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A neglected requirement for optimizing treatment of age-related osteoporosis: Replenishing the skeleton's base reservoir with net base-producing diets

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ABSTRACT

Osteoporosis is a disorder of bone in which the mass of the bone is reduced and the bone's architecture at the microscopic level is disordered. Together those abnormalities predispose affected individuals to experience fractures despite only minimal trauma (i.e., fragility fractures). Age related osteoporosis is a common type of osteoporosis that occurs with aging in both men and women usually beginning after the age of peak bone mass. Research has found that the disorder can be partially reversed by reducing the net amount of acid that is produced when consuming typical Western diets. However, the amelioration that results has not been so dramatic or so consistent that physicians have adopted the procedure as part of the standard treatment for age-related osteoporosis. We propose that reducing the net acid load from the diet is not sufficient to reverse age related osteoporosis because it fails to supply base needed to restore the large amount of base in bone that had been lost by reacting with the net acid load of the diet that had been consumed for years or decades. Reducing the net acid load from the diet might be expected to have little ameliorative effect or merely slow the progression of the disorder. We hypothesize that both to restore osteoporotic bone to, or nearly to, its pre-disease state, as well as to eliminate the risk of fragility fractures, requires consuming diets that produce net amounts of base to restore the base lost from years to decades of consuming diets that produce net amounts of acid. We hypothesize also that the excess base and attendant subclinical metabolic alkalosis will both stimulate the cellular process of bone formation and suppress the cellular process of bone resorption, and thereby implement the restorative process.

Introduction

Functions of the skeleton

The human skeleton is an adaptive, self-organizing, multifunctional organ-system vital to human health. It functions (a) as a structure supporting body movement through connections with skeletal muscles, and as trauma-defense through its structural surrounding of vital organs, (b) it contributes to cellular oxygenation throughout the body by generating and distributing red blood cells systemically via the circulation; (c) it contributes to systemic calcium and phosphorus homeostasis in virtue of its large reservoir of labile calcium and phosphorus; (d) it contributes to systemic acid–base homeostasis in virtue of its large reservoir of labile base equivalents residing in calcium hydroxyapatite, the major mineral component of bone; and, (e) contributes to the integration of body physiology through two-way endocrine communication with numerous organ systems of the body (pp. 3–4 [1]) (p. 3 [2]). Each subsystem of the human skeleton adapts to changing environmental conditions—rendering the skeleton a complex adaptive system.

Bone remodeling

Throughout one's life the skeleton continually remodels itself in response to changing mechanical loads and mechanical microdamage, through an interplay of osteoclasts resorbing bone and osteoblasts forming bone. During the first three decades of life, osteoblastic bone formation predominates over osteoclastic bone resorption, and bone mass increases. Once peak bone mass has been reached at around age 25 years a period of stabilization or a slow rate of bone mass decline may occur, then with menopause in women and further aging in women and men, osteoclastic bone resorption outpaces bone formation, often resulting in osteoporosis, a condition in which sufficient loss of bone mass and disruption of bone microarchitecture has occurred to increase the fragility of bone and the risk of fracturing (see Figs. 2 and 3 in [3]).

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The skeleton's role in mineral homeostasis

The skeleton's contribution to mineral homeostasis serves to benefit extra-skeletal systems, especially in contributing to the maintenance of plasma ionic calcium concentrations within a critical range. For example, if the concentration of calcium in the blood decreases owing to inadequate intestinal absorption of calcium, the skeleton releases calcium, which mitigates the decrease in plasma calcium concentration, calcium being vital for physiological functioning throughout the body [4]. But if the inadequate gastrointestinal absorption of calcium continues for a long period of time, the skeleton may lose substantial amounts of calcium and its associated minerals, resulting in osteopenia or osteoporosis. That is, if feedback inhibition fails to occur, due to continuing suboptimal intestinal calcium absorption, say, persistence of the homeostatic mechanism can have a negative trade-off effect on the skeleton itself [5,6]. Osteoporosis due to persisting dietary calcium insufficiency qualifies as a long latency nutrient deficiency disease [7].

The skeleton's role in acid–base homeostasis

Likewise, the contribution of bone to homeostasis of systemic acid–base balance can contribute to the pathogenesis of osteoporosis [5,6]. That can occur when the summed endogenous and exogenous non-carbonic acid load to the body exceeds that of the corresponding base load for a long period of time (years). The resulting chronic metabolic acidosis elicits osteoclastic bone resorption, which releases bone mineral, including calcium and its accompanying basic anions [8–15]. Most Americans suffer from a low-grade chronic metabolic acidosis owing to the fact that the typical American diet is net acid producing, that is, it produces non-carbonic acid in excess of base (alkali, bicarbonate) [16,17].

