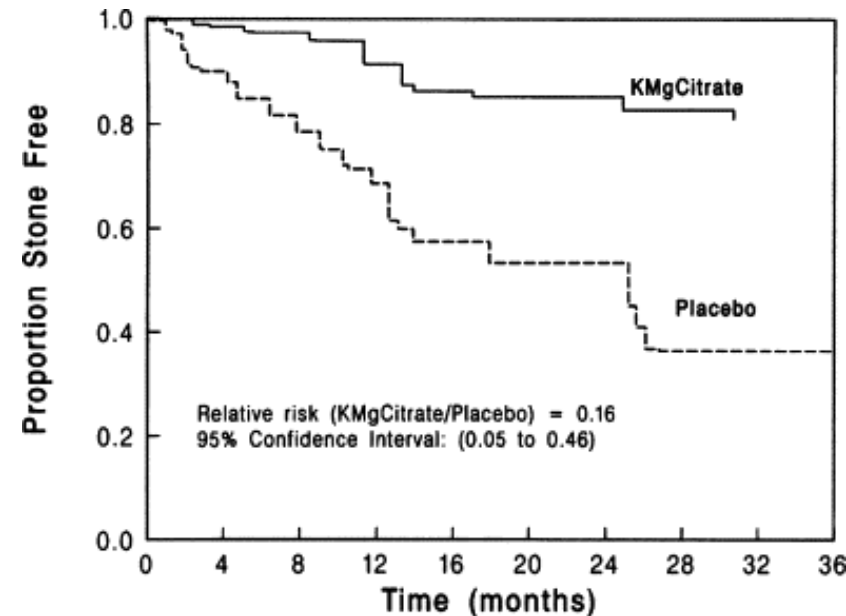
Schwille PO, et al. (1999) Magnesium, citrate, magnesium citrate and magnesium-alkali citrate as modulators of calcium oxalate crystallization in urine: observations in patients with recurrent idiopathic calcium urolithiasis. *Urol Res* 27, 117–126.

Kato Y, et al. Changes in urinary parameters after oral administration of potassium-sodium citrate and magnesium oxide to prevent urolithiasis. *Urology*. 2004 Jan;63(1):7-11;



K/Mg Citrate Prevents Kidney Stones

- Prospective & double-blind randomized trial
- 64 patients, received combo (42 mEq. potassium, 21 mEq. magnesium, and 63 mEq. Citrate) daily for 3 years
- Shown to **reduce the risk of calcium oxalate stone formation by 85%**
- KMg citrate had a statistically significant effect (RR 0.10) even after adjustment for possible confounders



Ettinger 1997



Renal Stone Dissolution with Oral Therapy?

- 8 patients with radiolucent stones ($<$ or $=$ 15 mm)
- Two study periods: first 6 weeks 1500mL water only, 2nd 6 weeks water plus potassium citrate 40 mEq (4g) and potassium bicarbonate 20 mEq (2.5g) - divided in two doses
- No change in 1st 6 weeks
- After 6 weeks of **potassium citrate/bicarbonate** treatment, complete stone dissolution was found in 3 patients
- In the other 5, a partial dissolution was observed, and two of them had complete dissolution after prolongation of the treatment for 4 and 6 month respectively.
- **5/8 complete dissolution in 6 mo**



Bone Health Among Stone Formers

- Prospective trial
 - 109 subjects (51 males and 58 females), idiopathic Ca oxalate stone formers
 - Hypocitraturia risk factor for stone formation
 - Treated with **K citrate for two years**
 - **Increased forearm BMD** (T-score (-1.43 +/- 1.02 vs -0.90 +/- 1.04))
 - This benefit attributed directly to alkalinization because urinary Ca excretion did not change



Acidosis & Pain

- Little clinical research, but mechanistic data suggests connection
- Mediated via **acid-sensing ion channels (ASIC)**
- An increase in ASIC activity in spinal dorsal horn neurons **promotes pain by central sensitization**, a mechanism documented in rats
- ASIC activity is tightly regulated by pH

Duan B, et al. (2007) Upregulation of acid sensing ion channel ASIC1a in spinal dorsal horn neurons contributes to inflammatory pain hypersensitivity. *J Neurosci* 27, 11139–11148.

Wang et al. (2006) Modulation of acid sensing ion channel currents, acid-induced increase of intracellular Ca²⁺, and acidosis-mediated neuronal injury by intracellular pH. *J Biol Chem* 281, 29369–29378.

