Detailed Study Notes

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Introduction to this Episode

Does sodium lead to calcium losses? Do high-salt diets harm bone health? At what thresholds could there be an impact? Does any of this change our recommendations around salt/sodium intake?

Thanks to Sigma Nutrition Premium subscriber Kate Wall for submitting a question in the member's area that inspired this episode.

Kate asks:

> *"Salt can impact calcium excretion in the urine and it is said that a high salt diet can increase risk of osteoporosis as it draws calcium from the bone and excretes it. How much of an impact does dietary salt intake actually have on bone health and how high would salt intake have to be for this to be a concern? Obviously high salt intakes are not something to aim for in general, but just wondered if this was a mechanism that could remove meaningful amounts of calcium in a way that I should be advising around this in those that we work with as nutritional professionals. Thanks!"*

So in this episode, Danny and Alan look at some of the evidence in this area to see if there are impacts that have pragmatic implications for nutrition and medical professionals, as well as health-conscious people.

Connection to Previous Episodes

#375: Salt, Sodium & Health

- In this episode Danny and Alan discuss the current evidence base related to sodium intake and health, most notably cardiovascular disease.
- The episode walks through understanding diet-disease relationships, the epidemiology of sodium and health outcomes, the reasons for conflicting conclusions, sodium measurements in research, intervention trials, and more.
- Importantly, the claim that the sodium-CVD risk relationship exhibits a "J-shaped curve" (i.e. risk is low at moderate intakes and higher at both low and high intakes) is dissected, with recommendations given on how to reconcile all the available evidence.
- You can find the episode here.

#410: Q&A: Sodium, Protein, Quackery Tactics & More!

- In this Q&A episode, at the [19:34] point of the episode, you will hear a question on sodium and hypotension. Specifically:
    - “Please could you go into the sodium needs of those with hypotension. Your podcast about normotension and hypertension was excellent, as was the section relating to athletes. I’d love to hear your thoughts on the sodium needs of a hypotensive person”
- Note: this topic of sodium and hypotension is better covered in episode 457 with Dr. Austin Robinson (see below).
- You can find the episode here.

#457: Austin Robinson, PhD – Salt Sensitive vs Salt Resistant, Impacts of Sodium on Health, & Racial Differences in Risk

- While, on average, blood pressure correlates with sodium intake, there is a wide range of responses on an individual level.
- People who see increasing sodium intake lead to increased blood pressure are termed “salt sensitive”.
- Others, however, don’t see much change in blood pressure with increased dietary sodium. Such individuals are classed as “salt resistant”.
- In this episode, Assistant Professor at Auburn University, Dr. Austin Robinson, is on to discuss whether people who are salt resistant need to keep their sodium intake low or not. And other individual and group differences that exist for hypertension risk and sodium physiology?
- You can find the episode here.

Bone Health: Background & Key Terms

Bone mineral is formed by small, imperfect hydroxyapatite crystals, which contain carbonate, magnesium, sodium, and potassium (Lorenzo et al., 2011).

Bone mineral content (BMC): as the name implies, the amount of mineral contained in bone.

Bone mineral density (BMD):

- BMD is the ratio of BMC to bone size
- *"the amount of mineral (calcium hydroxyapatite) per unit of bone and can be used as an indirect indicator of bone strength. The bone mineral density is used to determine if osteopenia or osteoporosis are present."* - *Source*

Bone mass in later life depends on the **peak bone mass** achieved during growth and the rate of subsequent age-related bone loss.

- About 90% of total adult bone mass is accrued by age 20, and a significant proportion of this is achieved during puberty alone (Cashman, 2002)
- The amount of bone at 30 years old is about the maximum amount that will be attained (Henry et al., 2004)

Osteoporosis - *"a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture"* - WHO

Osteopenia - bones have lost mass and are weaker, but not to the point where one has osteoporosis. Perhaps what osteopenia is to osteoporosis, what prediabetes is to diabetes.