Two homeostatic mechanisms operate to prevent a serious increase in the acidity and decrease in bicarbonate concentration of body water under conditions of endogenous generation of non-carbonic acids in excess of base: (a) generation of 'new' bicarbonate by the kidney and its delivery to extracellular fluid compartment in conjunction with the excretion of hydrogen ions in the urine as ammonium ions and titratable acid; (b) release of bone mineral base as hydroxyl, phosphate, and carbonate ions and their delivery to the extracellular fluid compartment [8,11,13,18–20]. Thus one of the negative trade-offs for the skeleton's continuing contribution to systemic acid–base homeostasis is continuing loss of the bone's alkaline mineral.

The kidney alone cannot generate sufficient new bicarbonate to fully neutralize non-carbonic acid generated in excess of base because it does not have access to all of the excess acid, inasmuch as the arterial blood flow exposes bone and kidney concurrently to the increase in acidity and decrease in plasma bicarbonate concentration. (The blood flow to the skeleton is a substantial fraction of the blood flow to the kidney [21].) The renal- and skeletal-based homeostatic mechanisms operate concurrently. Together the two mechanisms mitigate the severity of the metabolic acidosis and tend to stabilize it despite continuing endogenous generation non-carbonic acid in excess of base—at the expense of continuing net loss of calcium and its associated alkalinizing anions. In the case of bone's contribution to the homeostasis of acidity and bicarbonate concentration, the mechanism consists in stimulation, by acidity and reduced bicarbonate concentration, of osteoclastic bone resorption and suppression of osteoblastic bone formation, two events that can lead to osteoporosis [10,20].

In the treatment of osteoporosis, both of the postmenopausal and age-related types, numerous pharmacological agents have been developed to discourage osteoclastic bone resorption, though secondarily such anti-resorptive agents tend to discourage osteoblastic bone formation. A few agents have been developed to encourage osteoblastic bone formation itself [1,2].

Those pharmacological approaches, with or without accompanying lifestyle modifications, have significant but limited effectiveness in reducing the risk of the major deleterious consequence of osteoporosis, namely fragility fractures, in particular of the hip and spine.

By way of hypothesis, we offer here a therapeutic approach that might increase the effectiveness of current therapeutic measures and that, without drugs, might have satisfactory effectiveness both in prevention and treatment of osteoporosis.

The hypothesis

We offer the following explicit novel hypothesis:

In patients with postmenopausal or age-related osteopenia or osteoporosis, whatever therapeutic approach clinicians use in an attempt to restore osteopenic or osteoporotic bone to or close to its pre-osteopenic state, and to eliminate fragility fractures, that approach must include dietary consumption by the patients, at appropriate intervals and for appropriate durations, of a low-grade metabolic alkalosis-producing diet, one whose metabolism yields substantially more base/alkali (e.g., bicarbonate, bicarbonate-generating organic anions) than it yields non-carbonic acids (e.g., sulfuric acid, organic acids). The hypothesis presumes that net base loads constitute a *requirement* for the restoration of both bone mass, mineral density, and bone microarchitecture, additional to all other requirements, because net bone formation *requires* net base for normal bone matrix formation and for normal bone matrix mineralization, and because the mineral content of bone is an alkalinizing salt. The hypothesis does not claim that diet net base loads are *sufficient* to meet the stated goals, only that they are *necessary* to meet them.

Comments on hypothesis

Although research relating to acid–base physiology and bone health in humans remains active in the 21st century [14,19,22–26], its conceptual emphasis has been unidirectional in respect of acid–base balance. The cumulative evidence that chronic metabolic acidosis induces resorptive bone mass loss dominated the thinking on acid–base and bone, directing research toward reducing the net endogenous acid production's bone resorptive effect. Clinicians neglected consideration that inducing a substantial net rate of endogenous base production might have a potent bone formative effect as well as an anti-resorptive effect. No one recognized the requirement for a net base input to the body to restore osteoporotic bone to or close to its pre-osteopenic state, and eliminate fragility fractures, despite the knowledge that the mineral components of bone are alkali salts. Hence, our hypothesis represents a novel concept.

Note that the hypothesis posits a net base input as a *requirement* for restoration of osteoporotic bone, not as *sufficient* for doing so.

