Aging, metabolic acidosis and renal failure: Interactive accelerating processes

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ABSTRACT

In this article, we hypothesize that eating a low acid (and particularly a low phosphate) diet and/or supplementing the diet with base precursors such as bicarbonate would have a number of helpful effects on aging, by:

1) slowing progressive damage to the kidneys, which would help preserve the kidneys ability to excrete acid and minimize systemic acidosis;
2) avoiding the downregulation of klotho, a membrane and soluble factor associated with aging that decreases with constant high dietary phosphate intake and FGF-23 production; and.
3) potentially improving telomerase activity to help maintain telomere length, another factor associated with longer lifespan.

Although the present data is mainly from studies in invertebrate and small animal models, extrapolation of these results, as well as some associated results in human studies, suggests that low acid diets, or neutralization of the low grade metabolic acidosis seen in aging human subjects would possibly allow us to live longer and remain healthier.

Introduction

In many people with increasing age, renal function declines. And with declining renal function, the kidneys ability to excrete excess metabolic acids (such as phosphates, sulfates, chlorides and organic acids) also decreases.

However, it has recently been demonstrated that high acid levels themselves cause the kidneys to fail more quickly. Bicarbonate supplementation has been shown to increase the interval of time before dialysis needs to be initiated[1]. As such, many nephrologists now give bicarbonate supplements to subjects with low levels of kidney function and low serum bicarbonate levels.

One of the sources of metabolic acids is the diet. Diets high in phosphate have been shown to raise FGF-23 production, and FGF-23 lowers both 1,25 vitamin D (1,25VD) and klotho levels. Klotho is an important factor in increasing renal tubular excretion of phosphate, helping to maintain phosphate homeostasis.

But klotho has another interesting property; rats and mice that overexpress the klotho gene live 20–30% longer than wild type animals, while those that are klotho knockouts die rapidly of organ failure similar to rapid aging, including more rapid damage to the kidneys. In animals that are klotho deficient, treatment with bicarbonate lets them live longer.

Another factor associated with aging are telomeres; TTAGGG tandem repeats at the ends of the chromosomes that help control DNA replication. Longer lifespans are associated with longer telomeres and increased activity of the enzyme telomerase, which adds the TTAGGG units to the chromosomes. Diets high in metabolic acids such as phosphate are associated with both lower GFR and shorter telomere length. Diets with low levels of metabolic acids are associated with longer telomere length.

Hypothesis/theory

Thus, we hypothesize that eating a low acid (and particularly a low phosphate) diet and/or supplementing the diet with base precursors such as bicarbonate which would slow progressive damage to the kidneys which would help preserve the kidneys ability to excrete acid and minimize systemic acidosis. This in turn would 1) avoid the downregulation of klotho that occurs with constant high dietary phosphate intake and FGF-23 production, and 2) potentially improve telomerase activity to help maintain telomere length. And possibly allow such patients to live longer and remain healthier?

Evaluation of the hypothesis

Renal function and aging

In general, aging is associated with renal function decline, usually reported as about one mL/min/year. Many cellular and molecular
events are common to both aging and renal failure [2] (see Table 1).

| Cellular and molecular events common to both aging and uremia. |
|---------------------------------|-----------------|
| Aging                            | Uremia          |
| TGF-β↑                           | TGF-β↑          |
| Apoptosis↑ (muscle)              | Apoptosis↑      |
| Senescence↑                      | Senescence↑     |
| Telomere shortening↑             | Telomere shortening↑ |
| Klotho↓                          | Klotho↓         |
| Mitochondrial dysfunction↑       | Mitochondrial dysfunction↑ |
| Low grade metabolic acidosis↑    | Metabolic acidosis↑ |

Note: Adapted from White et al. [2].

Dietary acids and bases, and acid-base balance

All foods contain the above-mentioned diet acid precursors [14]. Phosphates and organic acids are common intracellular compounds. Only some foods, notably fruits and vegetables, contain organic anion salts metabolizable to base (e.g., bicarbonate) [15]. Diets low in fruits and vegetables will quantitatively add greater amounts of acid to the body, which needs to be buffered, neutralized and excreted to maintain systemic pH. Kurtz et al. [16] demonstrated more than 30 years ago that ingestion of more than approximately 1 milliequivalent/kg body weight will lead to positive acid balance in healthy humans with normal renal function.

Phosphate regulation and klotho

Phosphates are mainly intracellular ions, and therefore present in nearly all foods. Phosphate is a metabolic acid whose dietary restriction has been shown to improve survival in animals with renal disease [17]. Phosphate regulation is controlled by fibroblast growth factor (FGF) 23. FGF23 production in bone is increased by 1,25Vitamin D, PTH and hyperphosphatemia (or perhaps Ca-PO4 double product). FGF23 acts in the kidneys, and downregulates active VD and Klotho in both the kidney and the parathyroid gland. FGF23 works via the fibroblast growth factor receptor (FGFR). The FGFR forms a complex with membrane klotho, found mainly in the DCT kidney, and acts as a coreceptor for FGF23 [18].

