Evolving evidence supports that deviation from normal toward the acid spectrum of acid-base balance is associated with premature death compared to patients with normal acid-base status. Patients with non-dialysis-dependent CKD and metabolic acidosis have increased mortality compared to CKD patients without metabolic acidosis (5, 9). Furthermore, the risk for mortality and adverse cardiovascular outcomes increases in CKD patients as plasma total CO₂ (TCO₂) decreases due to metabolic acidosis and this increased risk extends into the normal range for plasma TCO₂ (9). Diets in developed societies are largely acid-producing due to comparatively higher intake of acid-producing animal-sourced protein compared to base-producing plant-sourced protein, the latter including fruits and vegetables (10). Consequently, individuals in developed societies are typically subjected to a constant dietary acid challenge with potential pathologic consequences which might be ameliorated by dietary acid reduction.

Human aging involves a complex set of pathophysiologic processes which often lead to cardiovascular disease, the leading cause of premature death in developed societies (3). Cardiovascular disease is mediated predominantly by arteriosclerosis which involves medial calcification due to altered osteogenesis, including altered mineral, mostly calcium and phosphate, metabolism (2, 4). Consequently, there is much interest in elucidating mechanism(s) for these processes, particularly vascular calcification. Chronic kidney disease (CKD) is a human model of accelerated aging given the shorter lifespans of CKD patients (11), mediated in large part by higher rates of cardiovascular disease (11) which includes vascular injury with calcification (4).

The k1/k1 mouse with deficient expression of the klotho gene is an animal model of accelerated aging (6). Kidneys are the main source of klotho (1, 4), klotho expression is considerably reduced in CKD patients with reduced GFR (1), and klotho deficiency is associated with vascular osteoinduction that is well-described in CKD (4). Accompanying their dramatic reduction in lifespan, klotho deficient animals have marked arteriosclerosis with extensive medial calcification, tissue calcification, and increased plasma levels of aldosterone (5, 6). Consequently, klotho deficiency might mediate premature death in CKD, possibly through accelerated arteriosclerosis with medial calcification. In addition, klotho
deficiency appears to be a laboratory model in which to test interventions purported to reduce aspects of
aging, particularly vascular calcification, in an effort to ameliorate progression of these processes in
conditions like CKD whose sufferers experience premature death.

In this issue of the journal, Leibrock and colleagues (7) examined effects of HCO₃ supplementation as
150 mM NaHCO₃ drinking solution in klotho-hypomorphic mice (kl/kl) on growth, lifespan, various
aspects of pathology, and serum levels of selected hormones including aldosterone. Previous studies from
their laboratory showed that dietary NaCl or treatment with the mineralcorticoid receptor antagonist
spironolactone increased the life span of these animals (8). The latter data suggest that volume depletion
(previously shown to be a feature of this model) and/or aldosterone (previously shown to be increased in
this model) contributed to its shorter life span. The effect of spironolactone was also associated with
decreased vascular calcification. Interestingly, Leibrock and colleagues showed that NH₄Cl, which added
metabolic acidosis to underlying respiratory acidosis due to emphysema that characterizes the kl/kl
model, abrogates tissue calcification and increases life span of these animals (8). The investigators
attributed this beneficial effect to alkalinization of acidic intracellular compartments, supported by higher
plasma ammonia (NH₃) associated with NH₄Cl intake, of kl/kl mice rather than to extracellular acidemia
because plasma pH was unchanged by NH₄Cl in kl/kl animals. Because kl/kl mice had respiratory
acidosis with acidemia, they subsequently examined the effect of NaHCO₃ that might alkalinize both
extracellular and intracellular compartments.