Basis of the hypothesis

We base our hypothesis on the plausible concept that realization of the full potential for osteoblastic bone formation requires supplying osteoblasts with all of the molecular materials needed to reconstruct bone or construct new bone. In relation to that aspect of our hypothesis, we focus on the need to provide the osteoblast not only with adequate calcium, phosphorus, and amino acids (for bone matrix formation), but also with adequate sources

of alkali, since the mineral composition of bone is largely composed of alkaline salts of calcium, such as calcium hydroxyapatite, calcium phosphate, and calcium carbonate [1]. Alkali is also required for normal bone matrix formation, as it stimulates osteoblasts to produce the predominant protein component of bone matrix, collagen [27,28], as it contributes to the formation of matrix collagen cross-linking [29], which are Schiff's bases that require alkalinity for cross-linking stability, and as it provides an environment favorable to mineralization.

Current therapeutic approaches for osteoporosis, however, never explicitly consider the alkali supply requirements for osteoblastic bone formation. Some studies have shown that alkali administration as supplement or as alkalinizing whole foods can improve skeletal health in terms of favorable changes in markers of bone formation and/or resorption, or improvements in bone mineral density [23–25,30]. But in those studies the objectives were to reduce the rate of endogenous non-carbonic acid production and reduce the degree of attendant metabolic acidosis. The studies were not designed specifically to substitute net endogenous base (alkali, bicarbonate) production (NEBP) for net endogenous non-carbonic acid production (NEAP), and were not designed specifically to induce a low-grade degree of metabolic alkalosis. Moreover, the studies did not produce improvements sufficient to motivate clinical adoption of alkali, or a net base load to the body, as a standard therapeutic modality for osteopenia or osteoporosis [31].

Clues inspiring the hypothesis

Our hypothesis evolved out of research in considering the role of the net acid producing effect of the Western diet in the pathogenesis of postmenopausal and age-related osteopenia and osteoporosis [19,26]. Though studies performed by our research group and others often showed promising results in improving bone health by partially or even completely reducing net acid production, the results were not particularly striking.

In one study of men and women over the age of 50 years, Dawson-Hughes et al. [23] administered bicarbonate as either sodium bicarbonate or potassium bicarbonate and found a variable degree of reduction of net acid excretion, with some subjects achieving levels of net base excretion of substantial degree. The authors found that those subjects with the negative net acid excretion rates showed the greatest reduction in the measured marker of bone resorption, N-telopeptide. In the bicarbonate treated group, among tertiles of net acid excretion, they found a linear relationship between the marker of bone resorption and net acid excretion.

A study by Jehle et al. in elderly but not osteoporotic women resulted in slightly negative net endogenous acid production rates by some participants and in those participants the best skeletal responses were observed [24]. Indeed, the authors of that study speculated that "*...it is possible that doses higher than neutralizing doses might be superior to neutralizing doses of alkali...*"

Those speculations of Dawson-Hughes et al. [23] and Jehle et al. [24] accorded with our earlier studies showing that administration of potassium bicarbonate in doses up to 120 milliequivalents per day both decrease markers of bone resorption and increased markers of bone formation [30].

They also accorded with our earlier discussion concerning the potential role of inducing a low-grade metabolic alkalosis in building bone mass [19,26,32]. In our 2007 book chapter [19], we wrote:

"In vitro studies show that metabolic acidosis leads to bone resorption [8,10]. In similar in vitro studies, metabolic alkalosis, by contrast, reduces calcium efflux from bone, and both suppresses osteoclastic bone resorption and stimulates osteoblastic bone formation [27]. Inspection of the data suggests that even minimal alkalosis has those anabolic and anti-resorptive effects. The findings suggest that, in vivo, sustaining a low-grade metabolic alkalosis with dietary base might amplify the anti-osteoporotic effects of simply zeroing out the diet's positive NEAP...Bone mass declines progressively after it peaks in young adulthood, because bone formation lags behind bone resorption. A small increase in the ratio of osteoblastic bone formation to osteoclastic bone resorption, such as might accompany low-grade, potassium-alkali-loading metabolic alkalosis, might tip the scales just enough to equalize the unfavorable formation–resorption coupling and prevent bone mass decline, or tip them enough even to reverse extant osteopenia [30,33]."

