Is NaHCO₃ an antiaging elixir?

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EVOLVING EVIDENCE supports that deviation from normal toward the acid spectrum of the acid-base balance is associated with premature death compared with patients with a normal acid-base status. Patients with nondialysis-dependent chronic kidney disease (CKD) and metabolic acidosis have increased mortality compared with CKD patients without metabolic acidosis (5, 9). Furthermore, the risk for mortality and adverse cardiovascular outcomes increases in CKD patients as plasma total CO₂ decreases due to metabolic acidosis, and this increased risk extends into the normal range for plasma total CO₂ (9). Diets in developed societies are largely acid producing due to comparatively higher intake of acid-producing animal-sourced protein compared with 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 pathological consequences that might be ameliorated by a dietary acid reduction.

Human aging involves a complex set of pathophysiological processes that 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. 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 kl/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 a reduced glomerular filtration rate (GFR) (1), and klotho deficiency is associated with vascular osteoinduction, which 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 the progression of these processes in conditions like CKD, which is associated with premature death.

Recently, Leibrock and colleagues (7) examined the effects of HCO₃⁻ supplementation as 150 mM NaHCO₃ drinking solution in klotho hypomorphic (kl/k₁) mice on growth, lifespan, various aspects of pathology, and serum levels of selected hormones, including aldosterone. A previous study (8) from their laboratory showed that dietary NaCl or treatment with the mineralocorticoid receptor antagonist spironolactone increased the lifespan of these animals. 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 lifespan. The effect of spironolactone was also associated with decreased vascular calcification. Interestingly, Leibrock and colleagues (8) showed that NH₄Cl, which added metabolic acidosis to underlying respiratory acidosis due to the emphysema that characterizes the kl/k₁ model, abrogates tissue calcification and increases the lifespan of these animals. The investigators attributed this beneficial effect to alkalinization of acidic intracellular compartments, supported by higher plasma NH₃ as associated with NH₄Cl intake, of kl/k₁ mice rather than to extracellular acidemia because plasma pH was unchanged by NH₄Cl in kl/k₁ animals. Because kl/k₁ mice had respiratory acidosis with acidemia, they subsequently examined the effect of NaHCO₃, which might alkalinize both extracellular and intracellular compartments.

The authors reported that NaHCO₃ increased lifespan, reduced vascular calcification as well as reduced calcification in the trachea, lung, and intestine, reduced plasma levels of aldosterone and antidiuretic hormone, increased plasma pH through increasing plasma HCO₃⁻ concentration but not changing PO₂, 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/k₁ model. They concluded that oral NaHCO₃ delays tissue calcification and premature death of klotho-deficient mice and attributed this effect, at least in part, to reversal of extracellular volume depletion and reversal of hyperaldosteronism as well as to a decline in intestinal phosphate absorption.

It is interesting that supplementation of kl/k₁ 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). The finding that the mineralocorticoid receptor antagonist spironolactone also increased lifespan in this model suggests an aldosterone role for the shortened lifespan of kl/k₁ animals.
animals and its reduced levels for the increased lifespan 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 the acid more toward the base spectrum of the 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, the respiratory acidosis remained, but they had additional metabolic alkalosis. The increase in plasma HCO3− concentration without a significant increase in PCO2 mediated the increase in plasma pH. The plasma pH increase is one difference between animals that received NaHCO3 compared with those given NH4Cl in earlier studies from this same investigator team, in which the baseline acidemic plasma pH did not change because the respiratory acidosis was replaced by metabolic acidosis. Nevertheless, both salts were likely associated with alkalization of acidic intracellular compartments, as noted by Leibrock et al. (8).

The results of the study 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 pathological tissue milieu that contributes to premature death, mediated in part through vascular injury, including vascular calcification. The importance of the authors’ 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 the cardinal features of this model. For example, oral NaHCO3 therapy in CKD patients with reduced GFR decreases uric 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.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

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