Published in final edited form as:

J Bone Miner Res. 2015 June ; 30(6): 967–969. doi:10.1002/jbmr.2526.

Do Nutrients Influence Bone Health? A Commentary on New Findings in the Field

Marian T. Hannan, D.Sc, MPH¹, Kelsey M. Mangano, RD, PhD¹, and Shivani Sahni, PhD¹

¹Institute for Aging Research, Hebrew SeniorLife, Beth Israel Deaconess Medical Center, and Harvard Medical School, Boston MA, USA

Food is always a good topic of conversation and inquiry. Humans require it, the variety of eating patterns spark personal debate, scientific measurement of dietary intakes are fraught with methodical issues, and the often changing (and inconsistent) nutrition messages in the media make for good discussion. The devil is in the detail when it comes to nutrients and the inferences to health beyond food intakes. Indeed, food is often the example when nuances of scientific inference are examined across time periods: “Is dairy good or bad for you?”, “should we consume more or less protein in our diet?” “how much fruit & vegetable is needed?”, or “should salt intake be limited”?

Macronutrients (carbohydrates, proteins and fats) as well as micronutrients (minerals and vitamins) are essential for the human body. Intakes of these nutrients have been the topic of bone investigations and patient questions for many years, especially as related to the occurrence of fractures. In this issue of *Journal of Bone & Mineral Research*, two exciting articles present their findings on first, serum sodium levels, and then, fruit and vegetable intakes, in relation to fracture risk. These topics are highly relevant to clinicians and researchers interested in bone outcomes. Patients are keenly interested in nutrition-related influences upon bone health, both those with positive as well as negative aspects. Examining nutrient intakes in relation to health outcomes is complicated, but can lead to significant risk factor modification as well as influence in food and health decisions, especially in older adults. Defining dietary intakes precisely is a major challenge in both clinical patients and participants of population-based studies as the scientific community continues to search for the long-term effects of dietary intakes. Nutrition studies are common in outcomes of cancer and heart disease, and less so with bone outcomes (with the exception of calcium and vitamin D). Prior to inference of causality, especially for dietary intakes, it is important to first document a significant association with outcomes and across populations.

Current work suggests

Jamal et al.¹ evaluated the relation between hyponatremia (low serum sodium concentration), the most common electrolyte imbalance encountered in clinical practice, and

Corresponding author: Marian T. Hannan, D.Sc, MPH, Institute for Aging Research, Hebrew SeniorLife, Beth Israel Deaconess Medical Center, and Harvard Medical School, 1200 Centre St., Boston, MA 02131, Phone: (617) 971-5366, Fax: (617) 971-5339, hannan@hsl.harvard.edu.

The authors state that they have no conflicts of interest.

subsequent fractures in older men. The Dietary Guidelines for Americans recommend limiting sodium to less than 2,300 mg/day, or 1,500 mg/day for adults aged 51 or older. Hyponatremia is rarely due to poor dietary intake of sodium and typically is managed with fluid restriction or correcting the underlying cause, and very infrequently by increasing salt intake. While it is well appreciated that very low intakes of dietary sodium is rarely the cause of hyponatremia, low intakes may exacerbate low serum sodium concentration. The etiology of hyponatremia is multifaceted, spanning a wide range of diseases, pharmacotherapy and pathophysiological variants each with different treatment modalities². Normal serum sodium levels are between approximately 135–145 mmol/L. Hyponatremia is usually defined as a serum sodium level below 135 mmol/L, with severe levels defined by serum sodium levels <125 mmol/L. Most cases of hyponatremia are chronic and mild (serum sodium 130–134 mmol/L) and is generally considered asymptomatic; however this silent condition is strongly associated with detrimental geriatric outcomes, such as cognitive impairment, abnormal gait patterns, falls, longer hospital stay and increased mortality³. Jamal and colleagues found that hyponatremia doubled the risks of hip fracture, and morphometric spine fracture in older men. Their study is one of only a few in humans to evaluate the risk of fracture. More work is needed to corroborate these results in other at risk populations. Further, it remains unclear whether more severe hyponatremia elevates the risk of fracture in their cohort. It is worth noting that only 1.2% of the cohort of 5,122 men had levels indicating hyponatremia, so markedly fewer would have severe levels. While rat studies have implicated reduced bone macro and microarchitecture in severe hyponatremia, no studies have examined severe levels in older humans as of yet. As the authors point out, the biological link between low serum sodium concentrations and fracture has not been determined. They suggest a possible pathway through increased risk of falls and gait instability; however taking past falls into account did not change the risks in their cohort. Further, it is unknown if correction of hyponatremia would decrease the risk of fracture. It may well be that hyponatremia is a marker of poor health and thus poses a high risk of concomitant illnesses and disorders, including fracture. Although many questions remain regarding the risk of fracture with chronic and acute hyponatremia, this study suggests the need for future studies with multiple measures of serum sodium over follow-up, perhaps with levels of severity, to determine whether targeting hyponatremia itself would have the potential to decrease falls and fractures in older people.