In 2005, in discussing the opposing effects of dietary protein and dietary acid load on bone health [32], we wrote in part:

"If a lower dietary net acid load permits greater anabolic effects of protein on bone [34], we might want to consider whether a negative dietary net acid load (i.e., net base-producing diets) might optimize the anabolic effects of dietary protein on bone. The metabolic alkalosis expected with a net base-producing diet itself has an anabolic effect on bone [27], and the metabolic acidosis expected with a net acid-producing diet, in addition to producing negative effects on the body's calcium economy, reduces serum IGF-I concentrations [35]. Therefore, the combination of a net base-producing, alkalosis-producing diet and a high-protein diet might optimize peak bone mass achievement during development and greatly mitigate or eliminate age-related decreases in bone mass. Indeed, from an evolutionary perspective, natural selection may have designed human physiology to best fit a dietary environment of high protein consumption and net base production [36]." The agricultural revolution thwarted achievement of that combination through its introduction of net acid-producing cereal grains as a major food source (see Table 1 in [37] for the impact of cereal grains on net acid production as indexed by renal net acid excretion).

Evaluation of the hypothesis/idea

Introduction

Osteoblasts construct a mineralized proteinaceous matrix in which the chief mineral is the cation, calcium. Approximately 99% of total body calcium resides in the skeleton. That amounts to some 22,000–30,000 mmoles of calcium at the age of peak bone mass. A large fraction of calcium's charge-balancing anionic components in bone consists of bases such as carbonate, phosphate, and hydroxyl ions.

Evidence supporting the hypothesis

Although we could find no explicit statement of hypothesis or assertion in the literature, other than our own, that inducing some degree of metabolic alkalosis with alkali supplements or diet might be required to restore osteoporotic bone to or close to its pre-osteopenic state, and to eliminate fragility fractures, we find many adumbrations of the concept:

- As early as 1968, in the context of prevention of osteoporosis and of mitigating the rate of bone loss, and in the context of evidence of the effects of acid on bone resorption, Wachman and Bernstein [38] suggested that:
  - o "Given an individual with decreased bone mass or one with a potential or long-continued loss of bone-mass, it might be worthwhile to consider decreasing the rate of bone attrition by the use of a diet favouring "alkaline ash"."

An alkaline ash diet would likely be a diet that is net base producing.

Prior evidence that alkalinity stimulates osteoblastic bone formation

Several investigators who found that alkalinity stimulated osteoblastic activity might have been inspired to consider that a net base-producing diet, with its attendant low grade metabolic alkalosis, might be required to restore osteoporotic bone to its pre-osteopenic state:

- In the early 1990s, Jacob Green and coworkers studied, in vitro, cells with the osteoblast phenotype and concluded that:
  - (a) "The process of bone formation depends on an optimal alkaline pH in the extracellular milieu surrounding the osteoblast" [39], and
  - (b) "In the process of bone formation, both the crosslinking of the collagen chains and the subsequent precipitation of hydroxyapatite are pH dependent and require an optimally alkaline pH in the bone formation site" [29].
- In 1994, Warren Ramp and colleagues studied the effects of medium pH on calvariae, tibiae, of osteoblast-like cells from chick embryos. They concluded:
  - "...the results of this study support the concept that acidic conditions in the BIF [bone interstitial fluid] stimulate Ca mobilization and impede mineralization and collagen synthesis, while alkaline conditions have opposite effects on these process [28]."
- In 1996, David Bushinsky presented extensive data in cultured osteoblasts demonstrating that differing degrees of metabolic alkalosis induced by varying bicarbonate concentrations stimulated osteoblastic activity as well as suppressed osteoclastic activity in conjunction with a reduction in flux of calcium from bone [27]. He stopped short of suggesting that bicarbonate-induced metabolic alkalosis might be more efficacious in treating osteoporosis than simply reducing endogenous acid production.
- In 1996, in the same study discussed above, Bushinsky also showed that alkalosis stimulates collagen synthesis directly with increasing pH in subclinical alkalosis [27].
- In 2000, Bollen and co-workers reported that an enzyme critical for mineralization (nucleotide pyrophosphatase/phosphodies terase), like alkaline phosphatase, has a pH optimum in the alkaline range [40,41].
- In 2005 Brandao-Burch and coworkers [42] pointed out that "although the pH of arterial blood is normally ~7.40, and that of venous blood ~7.36, the pH of the extracellular fluid bathing cells is likely to be lower, and subject to complex, dynamic gradients, depending on the metabolic activity of the cells and their distance from the nearest capillary."
  - That implies that to achieve an interstitial fluid pH of 7.40, blood pH would need to be greater than 7.40, that is, in the range of low-grade metabolic alkalosis. That might be particularly the case for osteoblasts mineralizing bone, since in the process as they deposit large amounts of base as hydroxyapatite, they are likely to generate hydrogen ions that make their way to the osteoblast's interstitial fluid compartment. From those considerations one might have surmised that a low-grade metabolic alkalosis as recognized in the blood compartment would provide a more favorable interstitial environment.
- In reviewing the effects of extracellular pH on bone cell function, Arnett [20] speculated in 2008, "Future therapies for treating bone loss disorders could be based on shifting systemic acid–base balance in the alkaline direction using diet (e.g., via fruit and vegetables and calcium salts) or drugs or by targeting H^+-sensing receptors on osteoclasts." Since a change in pH from 7.36 to 7.39 constitutes "shifting systemic acid–base balance in the alkaline direction," it is not clear Arnett was advocating inducing metabolic alkalosis.
- In assessing osteoclast activity in conjunction with the study of biomaterials as bone substitutes, Shen and coworkers [43] in 2012 found that "Osteoblasts, the cells responsible for bone formation, have a complex dependence on their immediate environment: not only does the drug dosage matter, but so does the pH. It is now confirmed that their activity is favoured at a pH value greater than that of normal physiological conditions, i.e., pH > 7.4. The results now indicate an optimum value around pH 8..."
- In 2015, Tabatabai and co-workers [14] studied the relationship between arterialized venous blood and change in bone mineral density over two years. They showed that participants with the lowest plasma bicarbonate concentrations (17.8–24.4 mmoles/L) had the greatest reduction in bone mineral density of four quartiles of bicarbonate concentration, whereas those in the highest quartile (26.0–31.8 mmoles/L) actually showed a slight increase in bone mineral density. They found a significant *p*-value for trend from lowest to highest quartile. They wrote:

  "These findings raise the possibility that even higher plasma bicarbonate concentrations, as would occur with habitual ingestion of net base-producing diets, could have even larger effects, potentially shifting the typical age-related bone mass decline to positive bone mass gain."

- Alkali provides the basic environment to ensure that the anions accompanying calcium in calcium hydroxyapatite (hydroxyl, phosphate, carbonate) are in the basic state needed to generate hydroxyapatite [$Ca_5(PO_4, CO_3)_3(OH)$] and thus restore the base reservoir of the skeleton.
- Alkaline phosphatase, essential for generating hydroxyapatite, has its pH optimum in the alkaline range [44].

Evidence opposing the hypothesis

Although not all studies have demonstrated that reducing net endogenous acid production improves bone health, no studies have addressed the question explicitly whether inducing a chronic degree of metabolic alkalosis with diet or alkali supplementation has either a positive or negative effect on bone health.

It might be argued that inasmuch as metabolic alkalosis is a clinical acid–base disorder, it might be unwise to produce that condition in patients with osteoporosis. However, as we have argued in extensive detail in previous publications, providing a net base load through diet or exogenous alkali (e.g., potassium bicarbonate or citrate) to produce a mild metabolic alkalosis would have no serious adverse effects compared to the clinical forms of metabolic alkalosis associated with potassium depletion, chloride depletion, or extracellular fluid contraction [19,26].

Role of potassium in protein-rich, net base-producing diets

Developing a protein-rich net base-producing diet of average energy content for an adult might be considered challenging. Yet, such a diet might be developed by adding as many net base-producing foods that their net base production exceeds the net acid production originating from catabolism of the protein. For example, a diet consisting predominantly of fruits and vegetables, and sufficient animal-source protein, might be net base-producing (see Tables 1 and 2 in [36]), with protein intakes as high as 2.2 g

per kg per day for a 65 kg adult and net base production rates as high as 200 mmol per day.

Because net base production from individual fruits and vegetables derive from metabolic precursors of bicarbonate [18], those precursors must be negatively charged and therefore charge-balanced by positively charged ions. The most common intracellular such cation is potassium. Hence bicarbonate-precursor-rich fruits and vegetables will also be potassium-rich (see Table 5 in [45]. Therefore, in using a protein-rich net base-producing diet for treatment of osteoporosis one must consider the role of a high potassium intake relative to the intakes of average Americans.

Unfortunately little has been published on the effects of potassium on bone. The fact that potassium has a vasodilator effect in many tissues [46], and that bone is highly vascularized, permits speculation that potassium may have a positive effect on bone by increasing blood flow. Potassium causes vasodilation predominantly through generation of nitric oxide [47]. Nitric oxide promotes bone formation [48–50]. Conceivably, potassium-induced nitric oxide production adds independent of pH to promote bone formation when consuming a protein-rich net base-producing diets.

Predictions of the hypothesis

Given the results of future experimental studies establishing the appropriate intervals, and duration of those intervals, for producing a diet, with or without base supplements, that yields net base and produces a low-grade metabolic alkalosis and that is protein-rich, the hypothesis predicts that:

- During growth and development, a greater peak bone mass will be achieved than normally occurs in individuals habitually consuming a net acid-producing Western diet;
- If net-base consumption begins only at age 50–55 years, age-related osteopenia and osteoporosis already extant will cease worsening and, given all other requirements to reverse osteopenia/osteoporosis (e.g., appropriate exercise, adequate vitamin D, essential nutrients, protein rich diet, and pharmacotherapy when indicated.), will rapidly reverse to the extent that the risk of fragility fractures becomes negligible;
- Attendant to the improvement in bone loss will be a corresponding improvement in bone microarchitecture, given the net-base producing diet is protein-rich, adequate vitamin D is provided along with an appropriate exercise regimen;
- Given all other requirements to reverse osteopenia/osteoporosis (e.g., appropriate exercise, adequate vitamin D, essential nutrients, protein rich diet, etc.), in postmenopausal and age related osteopenia or osteoporosis, bone mass will be restored to or nearly to its pre-osteopenic state with or without concurrent anti-osteoporotic pharmacologic therapy;
- When technology advances to the point that pH can be measured non-invasively in living remodeling bone sites, the pH of the matrix fluid compartments will approximate pH = 8;
- Calculated values of net endogenous base production (NEBP) will underestimate the measured values of net base excretion owing to titration of a portion of NEBP by hydrogen ion released into systemic extracellular fluid compartment by osteoblasts and their matrix vessels in the generation of base (bicarbonate) during the process of bone formation.
- The mild and subclinical alkalosis that accompanies consuming a net base-producing diet will increase matrix synthesis, in part by increasing collagen synthesis.

Those predictions are based on the premise that a net base input to the body is *required* to restore osteopenic or osteoporotic bone to or nearly to its pre-osteopenic state, and eliminate the risk of fragility fractures, not that it is *sufficient* to do so. Hence, testing the hypothesis would require that the bone formation process have access to all of the substances necessary for producing normal bone matrix and mineral.

Potential synergism of net base input and pharmacologic anti-osteoporotic treatment

Because the current anti-resorptive agents tend to reduce bone formation, addition of a net base input to the systemic circulation, with its stimulation of osteoblastic matrix and mineral anabolic effect, might improve the efficacy of the anti-resorptive agent.

Likewise, net base input might improve the efficacy of current anabolic pharmacologic agents. For example, the anti-sclerostin agent, romosozumab, at least temporarily increases bone formation markers while persistently reducing bone resorption markers, and leads to impressive increases in bone mineral density in women with low bone mass [51]. If the temporary reduction in bone formation markers indicates a corresponding reduction in actual bone formation, even more impressive improvements in bone mineral density might develop with the addition of net base input.

Conclusion

We hypothesized that, in patients with age-related osteopenia and osteoporosis, optimal treatment to approach full restoration of the skeleton and reduce incident fragility fractures to negligible rates requires induction of a mild metabolic alkalosis through consumption of a net base-producing diet that, like a hunter-gatherer diet, is also protein-rich. The intervals and interval-durations of consuming the net base-producing diet are not specified and would require experimental determination. We emphasized that the periods of alkalosis are necessary but not sufficient to reach the stated goal. The necessity arises in part from the need to supply base in excess of acid to replenish the enormous base reservoir of the skeleton inherent in its mineral component, the alkaline salt, calcium hydroxyapatite. In evaluating the hypothesis we learned from published ex vivo studies that alkalosis stimulates bone formation and suppresses bone resorption, that it stimulates the synthesis of the predominant protein of bone matrix, collagen, and that it provides a favorable environment for mineralization. We found clinical studies that the improvements in bone loss observed with reduction of the diet's net acid load by alkali supplementation continue further in the fraction of participants in whom the alkali administered happened to produce a net base load. The hypothesis offers numerous testable predictions that if confirmed would provide it supplemental support.

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None.

Conflict of interests

None.

