Not Salt But Sugar As Aetiological In Osteoporosis: A Review

by James J. DiNicolantonio, PharmD, Varshil Mehta, MBBS, Sojib Bin Zaman, MBBS & James H. O'Keefe, MD

The other ubiquitous white crystal, sugar, may lead to osteoporosis by increasing inflammation, hyperinsulinemia, increased renal acid load, reduced calcium intake, and increased urinary calcium excretion.

James J. DiNicolantonio, PharmD, (left), and James H. O'Keefe, MD, (right), MSMA member since 2003, are at Saint Luke's Mid America Heart Institute, Kansas City, Mo. Varshil Mehta, MBBS, is with Mount Sinai Hospital, New York and MGM Medical College, Navi Mumbai, India. Sojib Bin Zaman, MBBS, is with the International Centre of Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh.
Contact: jjdinicol@gmail.com

Abstract

Salt has notoriously been blamed for causing an increase in the urinary excretion of calcium, and thus is a considered a risk factor for osteoporosis. However, the increase in the urinary excretion of calcium with higher sodium intakes can be offset by the increased intestinal absorption of dietary calcium. Thus, the overall calcium balance does not appear to be reduced with a higher sodium intake. However, the other ubiquitous white crystal, sugar, may lead to osteoporosis by increasing inflammation, hyperinsulinemia, increased renal acid load, reduced calcium intake, and increased urinary calcium excretion. Sugar, not salt, is the more likely white crystal to be a risk factor for osteoporosis when overconsumed.

Epidemiology of Osteoporosis

Osteoporosis is considered to be a major concern for the elderly population which is characterized by decreased bone mineral density or mineral content affecting both the measures of bone quantity and quality.[1] Reduction in the bone mass or its architectural disruption often results in an enhanced risk of fragility and fractures.[2]

Osteoporosis-related fractures are known to cause significant morbidity leading to a permanent disability in the elderly population which increases the economic burden on the health care system.[3] Moreover, osteoporosis is not only under-diagnosed but also, under-treated even among those who are at high-risk or who have had previous fractures. Osteoporosis not only leads to a decline in quality of life (QOL) but also the quality-adjusted-life-year (QALY).[4] Therefore, osteoporosis is regarded as an important worldwide public health concern and its prevalence is continuing to escalate, especially in women and the elderly. It is estimated that 200 million people are suffering from the negative consequences of osteoporosis globally.[5]

Approximately one quarter of men and half of women over 50 years of age will have an osteoporosis-related fracture in their lifetime. Indeed, 1.5 million fractures are reported annually due to osteoporosis related causes which includes 0.25 million wrist fractures, 0.3 million hip fractures, more than 0.3 million fractures at other body sites, and 0.7 million vertebral fractures.[6] These fractures are associated with substantial pain, morbidity, and even mortality. Furthermore, a global increase in longevity has lead to a significant rise in the proportion of the population who are at risk for osteoporisis.[7]

While, it is obvious that the burden of hip fractures is increasing globally, the greatest impact is observed in Asia. It is hypothesized that due to the increased number of senior citizens

in Asia, the prevalence of hip fractures will rise to 37% in 2025 which was 26% in 1990.[8] Moreover, almost half of all hip fractures are projected to occur in Asia, particularly in China by the end of 2055.[9] Currently, 10 million Americans have either experienced or have osteoporosis.[10]

Various factors play a vital role in the pathogenesis of osteoporosis. However, the impact of salt or sugar on bone health is not well known. The aim of this review paper was to determine the impact of a diet high in salt and/or sugar on bone health and osteoporosis risk.

Risk factors for Osteoporosis

Among the non-modifiable risk factors, older age, gender, genetics, and ethnicity are associated with osteoporosis. Reduced sunlight exposure, lower intake of calcium-rich foods, as well as hypovitaminosis D are modifiable risk factors for osteoporosis.[7, 1] Lower amounts of estrogen can further decrease bone formation and growth of new bone leading to osteoporosis. Hence, post-menopausal women or women with low estrogen levels during the reproductive years may be at a higher risk of osteoporosis.[12]

Dietary consumptions of sodium chloride (salt) and excess protein are known to increase urinary calcium excretion.[13] Therefore, a high salt intake is considered one of the major risk factor for osteoporosis due to increased calciuria.[14-16] The calciuria can be hypothesized to be partly due to salt-induced volume expansion which might lead to an increase in glomerular filtration rate (GFR), and partly due to competition between sodium and calcium ions for reabsorption in the renal tubule.[17] Therefore, low calcium intakes may contribute to a compensatory response leading to increased bone remodeling and bone loss, which might be perpetuated by an increase in dietary salt consumption.