Byberg et al.⁴ investigated whether a dose-response effect was seen between fruit and vegetable intake and subsequent hip fracture in > 40,000 men and >34,000 women. One-third of their study participants met the dietary guidelines for fruit and vegetable intake (5 servings/day), 6% estimated 1 serving per day, 28% reporting between >1 to 3 servings per day and 33% reporting between >3 to 5 servings per day. The authors observed a 54% increased risk of hip fracture in their participants who reported 1 serving a day of fruits and vegetables compared to >3 but less than 5 servings a day. Interestingly, no strong evidence was seen of a dose-response relation. One could infer a threshold effect with intakes below the recommended 5 servings a day imparting greater risk of hip fracture compared to the recommended intakes. The authors note biological mechanisms for a possible effect between fracture risk and intakes of fruits and vegetables, in that higher fruit and vegetable intakes may reduce oxidative stress and decrease chronic inflammation

processes. While declarative empirical evidence at the level of five portions per day remains a bit unclear, it seems clear that the synergistic effects of antioxidants such as vitamin C and carotenoids along with phytochemicals⁵ in this food group are responsible for their potent antioxidant effect in decreasing oxidative stress. Consequently, lower intakes of fruits and vegetables show increased risk of fracture compared to higher levels of intake. Given the wealth of evidence supporting these intakes as part of a healthy diet in the cancer and cardiovascular fields, it certainly makes sense that fruit and vegetable intakes, and indeed a healthy diet, also have positive influences upon bone and muscle health. In addition to antioxidants, fruits and vegetables also provide other important nutrients (potassium, magnesium, folate and vitamin K) that have been linked with better bones. Further, greater fruit and vegetable intake also promotes a diverse microbiota which augments the absorption of other bone-benefiting nutrients (such as calcium and magnesium).

The Byberg article prompts thoughts of how to bolster this complex, inter-relation of nutrients and biological processes to build firm recommendations for patients that are easy to understand. The study of foods as consumed (also known as food patterns or dietary patterns) has not been fully embraced by the bone field as it is difficult to address possible mechanisms of single nutrients. Yet this type of work more directly reflects the 'exposure' of actual intakes that capture interactions across nutrients. Confounding must still be considered, as with most observational studies as well as other study designs, dietary patterns may follow other personal choices. For example, a dietary pattern of consuming a majority of energy from processed foods may be linked with a higher likelihood of unhealthy behaviors, such as smoking and lack of physical activity. Also a dietary pattern of higher fruits and vegetables may be confounded by a higher likelihood of using multivitamin supplements or higher socio-economic status. These factors and others may confound dietary patterns and possible confounders should be considered in studies.

We and others have shown the importance of single nutrients on age-related changes in bone and fracture risk but this approach is limited in that: i) it does not account for dietary quality or nutrient synergy,⁶ ii) it cannot isolate individual effects due to high correlation of nutrients within foods, iii) the effect of a single nutrient may be too small to detect, or a significant association might be found by chance alone due to an increased type I error rate when multiple comparisons are made among a large number of individual nutrients.⁷ Perhaps most importantly, isolating nutrients makes it difficult to translate results into dietary recommendations. Dietary patterns are also an 'exposure' that may be best understood by the public and perhaps more amenable to nutrition policy. The bone field is ignoring a key component and an important messenger by not including dietary patterns more often in our nutrition-related work.

Another area of contemplation prompted by the Byberg article is the importance of studying older adults. While bone health concerns run the lifespan from pediatric to geriatric, one wonders about older persons who are not highlighted by nutrition policy: those at greatest risk of fractures, namely the oldest old, those living in institutionalized settings (nursing homes, assisted living, communal living, group housing for elders) and persons with sarcopenia. These specific populations also tend to have lower intakes of fruits and vegetables. There is a shocking dearth of clinical trials directed towards nutritional

interventions in these populations, and there are just a few directed towards use of nutritional supplements, an intervention that we know does not confer the same benefit as direct consumption of nutrients. Therefore, greater focus should be placed on whole diet interventions specifically in older populations, whose dietary intakes change with age and spawn additional detriments to their overall health. Indeed, future studies may wish to consider a life course approach as major chronic exposures (such as dietary factors) across adult ages or even the lifespan may be powerful actors upon long-term skeletal outcomes or bone health. While hyponatremia is typically a geriatric condition, and while healthy intakes of fruits and vegetables may reflect a lifelong commitment or intermittent intakes, dietary patterns earlier in the life course may prove insightful in terms of biological markers, patterns of behavior, and/or a holistic approach to understanding links to bone health. A life course approach can be helpful to advance our understanding of complex exposures and chronic effects, such as osteoporosis.

Both studies had many strengths. There were large numbers of participants, with sufficient power to examine the research question under scrutiny. The study samples represent community populations of older adults, rather than a report from a clinical sample. The authors also used robust statistical methods with the ability to take the effects of confounders into account.