World Health Organization definitions based on bone density levels	
Level	**Definition**
Normal	Bone density is within 1 SD (+1 or −1) of the young adult mean.
Low bone mass	Bone density is between 1 and 2.5 SD below the young adult mean (−1 to −2.5 SD).
Osteoporosis	Bone density is 2.5 SD or more below the young adult mean (−2.5 SD or lower).
Severe (established) osteoporosis	Bone density is more than 2.5 SD below the young adult mean, and there have been one or more osteoporotic fractures.

Table from: bones.nih.gov

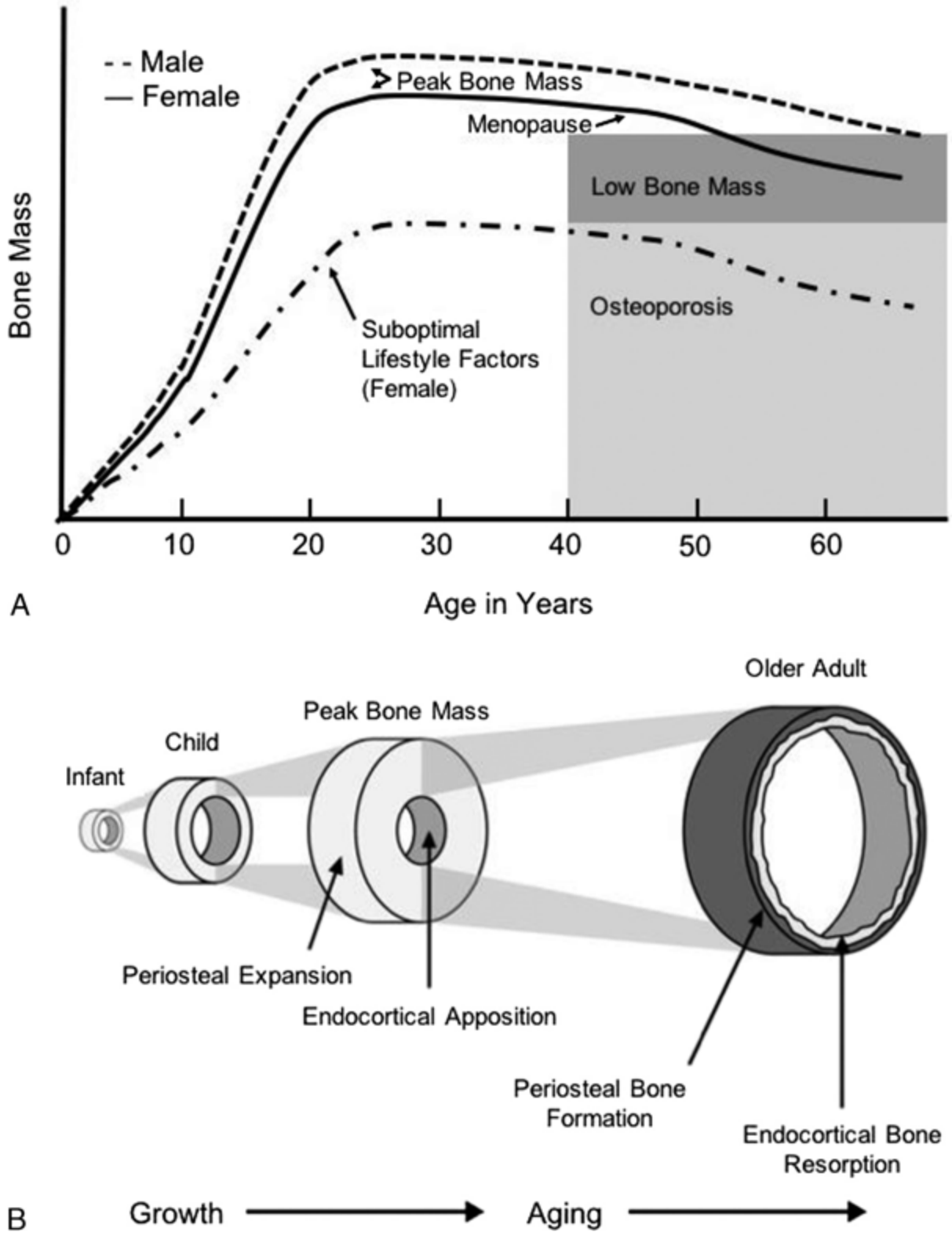


Image from: [Taylor, Nutrition Today 54(3):p 107-115, 5/6 2019](#).

Bone Remodeling

- Bone remodeling involves removal of old or damaged bone (by osteo*clasts*) and its replacement by new bone (formed by osteo*blasts*).
    - "osteo" = from the Greek word for bone
    - **Osteoclasts** are cells that *breakdown* the bone
    - **Osteoblasts** are the cells that *form new* bone
- The remodeling process is tightly regulated.
    - Bone homeostasis is maintained by a balance between bone resorption by osteoclasts and bone formation by osteoblasts.
- Remodeling repairs bone by removing old and micro-damaged bone, replacing it with strong new bone.
- The entire adult skeleton is replaced every 10 years in humans.
- When changes to the amount of bone resorption and/or bone formation lead to more breakdown than formation, then there will be a net bone loss.
    - This in turn results in the development of osteoporosis in both men and women.

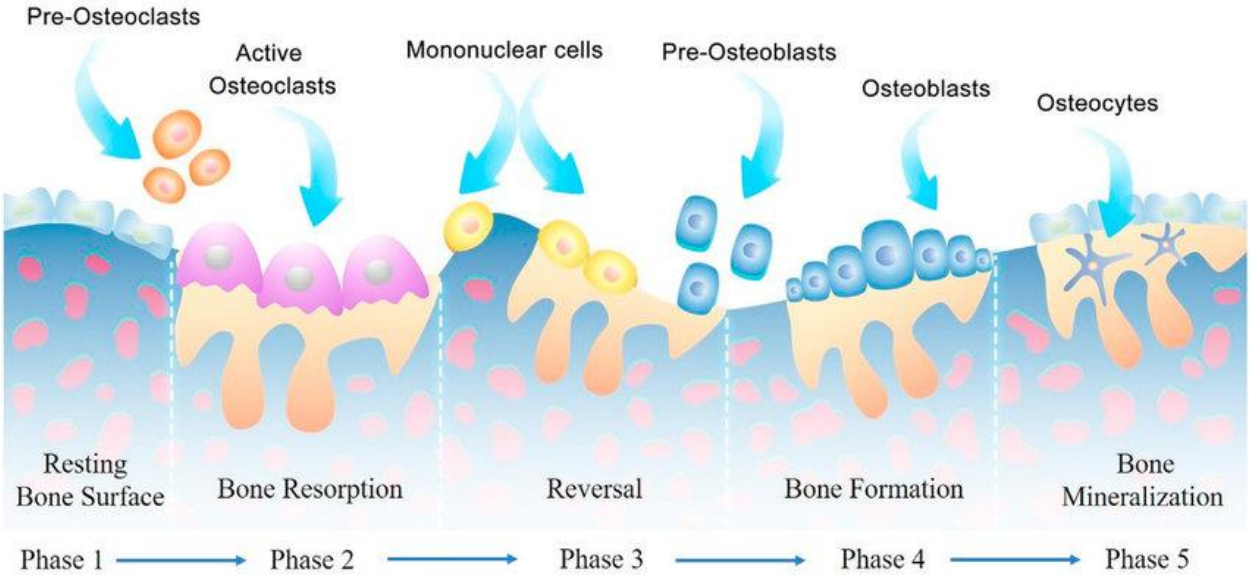


Image from: Black phosphorus-based 2D materials for bone therapy - Scientific Figure on ResearchGate.

Osteoporosis, Fractures and Implications

- Low bone mineral mass is the main factor underlying osteoporotic fracture.
- Fragility fractures are particularly common in the spine, hip, and distal forearm, although they can occur throughout the skeleton.
- Osteoporotic fractures are extremely common
    - In the US: 1.5 million fragility fractures each year
    - In the UK: one in two women and one in five men aged over 50 years will suffer an osteoporotic fracture in their lifetime (Clynes et al., 2020)
- There is a significant economic burden:
    - Osteoporosis-related fracture costs approximately $17.9 billion per annum in the USA and £4 billion in the UK (Clynes et al., 2020)
- Several factors are thought to influence bone mass. These can be broadly grouped into factors that cannot be modified, such as:
    - **Sex** – osteopenia and osteoporosis higher prevalence in women
    - **Age**
    - **Genetics** - Having a family history is a risk factor
    - **Ethnicity** – osteopenia more common in Caucasian or Asian populations
- And those factors that can be modified, such as:
    - **Hormonal status** (especially sex and calciotropic hormone status)
        - Sex hormones: The menopause transition is a critical period for bone health, with rapid losses in bone mass and strength occurring in a 3-year window bracketing the date of the final menstrual period.
        - Calciotropic = hormones involved in calcium homeostasis
            - E.g., parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D3
    - **Lifestyle factors**
        - physical activity levels, smoking and alcohol consumption
    - **Diet** (including functional foods)

Recap of Bone Health & Nutrients

For full details, see episode 411, where we discuss in detail the roles of:

- Calcium
- Vitamin D
- Vitamin K
- Phytoestrogens

Here's a quick recap of some key points…

Calcium

- Adequate calcium intake is critical to achieving optimal peak bone mass and modifies the rate of bone loss associated with aging.

Vitamin D

- Pivotal roles of 1α,25(OH)2D3 in calcium homeostasis, mineral metabolism, associated bone formation, and metabolism (Goltzman, 2018).
- These biological actions of 1α,25(OH)2D3 are believed to be mediated primarily through the nuclear vitamin D receptor (VDR).
- 1,25(OH)2D3 plays a role in bone turnover by affecting both osteoclast and osteoblast activity (Baldock et al., 2009).
- There is a considerable body of evidence that vitamin D deficiency is an important contributor to osteoporosis through:
    - less efficient intestinal absorption of calcium
    - increased bone loss
    - muscle weakness
    - weakened bone microstructure
- Vitamin D deficiency is characterized by inadequate mineralization, or demineralization
    - In children, severe vitamin D deficiency results in inadequate mineralization of the skeleton causing rickets
    - Whereas in adults, it leads to a mineralization defect causing osteomalacia.
        - Osteomalacia meaning "soft bones." Malacia is derived from Greek malakos = soft.
        - Osteomalacia is a disease that weakens bones and can cause them to break more easily

Vitamin K

- Osteocalcin is an important protein in bone.
- Osteoblasts synthesize osteocalcin, which is secreted into the bone extracellular matrix where it binds to hydroxyapatite crystals.
- Binding of osteocalcin to hydroxyapatite is dependent on the carboxylation of three glutamate residues by vitamin K (Cairns & Price, 1994)
- Gamma-carboxyglutamate binds calcium, which is essential for its activity.
- **Prospective cohort studies**:
    - In the Nurses' Health Study, vitamin K1 intakes of <109 µg/d were associated with an increased risk of hip fracture in 72,327 women.
    - In the Framingham Heart Study, elderly men and women in the highest quartile of vitamin K1 intake (median 254 µg/d) had significantly lower adjusted relative risk of hip fracture than did those in the lowest quartile of intake (median 56 µg/d)

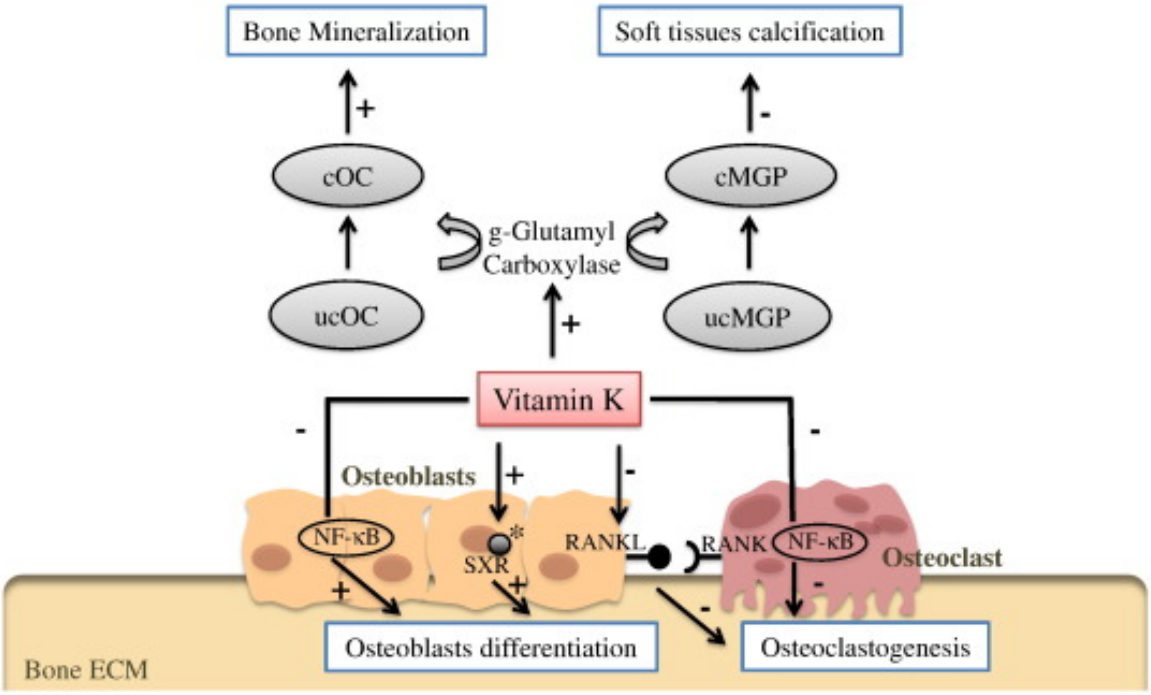
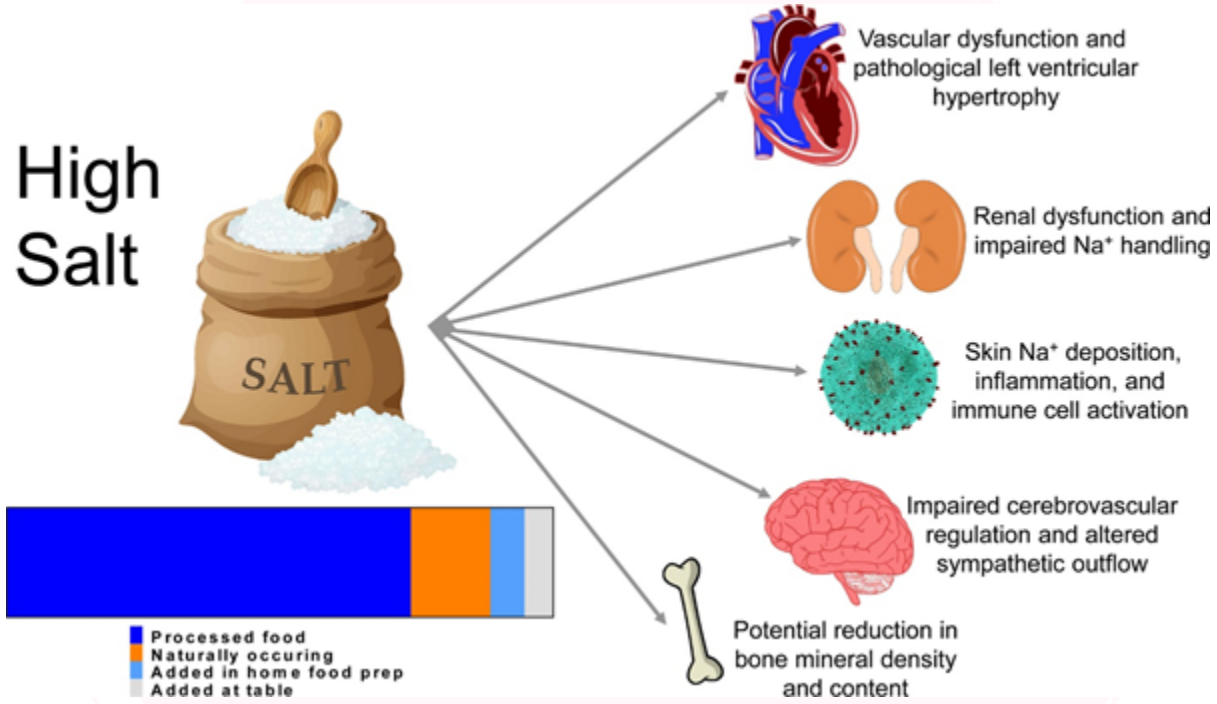


Image from: Palermo et al., Metabolism. 2017 May;70:57-71.

Salt/Sodium: Where Concerns Arise

Links to Osteoporosis Risk

- Associations between osteoporosis and high-salt diets.
- National Osteoporosis Foundation also recommends a low-salt diet for bone health.
- A meta-analysis by Fatahi et al. 2018, demonstrated that higher Na+ significantly increased the risk of osteoporosis, *however* there was a high degree of heterogeneity among studies.



From: Robinson et al., Curr Hypertens Rep. 2019 Apr 25; 21(6): 42.

Mechanism: Calcium Excretion

- Suggested mechanism is through lowering calcium:
  - As the body regulates sodium, with high intakes, we see high sodium excretion in the urine.
    - Hence why urinary sodium measures are such an accurate measure of sodium intake (see episode 375).
  - However, sodium brings calcium along with it. So increased sodium excretion means increased calcium excretion.
    - There is well-documented correlation between **urinary sodium and calcium** in 24-h urine collections

        - *Side note:* The correlation between urinary sodium and calcium is generally sodium driven, i.e., it is the sodium load that influences urinary calcium rather than vice versa (Nordin et al., 1993)
            - When sodium is the determinant, 100 mmol of sodium takes out approximately 1 mmol of calcium in the urine.
    - So the experimental evidence shows that both sodium and calcium compete for the same reabsorption mechanism in the kidney.
        - And if you've got an increase in the levels of sodium and calcium that the kidneys are trying to filter, that can actually lead to an increased excretion of both sodium and calcium.
    - And as we have associations between low calcium status and low bone mineral density, it is suggested that high-salt intakes could be detrimental to bone health.
    - Particularly given the fact that we reach peak bone mass in our late 20s, and so any loss of calcium from bone going forward could be problematic.
    - High sodium chloride intake increases urinary calcium excretion – Kim et al., 2015
- Heaney, 2006:
    - *"The calciuria is partly due to salt-induced volume expansion, with an increase in GFR, and partly to competition between sodium and calcium ions in the renal tubule."*

Mechanism: Acid-Base Balance

Other hypothesized mechanisms relate to acid-base changes.

- Salt = sodium chloride. Chloride is an acid. Some suggest that if chloride is excessive, then it's theoretically possible that the body will take base stores from the bone to maintain a balance.
    - This process would result in a net loss of calcium from the body
- Frasetto et al., 2008:
    - *"At baseline, in a steady state, diets that contain substantial sodium chloride and diets that are net acid producing each independently induce and sustain increased acidity of body fluid."*
    - *"With increasing age, the kidney's ability to excrete daily net acid loads declines, invoking homeostatically increased utilization of base stores (bone, skeletal muscle) on a daily basis to mitigate the otherwise increasing baseline metabolic acidosis, which results in increased calciuria and net losses of body calcium."*