Association of salt with osteoporosis

There is a large fraction of body sodium deposited in the bone,[18] suggesting that bone might serve as a sodium reservoir which is mobilized during homeostatic stress. Salt also has a crucial role in maintaining positive magnesium and calcium balance. If a reduction in serum sodium occurs, the bone may be stripped of sodium (as well as magnesium and calcium) to maintain normal serum sodium levels. Indeed, a low-salt diet has been shown to lead to negative calcium and magnesium balance which could result in osteoporosis.[19] Thus, a low-salt diet may cause osteoporosis by stripping the bones of sodium, calcium, and magnesium.

Theoretically, a high-salt diet may lead to hypercalciuria. However, its effect on bone health is unclear. Recent research indicates that a high-salt diet may increase bone resorption among postmenopausal women,[14] however other studies have not found this to be the case.[20] Animal studies also suggest that elevated levels of aldosterone may lead to magnesium and calcium loss in the urine potentially leading to a loss of bone minerals and bone strength.[21] Thus, a low salt diet, which increases aldosterone levels, may harm rather than improve bone health.

A previous study conducted on over 4,000 postmenopausal women from the Women's Health Initiative (WHI) concluded that, "Higher levels of sodium intake and intakes above the WHI population median were associated with significantly fewer hip fractures."[2] There are other studies which have not found any significant association between sodium intake and bone mineral density (BMD).[22,23] Another previous study also concluded that a high sodium intake may not be detrimental to bone health in elderly patients whose dietary calcium intake is adequate.[24]

A high sodium is consistently cited as a risk factor for osteoporotic fractures, especially if the calcium intake or calcium absorption is also low.[15,25-27] However, the regulation of sodium balance within the human body is quite complex. Normal sodium levels are of utmost importance and normal sodium intakes help to maintain central blood volume and renal perfusion. Thus, sodium levels in the body are tightly regulated by homeostatic defense mechanisms primarily mediated by the renin-angiotensin-aldosterone system (RAAS).

A lower sodium intake ($<$ 3,000 mg per day) in an average-weight adult can lead to low sodium levels in the blood and activation of the RAAS both of which may induce osteoclastic activity.[28-30] Osteoclasts resorb bone, and if bone breakdown exceeds bone building this can lead to osteoporosis. In experimental studies, it was shown that activation of RAAS or an infusion of angiotensin II lead to an increase in bone resorption with the absence of angiotensin receptor type 1 being associated with greater bone strength. It is interesting to note that greater salt intake was found to be associated with a high bone mineral densit .[31,32]

Sustaining low sodium levels in blood are not only potentially harmful for bone health but also seems to increase the risk of cardiovascular morbidity and mortality. In fact, even normal sodium levels at the lower-normal range (136-138 mEq/L) significantly increases the risk

of major morbidity (cardiovascular complications) when compared with the upper normal range of sodium (139-143 mEq/L).[33]

Hyponatremia or low sodium levels in the blood is most common electrolyte abnormality, and this condition occurs frequently in the elderly population both in and out of the hospital setting. Hyponatremia may lead to unsteadiness, which predisposes to falls and injuries particularly in older individuals.[33,34] For the elderly, falls can be hazardous, as they can lead to fractures and even death. A recent review paper noted that, "The increased bone fragility together with gait instability makes chronic hyponatremia a new risk factor for fractures, especially in the elderly."[35] The study even suggested that correcting even minor hyponatremia may help to lower the risk of fracture related events.[35] In fact, hyponatremia can potentiate the increased risk of fractures after a fall by around four-fold.[36]

Studies conducted on animals indicate that chronic hyponatremia can cause or accelerate the condition of osteoporosis, organ dysfunction, and senescence.[37,38] Moreover, two cohort and case-control studies suggest a significant association between osteoporosis or fracture and hyponatremia,[36,39-41] and a recent case report described a patient who had reversal of severe osteoporosis after correction of chronic hyponatremia.[42]