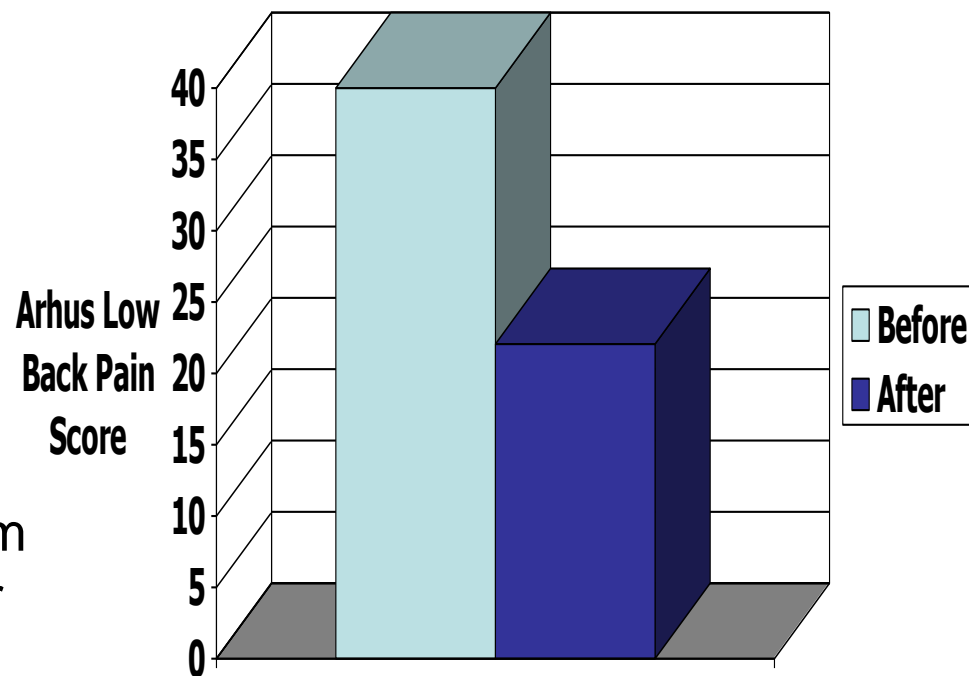


Complex Regional Pain Syndrome

- Able to induce pain in patients with complex regional pain syndrome with injection of acidic infusion into both muscle and skin
- No response in controls
- Suggests acidosis could be one possible mechanism via activation of nociceptors in deep tissues

Alkaline Minerals & Low Back Pain

- 82 patients with chronic low back pain
- ARHS scores decreased by 49% after 4 weeks
- Increase in buffering capacity & blood pH
- However, benefit could be due to nature of minerals, e.g. magnesium for muscle relaxation - intracellular magnesium increased by 11%





Assessment of Acidosis

- Currently no gold-standard
- Commonly used tests (plasma pH, bicarbonate, standard base excess) are not sensitive
- Measurement of net acid excretion (direct urine analysis) is best estimate of NEAP
- Calculations based on dietary factors, such as potassium and protein content, or PRAL, are often used instead
- **24-hour urine** is a reasonable estimation of renal NAE, and compares well with dietary-based calculations

First morning urine NOT a good measure of total acid load

MAY be a measure of metabolic acidosis

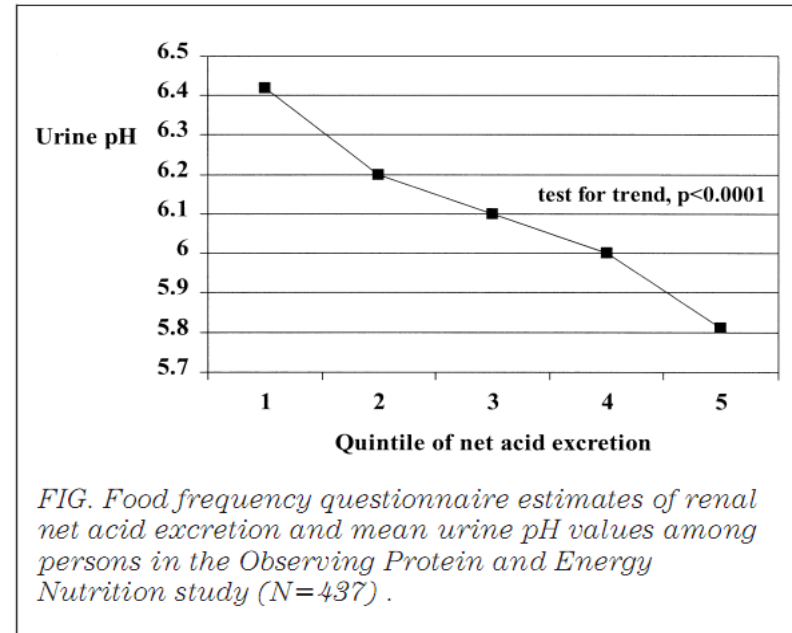
Frassetto L et al. 1996) Age and systemic acid–base equilibrium: analysis of published data. J Gerontol A Biol Sci Med Sci 51, B91–B99

Frassetto LA, et al. (2006) A practical approach to the balance between acid production and renal acid excretion in humans. J Nephrol 19, Suppl. 9, S33–S40.