References

[1] Burr DB, Allen MR. Basic and applied bone biology. Amsterdam: Elsevier/Academic Press; 2013.
[2] Marcus R, Feldman D, Dempster DW, et al. Osteoporosis. Amsterdam: Elsevier/Academic Press; 2013.
[3] Dawson-Hughes B, Fuleihan GE, Clark P. Bone care for the postmenopausal woman. In: International osteoporosis foundation.

[4] Higdon J, Drake VJ. Calcium. Oregon State University: Linus Pauling Institute; 2010.
[5] Alpern RJ. Trade-offs in the adaptation to acidosis. Kidney Int 1995;47:1205–15.
[6] Alpern RJ, Sakhaee S. The clinical spectrum of chronic metabolic acidosis: homeostatic mechanisms produce significant morbidity. Am J Kidney Dis 1997;29:291–302.
[7] Heaney RP. Long-latency deficiency disease: insights from calcium and vitamin D. Am J Clin Nutr 2003;78:912–9.
[8] Bushinsky DA. Acidosis and bone. Miner Electrolyte Metab 1994;20:40–52.
[9] Bushinsky DA. Acid–base imbalance and the skeleton. Eur J Nutr 2001;40:238–44.
[10] Bushinsky DA, Frick KK. The effects of acid on bone. Curr Opin Nephrol Hypertens 2000;9:369–79.
[11] Lemann Jr J, Bushinsky DA, Hamm LL. Bone buffering of acid and base in humans. Am J Physiol Renal Physiol 2003;285:F811–32.
[12] Lemann Jr J, Litzow JR, Lennon EJ. The effects of chronic acid loads in normal man: further evidence for the participation of bone mineral in the defense against chronic metabolic acidosis. J Clin Invest 1966;45:1608–14.
[13] Green J, Kleeman CR. The role of bone in the regulation of systemic acid–base balance. Contrib Nephrol 1991;91:61–76.
[14] Tabatabai L, Cummings S, Tylavsky F, Bauer D, Cauley J, Kritchevsky S, et al. Arterialized venous bicarbonate is associated with lower bone mineral density and an increased rate of bone loss in older men and women. J Clin Endocrinol Metab 2015;100(4):1343–9.
[15] Sellmeyer DE, Stone KL, Sebastian A, Cummings SR. A high ratio of dietary animal to vegetable protein increases the rate of bone loss and the risk of fracture in postmenopausal women. Am J Clin Nutr 2001;73:118–22.
[16] Frassetto L, Morris Jr RC, Sebastian A. Effect of age on blood acid–base composition in adult humans: role of age-related renal functional decline. Am J Physiol 1996;271:1114–22.
[17] Kurtz I, Maher T, Hulter HN, et al. Effect of diet on plasma acid–base composition in normal humans. Kidney Int 1983;24:670–80.
[18] Kleinman JG, Lemann J. Acid production. In: Maxwell MH, Kleeman CR, Narins RG, editors. Clinical disorders of fluid and electrolyte metabolism. New York: McGraw Hill; 1987. p. 159–73.
[19] Sebastian A, Frassetto LA, Morris Jr RC. The acid–base effects of the contemporary Western diet: an evolutionary perspective. In: Alpern RJ, Hebert SC, editors. The kidney: physiology and pathophysiology. Elsevier; 2007. p. 1621–44.
[20] Arnett TR. Extracellular pH regulates bone cell function. J Nutr 2008;138:415S–8S.
[21] Williams LR, Leggett RW. Reference values for resting blood flow to organs of man. Clin Phys Physiol Meas 1989;10:187–217.
[22] Jajoo R, Song L, Rasmussen H, et al. Dietary acid–base balance, bone resorption, and calcium excretion. J Am Coll Nutr 2006;25:224–30.
[23] Dawson-Hughes B, Harris SS, Palermo NJ, et al. Treatment with potassium bicarbonate lowers calcium excretion and bone resorption in older men and women. J Clin Endocrinol Metab 2009;94:96–102.
[24] Jehle S, Hulter HN, Krapf R. 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;98:207–17.
[25] Moseley K, Weaver C, Appel L, et al. Potassium citrate supplementation results in sustained improvement in calcium balance in older men and women. J Bone Miner Res 2012;2013(28):497–504.
[26] Sebastian A, Frassetto LA, Merriam RL, et al. An evolutionary perspective on the acid–base effects of diet. In: Gennari FJ, Adrogue HJ, Galla JH, Madias NE, editors. Acid–base disorders and their treatment. Boca Raton: Taylor & Francis Group; 2005 [chapter 8].