Another way that hyponatremia may lead to weak bones is by causing a deficiency of vitamin C. It is well documented that vitamin C absorption in the intestine depends on sodiu,.[43,44] Thus, hyponatremia may directly or indirectly worsen the bone health by causing vitamin C deficiency.[45] Interestingly, animal studies report that hyponatremia is responsible for decreased activity of the sodium-dependent vitamin C transporter, which not only reduces the uptake of ascorbic acid into the bone but also increases oxidative stress, which may also apply to humans.[46]

Sugar and Osteoporosis

The present literature suggests that nutritional deficiency (both the undernutrition and over-nutrition) may be a substantial risk factor for osteoporosis. The groups that appears to be most affected by both overnutrition with concomitant undernutrition are children and teenagers who consume excess refined carbohydrates and added sugars.[47] Adolescents who consume the greatest amounts of added sugar may be particularly vulnerable to the detrimental effects of dietary sugar on peak bone mass.

The regular consumption of soft drinks is a notoriously high source of added sugar, and is associated with an increased in the risk of developing fractures which may be in part due to the replacement of calcium-rich beverages.[48-51] Studies have found that soft drinks lack important nutrients.[48-51] Furthermore, the intake of sweet beverages, including non-carbonated fruit juices and carbonated cola beverages, are significantly associated with a higher risk of fractures. An increase of one-half of a can per day of fruit juice and cola beverages, increased the likelihood of developing bone fractures by 1.6-fold and 1.7-fold, respectively[5.

One study reported that the ingestion of 100 grams of galactose and glucose in healthy subjects significantly increased the urinary excretion of calcium, magnesium, and potassium (suggesting an increased need for these minerals after ingestion of sugar). The authors noted no effect of sugar consumption on sodium excretion.[52]

In another such study, by Lemann et al. it was observed that despite inducing a reduction in glomerular filtration rate leading to reductions in the rates of filtration of calcium and magnesium, glucose ingestion augmented urinary calcium and magnesium excretion. They further hypothesized that the reason behind this augmentation could be the inhibition of re-absorption of calcium and magnesium within the tubules.[53]

In a study conducted by Holl and Allen, there was a significant increase in both urinary calcium excretion (peak at 1.5 hrs) and serum insulin levels after ingestion of 2 gram/kg of sucrose. The reabsorption of calcium from the renal tubules first decreased from 99.1% at 0 min. to 97.3% at 90 mins. The investigators noted that sucrose consumption was responsible for an increase in the urinary excretion of zinc and sodium, however the renal re-absorption of zinc and sodium was not found to be impaired. The possible reason was due to increase in serum insulin levels, which might be responsible for inhibiting calcium reabsorption in the tubules.[54]

Experiments in animals have observed urinary mineral loss after the ingestion of dietary sugar.[55-57] Borle et al.[58] in their experiments on mouse metaphysis concluded that addition of glucose to the medium lead to a dramatic increment of bone lactate production. Lactic acid formed from osteoclast metabolism of glucose may dissolve the mineral salts from the bone and high glucose levels may reduce osteoblast proliferation.[5] Also, osteoclasts trigger the production of hydrolases which can dissolve the organic bone structures.[60,61]

In a study conducted by Ericson in subjects after consuming either 100gm of sucrose or glucose, a strong positive association between calcium and magnesium

excretion rates was observed ($P < 0.01$ to < 0.001).[62] This study showed that the consumption of dietary sugar leads to an increase in the urinary excretion of of both calcium and magnesium. The authors wrote, "[…] the calcium loss is not compensated for during the hours following the calcium hyperexcretion shown by the results of Thom et al. […] which reported an average net loss of 40 mg Ca/day during a week with doubled intake of sucrose and total carbohydrate, and 100 mg Ca/day during a week with three-fold intake."[62]

Furthermore, sugar consumption is also associated with a decrease in the active form of vitamin D, leading to a reduction in the intestinal absorption of calcius.[63] Thus, a diet high in sugar may drive both calcium and vitamin D deficiency. The overconsumption of sugar may also impair bone formation by causing high glucose levels in blood.[64] Moreover, hyperglycaemia (which is commonly driven by a diet high in sugar[65]) is associated with lower bone quality and density.[66]

