Kendall Williams, MD: Welcome everyone to the Penn Primary Care podcast. I'm your host, Dr. Kendall Williams. So we talk about things on this podcast that confuse everyone as primary care physicians. And I usually choose things that confuse me as good topics. So I found myself confused about a lot of things related to calcium and vitamin D, and I thought I'd ask two experts on to talk to us about it.

You have heard these voices before? They were on with one of our earliest podcasts on diabetes, so I invited them back. They are the co-directors of the endocrinology medical student course, so they're very comfortable teaching a lot of these concepts. So I've invited back Dr. Carrie Burns who is the professor of endocrinology at Penn. She is the director of the Diabetes and Pregnancy Center. Carrie, thanks for coming again.

Carrie Burns, MD: Thanks for having me, Kendall.

Kendall Williams, MD: And Dr. Christina Mitchell is an associate professor of clinical medicine in the division of endocrinology. And as I mentioned one of the great teachers of endocrinology at Penn with Carrie, they teach medical students and residents and fellows. And so they're frequently teaching about these issues. And today we're gonna do a popery of calcium problems. We're gonna talk about vitamin D. We're gonna talk about hyperparathyroidism and some hypercalcemia generally. And then I think that there was just some residual questions on osteoporosis, particularly in the use of infusion therapies that I thought would be helpful to review with them.

So that's what we're gonna cover today. So Christina, let's start with you. You teach the med students, let's talk about calcium metabolism generally. Talk about the role of calcium, where it's stored, Vitamin D and PTH, cause those are the big three that we're gonna be covering today?

Christina Mitchell, MD: Sure. In fact, this is the lecture that I give to the med students. the first lecture I give is the calcium metabolism and parathyroid lecture. So it's, Thank you for that question. And for the introduction. so calcium metabolism, we think about things in terms of the normal physiology and then the pathophysiology. And suffice it to say that parathyroid hormone and vitamin D, which is also a hormone work in concert to maintain a normal blood calcium. Effectively vitamin D helps to absorb calcium from the gastrointestinal tract, although in its hormonal role, it's also a co-factor for bone mineralization and plays a major role in the bone remodeling unit.

So, as our skeleton is undergoing normal remodeling, we have these bony pits where we're breaking down kind of demineralized bone. The osteoclast is doing

that and then there is new bone mineralization by the osteoblast. Vitamin D plays a key role in that remodeling step with the bone remineralization. But in any case, in normal physiology, our calcium levels are, kind of always ebbing and flowing and in order to maintain homeo. Vitamin D and, parathyroid hormone will work together. PTH produced by one of the four parathyroid glands that most of us have Their location is their name, parathyroid, para meaning near or beside the thyroid gland.

And effectively they will parathyroid hormone will take calcium from the greatest depot of the body, the bone, in order to maintain a normal blood calcium level. The way I like to describe it to students in the course is that if one or more than one of those parathyroid glands goes rogue, so to speak, and develops an adenoma, or alternatively, if there's multiple gland hyperplasia, there will be excess production of parathyroid hormone and then all of the normal physiologic actions are magnified. So effectively you'll have excess loss of calcium from the bones.

And in that way, hyperparathyroidism is a risk factor for osteoporosis. The parathyroid hormone also in its normal role will stimulate the, hydroxylation of vitamin D in the kidney so that you'll have the active form of vitamin D. And so that will happen then in excess as well. And so ultimately you have a couple different mechanisms through which you can develop hypercalcemia as a result of excess parathyroid hormone production by the glands.

Kendall Williams, MD: So taking it out of bone when parathyroid hormone is high, and you're also stimulating vitamin D. And so it's doing its job, which is partly to increase absorption from the gut, right? So both of those mechanisms are leading to a higher calcium. And the downside, if you let that happen and keep going over time, it's not only the effect on what it means if your serum calcium levels are high, but also the depletion of bone reserves and osteoporosis.

Christina Mitchell, MD: Right.

Kendall Williams, MD: So let's talk about vitamin D because vitamin D is a confusing thing, it's partly the names I think. There are two native forms of vitamin D. Vitamin D2 is ergocalciferol. Vitamin D3 is Coate Calciferol. Vitamin D three is made from the sun but from the sun interacting with our skin, it's made internally. We do not, as I understand it, make vitamin D2 in the body, but by do make vitamin D3. Vitamin D3 can also be obtained from animal sources, presumably animals that have themselves made it from the sun.