The authors report that NaHCO₃ increased lifespan, reduced vascular calcification as well as reduced
calcification in the trachea, lung, and intestine, reduced plasma levels of aldosterone and ADH, increased
plasma pH through increasing plasma [HCO₃] but not changing PCO₂, increased phosphaturia, and
decreased plasma PO₄ and K⁺. Importantly, supplementation with NaHCO₃ had no effect on plasma
ionized Ca²⁺ or on 1, 25 vitamin D, showing that NaHCO₃ supplementation improved lifespan and
reduced vascular calcification without correcting some of the cardinal features of the kl/kl model. They
concluded that oral NaHCO₃ delays tissue calcification and premature death of klotho-deficient mice and
attribute this effect, at least in part, to reversal of extracellular volume depletion and reversal of hyperaldosteronism, as well as to decline of intestinal phosphate absorption.

It is interesting that supplementing k1/k1 klotho deficient animals with the seemingly very different salts of NaCl, NH4Cl, and NaHCO3 all increased lifespan to various degrees. One common metabolic feature induced by all three salts was reduced plasma aldosterone although that induced by NaHCO3 did not reach statistical significance. Nevertheless, NaHCO3 reduced plasma levels and urine excretion of aldosterone in CKD patients with reduced GFR and did so more effectively than NaCl (12). Considering that the mineralocorticoid receptor antagonist spironolactone also increased lifespan in this model suggests an aldosterone role for the shortened life span of k1/k1 animals and its reduced levels for the increased life span in response to the three salts and the mineralocorticoid antagonist. Bicarbonate supplementation might also have reduced vascular calcification and thereby extended life of the k1/k1 model through reducing plasma phosphate levels.

Supplementation with NaHCO3 shifted k1/k1 animals from acid more toward the base spectrum of acid-base status. First, these animals ingested standard chow which has acid-producing casein as its nutrient protein. In addition, k1/k1 animals had baseline chronic respiratory acidosis as noted. After supplementation, respiratory acidosis remained but they had additional metabolic alkalosis. The increase in plasma [HCO3] without a significant increase in PCO2 mediated the increase in plasma pH. The plasma pH increase is one difference between animals receiving NaHCO3 compared to those given NH4Cl in earlier studies from this same investigator team in which the baseline acidic plasma pH did not change because the respiratory acidosis was replaced by metabolic acidosis. Nevertheless, both salts were likely associated with alkanization of acidic intracellular compartments as noted by Leibrock et al (8).

The studies by Leibrock et al (7) support the need for further studies of the potential benefits of oral alkali, or more broadly, dietary acid reduction (e.g., eating more base-inducing foods like fruits and vegetables). Emerging evidence supports that the largely acid-producing diets of developed societies induce a pathologic tissue milieu that contributes to premature death, mediated in part through vascular injury including vascular calcification. The importance of the author’s findings go beyond the particular
aging model they studied because the benefits of NaHCO₃, including increased lifespan and reduced
tissue, including vascular, calcification, were demonstrated without correction of cardinal features of this
model. For example, oral NaHCO₃ therapy in CKD patients with reduced GFR decreases urine excretion
of endothelin and aldosterone, surrogates of kidney levels of these substances (12), offering a possible
mechanism for the increasing benefits of alkali therapy being demonstrated in CKD patients.
Consequently, dietary acid reduction, including with NaHCO₃ and possibly other alkali salts might
abrogate the untoward effects of the acid-producing diets of developed societies.

References

1. Barker SL, Pastor J, Carranza D, Quiñones H, Griffith C, Goetz, R, Mohammadi M, Ye J,
   Zhang J, Hu MC, Kuro-o M, Moe OW, Sidhu SS. The demonstration of αKlotho deficiency in
   human chronic kidney disease with a novel synthetic antibody. Nephrol Dial Transplant 30:223-33,
   2015.


3. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence,
   prevalence, and years lived with disability for 301 acute and chronic diseases in 188 countries, 1990-
   http://dx.doi.org/10.1016/S0140-6736(14)62254-6.


5. Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Association of serum bicarbonate levels
   with mortality in patients with non-dialysis-dependent CKD. Nephrol Dial Transplant


