Episode Transcript

Danny Lennon: Hello and welcome to another episode of Sigma Nutrition Radio. This is episode 471 of the podcast. You are very welcome. My name is Danny Lennon, and beside me is Dr. Alan Flanagan. We obviously have a number of episodes previously that people may have heard about sodium intakes, most of that relating to cardiovascular disease outcomes.

And then we also have an episode specifically on bone health, where we talked about the impact of a number of nutrients in particular, but not sodium specifically. And so today we are going to look at the impact of sodium on bone health. And this actually comes off the back of a question that we were sent from one of our premium subscribers, Kate Wall. So thank you Kate for the question.

And in short to paraphrase, Kate essentially asked: *"how much of an impact does dietary salt intake have on bone health, and how high would salt intake have to be for this to be a concern?"*

So this leaves us with a number of questions that hopefully we can walk through today. First we can ask what are the mechanisms by which there could be potential harm? Is there actual evidence that high sodium intake

could harm bone health? If so, what do we see in terms of dose response or thresholds? What factors might impact someone's risk?

And then hopefully we'll end up with practically what this means on a couple of different levels. One, for our usual population guideline intakes or limits on sodium. And then also an individual advice that nutrition professionals may be giving to people; how does this tie into those?

As a way to start, and maybe I'll ask you to run us through some of this background context, Alan. If we think about back to our episode on bone health, where we cover this in more detail just for maybe people who didn't hear that, to get to some of the terminology or ideas that we're going to explore today, what is some of the background context we might have to set in terms of understanding sort of what bone mineral density is? Processes like bone resorption? Or probably more relevant to what we discussed there, what are the common nutritional links with things like osteoporosis risk? That we may have discussed previously or just at a very general overview level that you think are most relevant to catch people up on?

Alan Flanagan: Yeah, so we could probably start by saying, nutrients obviously have a particular role in the formation of the matrix that the tissue that we call bone. Typically most people will associate bone with calcium, and yes, that's the case that the majority of calcium in the body is deposited in bone and in our skeletal tissue and also in teeth. And then we have a role for a number of other minerals that we would've discussed on that episode. Phosphorus being one in particular that's really important but unheralded, certainly relative to calcium.

We would've talked about the role of vitamin D and the interaction with parathyroid hormone. And we would've touched on the fact there is this relationship between vitamin D status and between levels of, say, parathyroid hormone in the body and basically these concepts of bone breakdown and reabsorption or bone reabsorption. And really what we're talking about as a concept is a balance of factors from that relate to the breakdown and of minerals from bone and factors that relate to the uptake and accretion of those minerals in bone. And so that the process of bone mass accretion is something that develops particularly over childhood and adolescence. We reach peak bone mass somewhere around the age of 30, if I remember correctly.

And then over time, depending on external factors such as dietary intake of these minerals and dietary protein, vitamin D status, and also external factors like mechanical loading, exercise, physical activity, can all then influence the of bone retention mineral retention and bone mineral density, and bone mineral content.

And obviously then over time, that can influence the rate at which there may be progression of deteriorating mineral density and content of bone such that there is an increased risk for bone related outcomes like osteopenia, osteoporosis fractures. And there are of course then associations, particularly as we get into a much elderly age bracket of say the 75, 80 and over, and especially in the context of institutionalized care when people are in, for example, an old folks or a care home is the association between fractures and mortality. So it, it is a really important aspect of the overall health.

And I think the best way to think about this in a simple way, is to think about it as it relates to this balance of factors that then increase the mineral content and retention of that in bone and factors that may promote the release or the breakdown of those minerals such that over time there is potentially an increased risk of some of these outcomes like osteoporosis and osteopenia. And so we'll refer a lot to BMD, the density of these minerals in bones. And, this can be looked at using scans. (Bone) mineral content we might refer to in relation to a couple of studies as well, which is exactly that: it's the actual mineral content of the bone. And I think that's probably, for today's purposes, likely the main concepts in a general sense for the overview of bone. We can discuss the mechanisms of the relationship between sodium and calcium more specifically as we go.

Danny Lennon: So as some background context for where some of these concerns arise, and indeed some things that Kate had highlighted in our initial question, was that there have been associations noted between things like osteoporosis and high salt diets. Some of that we will get to there's a few associational cross-sectional studies. There's also some meta-analysis that mentioned that show these potential associations from high salt intake and osteoporosis. And indeed you can see organizations like the National Osteoporosis Foundation recommending low salt diets for bone health.