Another recent study concluded that dietary fructose can be responsible for a reduction in calcium transport in both the intestine and the kidneys due to reduced levels of 1, 25 dihydroxy vitamin D3 (1, 25(OH) 2D3). The hypothesis involved an increased expression of 24-hydroxylase (CYP24A1) and decreased expression of 1α -hydroxylase (CYP27B1), suggesting that fructose might enhance the renal catabolism and impairs the synthesis, respectively, of 1,25-(OH)2D3.[10]

Moreover, it is observed that a diet high in sucrose decreases the formation of dentin[67] and reduces the mineralization[68] during the primary dentinogenesis in rats. As the dentin and bone formations share a common matrix of calcium hydroxyapatite[69] it might be logical to infer that their osteoblastic activities may be similarly impacted by the influences of a high sucrose diet.

Saffar et al. observed adverse sucrose-induced changes that took place in the femurs of the young golden hamsters.[70] The researchers conducted another study where they found that the effect of diet-induced osteoporosis might involve not only the endosteal structure of bones but also the bone remodelling process.[71] According to the findings derived from the experiments on rats, glucose seemed to cause serious harm to the bones as compared to dietary sucrose.[72]

Lorincz et al.[73] presented a study on 9-week-old female C57BL/6 mice where they were given a high fat sucrose (HFS) diet for 10 weeks, and observed a detrimental impact on bone structure with negative morphological properties in cortical bone. Most of these effects were due to the increased osteoclastic activity, which was associated with an inflammatory environment. Moreover, long-term ingestion of an HFS diet for 24 months in female rats, also showed an adverse effect on the cortical bone, histology of the vertebrae and femoral neck, along with changes in mechanical properties.[73]

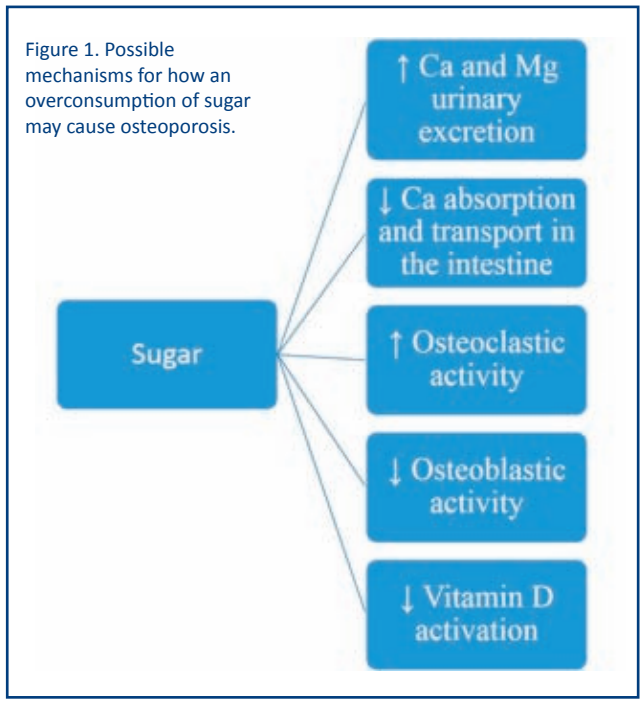

Figure 1. Possible mechanisms for how an overconsumption of sugar may cause osteoporosis.

In contrast to HFS studies, there are some experiments which used a fructose-rich diet (FRD) to forecast the metabolic syndrome (MS) animal model, where they assessed the consequences of FRD-induced MS on mice particularly focusing the growth in area of long bone histomorphometry and bone tissue regeneration.[74] Based on these FRD experiments, the researchers concluded that there was a 20% and 30% decrease in the osteocytic density of femoral trabecular bone and in osteoclast-covered (TRAP-positive) bone surface in the primary spongiosa, respectively.

Another study conducted by Felice et al. also evaluated the impact of FRD-induced MS on bone tissue regeneration, and concluded that fructose ingestion not only decreases the re-ossification, but also significantly reduces the osteocytic density. The study also suggested that further reduction of the osteoclastic activity particularly in the lesion site, might lead to a decrement in bone formation and remodelling. Moreover, it was also noted that the FRD-induced MS might diminish the ex-vivo osteogenic potential of marrow stromal cells (MSC) components and could lead to an increase in the ex vivo adipogenic potential of MSC,

which may lead to a reduction in Runt-related transcription factor (Runx2) and an increase in Peroxisome Proliferator Activator Receptorr γ (PPAR γ) expression under basal (undifferentiated) conditions. All the above mentioned data suggest that fructose can lead to a deleterious effect on overall bone health.[75] The final mechanism that by which fructose can lead to an overall negative impact on bone health is due to insulin resistance and hyperglycemia.[65,76,77] Indeed, diabetes and hyperglycemia are associated with higher risks for osteoporosis, bone fractures, impaired bone strength and bone remodelling. Figure 1 summarizes the possible mechanisms whereby an overconsumption of dietary sugar may lead to osteoporosis.

Conclusion

In summary it appears we have blamed the wrong crystal: it's not salt, but sugar that presents a greater risk factor for osteoporosis. The overconsumption of dietary sugar has the potential to increase the risk of osteoporosis by: a) increasing the urinary excretion of both calcium and magnesium, b) reducing the intestinal absorption of calcium by lowering the levels of active vitamin D, and c) impairing bone formation by reducing osteoblast proliferation and increasing osteoclast activation as well as lactic acid production.

References

1. Eaton-Evans J. Osteoporosis and the role of diet. British journal of biomedical science. 1994;51(4):358-70.
2. Kanis JA, Delmas P, Burckhardt P, Cooper C, et al. Guidelines for diagnosis and management of osteoporosis. Osteoporosis International. 1997;7(4):390-406.
3. Delmas PD. Treatment of postmenopausal osteoporosis. The Lancet. 2002;359(9322):2018-26.
4. Cheung EY, Tan KC, Cheung C-L, Kung AW. Osteoporosis in East Asia: current issues in assessment and management. Osteoporosis and Sarcopenia. 2016;2(3):118-33.
5. Reginster J-Y, Burlet N. Osteoporosis: a still increasing prevalence. Bone. 2006;38(2):4-9.
6. Masi L. Epidemiology of osteoporosis. Clinical cases in mineral and bone metabolism. 2008;5(1):11.
7. Khadilkar AV, Mandlik RM. Epidemiology and treatment of osteoporosis in women: an Indian perspective. International journal of women's health. 2015;7:841.
8. Gullberg B, Johnell O, Kanis J. World-wide projections for hip fracture. Osteoporosis international. 1997;7(5):407-13.
9. Tsang S, Kung A, Kanis J, Johansson H, et al. Ten-year fracture probability in Hong Kong Southern Chinese according to age and BMD femoral neck T-scores. Osteoporosis international. 2009;20(11):1939-45.
10. Bass EF, Baile CA, Lewis RD, Giraudo SQ. Bone quality and strength are greater in growing male rats fed fructose compared with glucose. Nutrition research. 2013;33(12):1063-71.
11. Khadilkar A. Vitamin D deficiency in Indian adolescents. Indian pediatrics. 2010;47(9):755-6.
12. Parker SE, Troisi R, Wise LA, Palmer JR, et al. Menarche, menopause, years of menstruation, and the incidence of osteoporosis: the influence of prenatal exposure to diethylstilbestrol. The Journal of Clinical Endocrinology & Metabolism. 2014;99(2):594-601.
13. Goulding A, Campbell D. Effects of oral loads of sodium chloride on bone composition in growing rats consuming ample dietary calcium. Mineral and electrolyte metabolism. 1984;10(1):58-62.
14. Harrington M, Cashman KD. High salt intake appears to increase bone resorption in postmenopausal women but high potassium intake ameliorates this adverse effect. Nutrition reviews. 2003;61(5):179.
15. Teucher B, Dainty JR, Spinks CA, Majsak-Newman G, et al. Sodium and bone health: impact of moderately high and low salt intakes on calcium metabolism in postmenopausal women. Journal of bone and mineral research. 2008;23(9):1477-85.
16. Cappuccio FP, Kalaitzidis R, Duneclift S, Eastwood JB. Unravelling the links between calcium excretion, salt intake, hypertension, kidney stones and bone metabolism. Journal of nephrology. 2000;13(3):169-77.
17. Heaney RP. Role of dietary sodium in osteoporosis. Journal of the American College of Nutrition. 2006;25(sup3):271S-6S.
18. Harrison HE. The sodium content of bone and other calcified material. Journal of Biological Chemistry. 1937;120:457-62.
19. Kodama N, Nishimuta M, Suzuki K. Negative balance of calcium and magnesium under relatively low sodium intake in humans. Journal of nutritional science and vitaminology. 2003;49(3):201-9.
20. Carbone L, Johnson KC, Huang Y, Pettinger M, et al. Sodium Intake and Osteoporosis. Findings From the Women's Health Initiative. The Journal of Clinical Endocrinology & Metabolism. 2016;101(4):1414-21.
21. Chhokar VS, Sun Y, Bhattacharya SK, Ahokas RA, et al. Loss of bone minerals and strength in rats with aldosteronism. American Journal of Physiology-Heart and Circulatory Physiology. 2004;287(5):H2023-H6.
22. Carbone LD, Bush AJ, Barrow KD, Kang AH. The relationship of sodium intake to calcium and sodium excretion and bone mineral density of the hip in postmenopausal African-American and Caucasian women. Journal of bone and mineral metabolism. 2003;21(6):415-20.
23. Greendale GA, Barrett-Connor E, Edelstein S, Ingles S, et al. Dietary Sodium and Bone Mineral Density: Results of a 16-Year Follow-up Study. Journal of the American Geriatrics Society. 1994;42(10):1050-5.
24. Ilich JZ, Brownbill RA, Coster DC. Higher habitual sodium intake is not detrimental for bones in older women with adequate calcium intake. European journal of applied physiology. 2010;109(4):745-55.
25. Nordin B, Need AG, Morris HA, Horowitz M. The nature and significance of the relationship between urinary sodium and urinary calcium in women. The Journal of nutrition. 1993;123(9):1615.
26. Jones G, Beard T, Parameswaran V, Greenaway T, et al. A population-based study of the relationship between salt intake, bone resorption and bone mass. European journal of clinical nutrition. 1997;51(8):561-5.
27. Need AG, Morris HA, Cleghorn DB, De Nichilo D, et al. Effect of salt restriction on urine hydroxyproline excretion in postmenopausal women. Archives of internal medicine. 1991;151(4):757-9.
28. Brunner HR, Laragh JH, Baer L, Newton MA, et al. Essential hypertension: renin and aldosterone, heart attack and stroke. New England Journal of Medicine. 1972;286(9):441-9.
29. Luft F, Rankin L, Bloch R, Weyman A, et al. Cardiovascular and humoral responses to extremes of sodium intake in normal black and white men. Circulation. 1979;60(3):697-706.
30. Hannon MJ, Verbalis JG. Sodium homeostasis and bone. Curr Opin Nephrol Hypertens. 2014 Jul;23(4):370-6.
31. Asaba Y, Ito M, Fumoto T, Watanabe K, et al. Activation of Renin-Angiotensin System Induces Osteoporosis Independently of Hypertension. Journal of Bone and Mineral Research. 2009;24(2):241-50.
32. Shimizu H, Nakagami H, Osako MK, Hanayama R, et al. Angiotensin II accelerates osteoporosis by activating osteoclasts. The FASEB Journal. 2008;22(7):2465-75.
33. Wannamethee S, Shaper A, Lennon L, Papacosta O, et al. Mild hyponatremia, hypernatremia and incident cardiovascular disease and mortality in older men: a population-based cohort study. Nutrition, Metabolism and Cardiovascular Diseases. 2016;26(1):12-9.
34. DiNicolantonio J. The Salt Fix: Hachette UK; 2017.