In the kidney, the FGF23/klotho/FGFR complex has a number of functions. This includes suppressing the production of CYP27B1 – which makes 1-alpha hydroxylase – and inducing CYP24A1 – which makes 24,25 hydroxylase that metabolizes VD. This combination results in decreased production of active 1,25 VD. Active vitamin D is a necessary factor in the production of klotho [19].

Membrane klotho is subject to ectodomain shedding by α- and β-secretases to release secreted klotho. Secreted klotho increases urinary PO4 excretion by decreasing the translocation of the NaPi-2a cotransporters in the proximal tubules, leading to decreased urinary uptake of phosphate and improved serum phosphate balance. Klotho is expressed also endogenously in the parathyroid gland, where FGF23 decreases PTH secretion, further suppressing 1,25 VD production by the kidney [19,20].

Ongoing high dietary phosphate intake, such as found in typical western diets, leads to a vicious cycle of ongoing high fibroblast growth factor 23 (FGF23) production, lower 1,25 VD and therefore lower klotho. Increases in serum FGF23 and serum PTH levels and decreases in serum vitamin D and urine klotho levels precede hyperphosphatemia during CKD progression from stage 1 to stage 5 [19].

Klotho, renal function and aging

Membrane klotho is a single pass transmembrane protein expressed primarily in the kidney [20]. The klotho gene appears to be an aging-suppression gene; mutations or deletion of the klotho gene leads to a syndrome resembling rapid aging [21], and overexpression increases lifespan in experimental animals by 20–30% [22]. Diets high in phosphate lead to increases in FGF23 and subsequent decreases in klotho expression.

Mice that are genetically klotho deficient (−/−) develop ectopic renal calcifications and rising serum creatinine [23]. As renal function declines, klotho expression declines even more [24]. In klotho deficient animals, low phosphate diets, low vitamin D diets and treatment with bicarbonate have been shown to help mitigate the effects on renal function and aging [25,26].

Telomeres and aging

Telomeres are DNA-protein complexes at the ends of human chromosomes that prevent the chromosomes from fusing with each other or from being recognized as a break by DNA repair enzymes. Telomere length is a biomarker of cellular aging, and telomere length shortens with normal aging, stress, infections, and chronic diseases [27].

Telomeres and diet acid loads

While there is no literature data on the effects of metabolic acidosis on telomere length, there are studies on the role of dietary effects and renal function on telomere length; those results are contradictory. In humans, high dietary phosphate intake has been linked epidemiologically with decreased telomere length [28]. Some studies suggest a Mediterranean or “vegetable-rich” diet is related to longer telomere length [29,30]. In subjects with CKD, telomere length has been associated with smoking, diabetes, and heart failure, all of which are associated with renal disease [31,32].

Some studies/meta-analyses demonstrated no effect of diet on telomere length [33,34]. In the German CKD study, subjects with moderate CKD of longer duration had longer telomeres than subjects with CKD of shorter duration [35]. But in a study of healthy Chinese over 3 years, telomere length was associated only with age, not with renal function [36].
Diet acid restriction and aging

So what data suggests that dietary acid restriction could potentially slow the aging process? In rats and mice, dietary methionine restriction of 65–80% led to an increase in longevity from 5 to 44% [37]. In rats with a mutation in the renal sodium-bicarbonate exchange transporter, treatment with bicarbonate slowed decline in renal function and improved survival rates [38], Ornish et al. [39] demonstrated improved telomere length and telomerase function in men with prostate cancer treated with a healthy diet and lifestyle changes. The Ornish diet is high in fruits and vegetables and therefore relatively low in acid.

Conclusions/predictions

While there is no definitive data that demonstrates that we would live longer if we maintained a low systemic acid load throughout our lifetime, there are clear hypotheses that can be tested. For example, klotho levels and telomere length/telomerase activity could be measured in samples from some of the long term bicarbonate trials in CKD, or in some of the CKD cohort studies such as CRIC (Chronic Renal Insufficiency Cohort). Studies could also be done in larger mammals with shorter life spans than humans (e.g., dogs or pigs). There will likely be other interventions that we will discover to help slow the aging process; lowering systemic acid load is something we can do right now. And, if lowering the systemic acid load has such positive outcomes, we should consider the possibility that inducing a moderate systemic base load would be even more ameliorative.

Grant support

None.

Conflicts of interest

The authors declare they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.02.015.

References