So really to think about what the basis for this is, let's start digging through some of the potential mechanisms first before we look at some outcomes.

And I think typically the mechanisms at least initially tend to center on that there can be essentially a lowering of calcium; so increased calcium excretion through high levels of sodium intake. And there's a few points of maybe nuance that we can work through with this.

Alan Flanagan: Yeah, so we focus a lot on calcium as it relates to bone health. It might be of some surprise to listeners to note that sodium in terms of its total body content, and that can range from about 90 to 130 grams in the body at any given time. But half of that is actually in bone. The remainder of it is in our extracellular fluid and is of course involved in the processes that we would most associate sodium with, which is the regulation of osmolarity, blood pressure, blood volume and the relationship with potassium in that regard.

But of that sodium content that's in bone it's exchangeable with sodium that we have in our extracellular fluid. In contrast, that's not the case with calcium. The calcium that we have in bone is really deposited there and doesn't really freely exchange with any calcium that we might have in the circulation.

Which isn't typically much. And so what we have really is a very. What's considered to be a superficial role for sodium in bone itself and that the sodium in bone is not necessarily an important part of the picture for sodium in the circulation and the relationship that would have for blood pressure or otherwise.

and. Ultimately, there's a line of experimental evidence that 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 we do know that if you increase, your dietary sodium, if we get someone into a lab and we feed a high sodium intake. Suddenly we will see that in terms of increased urinary sodium excretion as the body tries to compensate and maintain homeostasis. And we can also do the same with calcium.

But there, there is a potential other mechanism, which is that the role of sodium actually in the extracellular fluid and its role in plasma volume

expansion can also then the load of calcium that's filtered through the kidneys and that you get this induction of increased calcium excretion as a result of that increased sodium load on average urinary calcium can increase by between 20 to 60 milligrams for every 2,300 milligrams of sodium ingestion. So we do, in terms of experimental research, have a fairly good handle that this relationship primariliy is one of the effect of sodium increasing calcium excretion. When we get to discuss some of the interventions there are some interesting nuance there as it relates to the relationship with actual calcium intake.

And some experimental studies have used both high and low sodium intakes and high or low calcium intakes. And we can discuss some of the interesting findings from some of that. But ultimately this relationship holding other things relatively constant is one where there is an increase in calcium excretion increased sodium.

And that potentially is something that then is not just coming from the circulation because calcium is not necessarily that exchangeable in and out of between bone and the circulation itself. And ultimately the majority of our calcium is... so even in the context of a low calcium intake, it could be, for example, that there is an increased level of the breakdown and release of calcium from bone and that if we're having this process occur again over time, that could be something that's leading to calcium, depletion from bone and ultimately an increased risk for osteoporosis.

Danny Lennon: Excellent. So maybe as a way to recap that just for emphasis for people listening, a few really I important points there. First of all, we have this relationship between sodium and calcium that's important to note. So as we know, the body regulates sodium. So in other words, when we get these high intakes of sodium, we're going to see increased sodium excretion in the urine. And as we've talked about on some of our previous episodes, this is why sodium excretion in the urine is actually a really good measure of dietary sodium intake because as we increase intake, we get this increased excretion. But as you noted that with this sodium excretion, it can essentially bring calcium along, for lack of a better term, that we see this increase in calcium excretion. And this is a pretty well documented relationship between urinary sodium and urinary calciu m that we find. And one of those important points that we'll probably circle back to that you mentioned is that while there is a potential for say large increases in calcium to maybe impact this

relationship. By and large, that correlation between the urinary sodium and calcium is generally driven by sodium, so that it's the sodium low that's influencing the urinary calcium as opposed to vice versa.

And in most cases, but not all. And then there's probably something like a 100:1 ratio of this excretion; a hundred millimolars of sodium would be taking out about a one millimolar of calcium. One other point that was really important you mentioned was about the peak bone mass that one achieves and it's probably going to be achieved in someone's twenties.

And so therefore now we have, if there's this potential for increased calcium losses from bone, because this increase excretion over time, knowing that we've already achieved peak bone mass in our twenties, therefore give us pause for concern and maybe why there might be a potential relationship with negative outcomes like osteoporosis.

And then there's a few nuanced things that are going on in the kidneys and around both volume expansion could be one part of it. The other part could be this competition between sodium and calcium that occurs in the kidneys as well. So there's a couple of things going on there, but the big take home is that with this high sodium excretion occurs and that tends to be an increase in calcium excretion and therefore could set the stage for potential problems.

But there was a couple of cross-sectional studies, both of which I think came out of Korea, one of which was from like the Korean NHANES data their version of that. Is there anything that we should note about some of these studies that would add anything to what we've just said? Or just lend support to some of these ideas?

Alan Flanagan: I think the main. Issue in some of the epidemiology, and these are, I think, general points of critique that most of our listeners will now be familiar with is that most of the literature from the epidemiology of sodium as it relates to bone health is cross-sectional data. And so there are limitations to that because it's not necessarily a look prospectively over time.

So you are taking your participants as your current state of, or as their state of bone health overall at the time that you are looking at your healthy controls versus your controls with osteoporosis, osteopenia or indeed looking at their bone mineral density, that's always something that we need

to factor in terms of making inferences as it relates to the design of the studies themselves.

But these studies have primarily been interesting because they have suggested that yes, there is an increased, risk of lubar spine osteoporosis. In particular, there was a 34% higher prevalence of lubar spine osteoporosis in the highest quartile of sodium excretion compared to the lowest.

It wasn't a particularly precise finding; the competence intervals were very wide. But it also that particular study based on the, and this was the KNHANES data from 2008 to the 2011 also found a negative association between sodium excretion and bone mineral content and bone mineral density of the lumbar spine. And this was observed in women that actually had normal bone health status or osteopenia or osteoporosis, but it wasn't observed in men. So I think this is potentially important as we look at some of the other observational research. So this significant association between increased risk of osteoporosis or osteopenia and increased sodium excretion, primarily observed in women, was strongest as an effect in premenopausal women. But and that gives us some suggestions that potentially there is an effect of or an effect modifier of sex and of menopausal status. And that is something that will be consistent relatively with the wider literature of diet and bone health, generally speaking.

I think the major limitation for the study was that spot urine samples were used to estimate sodium. For our listeners that have listened to our previous episodes where we've really gone into some detail on the methodology of sodium measurement, they'll recognize that's really not a particularly accurate method. You are taking a single urine sample, a spot sample, so to speak, at a particular time of day, and you're using these various formulas to try and then estimate sodium, 24 hour excretion or otherwise. And the estimates are all fairly inaccurate relative to the gold standard method of assessing sodium.

So there's scope here for measurement error to be influencing the findings. But ultimately these KNHANES publications did suggest an association between: first, greater sodium excretion and lower bone mineral con content and density. Second, an association between higher intake or higher sodium excretion and osteoporosis.

Both of these findings specific to the lumbar spine region and not necessarily to others. And thirdly, primarily not in men, but specifically in premenopausal women, although there were associations observed for postmenopausal women as well. They just weren't as strong in the finding.

Danny Lennon: Yeah, and I think later on we will probably revisit this idea of the risk is probably going to differ depending on who we're talking about. And for example, we have issues here around sex differences potentially that emerge from these studies. And also there's another Chinese study that was done in a very similar fashion that showed similarly the findings were significant in females, but not in male participants.

So that's on some of this that would go to support the idea that this increased sodium intake or these high intakes could then therefore lead to potential issues for bone mineral content or bone mineral density and increase osteoporosis risk. Before we get onto maybe some of the findings that show a lack of association, one of the potential mechanisms that sometimes get discussed but maybe doesn't have the degree of evidence of what we've discussed to this point already is around the acid based balance type stuff. And if we have something like a high salt intake that could potentially cause an acidic environment and the body essentially to neutralize that can take base loads from something like calcium as a way to balance that out again. Would this go any way to explain some of these associations or are we pretty clear on the mechanisms we outlined earlier?

Alan Flanagan: Yeah, and I have seen some studies on this topic refer to like acid-based balance, but not in the way that I think the internet type of conversations in relation to acid alkaline play out because those assertions contend that a food is either net acid or alkaline, and that will then cause this shift in the body, particularly a shift in pH that we then compensate for by, for example, breaking down more alkaline, minerals to release to balance.

But the problem I think with that is it just doesn't really seem to account for how narrow a pH range that the body maintains for a pH homeostasis, which is incredibly tight. To go outside of those ranges is to enter into very life critical states of metabolic alkalosis or metabolic acidosis, respectively.

And while, yes, there are these processes that. can influence mineral uptake or breakdown from bone, they don't necessarily seem to relate, to, the

concept I think that people are generally talking about where they're referring to acid- base or acid-alkaline, certainly the alkaline theory.

Now there is obviously some clinical context where this is important and there, there also is as we'll discuss with the evidence from intervention. There is an attenuating effect of, for example, experimental studies that have looked at giving people a high sodium intake and then looking at, calcium excretion and then also looking at that sodium intake with a concomitant high potassium intake or the addition of some more base, mineral content to that sodium load.

And we can see an attenuating effect of calcium excretion from that high sodium intake. But that may not necessarily relate to preventing or providing a more alkaline environment. It may relate coming back to these factors of like renal processing of these minerals and the impact then that sodium has on on promoting this calcium excretion.

Danny Lennon: Yeah. And that's going to m my sense of it, that rather than driving this in the first place, it's actually something that might be a more relevant factor to certain at-risk group. For example, one of the researchers in nephrology, Linda Frasetto, who was on the podcast before some of her work has mentioned that it's actually with age we see it's pretty normal for this decline in the kidneys function to be able to actually clear some of those net acid loads. And so it's just the function of age that over time you have this more poor ability to do that and therefore it might end up taking some more calcium within the body to try and balance that out.

And that's what's going on as opposed to someone's salt intake, primarily driving that particular mechanism. And so in that case, yeah, someone could make a case that you don't want to do things to exacerbate it, but probably what's going on is you've this change in kidney function that's happening with age as opposed to something else from an acidic type of food they're eating per se.

So with that, I think one of the useful studies to maybe. Bring up here is data that came from the WHI, so the Women's Health Initiative, this was a paper published by Carbone and colleagues 2016. And this had a pretty large cohort perspective cohort study, decent amount follow up, and they were looking at changes in bone mineral density and again, looking at things like sodium as

well as potassium and calcium intake. And I think this gives us some useful base to get into some of the nuances of this area and why there might be some conflicting results we find that we might need to reconcile a bit later on. So for the moment, let's maybe introduce people to some of the findings of the Carbone study.

Alan Flanagan: To start with this did use a 24 hour urine concentration as far as the estimate of sodium goes. But it also was a single 24 hour, so it's better than a spot urine sample. But it's not it's somewhere sitting above that in terms of, sodium estimates, but it's still prone to a lot of variation. And again, would be, will be less accurate than gold standard measurement methods. The average intake from biomarker calibration, so the urinary concentrations that were taken of sodium was about 2,900 milligrams per day. ,And a range of 1200 up to up to 7,000 500 milligrams a day of sodium. Any range from under the actual, current recommendations for less than 2,400 milligrams up to relatively high sodium intakes.

But the main finding for this, and this, there was an average of about 11 years follow up. But they looked at fracture risk over three year increments and increasing sodium intake by 20%. So in these 20% increments or quintile increments wasn't associated with any change in bone mineral density over three or six years. And that included hip bone mineral density, total hip or femoral neck bone mineral density. When looking at the actual hip fracture incidence risk there was actually even evidence of a lower of a 19% lower hip fracture with these 20% increment increases in sodium intake. And then when they looked at sodium intake above or below the current recommendations for sodium, which is less than 2,300 milligrams a day. Again, there was no significant association with change in bone mineral density at any of the actual skeletal sites that were analyzed at either three or six years.

And then they also considered calcium intake of, because some of the contentions for calcium intake are that there's this maybe 500 milligram per day threshold at which there's a certainly at least a minimum amount for adequate, bone related processes. And looking at around that marker, there was again, no evidence of any relationship between sodium and fracture risk at a calcium intake that's at that, what we might term as a minimum effective dose or even under that minimum effective dose of calcium.

So overall, essentially the opposite it's designed as a prospective study would certainly have stronger inference than the cross-sectional studies that we discussed previously. But I think potentially surprising is not that there was null associations or perhaps weak positive or weak inverse associations. But actually in a lot of these outcomes, evidence of a lower actual risk of fracture incidents with these 20% increment increases in sodium.

Danny Lennon: Yeah. And we'll probably go somewhere to try and reconcile that, or at least maybe explain some of that in. But for now, I think there's a couple of interesting elements that regular instance of this podcast might want to pick up on.

So first of all, we know this is a prospective cohort study, and so there's about 70,000 postmenopausal women here, but we've also noted that there was 24 hour urine measures. So hopefully people are thinking "something's up here: there couldn't have been 24 hour urine measures for 70,000 people", which is why you mentioned that the calibration.

So here we have food frequency questionnaires being calibrated with these 24 hour urine measures with a subset of those women. Just for, maybe for people who haven't came across this before, can you just briefly explain that?

Alan Flanagan: Yeah so for food frequency questionnaires, the validation of the assessment of a nutrient in a food frequency questionnaire will often be against another reference, dietary assessment method. Commonly this is done in relation to 24 hour recalls, but for sodium specifically, the issue is that neither food frequency questionnaires nor 24 hour recalls are particularly accurate when it comes to quantifying sodium intake. And as we've discussed on previous episodes, the excretion of sodium that we have is almost exclusively through urine, 95 to 98%.

And so urinary sodium is a robust reflection of sodium intakes, the challenge then becomes obviously getting an accurate quantification of those urinary samples because it varies from person to person and it varies across the day. So to calibrate a dietary assessment method, you can use a reference instrument or against biomarkers.

And so one method of doing that, for example, will be to take some samples from a subset of your cohort and then to look then at the levels of intake in

those biomarker samples. So in this case, 24 hour urinary samples from a subgroup of your participants. And then you look at the food frequency questionnaire data and you are essentially looking for how well those two methods correlate with each other.

And it gives you an opportunity then to try to correct potentially for measurement error that you've observed in your main dietary assessment instrument, such as a food frequency questionnaire. So in the FFQ used, the average assessed sodium intake was about 2,500, give or take milligrams a day. And then for the biomarker calibrated sodium, that was 2,900 like we said. So you're getting slightly different estimates. You're getting a slightly higher estimate with the biomarker calibrated sodium intake. but this is really giving us an insight into: A) the challenges of assessing sodium with a degree of accuracy in nutritional epidemiology; B) the fact that food frequency questionnaires and those types of dietary assessments are poor reflections of sodium intake, urinary samples are typically the best.

But even calibrating against a subset of the cohort based on a single 24 hour measurement is likely to have a substantial error and that appears to be the with quite a big difference between the mean food frequency questionnaire, sodium estimate, and the biomarker calibrated sodium estimate.

Danny Lennon: And so maybe as a way to explain how that differs from some of those cross-sectional studies, I think this is an area where the concept of the background diet is probably really important to consider, as it always is, but particularly here for understanding what's going on and in particular looking at both the background sodium intake, but then also calcium intake and potassium intake and how that might lead us to get to different conclusions.

So one of the studies that's really useful here to look at was a randomized control trial done by a group at the MRC, so based out Cambridge, that looked at the impact of high and low calcium and salt and found some quite interesting studies findings. And there was some interesting elements to this. For this, do you want to kinda walk us through some of the interesting aspects of the study design here?

Alan Flanagan: Yeah, so this is the Teucher and colleagues study, published in 2009. And this was an interesting study because we've noted as we've gone

along and indeed with some of the epidemiology that yes, there is this potential relationship with sodium.

Mechanistically, the purported explanation is that it's related to the increased calcium excretion that we would have with high sodium intakes. But we also know that both of these calcium and sodium may also, if we're consuming a high amount, be increased in excretion. So there's a couple of interesting potential interactions and methodological approaches that can be taken.

So this study used a was a randomized crossover intervention trial, very strong design, looking at high or low salt intakes. So this was either 11.2 grams of salt in the high condition, which is 4.4 grams of sodium, or 3.9 grams of salt, which is 1.6 grams of sodium in the low salt condition. And it was also then looking at those high and low salt diets in the context of high or low calcium intake, which was over just under 1300 mg of calcium per day in the high calcium diet and just over at just 500 milligrams per day in the low calcium condition. And so these were followed for 40 days each dietary intervention period. So there was four conditions being tested. So there was: low salt/low calcium, low salt/high calcium, high salt/high calcium, high salt/low calcium.

So these four periods and they had a washout period of a month in between each of these diets where participants just went back to their normal day-to-day diet. And as we could expect from some of the mechanistic research consuming both a high sodium intake and a high calcium intake, both independently increased respective levels of sodium and calcium excretion.

But what was interesting is they both specifically increased urinary calcium excretion, so feeding high sodium. And a high calcium intake or a high calcium intake led to increased urinary calcium excretion. But what was interesting was that the increase in urinary calcium excretion was observed on, in the context of the low salt diet.

So that is coming back to what we said at the very start, where you have the ability for both of these to independently increase the renal load of these minerals and to increase resulting excretion. But what was I think probably the most interesting finding from the study was that the increase in urinary

calcium in response to the high salt intake was observed in participants consuming either low or high calcium diet.

Okay, to summarize, if you give people a high calcium intake, you will see an increase in urinary calcium excretion. But that's probably just a reflection of the increased level of calcium in the diet being absorbed. But if you've got actually low calcium intake and you feed someone high sodium intake, you'll still get an increase in urinary calcium excretion. And that's the finding that may be particularly relevant for obviously osteoporosis risk over the longer term.

Danny Lennon: Yeah. And this is one where there are some questions about, because the level of calcium has been seen as the thing that may determine how much of an issue salt is or not. So as you note that we have this adaptive capacity to. Increase calcium absorption in times where there is maybe low calcium intakes, but if we then have a high salt intake layered on top of that could be potentially problematic. Versus if someone has a high enough level of baseline calcium, the idea put forward as well, if someone does have a pseudo amount of calcium is even increased amount of salt problem for the bone. In the same way it would be if someone has low calcium and now they're having high salt intake as well. And so what we're getting at here is this idea of what is someone's level of calcium and if it's low or adequate, does that give us a different view on how much of an issue salt is? Which I think is a fair question for people to pose.

Alan Flanagan: Yeah, I think so. If you look at the actual levels of calcium excretion in that study, in on the high salt diet, there was, with the high calcium intake you had a, an excretion of about 51 milligrams of calcium a day. So you're certainly seeing an additive effect of both high sodium and calcium. And then what becomes difficult then is okay, we're going to get an increased re we're going to get an increase in calcium excretion in the urine, even if we just fed someone high levels of calcium intake.

So is it not just coming back to make sure you're getting adequate calcium? And that's the main take home point and the actual level of, in milligrams per day, excretion of urinary calcium with the high salt intake when it was on the low calcium diet was 18 milligrams per day. The question then is, okay, that appears to be a much smaller magnitude of effect.

But actually, if we're talking about feeding a high salt intake with a low calcium diet, versus the high calcium diet with the high salt, yes, there is a difference. That difference could reflect just simply the increased calcium load in the high calcium condition.

It's still suggestive of an increased calcium excretion in urine. Where you've got a high sodium intake and a low calcium intake. Although the magnitude of that certainly differs relative to the level of calcium.

Danny Lennon: For the moment we're going to put that calcium is something that should be taken into account and certainly for as we discussed in our previous bone health episode, we probably don't want to be recommending low calcium intakes anyway. And then we have this question of, okay once adequacy there is achieved, how might that impact this issue around, around sodium? One of the other aspects then that we could look at is potassium. And this relationship with potassium and sodium is something we've noted in other outcomes in cardiovascular disease outcomes in previous episodes, but rears its head here as, as well.

And there's a few different ways we can take this. I think one of the reviews we had noted was one from Cashman and colleagues, and there's some others in this area as well. I think Robert Heney has a nice piece on the potassium and sodium stuff too. So from here what do we see? In this impact of potassium, and does this actually allow one to prevent any of these negatives that we're seeing with the high sodium intake, once we're getting enough potassium? What does the literature seem to indicate here?

Alan Flanagan: Yeah, it does seem to suggest that you have an attenuating effect of the addition of potassium. And one of the nicest, in terms of well-designed interventions ,was from Sellmeyer and colleagues, and it was published 20 years ago in the Journal of Clinical Endocrinology and Metabolism. And it's referred to commonly in the review papers, but essentially they looked at the effects of differing levels of salt with or without supplemental potassium in postmenopausal women. So they were and, again, in terms of a really well thought through methodological approach, what we've discussed before with nutrition RCTs is not considering maybe baseline levels of intake. And it's always a contrast between a spectrum of intake of a nutrient. So what they did was they did a three week run-in period where the participants were consuming five grams of salt a day, so a low sort

diet for a run-in period, and then they were randomized to either consume 13 grams of salt today. So a big jump up then in that salt intake, or they were randomized to the same level of salt; 13 grams of salt a day, with the addition of 29 grams of potassium. And what you saw in terms of urinary calcium excretion was the high salt intake, jumping from five grams to 13 grams of salt a day did bump up, highly significant increase in urinary calcium excretion, but actually the addition of that 29 grams of potassium to that 13 grams of salt all but abolished that increase in urinary calcium excretion. So very suggestive that the increase in calcium excretion and the increase in markers of bone resorption of this process of bone mineral breakdown what wasn't just attenuated necessarily, the effect was entirely abolished by the addition of that high potassium intake to that salt load.

Danny Lennon: If we think back through some of what we've just said, we have thinking about sodium intake, thinking about calcium intake and thinking about potassium intake. And that's going to be important when we get to some practical conclusions. But before we get to that point, I did want to revisit something we had opened a tab on earlier in thinking about other factors beyond background diet that could have a difference on the conclusions we may get from different studies or that we may see in practice. One of which that you mentioned earlier was potential sex differences between men and women. And then there's also been a decent amount of literature looking at differences between pre- and post-menopausal women here, and the impacts on that with regard to either or both of these. What do you think are maybe some fair conclusions to come on of where do we see differing results, maybe in this area or are there particular groups, based on sex or age that we might see higher risk from sodium intakes or other groups where it's probably not as much of a concern?

Alan Flanagan: Certainly as in relation to bone health and dietary interactions with bone health over the lifespan, a lot of what we're seeing here is not necessarily either novel or inconsistent. It is a feature of the bone health and diet literature that there are variations in risk associated with sex where women tend to be at higher risk than men. And where that risk is also further stratified upon menopausal status where there typically is an increased risk in the postmenopausal period relative to premenopausal. And that relates to the loss of ovarian estrogen production and again, this explains the general sex difference in bone health risk over the lifespan. But there is typically a protective effect of estrogen. And of course with the shift in the

postmenopausal period, there can often be then an increased risk of osteoporosis in postmenopausal women.

A lot of the interventions have been conducted in post-menopausal women that have suggested attenuating or abolishing effect of a hypo-potassium intake. And the observational data that we have again suggesting potentially differential effects based on menopausal status.

Although I think even with that and the limits of the observational epidemiology in this area the preponderance of cross-sectional rather than prospective data and the discrepancy in the findings between some of the cross-sectional and prospective data I don't know that I would be to any hard conclusions as to where the apportionment of risk truly lies, from that research alone , that would be anything above and beyond what we would ordinarily just conclude in relation to bone health status, which is this potentially higher risk in post-menopausal women.

Although as noted earlier, one of the Korean studies did find the was stronger in premenopausal women. So yeah, I think overall the increase in bone resorption markers that is typically observed. In the postmenopausal period is something that is known just outside of the sodium and bone literature. There are sex-based differences hormonally that may explain some of these findings. And overall, a lot of the intervention trials that are suggesting this effect modification of calcium excretion and bone resorption markers is in postmenopausal women. But yeah I don't know that there's anything necessarily novel in any of this as it relates to bone related outcomes.

Danny Lennon: And certainly I think a point, just to be clear for people, is that when we start talking about things like calcium excretion and sodium excretion, that always isn't a discussion about dietary intake, for example. And we can get shifts in these things for a variety of reasons and if we're talking about a population of post-menopausal women here, I think one of the findings that you do see is this increased calcium excretion over time that happens in that period that isn't just down to changes in sodium or calcium intake per se, that this is something that is obligatory that occurs at menopause.

Some of the interesting things I found that area has been published by Borge Nordine in the early nineties, and some of that showing that while we do

have this correlation between calcium and sodium in fasting urine in all women, whether that's pre or postmenopausal, that there is more calcium relative to sodium in postmenopausal women. It seems at least from some of that work. But then the bigger point was that we have this twofold issue of in general, this increased calcium excretion that happens at menopause. And then potentially that you could have a higher fasting urinary sodium, which then theoretically could mean even more calcium excretion.

And I think wha that research group put down to this increased fasting urinary sodium was representing a delay in sodium excretion, and so potentially there if you have this higher sodium excretion, because of that, potentially you get more calcium excretion that would be on top of an already higher calcium excretion due to menopause and age as we outlined earlier.

But by and large, the main point that I'm trying to make here is that some of these are physiological changes that are occurring with age and changes in hormones that are affecting things like calcium and sodium excretion that are different questions per se to just looking at dietary intake.

So just to flag that, to be clear for people I guess. I think maybe one final thing before we get to some conclusions is just on a, when we're looking at research in this area and what we might want to keep an eye out for is, as we've noted, there's many things that could modify this relationship, but one that maybe isn't always controlled for in some of these that probably should be based on something you said earlier is physical activity. Because you noted how much of a modifier exercise can be, and so if we're not accounting for that could potentially be a problem.

Alan Flanagan: Yeah, there are factors that are obviously dietary related. And then there are non dietary lifestyle factors that are crucial in terms of the potential rate of bone mineral density loss over, over the lifespan and from peak bone mass onwards as people age. And of these various factors physical activity or mechanical stimulation of the skeletal system is one of the most important. It appears factors in influencing not just the stimulation of the bone building and uptake processes that occur. And obviously by implication preservation of bone mineral density and mineral content and lower osteoporosis fracture risk and otherwise.