35. Giuliani C, Peri A. Effects of Hyponatremia on the Brain. Journal of clinical medicine. 2014;3(4):1163-77.
36. Gankam Kengne F, Andres C, Sattar L, Melot C, et al. Mild hyponatremia and risk of fracture in the ambulatory elderly. QJM: An International Journal of Medicine. 2008;101(7):583-8.
37. Verbalis JG, Barsony J, Sugimura Y, Tian Y, et al. Hyponatremia-induced osteoporosis. Journal of Bone and Mineral Research. 2010;25(3):554-63.
38. Barsony J, Manigrasso MB, Xu Q, Tam H, et al. Chronic hyponatremia exacerbates multiple manifestations of senescence in male rats. Age. 2013;35(2):271-88.
39. Sandhu HS, Gilles E, DeVita MV, Panagopoulos G, et al. Hyponatremia associated with large-bone fracture in elderly patients. International urology and nephrology. 2009;41(3):733-7.
40. Hoorn EJ, Rivadeneira F, van Meurs JB, Ziere G, et al. Mild hyponatremia as a risk factor for fractures: the Rotterdam Study. Journal of Bone and Mineral Research. 2011;26(8):1822-8.
41. Jamal SA, Arampatzis S, Harrison SL, Bucur RC, et al. Hyponatremia and fractures: findings from the MrOS study. Journal of Bone and Mineral Research. 2015;30(6):970-5.
42. Sejling A-S, Thorsteinsson A-L, Pedersen-Bjergaard U, Eiken P. Recovery from SIADH-associated osteoporosis: a case report. The Journal of Clinical Endocrinology & Metabolism. 2014;99(10):3527-30.
43. Said HM, Mohammed ZM. Intestinal absorption of water-soluble vitamins: an update. Current opinion in gastroenterology. 2006;22(2):140-6.
44. Figueroa-Méndez, R., & Rivas-Arancibia, S. (2015). Vitamin C in Health and Disease: Its Role in the Metabolism of Cells and Redox State in the Brain. Frontiers in Physiology, 6, 397. http://doi.org/10.3389/fphys.2015.00397
45. Xiao X, Liao E, Zhou H, Dai R, et al. Ascorbic acid inhibits osteoclastogenesis of RAW264. 7 cells induced by receptor activated nuclear factor kappaB ligand (RANKL) in vitro. Journal of endocrinological investigation. 2005;28(5):253-60.
46. Barsony J, Sugimura Y, Verbalis JG. Osteoclast response to low extracellular sodium and the mechanism of hyponatremia-induced bone loss. Journal of Biological Chemistry. 2011;286(12):10864-75.
47. Marriott BP, Cole N, Lee E. National estimates of dietary fructose intake increased from 1977 to 2004 in the United States. The Journal of nutrition. 2009;139(6):1228S-35S.
48. Wyshak G, Frisch RE. Carbonated beverages, dietary calcium, the dietary calcium/phosphorus ratio, and bone fractures in girls and boys. Journal of Adolescent Health. 1994;15(3):210-5.
49. Wyshak G. Teenaged girls, carbonated beverage consumption, and bone fractures. Archives of pediatrics & adolescent medicine. 2000;154(6):610-3.
50. Ma D, Jones G. Soft drink and milk consumption, physical activity, bone mass, and upper limb fractures in children: a population-based case-control study. Calcified tissue international. 2004;75(4):286-91.
51.Petridou E, Karpathios T, Dessypris N, Simou E, et al. The role of dairy products and non alcoholic beverages in bone fractures among schoolage children. Scandinavian journal of social medicine. 1997;25(2):119-25.
52. Lindeman RD. Influence of various nutrients and hormones on urinary divalent cation excretion. Annals of the New York Academy of Sciences. 1969;162(1):802-9.
53. Lemann J, Lennon EJ, Piering WR, Prien EL, Ricanati ES. Evidence that glucose ingestion inhibits net renal tubular reabsorption of calcium and magnesium in man. The Journal of laboratory and clinical medicine. 1970;75(4):578-85.
54. Holl MG, Allen LH. Sucrose ingestion, insulin response and mineral metabolism in humans. The Journal of nutrition. 1987;117(7):1229-33
55. Ferretti JL, Locatto ME, Savino D, Puche RG. The effect of galactose on bone metabolism. Calcif Tissue Res 1974;14:169-175.
56. Saffar JL, Sagroun B, de Tessieres C, Makris G. Osteoporotic effect of a high-carbohydrate diet in golden hamsters. Arch Oral BioI1981;26:393～397.