Observations: KNHANES

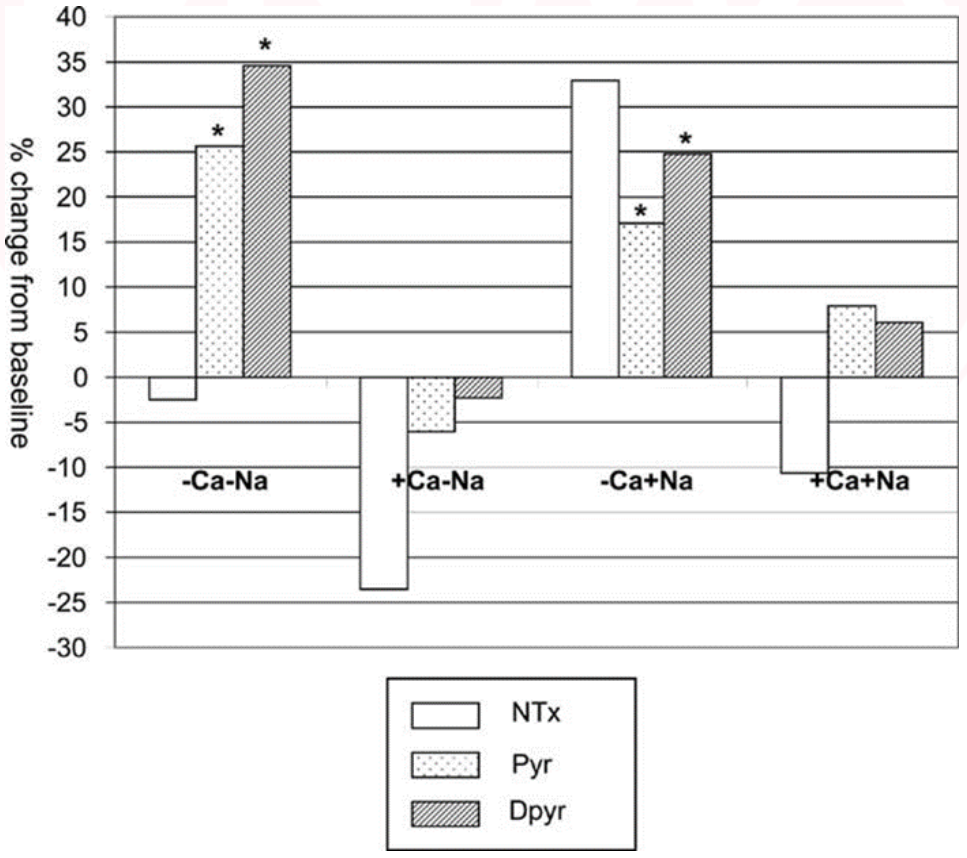
- KNHANES: Cross-sectional study of postmenopausal Korean women higher urinary Na+:creatinine was positively associated with osteoporosis and negatively correlated with bone mineral density (Kim et al., 2014)
- In another cross-sectional Korean study, urinary Na+ excretion was negatively associated with bone mineral content (BMC) and BMD in female, but not male participants.
- In a cross-sectional study of Chinese adults, urinary Na+:K+ was inversely associated with BMD in female, but not male participants (Cao et al., 2017).

Carbone et al., 2016 – Women's Health Initiative

- Study: Carbone et al., Journal of Clinical Endocrinology & Metabolism, Volume 101, Issue 4, 1 April 2016, Pages 1414–1421
- Prospective observational cohort study including ~70,000 postmenopausal women (part of the Women's Health Initiative)
- Average 11.4 years of follow-up
- Looked at whether sodium intake is associated with changes in BMD and with incident fractures
    - Also examined whether this relationship is modified by potassium and/or calcium intake.
- FFQ which was *calibrated* using 24-hr urine measures from a subset of 450 women
- They looked at fracture risk over three year increments and increasing sodium intake by 20% (quintiles).
- In adjusted models, there was **no association** of calibrated sodium intake with changes in BMD at the hip or lumbar spine from baseline to 3 or 6 years
- Levels of sodium intake above or below currently recommended guidelines for cardiovascular disease (≤ 2,300 mg/d) were **not associated** with changes in BMD at any skeletal site from baseline to 3 or 6 years or with incident fractures.

