Age-related Disease: A Revolution is Coming, Part 2—Dietary Acid Load, Hypertension, and Cardiovascular Disease

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Abstract

We are starting to develop the analytical tools to examine damage to our DNA and screen for the presence of clonal hematopoiesis of indeterminate potential. This type of technology will soon support the personalization of approaches to both the prevention and treatment of age-related diseases, which have historically been characterized as beyond our control. We are at the start of an era that will one day be looked upon as the age of precision personalized lifestyle health care. This article is the second in a series in which I will be examining new tools and research that I believe is paving the path forward and leading to exciting times ahead.

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In 1978, I was a biochemistry professor and I became very interested in a relatively new clinical test called the ionized serum calcium test, which was used to assess parathyroid function, as well as vitamin D and calcium status.[1] At that time, it had become well understood among clinical researchers that measuring "free calcium" in serum (as opposed to total calcium) was a sensitive and useful tool for assessing the endocrine control of calcium physiology that is dependent on parathyroid function and vitamin D metabolism and activity. The ionized serum calcium test was recognized as having improved diagnostic value for the early assessment of parathyroid function and its relationship to "normocalcemic" secondary hyperparathyroidism. Calcium physiology influences a number of factors, including bone mineral metabolism, vascular biology, and neurological function, and "free calcium" is related to, but not the same as, total serum calcium due to changes in both the albumin and pH levels in the serum. These 2 factors—along with parathyroid hormone level and its relationship to vitamin D status—affect protein-bound (versus unbound) serum calcium levels.[2] It is well known that insufficiency or improper activity of the vitamin D-derived hormone calcitriol, as well as suboptimal calcium dietary intake or malabsorption, can result in secondary hyperparathyroidism.[3]

My interest in this area was further fueled in 1980 when, by chance, I met 2 principal leaders in this field: Dr Mildred Seelig and Dr David McCarron. Dr Seelig and I shared the podium at a medical meeting that year, and this is where I became aware of her important pioneering work on the influence of magnesium in cardiovascular function and hypertension.[4] Dr Seelig's research demonstrated that the physiological stress response was amplified when magnesium status was compromised and that stress itself resulted in the urinary loss of magnesium.[5,6] The same meeting introduced me to Dr McCarron's work on the influence of dietary calcium on blood pressure.[7] As research continued, numerous investigators subsequently demonstrated that ionized serum calcium and ionized (or "free") serum magnesium and intracellular magnesium levels are sensitive indicators of the influence of these minerals in vascular function and blood pressure.[8,9,10,11] It has also now been shown that compromised magnesium status is independently associated with greater odds of decline in kidney function with age.[12]

In 2003, Robert P. Heaney, MD, a clinician I had admired and followed for many years, received the prestigious EV McCollum Award from the American Society for Clinical Nutrition. In his acceptance address, Dr Heaney discussed his findings that suboptimal status of calcium and/or vitamin D can result in long-latency deficiency diseases, which are conditions in which many years—and possibly decades—of insufficiency can pass before the onset of pathophysiology or diagnosis of disease takes place.[13] The adverse functional effects of chronic secondary hyperparathyroidism, which can include increased bone loss, hypertension, and risk to cardiovascular disease, might not be recognized early in the absence of knowing a person's ionized serum calcium level. As Heaney pointed out: "Because the intakes required to prevent many of the long-latency disorders are higher than those required to prevent the respective index diseases, recommendations based solely on preventing the index diseases are no longer biologically defensible."

Today, it is recognized that many variables, both genetic and lifestyle related, can influence parathyroid function and calcium metabolism, including vitamin D conversion to calcitriol and vitamin D receptor polymorphisms.[14]

Diet, Urinary Acid-Base Excretion, and Hypertension

Many years have now passed since my initial interest in ionized serum calcium as a functional assessment test for the relationship of calcium to parathyroid function and vascular function took form, and there has been considerable progress made in understanding how the divalent calcium and magnesium and monovalent sodium and potassium electrolytes play functional roles in the pathogenesis of hypertension and its influence on cardiovascular and kidney diseases. It is now recognized that the function of these electrolytes on cardiovascular, renal, and neurological function is intimately connected to intracellular and extracellular pH.[15] Findings of lower intracellular pH (ie, acid drift) in the red blood cells of patients with essential hypertension indicate a defect in cellular acid-base regulation in hypertension.[16]