57. Tamura T, Fujii A, Kobayashi S, Kuboyarna N. Relationship between prolonged excess intake of sucrose and calcium balance. J Dent Res 1983;62:Abstr. 31.
58. Borle AB, Nichols N, Nichols G. The metabolic patterns of accretion and resorption. J BioiChern 1960;235: 1211-1214.
59. Lorincz C, Manske SL, Zernicke R. Bone health: part 1, nutrition. Sports Health. 2009 May;1(3):253-60.
60. Vaes G. Lysosomes and the cellular physiology of bone resorption. In Dingle JT, Fell HB, eds. Lysosomes in biology and pathology. Amsterdam: Elsevier, 1969;217-253.
61. Baron R, Neff L, Louvard D, Courtoy PJ. Cell-mediated extracellular acidification and bone resorption: evidence for a low pH in resorbing lacunae and localization of a 100-kD lysosomal membrane protein at the osteoclast ruffled border. The Journal of cell biology. 1985 Dec 1;101(6):2210-22.
62. Ericsson Y, Angmar-Månsson B, Flores M. Urinary mineral ion loss after sugar ingestion. Bone and mineral. 1990 Jun 1;9(3):233-7.
63. Douard V, Sabbagh Y, Lee J, Patel C, Kemp FW, Bogden JD, Lin S, Ferraris RP. Excessive fructose intake causes 1, 25-(OH) 2 D 3-dependent inhibition of intestinal and renal calcium transport in growing rats. American Journal of Physiology-Endocrinology and Metabolism. 2013 Jun 15;304(12):E1303-13.
64. Terada M, Inaba M, Yano Y, Hasuma T, Nishizawa Y, Morii H, Otani S. Growth-inhibitory effect of a high glucose concentration on osteoblast-like cells. Bone. 1998 Jan 31;22(1):17-23.
65. DiNicolantonio JJ, O'Keefe JH, Lucan SC. Added fructose: a principal driver of type 2 diabetes mellitus and its consequences. Mayo Clin Proc. 2015 Mar;90(3):372-81
66. Montagnani A, Gonnelli S, Alessandri M, Nuti R. Osteoporosis and risk of fracture in patients with diabetes: an update. Aging clinical and experimental research. 2011 Apr 1;23(2):84-90.
67. Bäckman T., Larmas M. (1997) Chronic metabolic alkalosis, sucrose diet and dentine formation in young rats. Arch. Oral Biol. 42:299–304.
68. Tjäderhane, L. (1996) The effect of high sucrose diet on dentin minerals measured by electron probe microanalyzer (EPMA) in growing rat molars. In: Dentin/Pulp Complex (Shimono, S., Maeda, T., Suda, H. & Takahashi, K., eds.), pp. 293–296. Quintessence Publishing, Tokyo, Japan
69. Linde A., Goldberg M. (1993) Dentinogenesis. Crit. Rev. Oral Biol. Med.4:679–728.
70. Saffar J. L., Sagroun B., de Tessiers C., Makris G. (1981) Osteoporotic effect of a high-carbohydrate diet (Keyes 2000) in golden hamsters. Arch. Oral Biol.26:393–397.
71. Saffar J. L., Makris G. P. (1982) Further data on the osteoporotic effect of the Keyes 2000 diet in the hamster. Arch. Oral Biol. 27:181–182
72. Tsanzi E, Light HR, Tou JC. The effect of feeding different sugar-sweetened beverages to growing female Sprague–Dawley rats on bone mass and strength. Bone. 2008 May 31;42(5):960-8.
73. Lorincz C., Reimer R.A., Boyd S.K., Zernicke R.F. High-fat, sucrose diet impairs geometrical and mechanical properties of cortical bone in mice. Br. J. Nutr. 2010;103:1302–1308. doi: 10.1017/S0007114509993084.
74. Zernicke R.F., Salem G.J., Barnard R.J., Schramm E. Long-term, high-fat-sucrose diet alters rat femoral neck and vertebral morphology, bone mineral content, and mechanical properties. Bone. 1995;16:25–31. doi: 10.1016/8756-3282(95)80007-D.
75. Felice J.I., Gangoiti M.V., Molinuevo M.S., McCarthy A.D., Cortizo A.M. Effects of a metabolic syndrome induced by a fructose-rich diet on bone metabolism in rats. Metabolism. 2014;63:296–305. doi: 10.1016/j.metabol.2013.11.002.
76. Merlotti D, Gennari L, Dotta F, Lauro D, Nuti R. Mechanisms of impaired bone strength in type 1 and 2 diabetes. Nutr Metab Cardiovasc Dis. 2010 Nov;20(9):683-90
77. Pietschmann P, Patsch JM, Schernthaner G. Diabetes and bone. Horm Metab Res. 2010 Oct;42(11):763-8.

Disclosure

None reported.

MM