[27] Bushinsky DA. Metabolic alkalosis decreases bone calcium efflux by suppressing osteoclasts and stimulating osteoblasts. Am J Physiol 1996;271:F216–22.
[28] Ramp WK, Lenz LG, Kaysinger KK. Medium pH modulates matrix, mineral, and energy metabolism in cultured chick bones and osteoblast-like cells. Bone Miner 1994;24:59–73.
[29] Green J, Kleeman CR. Role of calcium and cAMP messenger systems in intracellular pH regulation of osteoblastic cells. Am J Physiol 1992;262:C111–121.
[30] Sebastian A, Harris ST, Ottaway JH, et al. Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. N Engl J Med 1994;330:1776–81.
[31] National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis, 2014.
[32] Sebastian A. Dietary protein content and the diet's net acid load: opposing effects on bone health. Am J Clin Nutr 2005;82:921–2.
[33] Marangella M, Di Stefano M, Casalis S, et al. Effects of potassium citrate supplementation on bone metabolism. Calcif Tissue Int 2004;74:330–5.
[34] Alexy U, Remer T, Manz F, et al. Long-term protein intake and dietary potential renal acid load are associated with bone modeling and remodeling at the proximal radius in healthy children. Am J Clin Nutr 2005;82:1107–14.
[35] Brungger M, Hulter HN, Krapf R. Effect of chronic metabolic acidosis on the growth hormone/IGF-1 endocrine axis: new cause of growth hormone insensitivity in humans. Kidney Int 1997;51:216–21.
[36] Sebastian A, Frassetto LA, Sellmeyer DE, et al. Estimation of the net acid load of the diet of ancestral preagricultural *Homo sapiens* and their hominid ancestors. Am J Clin Nutr 2002;76:1308–16.
[37] Dawson-Hughes B, Harris SS, Palermo NJ, et al. Potassium bicarbonate supplementation lowers bone turnover and calcium excretion in older men and women: a randomized dose-finding trial. J Bone Miner Res 2015;30:2103–11.
[38] Wachman A, Bernstein DS. Diet and osteoporosis. Lancet 1968;1:958–9.
[39] Green J. Cytosolic pH regulation in osteoblasts. Miner Electrolyte Metab 1994;20:16–30.
[40] Bollen M, Gijsbers R, Ceulemans H, et al. Nucleotide pyrophosphatases/phosphodiesterases on the move. Crit Rev Biochem Mol Biol 2000;35:393–432.
[41] Simao AM, Bolean M, Hoylaerts MF, et al. Effects of pH on the production of phosphate and pyrophosphate by matrix vesicles' biomimetics. Calcif Tissue Int 2013;93:222–32.
[42] Brandao-Burch A, Utting JC, Orriss IR, Arnett TR. Acidosis inhibits bone formation by osteoblasts in vitro by preventing mineralization. Calcif Tissue Int 2005;77:167–74.
[43] Shen Y, Liu W, Wen C, et al. Bone regeneration: importance of local pH-strontium-doped borosilicate scaffold. J Mater Chem 2012;22:8662–70.
[44] Crofton PM. Biochemistry of alkaline phosphatase isoenzymes. Crit Rev Clin Lab Sci 1982;16:161–94.
[45] Cordain L, Eaton SB, Sebastian A, et al. Origins and evolution of the Western diet: health implications for the 21st century. Am J Clin Nutr 2005;81:341–54.
[46] Haddy FJ, Vanhoutte PM, Feletou M. Role of potassium in regulating blood flow and blood pressure. Am J Physiol Regul Integr Comp Physiol 2006;290:R546–52.
[47] Oberleithner H, Callies C, Kusche-Vihrog K, et al. Potassium softens vascular endothelium and increases nitric oxide release. Proc Natl Acad Sci U S A 2009;106:2829–34.
[48] Turner CH, Owan I, Jacob DS, et al. Effects of nitric oxide synthase inhibitors on bone formation in rats. Bone 1997;21:487–90.
[49] Fox SW, Chambers TJ, Chow JW. Nitric oxide is an early mediator of the increase in bone formation by mechanical stimulation. Am J Physiol 1996;270:E955–960.
[50] van't Hof RJ, Ralston SH. Nitric oxide and bone. Immunology 2001;103:255–61.
[51] McClung MR, Grauer A. Romosozumab in postmenopausal women with osteopenia. N Engl J Med 2014;370:1664–5.