Assessment – 24 hr Urine

- 24 hr urinary pH represents an index of the diet dependent net acid excretion, as well as the PRAL
- Additionally, urine pH can be adjusted to a target pH based on PRAL calculations for dietary intake.
- **pH strip measurement of the first voided urine was not found to be predictive of the NEAP reflected by the 24 hr urine NAE**



Remer T et al. (1995) Potential renal acid load of foods and its influence on urine pH. J Am Diet Assoc 95, 791–797.

Michaud DS, et al. (2003) Comparison of estimated renal net acid excretion from dietary intake and body size with urine pH. J Am Diet Assoc 103, 1001–1007.

Whiting SJ et al. (2005) Measurement of net acid excretion by use of paper strips. Nutrition 21, 961–963.



Intervention

- Diet
 - Increase:
 - Citrus fruits
 - Fruits and vegetables
 - Decrease
 - Salt
 - Sulfur-containing proteins
- Supplements
 - Citric acid mineral salts
 - Magnesium and potassium



Meta-Analysis – “Alkaline Diet” Not Justified?

- 2009 meta-analysis “does not support the concept that the calciuria associated with higher NAE reflects a net loss of whole body calcium”
- “No evidence from superior quality balance studies that increasing the diet acid load promotes skeletal bone mineral loss or osteoporosis. Changes of urine calcium do not accurately represent calcium balance”
- However
 - The studies included did not directly measure bone health or the progression of osteoporosis
 - **Only studies which modified protein intake were included**
 - **Studies which examined the effect of changes in NAE from either bicarbonate salts or altered intakes of fruit and vegetables or grain foods were excluded!**



Treatment and Prevention of Acidosis

- A diet high in fruits and vegetables and low in animal protein and sodium chloride reduces acid load
- Increased fruit and vegetable consumption, as well as K and Mg alkali intake, is consistently associated with a base-producing diet & greater BMD

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 Nov;17(11):3213-22.

Tucker KL, et al (1999) Potassium, magnesium, and fruit and vegetable intakes are associated with greater bone mineral density in elderly men and women. *Am J Clin Nutr* 69, 727–736.



Protein Intake

- Veggie vs. Animal
 - Vegetarian diet has a considerably lower NEAP than both a high and moderate omnivorous protein intake
- Not too high or too low
 - Reducing protein consumption down to the 0.8 g/kg (the US DRI) in a trial of thirty-nine healthy premenopausal women has also been shown to reduce Ca excretion and raise urinary pH, as well as reduce markers of bone resorption
 - Low protein diet could also induce acidosis

Remer T et al. (1994) Estimation of the renal net acid excretion by adults consuming diets containing variable amounts of protein. *Am J Clin Nutr* 59, 1356–1361.

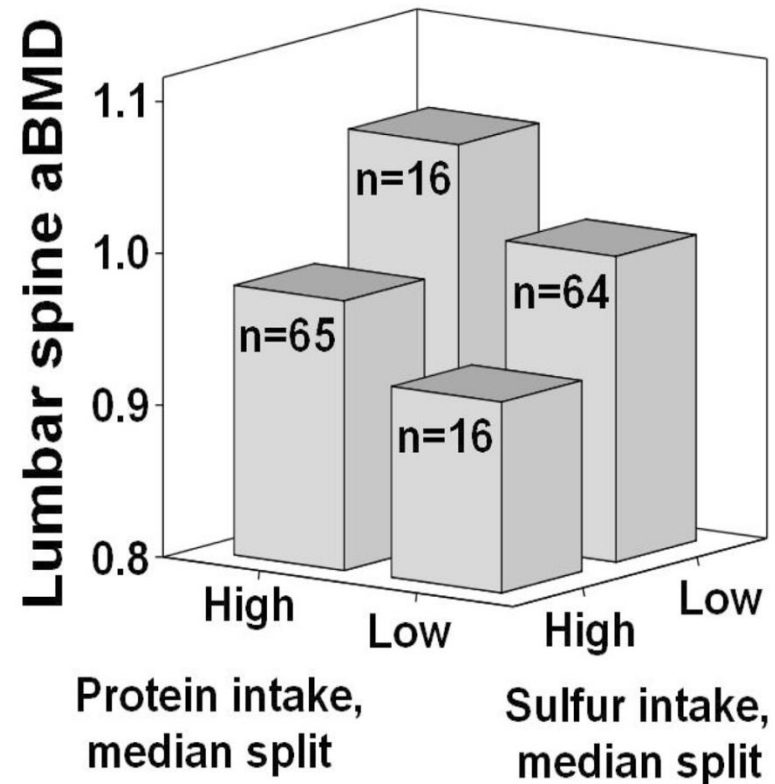
Ince BA, et al. (2004) Lowering dietary protein to U.S. recommended dietary allowance levels reduces urinary calcium excretion and bone resorption in young women. *J Clin Endocrinol Metab* 89, 3801–3807.

Remer T (2001) Influence of nutrition on acid–base balance – metabolic aspects. *Eur J Nutr* 40, 214–220.



Protein Intake – Depends on Type

- In 161 postmenopausal women, protein intake had a positive association with lumbar BMD
- But only after adjusting for the negative effect of the sulfur content of the protein (sulfate)
- Authors: ‘reconciling reports of positive impacts of dietary protein on bone health with reports of a negative impact of the acid load from **sulfur-containing amino acids**’



NCBI Pubic Domain



Protein Intake – Also Depends on Diet

- 229 healthy children and adolescents aged 6-18 y
- A greater protein intake was associated with greater bone strength, **BUT**
- This effect negated if alkalinizing nutrients were lacking, i.e. children with a higher dietary PRAL had significantly less cortical area ($P < 0.05$) and bone mineral content



Salt Intake

- Sodium chloride intake dose-dependently decreases blood pH and plasma bicarbonate levels
- Individuals who are particularly sensitive to salt, (generally defined as an increase of 3-5mm Hg for a given salt load), have more of a metabolic acidosis than those subjects who are salt resistant

Frings-Meuthen P, et al. (2008) Low-grade metabolic acidosis may be the cause of sodium chloride-induced exaggerated bone resorption. *J Bone Miner Res* 23, 517–524.

Sharma AM, et al. (1990) Salt sensitivity in humans is associated with abnormal acid–base regulation. *Hypertension* 16, 407–413.



Supplemental Interventions

- Alkali salts are available as salts of carbonic acid, and as citrates, carbonates, acetates or hydroxides
- **Na salts counterproductive**
- Calcium and potassium most commonly used
- Dose-dependently decrease net acid excretion

Lemann J Jr, et al. (1989) Potassium bicarbonate, but not sodium bicarbonate, reduces urinary calcium excretion and improves calcium balance in healthy men. *Kidney Int* 35, 688–695.

Frassetto L, et al. (2004) Diet acid load and bone health. In *Nutritional Aspects of Osteoporosis*, 2nd ed., chapter 22, pp. 273–290 [P Burckhardt and B Dawson-Hughes, editors]. San Diego, CA: Academic Press



Contraindications to Alkali Supplementation

- Caution if heart, lung or kidney disease
 - In CHF, sodium bicarbonate impairs arterial oxygenation and reduces systemic and myocardial oxygen consumption in these patients, which may lead to transient myocardial ischemia
 - Additionally there may be several simultaneous processes affecting acid–base status among patients with congestive heart failure
 - In COPD bicarbonate loading may worsen exercise response
 - Subjects with kidney failure may develop elevated blood K levels and potentially fatal cardiac arrhythmias if given K alkali salts, or volume overload and breathing problems if given Na alkali salts.

Bersin RM, et al. (1989) Metabolic and hemodynamic consequences of sodium bicarbonate administration in patients with heart disease. *Am J Med* 87, 7–14.

Frangiosa A, et al. (2006) Acid–base balance in heart failure. *J Nephrol* 19, Suppl. 9, S115–S120.

Coppoolse R, et al. (1997) Effect of acute bicarbonate administration on exercise responses of COPD patients. *Med Sci Sports Exerc* 29, 725–732



Conclusion

- Low grade, chronic diet-induced metabolic acidosis is a clinically relevant phenomenon, attributed to a Western diet, poor in fruits and vegetables, and high in salt
- Long-term effects:
 - Bone and muscle loss
 - Kidney stones
 - Impaired insulin sensitivity and renal health
 - Increased susceptibility to cancer and aging
 - Loss of kidney function
 - Impaired ability to detoxify environmental toxins
- Dietary & supplemental therapy have proven clinical effectiveness for reversing diet-induced acidosis, as well as its consequences