Prevention and treatment of osteoporosis: a missing factor for full efficacy in restoring the skeleton and eliminating the risk of fragility fractures

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ABSTRACT

This article reviews an hypothesis we put forward in 2005,[1, 2] and refined in 2007,[3] 2015,[4] and 2016.[5] We hypothesized that to fully restore osteoporotic bone to its pre-osteopenic state, and eliminate the risk of osteoporotic fragility fractures, requires replenishing the base (alkali) reservoir of the skeleton by providing a net base load to the body, preferably by having the patients consume a net base-producing, subclinical metabolic alkalosis-producing, protein-rich diet.

INTRODUCTION

If you had a currently non-existent imaging device that could resolve from Earth's orbit individual human beings, and could locate individuals in the act of sustaining an osteoporotic skeletal fracture, whether the individuals were indoors or outdoors, you would find persons sustaining osteoporotic skeletal fractures every three seconds on average.6 That amounts to 8.9 million osteoporotic fractures annually.6 The most common form of osteoporosis is age-related osteoporosis in women, ranging from 10% of women afflicted at age 60 to 67% of women afflicted at age 90.6 Those statistics reveal that effective prevention and treatment of age-related osteoporosis has not yet been achieved. A large variety of drugs are available for treatment of age-related osteoporosis none of which are capable of achieving anything near 90% efficacy and most achieve less than 40% efficacy in reducing the risk of fracture even with good patient compliance.6

What are we missing?

Perhaps we have failed to look closely enough at the fundamentals of skeletal anatomy and physiology. What is bone fundamentally? Fundamentally it consists of protein and alkalinizing mineral salts of calcium, phosphorus, carbonate, and hydroxyl ions, the latter a variant of hydroxyapatite.[7, 8] Protein forms the matrix and the mineral salts of calcium, phosphorus, carbonate, and hydroxyl ions crystalize between cross-linking proteins of the matrix, thereby stiffening and strengthening the structure. Because the cross-linking proteins of the matrix are basic proteins and the mineral salts are alkalinizing, the skeleton constitutes an enormous reservoir of base (mono and dibasic phosphate, bicarbonate and carbonate, hydroxyl ions, and base-producing proteins). Therefore, large amounts of base had to have been available for the formation and the development of the skeleton. It would seem from those facts that the development of age-related osteoporotic bone could not be fully restored to healthy bone without fully replenishing the base reservoir of the skeleton.

Is that what we are missing in the treatment of osteoporosis, viz., failure to replace the lost base component of the skeleton's enormous base reservoir following the loss of bone mass characteristic of osteoporosis? If so, how could we achieve that replacement? First, we would need to know where the base comes from when non-osteoporotic bone is formed normally.

Obviously it must come proximally from osteoblastic activity, the bone formation element of the bone modeling and remodeling process during growth and development and maintenance of the skeleton. Activated osteoblasts have an epithelioid character consisting of an apical and a basolateral membrane. The apical membrane abuts the matrix and secretes both the matrix proteins and the alkalinizing minerals. The base necessary for maintaining the mineral salt of calcium in their basic form is generated in part from carbon dioxide hydration to carbonic acid, the latter of which dissociates to hydrogen ions and bicarbonate ions. The hydrogen ions are prevented from accumulating in the osteoblast by secretion

into the bone interstitial space at the basolateral membrane. Clearly, during bone formation, the hydrogen ions secreted into the interstitial space would require neutralization by extracellular base in order to prevent the development of progressive intracellular and extracellular acidosis and to prevent accumulation of hydrogen ions in the osteoblast. Neutralizing the hydrogen ions in the interstitial fluid facilitates bicarbonate generation within the osteoblast.

HYPOTHESIS

We therefore hypothesized that to fully restore osteoporotic bone to its pre-osteopenic state requires producing a low grade subclinical state of metabolic alkalosis by supplying a dietary net base load to the body preferably in conjunction with one that is protein-rich.[1, 3-5] The hypothesis did not specify that such treatment is sufficient to fully restore osteoporotic bone to its pre-osteopenic state, rather it specifies that such treatment is required to do so. We based our hypothesis, in part, 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 focused on the need to provide the osteoblast not only with adequate calcium, phosphorus, and amino acids (the latter 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. Alkali is also required for normal bone matrix formation, as it (a) stimulates osteoblasts to produce the predominant protein component of bone matrix, collagen,[9, 10] (b) contributes to the formation of matrix collagen cross-linking,[11] which are Schiff's bases that require alkalinity for cross-linking stability, and (c) provides an environment favorable to mineralization.

HISTORICAL BACKGROUND

It seemed reasonable to consider that if reducing net endogenous acid production (NEAP) tended to improve bone mineral density and ameliorate negative calcium and phosphorus balances in older women, further reductions in net endogenous acid production into the negative range might further improve the healing of osteoporotic bone. Such further reductions in NEAP, leading to positive net endogenous base production (NEBP), might be achieved by administering net base producing diets or by administering supplements of alkali.

In 2005, we discussed an article that considered the opposing effects of dietary protein and dietary acid load on bone health.[1] We wrote in part:

"If a lower dietary net acid load permits greater anabolic effects of protein on bone,[12] 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,[9] 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-1 concentrations.[13] IGF-1 is important for bone growth and development as well as for maintenance.

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.[14]„

The agricultural revolution thwarted achievement of that combination through its introduction of net acid-producing cereal grains as a major food source (see[15] for the impact of cereal grains on net acid production as indexed by renal net acid excretion).