Surrogate markers for a shift in physiology toward lower cellular pH include serum lactate and reduced urinary pH. Dietary acid-alkaline balance is reflected in measurements of urinary pH, and studies indicate that processed diets (high in protein, saturated fats, refined carbohydrate, and fructose; low in plant-based foods) result in an acid shift in cellular pH and a decreased urinary pH.[17,18] Excessive consumption of diets with high acid load is associated with increased blood pressure, reduced kidney function, insulin resistance, and reduced metabolic performance.[19,20] Higher dietary acid load has also been found to be associated with increased incidence of peripheral artery disease and type 2 diabetes.[21,22] In contrast, numerous studies have shown that vegan diets (which have a low acid load) can reduce urinary pH and improve blood pressure, exercise tolerance, and kidney function.[23-25]

As the dietary acid load increases, parathyroid function and its relationship to vitamin D and endocrine regulation of calcium metabolism is affected. In a study of the influence of the processed Western-style diet on calcium metabolism, researchers determined that the dietary acid load was responsible for an alteration in endocrine function that, in turn, had adversely affect markers of bone mineral metabolism. They wrote: "An acidogenic Western diet results in mild metabolic acidosis in association with a state of cortisol excess, altered divalent ion metabolism, and increased bone resorptive indices."[26]

Metabolic effects associated with an elevated dietary acid load are part of a systems biology alteration in endocrine function, not only the parathyroid glands, but also the thyroid, endocrine pancreas, and adrenals. This functional state could be called "metabolic-endocrine stress." Clinical characteristics would include alterations in ionized serum calcium, insulin sensitivity, serum cortisol, and markers of bone loss such as *N*-telopeptide.

Dietary Principles Associated With a Lower Acid Load

What are the important nutrient components of the lower acid load diet and its connection to improved metabolic function? I am often asked about this. There is evidence that a lower intake of processed carbohydrate, fructose, animal protein, and saturated fat reduces the acid load of the diet. Increasing the plant food component of the diet has also been found to reduce the acid load, as does increasing the intake of prebiotic dietary fibers, which can help regulate the composition and function of the microbiome. A high acid load, energy-dense diet has been found to trigger changes in gut microbiota and alter the gut-brain communication, which can result in increased body fat.[27] This effect is due in part to the influence that specific gut microbes have on the expression of the ionized calcium binding adapter molecule 1 in the gut mucosa that contributes to the regulation of inflammatory response of macrophages. This is an interconnected signaling network made up of the gut microbiome, the macrophages of the intestinal immune system, the macrophages resident in the adipocyte fat mass, and the microglia of the brain. This calcium-sensing system represents an important part of the inflammatory signaling process that is communicated across multiple organs and contributes to metabolic-endocrine stress.[28]

One of the more important and unique aspects of a plant food-rich diet is that it is high in potassium and magnesium and low in sodium. A recent clinical intervention trial demonstrated that a low dietary acid load and increased potassium intake resulted in lowered blood pressure.[29] This is a very interesting observation in that it once again demonstrates the important role that mono and divalent minerals associated with dietary acid load have in regulating vascular function.

In 2014, 2 large studies[30,31] were published in the *New England Journal of Medicine* that discussed the monovalent cations sodium and potassium and their relationship with blood pressure and cardiovascular events. The first of these 2 studies is titled "Association of Urinary Sodium and Potassium Excretion with Blood Pressure."[30] This study found that people consuming processed diets high in sodium had increased urinary sodium excretion that was associated with increased blood pressure. The second study is titled "Urinary Sodium and Potassium Excretion, Mortality, and Cardiovascular Events."[31] In this study, sodium intake more than 6 grams per day was associated with increased risk to cardiovascular disease and death versus daily intakes of 3 to 6 grams per day. An important feature of these studies was the recognition that higher urinary potassium to sodium urinary excretion ratio is associated with better health. The only practical way to achieve a higher potassium to sodium urinary excretion ratio is to consume a diet that is higher in plant foods. Based on my research on serum ionized calcium levels (which began in 1978 and continues

today), this is the diet associated with improved parathyroid endocrine and metabolic function.