So this is something that is a. Acrucial factor in the equation, and yet it's not necessarily something, at least in the epidemiology that is often, considered or accounted for. If we, consider some of the, epidemiology of this and you look at, say, for example, some of the adjustment models that have been used.

You're often seeing things like age, sex, BMI and smoking status, alcohol. And these are fairly typical fairly typical factors that are adjusted for in models, in epidemiology. But so is physical activity. There are ways of quantifying it in terms of observational research metabolic equivalence or other, or even just minutes per week in a more crude estimate.

It is just a factor to bear in mind that a really crucial effect modifier is often in some of the observational studies not well accounted for. And this is something that could be, and lightly is playing a very important role in the overall picture. So not accounting for it is really leaving an important variable out of the analysis.

Danny Lennon: Okay. So maybe to finish on the pragmatic conclusions from at least a dietary perspective, which what really the initial question we set out to address was looking to get to. So in a roundabout way, we've maybe hopefully explained some of the background mechanisms and some of the work there. But on a very direct answer to that question, really we are left with twofold thing that I'll ask. Based on anything we've discussed here, is there any reason you would suggest that we might need to change either: 1) sodium intake recommendations at a general population level that are different from the typical limits that are set, which are mainly based on cardiovascular disease? And 2), on an individual level, is there any reason to think that sodium intakes within those typical limits might need to be decreased even further on the basis of bone health? Is there anything specific about bone health here that you think would any differential recommendations for sodium intake?

Alan Flanagan: No, not really. I'm not even particularly convinced based on the available research that, that we can even come to any strong conclusions in relation to sodium and bone health.

Certainly not in contrast, for example, the conclusions that we could come to in relation to hypertension, stroke, cardiovascular disease, where, you're

capable of really of forming a much more robust evidential support of the causal chain between those factors and those outcomes.

I think with this literature it's quite messy. We have better experimental data on the relationship between increasing sodium intakes, leading to increased urinary calcium excretion. We have good experimental data, some of these nicely controlled crossover, randomized controlled trials where we've got evidence of an attenuating effect of potassium, which is something that we would generally recommend for sodium and cardiovascular disease, where we've got evidence that higher calcium intakes are preferable to lower, which is just consistent with general bone health research, and I don't necessarily see anything in terms of the experimental research or even the epidemiology that would suggest that there is a more unique recommendation for sodium, that are different to our current general population advice, which largely is derived from cardiovascular disease risk reduction levels.

And yeah, and I don't even yeah I wouldn't be confident making any sort of strong conclusions about the isolated role of sodium in relation to osteoporosis based on the current literature, and how deterministic that is, as a factor. Whereas obviously, we can come to some stronger conclusions as it relates to cardiovascular disease.

So I don't think best practice nutrition advice for bone health changes in this context. I don't think the general targets for sodium intake change based on the sodium and bone health research. And I'm not even entirely confident of this literature as it relates to sodium or the role of sodium specifically in terms of long-term osteoporosis risk.

Danny Lennon: So in relation to our initial question, we have that overall there is evidence showing that with increasing sodium intakes, you're going to potentially get increased calcium excretion. However, for actual more hard outcomes, let's say for things like osteoporosis or even changes in bone or fractures or any other outcome like that, we don't have a really good solid evidence base that we could have really any confidence in to even conclude high salt intakes are actually having these clear negative impacts on bone in above themselves and of the evidence we do have. We could probably see that there are, if the focus is bone health, other nutrients and other dietary interventions that we'd have much more focus on that would probably do you fine.

For example, we mentioned calcium or potassium, or in our bone health episode we focused in on calcium, vitamin D, vitamin K potentially things like phytoestrogens. But there are other areas where one would place their focus. That probably looking at sodium in itself is probably not where you would go right now.

And even within that, there's already enough reason from other outcomes, predominantly cardiovascular disease, but also beyond that too, that we would already have limits for people's sodium intake, that it shouldn't be excessively high anyway. So all that leads us to say is that by the end of this discussion, working kind at a point where don't worry about any differential outcomes based on current literature for sodium and bone health.

So with that thank you Kate for the question. Thank you everyone for listening. Hopefully found this useful and at a way of walking through some of the literature. We'll be back with another episode very soon. I hope you are enjoying the podcast. And with that, I hope you have a great week and let you stay safe and take.