Teucher et al. (Medical Research Council) RCT

- Study: Teucher et al., J Bone Miner Res. 2008 Sep;23(9):1477-85.
- Eleven women
- Randomized cross-over trial
- Four successive 5-week periods of controlled dietary intervention, each separated by a minimum 4-wk washout.
- Moderately low and high calcium (518 versus 1284 mg) and salt (3.9 versus 11.2 g) diets were provided.
- Stable isotope labeling techniques were used to measure calcium absorption and excretion.
- **Moderately high salt intake (11.2 g/d)**:
    - Elicited a significant increase in urinary calcium excretion
    - Significantly affected bone calcium balance with the high calcium diet
- Efficiency of calcium absorption was unaffected by salt intake.
- Adaptive increases in calcium absorption offset the increased urinary loss.
- Mean percent change in bone resorption markers after 4 wk of diets low (−Ca) or high (+Ca) in calcium and low (−Na) or high (+Na) in sodium:



Sellmeyer et al. - Effects of Potassium

- Study: Sellmeyer et al., J Clin Endocrinol Metab. 2002 May;87(5):2008-12.
- Looked at the effects of differing levels of salt with or without supplemental potassium in postmenopausal women.
- Three week run-in period where the participants were consuming five grams of salt a day (relatively low salt diet), and then they were randomized to either consume:
    - 13 grams of salt per day
    - 13 grams of salt per day *plus* the addition of 29 g/d of potassium.
- Urinary calcium excretion:
    - Going from low to high salt (i.e. 5 g/d to 13 g/d) significantly increased urinary calcium excretion
    - But the addition of 29 g of potassium abolished that increase in urinary calcium excretion.
- Suggestive that the increase in calcium excretion from high-salt was entirely abolished by the addition of that high potassium intake to that salt load.
- Result shown over page.

Change in calcium, bone turnover markers, and hormones from low salt (87 mmol/d sodium) to high salt (225 mmol/d sodium), placebo *vs.* potassium citrate (90 mmol/d)

	Change from low salt to high salt + placebo	**Change from low salt to high salt + potassium citrate**	***P* value placebo *vs.* potassium citrate**
Urine calcium (mg/d)	42 ± 12	−8 ± 14	0.008
Urine NTX (nMBCE/mmol Cr)	6.4 ± 1.4	2.0 ± 1.7	0.049
Serum calcium (mg/dl)	0.04 ± 0.06	0.05 ± 0.05	0.89
Osteocalcin (ng/ml)	−0.57 ± 0.21	−0.22 ± 0.23	0.26
Fasting PTH (pg/ml)	0.97 ± 1.5	−0.74 ± 1.8	0.46
cAMP (nmol/liter)	142.2 ± 99.2	106.7 ± 135.6	0.83
Urine potassium (meq/d)	2 ± 3	72 ± 5	<0.001
Net acid excretion (meq/d)	3 ± 3	60 ± 5	<0.001

Table from: Sellmeyer et al., J Clin Endocrinol Metab. 2002 May;87(5):2008-12.

Conclusions

- There is evidence suggesting salt intake could influence calcium excretion and some markers of bone. Similarly, associations between high-salt intakes and osteoporosis have been noted.

- However, the current evidence base is mixed with very little clear signal. And the evidence for uniquely harmful effects of salt on actual important outcomes related to bone health is very weak.

- In addition, it seems that for those aiming to maintain good bone health, there are far more useful areas to look to, both generally (e.g. physical activity) and in relation to nutrition (e.g. calcium, vitamin D).

- In addition, for cardiovascular health, there are already limits suggested for overall salt/sodium intake. And therefore high-salt diets are already advised against.

- Therefore, there is currently no basis for making any specific dietary recommendations related to sodium/salt intake, on the basis of bone health.