And then we eat, so you have vitamin D2 and vitamin D3, Vitamin D2 from

plant foods, right? Mushrooms and some other places. And so, there's no real meaningful difference. However, in the body between Vitamin D2 and vitamin D3, they are. Sort of pro hormones, if you will, for the eventual hydroxylation process that will lead to the die hydroxy vitamin D that will eventually be formed after hydroxylation in the liver, in the kidney, right?

Carrie Burns, MD: Right. I think that's a great summary.

Christina Mitchell, MD: Yeah, it is.

Kendall Williams, MD: Okay, so we have Ergocalciferol, coli calciferol, vitamin D2, vitamin D3, So this leads to a question of how much, how do we get vitamin D deficient? It's either from decreased intake from the gut or from lack of access to the sun, or both, Right,

Carrie Burns, MD: Right.

Kendall Williams, MD: Vitamin D deficiency is very common.

Carrie Burns, MD: Correct. Most of the vitamin D that we have that is available is from the sun. It's difficult to obtain enough from the diet, as you know milk is frequently supplemented with D most of the time. I think every, homogenized milk product has vitamin D. And other than what you mentioned, Kendall mushrooms the fatty fishes have probably the highest amount of dietary vitamin D. So that is why vitamin D deficiency is so common, especially in this part of the world in the latitudes that are further from the equator. The other items that cause vitamin D deficiency would be using, sunscreen, being institutionalized. Being in an inner city.

The more pigment you have in your skin, the less efficient you are at the hydroxylation of D in your skin. Although there is. confusion about how we measure vitamin D in different populations. So we may not be always measuring vitamin D correctly as there's different vitamin D carrier proteins in different populations. So it's unclear for always measuring vitamin D correctly. Obesity also seems to be a risk factor for low vitamin D.

Kendall Williams, MD: I remember reading that the amount of sun you need in order to produce enough vitamin D is 15 minutes of sun a day on your elbow.

Carrie Burns, MD: I think forearms.

Christina Mitchell, MD: So, it's, interesting. That's a question that comes up a lot in the student course actually. And what has been defined is that a full body,

minimal erythema dose, so meaning that, head to toes the body completely exposed that if one full body minimal erythema dose would result in the release of 10,000 to 20,000 international units of vitamin D into circulation. And by minimal erythema dose, that's about probably about 15 minutes for most of us, where unprotected exposure to the sun is causing some redness to develop of the skin, some inflammation and releases about 10,000 to 20,000 units of vitamin D into circulation.

Kendall Williams, MD: Reminds me of the rule of nines, when you were learning about burns, you to try to divide the body up into different percentages. So if you're getting that much vitamin D, most of us aren't going out and standing naked in the sun every day, thankfully to my neighbors will. Thank me for not doing that. But you're getting a percentage of that if you're exposing, so vitamin D deficiency is mostly sun deficiency is your point, right?

Carrie Burns, MD: Yes.

Kendall Williams, MD: So, vitamin D is then, comes into the body through those mechanisms. It's then as we noted, hydroxylated in the liver. It's then known as Calcidiol. And that is the major storage form, which is what we measure when we measure vitamin D levels. Right? Even that's not the act of hormone, right? But that's what we measure. 25 hydroxy vitamin D.

Christina Mitchell, MD: Correct and then I think that's really clinically relevant. I think that point's really clinically relevant because I will say that sometimes patients will come to the office with a concern about vitamin D deficiency or even vitamin toxicity. But what has been measured leading to that visit is actually 125 dihydroxy vitamin D. And these are usually referrals from outside the health system. I will say that it's become more clear in our electronic medical record. what we should be measuring for, to assess vitamin D stores as far as measuring 25 hydroxy versus 125 dihydroxy. but it can be, that can be confusing since both of those lab orders are available. But we do the 25 hydroxy is what we use to assess vitamin D. Deficiency Insufficiency, sufficiency. Whereas the 125 Dihydroxy D, we reserve for evaluation of folks with hypercalcemia.

Kendall Williams, MD: And then when we're supplementing vitamin D we're giving vitamin D2 or D3. as we mentioned, the Ergocalciferol Coli Calciferol. And it doesn't really matter which you give if you're supplementing it. Is that right?

Carrie Burns, MD: I think vitamin D3 is thought to be more bioavailable. Ergocalciferol was a little more popular, I would say, five to 10 years ago and

was used more as a quote unquote loading dose. Patients whose vitamin D levels were found to be quite low, maybe in the 10 to 20 nanograms per deciliter range. And we would dose with 50,000 international units of ergocalciferol weekly for about three months, and then go revert to a maintenance dose. I find that we're not doing that as frequ3 it could be a slippery slope because sometimes that prescription gets renewed and patients remain on that 50,000 international unit dose per week and can be at risk for vitamin toxicity, which could lead to hypercalcemia for one thing.