In our 2007 book chapter,[3] we wrote:

"In vitro studies show that metabolic acidosis leads to bone resorption.[16, 17] In similar in vitro studies, metabolic alkalosis, by contrast, reduces calcium efflux from bone, and both suppresses osteoclastic bone resorption and stimulates osteoblastic bone for formation.[9] 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.[18, 19]„

EVIDENCE CONSISTENT WITH THE HYPOTHESIS

We could find no statement of hypothesis or assertion in the literature that inducing metabolic alkalosis with alkali supplements or diet is required to restore osteoporotic bone nearly to its pre-osteopenic state, and to eliminate fragility fractures. We did find many forerunners of the concept:

A theoretical argument

As early as 1968, Wachman and Bernstein[20] suggested that:

"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'."

In vitro studies

In the early 1990s, Jacob Green and coworkers concluded from in vitro studies that:

(a) "The process of bone formation depends on an optimal alkaline pH in the extracellular milieu surrounding the osteoblast,[21]" 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.[11]"

In 1994, Warren Ramp and colleagues concluded from in vitro studies 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.[10]"

In 1996, David Bushinsky found that metabolic alkalosis stimulated osteoblastic activity as well as suppressed osteoclastic activity in conjunction with a reduction in flux of calcium from bone.[9] He also reported that mild alkalosis simulated the synthesis of collagen, the major component of matrix protein.

In assessing osteoclast activity in conjunction with the study of biomaterials as bone substitutes, Shen and coworkers[22] in 2012 reported 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. . ."

Clinical observations

In men and women over the age of 50 years, Dawson-Hughes et al.[23] administered 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—i.e., net base delivery to the body-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]. The authors speculated that "*...it is possible that doses higher than*

neutralizing doses might be superior to neutralizing doses of alkali..." The study has not been replicated by other investigators.

In 2015, Tabatabai and co-workers[4] 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*." The study has not been replicated by other investigators.

EVIDENCE CONTRARY TO THE HYPOTHESIS

In 2015, Bess Dawson-Hughes and colleagues compared the effect of low-dose (median 81 mmol/day) with high dose (median 122 mmol/day) bicarbonate supplementation for approximately three months on bone turnover markers and reported that the lower dose significantly reduced bone turnover whereas the higher dose did not significantly reduce bone turnover.[15] The lower dose significantly reduced renal net acid excretion to approximately zero whereas the higher dose reduced renal net acid excretion to a negative value. They concluded: "*KHCO3 has favorable effects on bone turnover and calcium excretion and the lower dose appears to be the more effective dose. Long-term trials to assess the effect of alkali on bone mass and fracture risk are needed.*" The study has not been replicated by other investigators.

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. Such a diet might be developed by adding net base-producing foods in amount that their net base production exceeds the net acid production originating from catabolism of the protein. For example, a diet consisting largely of fruits and vegetables, and sufficient animal-source protein, might be net base-producing[14], with protein intakes as high as 2.2 g/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[25], 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[26]. 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 is known about the effects of potassium on bone. The fact that potassium has a vasodilator effect in many tissues,[27] 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.[28] Nitric oxide promotes bone formation.[29-31] Conceivably, potassium-induced nitric oxide production, independently of pH, promotes bone formation when consuming a protein-rich net base-producing diets.

PREDICTIONS OF THE HYPOTHESIS

- Assuming future experimental studies establish the appropriate periods of time, and duration of those periods, for producing a net base-producing diet and a low-grade metabolic alkalosis and that is protein-rich, the hypothesis predicts: During growth and development, peak bone mass will increase to greater levels than normally occurs in individuals habitually consuming a net acid-producing Western diet;

- When net-base consumption is begun only at or after age 50–55 years, extant age-related osteopenia and osteoporosis will not get worse 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.) are met, osteopenia/osteoporosis will rapidly reverse to the extent that the risk of fragility fractures becomes negligible;

- The improvement in bone loss will be accompanied by an 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 technological advances enable measurements of pH non-invasively at 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. The underestimation is due 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 collagen synthesis, hence will increase matrix synthesis.
- The above predictions rest on the premise that 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, to test the hypothesis one would need to ensure that all other anti-osteoporotic factors accompany the net base-input to the body.

CONCLUSION

We recognized that the weight of evidence accumulated over some 50 years is consistent with the hypothesis that the net acid-producing Western diet contributes at least in part to the development and progression of age-related osteopenia and osteoporosis. We also recognized that partially or completely neutralizing the Western diet's net acid load to the body, either with diet modification or alkali supplements have failed to produce sufficiently dramatic results that neutralizing the diet's net acid load has not been adopted as recommended standard therapy for age-related osteopenia or osteoporosis. In 2005, our research group began to realize that neutralizing the diet's net acid load might only slow or stop the progression of osteopenia/osteoporosis but not necessarily reverse the long-term damage to the skeleton caused by the diet's net acid load. Accordingly, we hypothesized that, in patients with age-related osteopenia and osteoporosis, optimal treatment to achieve 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. We emphasized that periods of metabolic alkalosis are ***necessary*** but not ***sufficient*** to reach that goal. The necessity arises in part from the need to supply base in excess of acid to replenish the substantial loss of the base reservoir of the skeleton inherent in its mineral component, the alkalinizing salt, calcium hydroxyapatite. We learned from published ex vivo studies that metabolic alkalosis stimulates bone formation and suppresses bone resorption, that it stimulates synthesis of the most abundant protein of bone matrix, collagen, and that it provides a favorable alkaline environment for mineralization. We noted clinical studies showing that the improvements in bone loss observed with reduction of the diet's net acid load by alkali supplementation are amplified in the fraction of participants in whom the alkali administered happened to produce a net base load. The hypothesis offers numerous testable predictions.

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