Investigators have long been exploring the question of how to conveniently measure urinary potassium to sodium excretion. In 2018, the *Journal of the American Medical Association* published an important study that provides valuable insight into this issue; it is titled "Estimated 24-Hour Urinary Sodium and Potassium Excretion in US Adults."[32] This was a study of 827 randomly selected, nonpregnant participants aged 20 to 69 years in the NHANES study group who provided at least one 24-hour urine specimen for analysis in 2014. The result of this study was that the mean daily urinary sodium excretion of this group was 3.60 g. The mean daily urinary potassium excretion was 2.15 g. The recommended adult daily sodium intake is 2.3 g and daily potassium intake is 4.5 g. What does the data from this study indicate? As a nation, people in the United States are consuming, on average, a daily diet that has a ratio of potassium to sodium that is approximately 2:3 rather than 2:1, which is the recommendation according to the US Dietary Guidelines. This represents a significant dietary deviation from what individuals should be eating for good endocrine and metabolic health.

In an editorial that accompanied the 2018 *JAMA* article, 2 authors pointed out that within the United States, consumption of diets that are imbalanced in sodium and potassium has resulted in widespread stressed metabolic function.[33] When considered in the context of potential lifespan and duration of stressed metabolic function, the significance of Dr Robert Heaney's study of "long latency nutritional diseases"—hypertension, coronary heart disease, peripheral artery disease, and type 2 diabetes—becomes all the more apparent.

How can we conveniently evaluate diet quality to see if a person is consuming a high acid load diet? Traditionally, the easiest method to monitor net acid excretion has been to measure the first morning urine pH with pH test strips. Unfortunately, studies indicate this method is not accurate in evaluating the overall quality of the diet relative to the potassium to sodium ratio and its relationship to magnesium and calcium intake.[34] It appears that a more accurate method is to measure the urinary potassium and sodium to creatinine ratios in a morning spot urine sample.[35] From published comparative studies, it is clear that diet diary or food frequency questionnaire data is of low validity in determining dietary sodium and potassium intake and its relationship to dietary acid load.

A clinical trial comparing the endocrine and metabolic effects of the Dietary Approach to Stop Hypertension (DASH) diet versus a fruit and vegetable-enriched diet or a control diet was recently published.[36] The participants had their parathyroid hormone, vitamin D_3, ionized serum calcium, and urinary calcium levels measured along with their blood pressure. The DASH diet and the fruit and vegetable rich diets were lower in sodium and higher in potassium and magnesium than the control diet. Although blood pressure was reduced in the DASH diet group, there was no statistically significant change in ionized serum calcium or parathyroid hormone levels after the 11-week dietary intervention, but a statistically significant reduction in vitamin D_3 (calcitriol) was observed. It may be that the 334 participants in the study group of men and women whose initial systolic blood pressure had to be less than 160 mm and their diastolic pressure from 85 to 90 mm did not represent a large enough study group or their inclusion criteria were too moderate to determine the endocrine effects from the DASH diet. This study leaves open the question of the mechanism by which the DASH diet has a favorable influence on blood pressure.

Taken as a whole, there has been significant progress made over the past 40 years in understanding the endocrine and metabolic effects of a diet that is imbalanced in mono and divalent cations and its relationship to dietary acid load. The value of the morning spot urine analysis of sodium, potassium, and creatinine has emerged to be a potentially useful screening tool as a surrogate marker for determining overall dietary quality and its potential relationship to endocrine function. It is also important to understand how dietary imbalances such as the potassium to sodium ratio can create metabolic and endocrine stress. From the perspective of clinical importance, it appears the role that mono and divalent cations play in endocrine and metabolic stress is an important area of need for clinical evaluation and intervention. Implementation of plant food-based diet approaches is an important therapeutic tool for reducing this important contribution to the prevention and treatment of age-related endocrine and metabolic diseases.

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