So I think that's fallen mostly out of favor, and I think the availability of D3 in the marketplace for patients to purchase is so much more available than it was 10 to 15 years ago. So, mostly you'll see D3 available in most supermarkets and pharmacies for patients. And that's typically what we recommend are maintenance doses of D3.

Kendall Williams, MD: And Carrie, this gets to the issue of item D deficiency and how we treat it and so forth. If we test for it and we want to supplement. I mean, one thing we could tell people is to get more sun exposure, as you noted. The other thing we'd wanna do is to then supplement it with vitamin D3 and now how much are you telling them to get and take?

Carrie Burns, MD: Right. I think the concept of vitamin D sufficiency is becoming more popular, I think with recent data and the literature, vitamin D is not the panacea that has been hoped for. And idea of the goal being sufficiency therefore for most 800 to 1000 international units daily should be enough. I would say the high end of the RDA I believe is 5,000. So taking 5,000 per day should not result in toxicity. But once you may go above that, dose, which is easy to do with over the counter products, may be at risk for vitamin D toxicity, since it's a fat soluble vitamin. So I think for most I would say 800 to 1000 international units daily.

Kendall Williams, MD: And other than osteoporosis, are there other situations in which you are routinely testing for vitamin D?

Carrie Burns, MD: I personally am not.

Kendall Williams, MD: Yeah, it's not recommended per se. I wanted to highlight that. Yeah.

Carrie Burns, MD: Right. Absolutely. And, this is a test that should be done at the most yearly in a patient that has osteoporosis. The 25 hydroxy concentrations in the liver do not change rapidly. Therefore, a dose increase in a supplement should not be tested again in a few months unless there's primary

hyperparathyroidism going on, perhaps. But in someone who has osteoporosis and. You're checking to see if someone is vitamin D sufficient. For example, for one of the treatment options, yearly is definitely enough to test and won't be paid for lack of a better way to say it by most insurers including Medicare, if it is measured more than once per day, I think it's reached a target status for insurance companies because that's a, costly test that's being over ordered.

Kendall Williams, MD: I'll have patients come in to me not infrequently to ask me to check their vitamin D because it had been low in the past and they want me to check it. It happens, I don't know, a couple times a month. So I, might check it in that circumstance, but I really shouldn't be, should I?

Carrie Burns, MD: If there's a history of deficiency, I think it's okay to check in occasionally. I don't think that's outrageous.

Christina Mitchell, MD: And I wanted to mention and, we may get into this in a bit. Regarding the osteoporosis reason to check it, as for example, a secondary risk factor. Vitamin D deficiency is a secondary risk factor. And again, we may get into this, but as part of just kind of the evaluation for other secondary risk factors for osteoporosis, one of those risks is excess loss of calcium in the urine, hypercalciuria. and in fact we must know the patient's vitamin D status before we have them do that onerous 24-hour urine collection. Because a low vitamin D I mean actually probably anything less than 25 nanograms for deciliter is associated with a spuriously low urine calcium.

So that you kind of can't rely on that urine calcium result unless you're pretty sure that their vitamin D is okay. Now, if it was checked six months ago, I don't necessarily need to recheck it, but the idea that you need a something that's probably been done at least within the year to make sure that you're not gonna have a spuriously low urine calcium.

Kendall Williams, MD: So before we leave vitamin D, is there anything more to be said about it from your perspective, things you see in practice that maybe primary care physicians should know more about?

Christina Mitchell, MD: I'm gonna mention, I'm gonna mention the liver here because I feel at Penn we're such a big transplant center and honestly just the rise of cirrhosis secondary to fatty liver disease. obviously we see a lot of patients, with incidental discovery of hepatic theosis and fatty liver disease, and unfortunately sometimes that progresses to fibrosis and cirrhosis. But Liver disease becomes another risk for very low vitamin D levels. And certainly if the liver synthetic function is impaired, you're not gonna have that hydroxylation, that 25 hydroxylation of the vitamin D.

But there may also be an impairment of absorption too conferred by liver disease, so that's a population too that I find is very deficient in vitamin D and can require very high doses of vitamin D supplementation. And actually as dare I say that I will sometimes use ergocalciferol in those patients just by virtue of being able to get it in that 50,000 unit dose in order to kind of overcome the issues with absorption for some of those liver patients.

Carrie Burns, MD: I think another population that we are seeing more of is the transplant population and due to the immunosuppressants, they are at very high risk for skin cancer and are read the riot act in regards to prevention of skin cancers and wearing sunscreen and avoiding the sun. So that might be group that you may wanna screen for low vitamin. Besides your institutionalized inner city patients.

Kendall Williams, MD: I suppose it also should be said if somebody has markedly low vitamin D levels, then, being a fat soluble vitamin, we should be considering other malabsorption syndromes like celiac disease or other things. So, I dunno if you have any comment on that, but.

Carrie Burns, MD: I'm concerned typically if someone has of either B12 deficiency and vitamin D deficiency, that there may be either celiac disease or IBD or some other sort of mal-absorption in the small bowel perhaps.

Kendall Williams, MD: Well, that was great. I mean, Vitamin D can be very confusing in all the different names and how different forms and so forth and how you supplement it. So that was very helpful. So let's talk about high calcium levels. We all had this board question that an outpatient and we had to learn it for the boards. The answer to the question, what are the most common causes of hypercalcemia? And we all learned that in outpatient settings, primary hyperparathyroidism is the most common cause of hypercalcemia. And in the hospital it's metastatic cancer, usually due to breast and so forth.

But let's talk about you get a calcium level. It's high, the patient's feeling fine, but it's maybe 11.4. And Christina, what do you do with that information? If it comes to you? What do start to test?

Christina Mitchell, MD: I'm lucky that in so far as typically someone isn't coming to me until they've already had the PTH done. So in some ways, that heavy lifting has already been done by the time they're arriving at an endocrinology visit. But definitely that first decision point or that tree. Is it PTH or non PTH mediated? And when it's PTH mediated, which are typically the patients we're seeing then. the next question is asymptomatic versus

asymptomatic. And these are fairly defined terms in so far as we consider symptomatic, someone who has had a fragility fracture or someone who is a kidney stone former in the past or in the present, or maybe even has asymptomatic stones in the cortex of the kidney.

So these would define the symptomatic patient. The asymptomatic patient. IE. No recent fragility fractures or stones is someone that may also meet criteria for surgical intervention. Certainly the symptomatic patient has bought themselves consideration for surgery for Parathyroidectomy, but there are a number of criteria for the asymptomatic patient as well.

Kendall Williams, MD: So it's not the calcium level per se, or even the PTH level per se, that lead you as an endocrinologist to then refer to surgery? Well, in the asymptomatic population, I suppose it is the PTH level, right?

Christina Mitchell, MD: The asymptomatic patient calcium level is one of the defining characteristics. So protocols that stands now if the calcium is one above the upper limit of normal for the lab. So I, can quote that our lab. If I'm still correct about this, is 10.3 calcium milligrams per deciliter, that's the top normal. So the calcium that you quoted of 11.4 would actually meet muster being greater than one above the upper limit of normal for the lab. That's one possibility for the asymptomatic patient that would qualify them for surgery. Having the presence of renal insufficiency, so a creatinine clearance less than 30 becomes a reason that that person may be a candidate for parathyroidectomy.

Having osteoporosis on Dexus scan is a qualifying feature to consider parathyroidectomy and age less than 50. Years is another feature. And couple reasons for that. One, the longitudinal studies that have looked at hyperparathyroidism and progression shows that if you're diagnosed before the age of 50, it's very likely that you're going to meet one or more than one of these criteria at some point in your later life. So intervention then is warranted. And the other part of it is, is that you're more likely to potentially have a syndrome that causes hyperparathyroidism if you're diagnosed before the age of 50.

Kendall Williams, MD: Like an MEM syndrome you mean?

Christina Mitchell, MD: Right. And one of the multiple endocrine neoplasia type syndromes. Yes. As being responsible for causing hyperpara or even autoimmune polyglandular syndromes as well.

Carrie Burns, MD: And just a word about the parathyroid concentrations. So I think in endocrinology, Dr. Mitchell and I are familiar with the concept of

inappropriately normal hormone concentrations in a couple of situations. So parathyroid hormone is one of those situations if there is an elevated serum calcium and there is a normal, in the normal range, parathyroid level, that's inappropriate. So with an elevated thinking about feedback loops and thermostats, if there is an elevated serum, Calcium parathyroid hormone should be low, almost nil.

So if one has a comfortably normal in the middle of the normal range, parathyroid hormone concentration with a calcium in the 11 range, there's your diagnosis. Most patients do have an elevated parathyroid hormone level when that is drawn, but typically not terribly high, usually up maybe two times the upper limit of normal is where they usually are. But I would say most patients have an elevated PTH at the time of diagnosis. Again, depending on how long this has been going on. But there are many that have parathyroid hormone concentrations in the normal range.

And I think it's important to know that most of our patients have calciums that have been noticed relatively quickly because of the availability of serum calcium levels on comprehensive metabolic panels or basic metabolic panels.

Kendall Williams, MD: So that's interesting, Carrie. So if you have a, if you have hypercalcemia and you get a PTH back and it's normal, that can be inappropriately normal and that can still mean they have primary hyperparathyroidism. I just wanna highlight that point because I think that's a point that a lot of us don't know. And I don't keep the upper limit of parathyroid hormone levels in my head. I don't know if you do, but I don't know. Is it four or something like this?

Christina Mitchell, MD: Well, I know Op Pen has a very, our assay, So the assay at Penn is its own unique assay and I believe the top normal for our assay is 6.4. I believe it's 6.4, whereas if you get labs back from LabCorp picking on them just because they're the preferred for ibc. So of course we get a lot of Labcorp labs back. I mean, I think their top normal is 72 obvi different units, mind you. It actually becomes really relevant at that point. Because I will tell you that I recently had a patient who, I saw the PTH flagged. The person has hypercalcemia. The PTH was Suffice it to say that I assumed it was from, the Penn lab and it was not, and so actually the PTH was not high.

It was in fact low. And when I did not pay attention to the fact that it was, I only took note of the flag and not where the lab was coming from. And the designation of high versus low and of course, obviously a very different treatment strategy. So, thankfully that error didn't reach the patient, but it becomes relevant that we use a completely different ass. With a very different

reference range than the commercial labs that we often get results from.

Kendall Williams, MD: So to summarize on this if your calcium is high and your PTH is normal or high, then the patient has likely hyperthyroidism. The decision on surgery is going to depend on the factors You mentioned, Christina, a GFR less than 30 and age less than 50. Presence of osteoporosis. So I assume anybody that comes to you in this situation, you will do a dexa scan, a woman over 50, for instance, you'll do a dexa to assess for that, right? Is there anything else you do?

Christina Mitchell, MD: I'll mention here that the workup one of the criteria that I didn't mention because it's actually not part of the criteria anymore, is a 24 hour urine calcium greater than 400. The idea that hyperparathyroidism Causes, Hypercalciuria causes loss of excess calcium in the urine. So you would expect the urine calcium to be normal to high. And in fact, it used to be one of the criteria that if you had a very high urine calcium. See normal for women being less than 200 milligrams per day, normal for men being less than two 50 milligrams per day. That if you had a urine calcium greater than 400, that that also met mustar for surgery.

That criteria has been removed, but it's relevant that a condition that can be confused with primary hyperparathyroidism can present with the serum values looking very similar, but have a very low urine calcium. And that's, what goes by the acronym? FHH familial Hypo Calciuric hypercalcemia.

Kendall Williams, MD: which is very common. I, don't recall the actual data. It's 1%, 10%. It's some sort of round number percentage that's fairly high on a population level?

Christina Mitchell, MD: It's an autosomal dominant inheritance. So I, think it's along the lines of one to 3% as far as the incidence of that goes. But what's really relevant is that before I would ever have the patient consult with endocrine surgery, I do check a 24 hour urine calcium to assess for that. There are some things that to be aware of when you do that 24 hour urine calcium. If someone is taking hydrochlorothiazide. which of course is such a common blood pressure agent, and so many of our patients may be on it. They are going to have a low urine calcium.

That's just through its mechanism of action, it inhibits the loss of calcium in the urine, so It becomes difficult to use that as a deciding factor if someone is on each hctz because of that issue. And then another thing just to be aware of is if someone is taking a calcium supplement. Now, admittedly, If you're working them up for hyperparathyroidism, you, perhaps you've already told them to stop

the calcium supplement. I think most of us would have done that at that point. But if they are actively taking a calcium supplement that can cause a spuriously high 24-hour urine calcium. So, I do ask patients to hold it for a few days before the collection. And on the day of the collection.

Carrie Burns, MD: But I think that's important, Christina too, for patients with osteoporosis that may have a normal serum calcium, we do a urine calcium collection as part of that evaluation. So I think it's important for 24 hour urine collections in general, for whichever purpose you're performing them to have your patients stop calcium supplementation. I usually stop them two weeks before the collection to make sure it's not affecting the measurement.

Kendall Williams, MD: What's a circumstance in which you're comfortable simply monitoring a patient with primary hyperparathyroidism without sending them to surgery. And what percentage of patients are you doing that with?

Carrie Burns, MD: I would say a patient that does not have a serum calcium above one microgram per deciliter above the upper limit of normal. Maybe a patient who is older, , in their eighties or nineties in which the long term effects of elevated serum calcium won't affect longevity or cause any end organ damage. A patient maybe in which surgery is not safe and there are other medication. Such as Cynic Cal that could be utilized or sometimes even biphosphates are helpful to help control elevated serum concentrations in patients who are not surgical candidates. I think those are the main populations.

I think I see a lot of patients, maybe I uncover their elevated serum calcium myself on their metabolic panel. I see them for diabetes, for example. And it's slightly elevated, so I monitor them. Maybe I'll grab a PTH the next time I measure it. Frequently, I find our lab has spuriously, high serum calciums from time to time, I feel sometimes they go in cycles. I feel like I'll have really common calciums in the 10.4, 10.5, 10.6, and the next time I check it, it's resolved. It's normal. There are other medications you have to think about besides the thiazide diuretics. Lithium is another one. I don't think we also talked about vitamin A supplementation can cause elevated serum calcium.

And that might be something that comes and goes as patients may take supplements and then maybe run out of them. So maybe one time they're taking the supplements in high doses, and then the next time they see you, they've stopped. I've seen in my patients that have diabetes who may be read up on supplements. Bitter melon extract is a common supplement that patients with diabetes sometimes take and that can elevate serum calcium, sometimes So those are patients I'll monitor, and maybe the next time I see them, I'll measure a serum pth.

Kendall Williams, MD: Those are really all valuable insights. We all get these labs back and we're Stuck trying to figure out what to do. I have the advantage of having Carrie pass by my office a couple times a week, so I'm able to ask her if she walks past. But for the rest of us, we're trying to figure these out. So let's move on to osteoporosis because we had a great podcast with your colleague Mona Almukadam, which I. think everyone should listen to. It was very informative and Mona was terrific. But there's some residual issues since that podcast, which was about a year ago. I know for me, I've diagnosed more patients with osteoporosis.

I've had patients come to me who are already on prolia or one of the other infusions and asking me to order it and so forth. And so I wanted to kind of go through this a little bit, focusing a little bit on therapy specifically. So, most of the time I think for many of us, internist, we diagnose somebody with osteoporosis and our reflexes to do Fosamax weekly. Which is well tolerated. Carrie, a question I asked you before and probably one of our hallway conversations is, when do you just jump right to zoledronic acid or consider Demusemab as opposed to just starting somebody on Fosamax?

Carrie Burns, MD: Right. So I do like to use, resendronate or alendronate as first line, especially for patients who maybe have T scores around 2.5, maybe 2.6, 2.8, not in that negative three to negative 3.5 range. If, especially if they have not had a history of fracture. So kind of your entry patient. I think resendronate and alendronate are great treatment options. They're inexpensive, they're for the most part well tolerated and are really effective at preventing fractures . And I think for the most part, I do like to use them first line. When do I think about zoledronic acid? I think if there's. been a history of intolerance. Patient has tried alendronate and had intolerance, which is usually in the form of reflux.

Occasionally diarrhea or constipation or that's usually the situation. So if someone has a history of severe reflux, I think about starting with zoledronic acid. However, if someone has not tried alendronate or resendronate, I usually ask them to give it a try. Because usually the reflux, if it's taken appropriately, occasionally I'll have a patient that does have new onset GERD with an oral, a bisphosphonate. For the most part though, they are well tolerated, so usually I give it a try. But if, someone has a history of severe GERD or prior into erancel I would go straight to the zoledronic acid or if it's someone that can't do the protocol of how to take alendronate correctly.

So just to review that that is taking the tablet once weekly on an empty stomach, 30 minutes before food or other medications, and being able to remain upright

for a long period of time after that. , So not taking it at three in the morning and going back to bed. We have our, patients on Levothyroxin that sometimes do that, and that's not a problem. But doing that with alendronate is a problem. I also think about going to zoledronic acid if they've quote unquote failed alendronate or Risedronate as zoledronic acid is a notch more potent than, alendronate. So if someone's taking alendronate. Their T score was negative 2.6, and now you've done a dexa two years later it's, negative 2.7, but no history of fractures and maybe, you try zoldronic acid.

Christina Mitchell, MD: And I think to that point Carrie, you mentioned about, failure of the oral bisphosphonates and, perhaps that's going to emerge as a fragility fracture. I say, here, God forbid, but, and even then, you're not sure that it, would be failure of the med because of course there's just a high likely, I mean, there's unfortunately an increased likelihood in the presence of osteoporosis anyway, but this is gonna bring up something a little off, the beaten track in terms of evidence based. But there are, in endocrinology, we will sometimes use bone turnover markers.

The serum C tele peptide, not so much that the absolute value is helpful, but in other words, if you are starting a patient on an oral bisphosphonate and you check a baseline c tele peptide, so it is a marker of bone resorption, a marker of osteoclastic activity, you have a sense of what that baseline is. And if the patient is adequately absorbing the oral bisphosphonate, because that's the other thing, that they may be tolerating it, but whether or not there's adequate absorption is it becomes a question for many people. There is, for most people there, there is adequate absorption, but for some people there isn't very large nitrogen containing molecules.

Studies suggest that we probably absorb less than 1%, of the dose. But that's made up for concentration. So for example, alendronate 70 milligrams once a week versus Zoledronate five milligrams once a year, because you're getting an infused IV, so you're observing a hundred percent of it. But in any case, if someone is adequately absorbing the oral bisphosphonate, you'd expect that baseline c tele peptide to decrease significantly after a few months of therapy. So that becomes another way to kind of gauge the success of the oral bisphosphonate in addition to symptoms. Are they tolerating it? And then the future Dexa scan.

Carrie Burns, MD: The only issue with measuring the C tele peptide is frequently that's not being covered by insurance companies any longer as well. So that's something that. You have to just have a caveat that it may not be covered and maybe have a discussion with your patient about that. Because that's been a recent and a popular target of insurance companies of late to not

pay for that measurement.

Kendall Williams, MD: And so you have somebody on Fosamax, you treat them for five years and then you give them a holiday. Carrie, you mentioned a circumstance in which somebody might be on for two years and then you switch them to zoledronic acid, which I believe you do a holiday after three years, right, . So, I just wanna address that holiday issue.

Carrie Burns, MD: Right. So I think when these medications first came out I believe it was the 1990s patients were prescribed them maybe a little too frequently, maybe premenopausal, maybe with low bone mineral density and not true osteoporosis. So these drugs were really very popular and probably over-prescribed and prescribed for a long period of time. And that's when in the earlier two thousands you started to see these rare side effects come out such as atypical femur fracture and osteonecrosis of jaw.

The atypical femur fracture, which is still exceedingly rare, I would say somewhere in the one in 10,000 to one in 100,000 is likely linked to a dose dependent use of bisphosphonates. Both and denosumab. Denosumab is, not free from that. And osteonecrosis of the jaw, which is an unhealing ulcer in the mouth, usually after an extraction or perhaps an implant of a tooth. And it's very difficult to heal. Very upsetting to the patient. And that population in which that scene is, patients that are dosed frequently, zoledronic acid, frequently, patients with metastatic breast cancer, who are dosed quarterly, or maybe even more frequently, with zoledronic acid.

So the, but these effects started to become clear that they were likely linked to bisphosphate and denosumab, and that's where you saw the FDA come out. And basically that statement was they recommend five years of oral bisphosphonate therapy and three doses of zoledronic acid. But at that point you should reassess. So it's not like it's a hard stop. You should stop therapy. A reason to continue those drugs is if the patient still has osteoporosis. So if patient has been on, you start a patient on, they have a T score of negative 2.7 at the HIF. You treat them with five years with oral resedronate let's say .

You check a dexa at that five year mark and they're now negative 2.4. They haven't fractured. That's a great time to have a drug holiday. , Let's say that same patient has the same T score, maybe you continue it or maybe you intensify treatment. So if they have osteoporosis, they should still be treated and should not necessarily have a drug holiday. Sometimes switching medications is a good idea, especially in your highest risk patients. If they've been on one of those medications for a long period of time. So thinking about if they still have osteoporosis it's still okay to treat them, but thinking about things like asking

about dental health at every visit to make sure there's nothing coming up that maybe you'd wanna delay every class infusion, perhaps if there's a dental implant that's about to happen.

Kendall Williams, MD: So let's talk about this issue of zoledronic acid versus, denosumab. Thank you for correcting my pronunciation there. Carrie otherwise known as Prolia.

Carrie Burns, MD: You're assuming I'm right.

Kendall Williams, MD: So, Christina, when do you choose one or the other? Do you have a preference? How do you go about making that decision?

Christina Mitchell, MD: That's a tough one. That's a tough one. I mean, so, okay, so you've established that the patient has either failed or hasn't tolerated an oral bisphosphonate and hence what's next? I think in general, I will go with the IV bisphosphonate. But denosumab remains a niche choice for some people. So the patient with renal insufficiency we can safely use a bisphosphonate up to a GFR of 30 but as you get closer to 30, there is the concern, there is the concern that the IV bisphosphonate could potentially, hasen a demise of renal function, so that certainly sticks with me. And ultimately you don't have the same concerns at all with renal function, with denosumab.

So certainly the patient who's has borderline renal function, denosumab is gonna be a great choice. The person who has very low T scores, so minus three and lower. While denosumab is not by definition an anabolic agent, most of the time we do see T-score improvements with denosumab. And that's one of the situations where maybe you consider using it to improve the T scores to get them back into a reasonable range. And then maybe you do end up replacing it with Reclas. So there, there are a couple. So, perhaps based on renal dysfunction or based on severity of osteoporosis Prolia may be a good choice.

Kendall Williams, MD: There was this issue that Dr. Almukadam had raised in the last podcast about osteoporosis, about us not knowing how to stop Denosumab. You were getting it every six months and then you would get this sort of rebound bone loss if people kind of fell off schedule, but it seems like there's been some movement in that area. Carrie, can you speak to that?

Carrie Burns, MD: Sure. So I like to think the osteoclast as the main actor here. So both bisphosphonates and denosumab affect the osteoclast. So bisphosphonates such as alendronate, will cause osteoclast apoptosis. Once the osteoclast have already left the bone marrow and are in circulation. I like to think of denosumab, which is a monoclonal antibody to rank ligand as basically

never letting those osteoclasts out of the. So they don't even, they don't even come out. They're just completely suppressed with denosumab. And as denosumab is twice a year and its action starts to wane towards the end of that time. What we started to see again first anecdotally, and now in the literature is patients that missed the next denosumab injection.

Once that action went away and Rank Ligand was able to go onto its downstream events that this lack of suppression of osteoclas cells. Now these osteoclas cells started coming outta the bone marrow quite fervently, and we started to see rebound, especially for teal fractures in patients who missed Prolia dosing. And this became apparent and obviously concerning. We think typically you have about a month grace period after the last dose. So that sometimes is a time to get that dental work in to see how it's going. But the expert opinion that came out following the identification of this problem is that if you do wanna stop denosumab, let's say it's time for a drug holiday or there's intolerance, or there's an issue.

That waiting until typically a month after the next expected dose of denosumab, you could dose either oral alendronate or zoledronic acid to then take down some of that osteoclas activity, causal apoptosis of that resurgent of osteo resurgence of osteoclas. And that would likely, again, there's no, not a lot of data. Because it's a low number, but would likely reduce the risk of rebound for T bone fracture. And it's also important to know that once you stop Prolia, all of that benefit kind of, it kind of comes right back down again. So not just the fracture, I mean, so the fracture risk does kind of come back down again pretty rapidly.

So I personally like to utilize Prolia as kind of a second line agent because of that risk. But I do use it in my practice quite a bit. If I have patients that are arians nonagenarians that have pretty severe osteoporosis or fractured, they're staying on Prolia, we don't do a holiday in some of those patients. So I'm really careful about who I select for denosumab from the start.

Kendall Williams, MD: Carrie, that's very helpful. I, think we are thinking about these issues, talking about them with patients. They're asking us questions, bouncing off what they've heard from the endocrinologist. And so, knowing this information's very helpful. This has been terrific information. I wanted this podcast to be sort of practical pearls of managing various calcium difficulties we have in primary care, including hyperparathyroidism, learning more about vitamin D and osteoporosis, and we've really accomplished that. So I'm sure everybody will very much appreciate listening to the thoughts You, Brought to the table here, Christina and Carrie, and so I'm looking forward to having you back to discuss another thing. We wanna do another diabetes one

and talk about some of the updates there, so hopefully we'll be able to get you back for that soon.

Christina Mitchell, MD: Thank you.

Carrie Burns, MD: Thank you.

Kendall Williams, MD: So thank you for listening to the Penn Primary Care podcast. Please join us again next time. Please note that this podcast is for educational purposes only. For specific questions, please contact your physician. And if an emergency, please call 911 or go to the nearest emergency departments.