Yet the puzzle remains

Both of the excellent articles make one ponder how to get our patients and the population to adopt “a healthier lifestyle”. Both articles remark that their findings are in-line with the exposure (whether fruits and vegetables, or not-hyponatremic) being a marker of health or the reference groups being composed of those persons with “a healthier lifestyle”. Both articles attempt to address this issue through sensitivity analyses and consideration of confounders related to health status. Their findings are compelling and convincing, but for the readers of JBMR, who are trained to examine every nuance of reported findings and consider how generalizable research conclusions may be to our patients, further work is indeed needed.

These papers and their findings are a piece of the puzzle that lead us (as consumers of the medical literature) to advocate for a change in the paradigm of how older persons at risk for fracture should be evaluated. While hyponatremia is relatively rare in populations (ranging from 1–10%), it appears to place one at high risk for fracture and may be amendable to treatment (still yet to be investigated directly). Higher fruit and vegetable intakes confer benefit for overall health, and the recommended level appears to meet our skeletal needs but one wonders about our highest risk populations. In science, we have been trained to be conservative in our conclusions and to ‘build the pyramid of evidence’ one brick at a time until the evidence points to the truth and the light. More bricks are needed.

Future directions

Longitudinal studies are needed to clarify the role of single nutrient intakes on the progression of health outcomes across the lifespan. Perhaps more importantly, we need to

examine dietary patterns as a part of a larger causal chain that may be leading to overall poor health (or better health), including bone as one of many outcomes. We also need clinical trials addressing whether acute nutrition intervention can impact bone parameters, as well as research that addresses our most vulnerable populations at the highest risk for fracture.

The public health impact of fracture is large and growing with the aging of many populations. Nutritional influences, whether in the causal pathway, related directly to osteoporosis, or as a result of treatment, become even more essential to describe and investigate. The long-term consequences of fracture alone have a major impact, but in synergy with poor nutrition, whether a marker for poor health or not, the burden is even greater. One anticipates a better understanding of these nutritional components as the bone field encourages these complex investigations involving crucial groups of osteoporotic patients and those at highest risk. Such studies will encourage new ideas and promote a more integrated evaluation of these nutritional and ‘healthy lifestyle’ effects.

These two papers in this issue of JBMR, and indeed the published works in JBMR, are intended to shed light into unknown areas and to spark intellectual curiosity to further more systematic evaluation into the amenable factors that influence osteoporotic fracture outcomes. We look forward to a better understanding of nutritional influences and their synergies in bone health as this area of research comes under greater examination in the years ahead.

Acknowledgments

MTH, KMM, and SS discussed the concepts and wrote the commentary; All authors were responsible for the final content. All authors read and approved the final manuscript.

Source of Funding:

Their research work is funded by NIAMS/NIH R01-AR060145 (MTH), R01-AR060816 (MTH), R03-AR062808 (SS), the American Society of Bone and Mineral Research Junior Faculty Osteoporosis Research Award (SS), unrestricted research grant from Policy Analysis Inc. (MTH & SS), unrestricted research grant from General Mills Bell Institute of Health and Nutrition (SS), and NIA/NIH T32-AG023480 (KMM), and Academy of Nutrition and Dietetics, Healthy Aging DPG Research Award (KMM). The content is solely the responsibility of the authors and does not necessarily represent the official views of any sponsors or agencies.

REFERENCES

1. Jamal SA, Arampatzis S, Litwack Harrison S, Bucur RC, Ensrud K, Orwoll ES, Bauer DC. Hyponatremia and Fractures: Findings from the Osteoporotic Fractures in Men Study. JBMR. 2015
2. Cumming K, Hoyle GE, Hutchison JD, Soiza RL. Prevalence, incidence and etiology of hyponatremia in elderly patients with fragility fractures. PLoS One. 2014; 9:e88272. [PubMed: 24505459]
3. Cumming K, McKenzie S, Hoyle GE, Hutchison JD, Soiza RL. Prognosis of hyponatremia in elderly patients with fragility fractures. Journal Clin Medicine Research. 2015; 7:45–51.
4. Byberg L, Bellavia A, Orsini N, Wolk A, Michaëlsson K. Fruit and vegetable intake and risk of hip fracture: A cohort study of Swedish men and women. JBMR. 2015
5. Liu RH. Health benefits of fruit and vegetables are from additive and synergistic combinations of phytochemicals. Am J Clin Nutr. 2003 Sep; 78(3 Suppl):517S–520S. [PubMed: 12936943]
6. Jacobs DR Jr, Gross MD, Tapsell LC. Food synergy: an operational concept for understanding nutrition. Am J Clin Nutr. 2009 May; 89(5):1543S–1548S. [PubMed: 19279083]

7. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. *Curr Opin Lipidol.* 2002 Feb; 13(1):3–9. [PubMed: 11790957]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript