DIANA PINKHASOVA: Hello. I'm Diana Pinkhasova. I'm the Clinical Assistant Professor of Medicine in the Division of Endocrinology and Metabolism, and one of my interests is in bone metabolism and osteoporosis. So I will be talking today on the update and management of osteoporosis.

I have no disclosures. Some of my objectives will be to highlight the morbidity and mortality associated with fragility fractures to determine who and how to screen for osteoporosis, to review initial evaluation of secondary causes of osteoporosis, and to review pharmacological management and highlight more newly available options.

So just a little bit about the normal homeostasis of bone. So in the first slide you see here, there's an equal balance of osteoblasts and osteoclasts. Osteoblasts are what lays down osteoid, so we call them the bone builders. And then osteoclasts are the ones that reabsorb the bone.

So you see with normal homeostasis, osteoblastic activity is equal to the osteoclastic activity. And then down here, for the postmenopausal osteoporosis, you see that there's an imbalance in remodeling of bone. So there's more osteoclastic activity versus osteoblastic activity, which leads to negative bone balance and osteoporosis. And this bone remodeling is accelerated in settings of chronic disease, aging, and a variety of mechanical or hormonal and biochemical exposures, such as glucocorticoids.

So here, you can see the stages of osteoporosis. So you can see there is normal bone, and then the next stage after that is osteopenia, then osteoporosis, and then severe osteoporosis. And then in the figure right next to that, you have a micrograph of normal bone, which is on the left side, and then osteoporotic bone, which is on the right side. And you can see that as trabecular mineral is depleted, individual bony plates and connecting branches are lost. So it leaves less resilient, weaker bone that is most likely to fail under normally tolerated mechanical Loads.

So some introduction. Osteoporosis is the most common metabolic bone disease in the United States and the world. Any new fracture in an adult signifies 50 years or older imminent elevated risk for subsequent fractures, particularly in the year following the initial fracture, which is why it's really important to get these patients treatment so that they don't have another fracture after the initial one.

And untreated osteoporosis can lead to a vicious cycle of recurrent fractures, often resulting in disability and premature death. Primary care providers and medical specialists are critical gatekeepers who can identify fractures and initiate proven osteoporosis interventions.

So there is a really disturbing gap. At-risk patients are often not screened. A majority of highest risk women, and especially men, who have a fracture or fractures, are not diagnosed and do not receive effective FDA-approved therapies. Even those prescribed appropriate therapy are sometimes unlikely to take the medication as prescribed. So it's something that really needs to be monitored once you do prescribe the medication, and the patients really do need to be educated about fracture prevention.

So fractures can occur in any bone. Hip and spine fractures are the most common and account for all the osteoporotic fractures. An estimated 10.2 million people aged 50 years and older in the United States have osteoporosis, and about 43 million have low bone mass. And this is greater than 40% of older US adults. And the low bone mass is associated with a high risk for progression to osteoporosis.

At present, there are two million new cases of osteoporotic fractures per year. And this is actually a really, really good point, is that it exceeds the annual number of new cases of MI, breast cancer and prostate cancer combined. So this is a really, really big problem.

Annual fracture incidence is expected to increase 60% to 3.2 million by 2040, and the personal and economic costs of fractures are enormous. So fractures result in more than 432,000 hospital admissions. Annual fracture-related costs are expected to increase from $57 billion to over $95 billion by 2040, and this heavy toll could be significantly reduced with routine use of effective treatment and screenings.

Here is a slide that really shows what happens to these patients when they have a fracture. So 50% of people with one osteoporotic fracture will have another one, and usually in the first year. 40% will be unable to walk independently. 60% will require assistance a year later. The mortality is up to 20% to 24% in the first year after a hip fracture.

So if you have a patient that just had a hip fracture and you're talking to them about starting treatment for osteoporosis, this is sometimes the point that really gets to the patient, is that there's an increase in mortality, and a really substantial increase. And 33% dependent or in a nursing home in the year following a hip fracture. So if you have patients that are very independent, you have to tell them that they have to get treatment for their osteoporosis or they may end up in a nursing home.

So screening is really, really important. So please perform screening in women aged 65 years and older and men aged 70 years and older. There's definitely a really high gap in patients in men who are over the age of 70 that are not screened, so that is definitely something to start doing. Postmenopausal women and men aged 50 to 69 years, based on risk profile. Postmenopausal women and men aged 50 years or older with a history of adult age fracture. And the DXA facilities that employ accepted quality assurance measures.

And this is a really important point. Please try to use the same facility and on the same densitometry device for each test whenever possible. So if you have a patient that had a DXA scan at UPMC McGee, then make sure they have their next DXA scan at McGee as well so that we can actually look at the differences, because each DXA scan is actually calibrated a little bit differently.

So some diagnostic categories for osteoporosis and low-bone mass. So normal is a T-score greater than or equal to negative 1 standard deviation. Low bone mass is a T-score score less than negative 1 and greater than negative 5 standard deviation. Osteoporosis is a T-score less than or equal to negative 5, and then severe osteoporosis is when you do have a T-score less than or equal to negative 5, and you also have presence of one or more fragility fractures.

So this is the FRAX score. So as you guys know, the FRAX score is the National Osteoporosis Foundation clinician's guide. Focuses on its utility in postmenopausal women and men aged 50 years and older. It's validated to be used only in untreated patients. So this is for those patients that have osteopenia on DXA scan, but they have risk factors, and you want to know what is their 10-year risk of a hip fracture or a major osteoporotic fracture.

And then you can use the calculation tool, which will ask you if they've had a previous fracture, if they have a parent who had a fractured hip, if they smoke, if they're on steroids, if they have a history of rheumatoid arthritis, if they drink more than three alcoholic beverages a day.

And then once you plug that in, you get the scoring. And if you get a score of 3% or more for hip fracture, or 20% or more for major osteoporotic fractures, then you do have to treat these patients for osteoporosis, because they are at high risk of fracture.

Now, there's also a FRAX with-- we call it TBS, Trabecular Bone Score. This is a newer technology. It is an assessment of how evenly or unevenly mineral is structured, structurally distributed in trabecular bone. So adding the TBS to a FRAX score, which is possible on late model densitometry devices, actually increases the ability of FRAX to predict fractures.

We call it the TBS-adjusted FRAX. TBS is most applicable to patients who have low bone mass rather than those with osteoporosis according to BMD criteria, for whom treatment is already indicated. It is FDA-approved, and it is generated from lumbar spine BMD images using software installed on a DXA machine. No additional scan time or radiation exposure is required.

So you know, I always think of the TBS as literally assessing the bone structure. And the TBS for L1 to L4, you can see here, there's a scoring device. And it goes anywhere from 0.8, which is severely degradated microarchitecture to 1.8, normal microarchitecture. And then in the spine, the trabecular bone scores are also listed here.

So if you have a score greater than 1.31, that's normal. If it's 1.23 to 1.3, that's partially degraded. And if it's less than 1.2, then that is degraded microarchitecture. And then you might ask, you know, what do you do with that number. So you can actually go back to your FRAX score and then add-- there's a tab that will say, Adjust with a Trabecular Bone Score, and you can actually put in the trabecular bone score for your lumbar spine in the box right here.

And then you hit Calculate, And it gives you the 10-year probability of fracture adjusted for TBS. So it's a more accurate assessment than using the FRAX score. So this is the adjustment of FRAX based on TBS. And we do have some machines in the UPMC system that are able to calculate the TBS, but we are hoping that we get more machines with TBS in the near future, because it is just a more accurate tool.

OK, so here we have some causes of secondary osteoporosis. So there's a lot, but some of the ones that you should be thinking of when you see these patients with osteoporosis is, do they have a history of-- is there primary hyperparathyroidism? Do they have hypogonadism? Do they have a history of premature menopause? Do they have a history of diabetes? Do they have a history of thyroid toxicosis?

And then patients that have a history of gastric bypass are more prone to vitamin D deficiency, which becomes very chronic in nature and can lead to osteoporosis as well. So I always ask the patients if they've had a history of gastric bypass, if They have any history of celiac disease or malabsorption.

And then you can ask if they have any history of liver disease, if they have malnutrition, history of anorexia, history of rheumatoid arthritis, renal insufficiency. And then some of the most important things to ask about is medications. So anticonvulsants such as phenobarbital and Dilantin are commonly a cause of secondary osteoporosis, same with glucocorticoids.

So I always ask the patient if they've been on chronic steroids before, especially injectable steroids, because sometimes you forget to ask that. But I have some patients who have been getting injections into their shoulder, spines, knees, for the past 10 years, and they have terrible osteoporosis.

And then if they've been on tamoxifen, chronic PPI therapy. So these are just some important medications to ask about to kind of try to figure out why they have osteoporosis. So history and physical exam is really important. Most of the conditions causing osteoporosis can be excluded with a careful history and physical exam.

Lifestyle factors that contribute to bone loss. So ask about alcohol abuse, If they have a history of anorexia nervosa, low BMI, excess vitamin A, frequent falling, immobilization, inadequate physical activity, low calcium intake, smoking, vitamin D deficiency. Living in Pennsylvania, a lot of us have vitamin D deficiency because we don't get a lot of sunlight. So that's definitely something to ask.

So then evaluation. So when you see these patients for osteoporosis, you know, what testing should you do? So should definitely get their albumin-adjusted calcium, their renal function, phosphorus, and magnesium. You should get their parathyroid hormone, because if they have an elevated calcium and an elevated parathyroid hormone, then that can be primary hyperparathyroidism, which can definitely lead to secondary osteoporosis.

You want to make sure their vitamin D is replete. And then if you have a male patient, always check their 8:00 AM testosterone. And make sure it's at 8:00 AM, because that's when testosterone levels peak, because one of the major causes of osteoporosis in men is hypogonadism. And then in some select patients, if you're concerned about multiple myeloma, you can get an SPEP. You should get some thyroid labs.

If you're concerned about celiac disease or malabsorption, you can get a celiac panel. And then other testing is something that you can do if you are-- for example, a 24-hour urine for calcium is useful to assess for adequate calcium intake and absorption, if you have a woman with a history of GI disorders, such as IBD or celiac disease, or after GI surgery, such as gastrectomy or bariatric surgery.

An assessment of urinary calcium is also necessary in women with kidney stones. And it may be helpful in women with osteoporosis and no risk factors beyond age to identify idiopathic hypercalciuria. And then if you're suspecting Cushing's disease, then you can get a urinary free cortisol level or salivary cortisol, or do a dex suppression testing.

Calcium and vitamin D are the building blocks of bone. So it's really important that you ask about their calcium, vitamin D. So we recommend a diet with adequate total calcium intake, so 1,000 milligrams a day for men aged 50 to 70 years old, and 1,200 milligrams for women greater than 51 years and men greater than 71 years. So what I usually say is 600 milligrams can come from your diet, and then 600 milligrams can come from a supplement.

Vitamin D levels are really important as well, so we want to maintain their vitamin D levels greater than 30. And then please make sure you're checking 25-OH. Vitamin D levels and not the 125, because we want to know the total vitamin D level. And I usually have my patients on about 1,000 international units a day, but if their vitamin D levels are really low, like less than 10, then I usually put them on 50,000 international units once a week for eight weeks. And then I retest their level.

So just remember, vitamin D and calcium are really important for osteoporosis. So treatment. Strongly consider pharmacological treatment in postmenopausal women and men over the age of 50 who have T-scores less than 2.5. So that's osteoporosis. Or if they have low bone mass by DXA with a 10-year hip fracture risk greater than 3%, or a 10-year major osteoporosis-related fracture risk greater than 20%, based on the FRAX model.

And also strongly consider initiating pharmacological treatment in postmenopausal women and men 50 years of age or older who have fracture of the hip, regardless of BMD or the vertebra, fracture of proximal humerus, pelvis or distal forearm in persons with low bone mass. And the decision to treat should be individualized in persons with a fracture of the proximal humerus, pelvis, distal forearm, who do not have osteopenia or low BMD.

OK, so there are quite a few drugs that are approved by the FDA for osteoporosis. So I will talk about some of them. So here, we have the bisphosphonates. So there's alendronate that you all know as Fosamax. There is ibandronate, which is Boniva, risedronate, which is Actonel, and then zoledronic acid, which is Reclast, and that's the IV infusion

Then we have the parathyroid hormone analogs. So these are anabolic agents. That's abaloparatide, teriparatide. Then we have the RANKL inhibitor, which is denosumab, or you may know it as Prolia. Then we have the newer agent, which is the sclerostin inhibitor romosozumab. We call it Evenity. And then some of the older options that we really don't use, calcitonin, which is a nasal spray

So alendronate or Fosamax is usually first line for patients with osteoporosis that are able to tolerate oral bisphosphonate. So really important to know that it reduces incidence of spine and hip fractures by 50% over three years in patients with osteoporosis, or if they've had a prior vertebral fracture.

So I think it's something important to tell patients when you're talking about treatment options, because if you tell them that this is a way to reduce their fracture risk by 50%, I think they'll understand it better than just, oh, here's some Fosamax. You know, it's good for your bone. So yeah, 50% for Fosamax.

Now, as far as side effects, so side effects are actually similar for all oral bisphosphonates. So they include gastrointestinal problems, esophageal inflammation, rare cases of atypical femur fractures, and osteonecrosis of the jaw. Ocular inflammation has been documented. It's really, rare though. And then this is really important, is all bisphosphonates can affect renal function and are contraindicated in patients with estimated GFR below 30 to 35. So if you have somebody with CKD, their GFR is less than 35, then you cannot use bisphosphonates.

So another bisphosphonate here is Boniva or ibandronate. So it reduces incidence of vertebral fracture by 35% to 50% over three years, but does not reduce risk of non-vertebral fractures in the hip or non-hip. So meaning if you have finally convinced your patient to get treatment for their osteoporosis, make sure it's not Boniva, OK, because again, it only reduces fracture risk for vertebral fractures but not the hip.

Actonel reduces incidence of vertebral fractures by 39% and hip fractures by 27%. So still, Fosamax is better as far as reduction of hip fractures and vertebral fractures, but Actonel is better than Boniva, because it actually reduces both hip and vertebral fractures.

Now, if you have a patient on Fosamax and they've been on it for a few months, and they start complaining of heartburn, so GERD, gastritis, they're unable to swallow the pill and they just can't tolerate it, then you can switch them to zoledronic acid or Reclast, which is-- you know, I kind of call it, it's IV formulation of a bisphosphonate.

So it's approved by the FDA for prevention and treatment of osteoporosis in postmenopausal women. So we use 5 milligrams once a year for treatment of osteoporosis, and once every two years for prevention. Zoledronic acid, so it reduces incidence of vertebral fractures by 62% to 70%, and hip fractures by 41%, and non-vertebral fractures by 21% to 25%.

So it's a very effective medication, and it's an infusion. So it's 5 milligrams. It's given once a year by intravenous infusion, and administered over at least 15 minutes. The most likely side effect the patient might have is flu-like symptoms. So they might have a headache, myalgias, fevers. And this does commonly occur after the first dose. So I usually tell patients to be really well hydrated before the infusion, and I pre-treat them with Tylenol.

And then if they go for their second dose, only 7% after the second dose will have the flu-like symptoms, and 3% after the third dose. So if you have a patient that had symptoms after the first infusion, just tell them that it will definitely be better after the second infusion.

And again, to reduce the likelihood of acute-phase reaction, patients should be well hydrated. Drink two glasses of water before the infusion, and I usually give them about 650mg of Tylenol beforehand. Another way to decrease acute-phase reactions is to actually increase the infusion time to 45 minutes.

So some things about Reclast. You know, vitamin D should be replete before treatment, so I always get a vitamin D and a kidney function before every infusion. It may cause or exacerbate hypocalcemia, which is why you have to make sure that, again, the vitamin D and calcium is something the patient is taking. And again, it's contraindicated in patients with creatinine clearance less than 35, or in patients with evidence of acute renal impairment.

So bisphosphonate holiday. So this is also very important, because if you have somebody on a bisphosphonate and they're on oral bisphosphonates, then after five years, you have to assess, do they have a hip, spine or multiple fractures before or during therapy.

If they have not, and their hip bone mineral density is less than 2.5, then you can consider a drug holiday and then reassess after two to three years. If they have been on oral bisphosphonates for five years, but they have had a hip spine or multiple other fractures during therapy, then you can either continue it or change to another anti-fracture therapy and reassess every two to three years.

Or if you have a patient that's been on bisphosphonates for more than five years, and their hip BMD T-score is less than 2.5 still, then you can actually continue bisphosphonates for up to 10 years. So that's the oral. And then I usually do the intravenous bisphosphonate or Reclast for up to five years.

And then please keep track of bisphosphonate's start date. So there's a lot of patients out there that have been on bisphosphonates for many, many years, and because there's no clear start date, they're continued on it. And if you go over the 10-year mark, again, we don't know if there's much benefit. But we do know that it increases your risk of atypical femur fractures. So please keep track of the start date.

Then we have the RANKL inhibitor, which is denosumab. It suppresses osteoblastic formation, leading to less bone resorption and higher bone density. It's one of the most potent drugs available. It reduces incidence of vertebral fractures by about 68%, hip fractures 40%, and non-vertebral fractures by about 20%.

It may cause or exacerbate hypercalcemia. So you have to make sure you check their calcium levels, vitamin D levels beforehand. And it has been associated with rare cases of atypical femur fractures and ONJ. Now, discontinuation of denosumab is associated with very rapid bone loss. That may result in multiple vertebral fractures, especially in patients with a prior vertebral fracture.

So if you have a patient on denosumab and they've been on it for five years, you cannot just stop it. So a drug holiday is not appropriate with denosumab because if you just stop it, they'll actually either get multiple vertebral fractures, or their BMD will decrease substantially. And during periods of suspended treatment, and as recommended by the FDA, alternate anti-resorptive therapy should be considered. So we usually either switch to Fosamax or zoledronic acid infusions.

Now parathyroid hormone analogs, we have Tymlos and Forteo. So here, we'll talk about Forteo again. It's an anabolic agent. It reduces risk of vertebral fractures by 65% to 77%, non-vertebral by 35% to 53%. And also important to follow, teriparatide with an anti-resorptive agent, usually a bisphosphonate or denosumab, to maintain or further increase BMD.

I really like this depiction right here, because it really shows severely osteoporotic bone on the left, and then the anabolic effect of the Forteo after 21 months on the right. So it is an injection that the patient does themselves. It's a daily injection, 20 mics subcutaneously.

And again, when treatment is discontinued, bone loss can be rapid. So you have to treat with another agent, which we typically switch them over to either denosumab or zoledronic acid. And then treatment duration used to be 24 months, but this was recently changed to open the possibility of longer treatments in high-risk patients.

So some of the side effects, transient hypotension, leg cramps. It can transiently increase serum calcium. It should be used in caution with patients with active or recent kidney stones. And then it should be avoided in settings of increased risk of osteosarcoma.

So if you have a patient that has a history of Paget's disease of the bone, if they've had extensive prior radiation therapy involving the skeleton, they have a history of bone mets or malignancies, if they have elevated alk phos or hereditary disorders predisposing to osteosarcoma, this is definitely not the agent to use.

Then we have abaloparatide, which is Tymlos. It's also an anabolic agent and reduces risk of vertebral fractures by about 86% and then non-vertebral by 43%. And Tymlos is actually at this point preferred by UPMC Insurance versus Forteo. It's also a daily subcutaneous injection. The duration is still not to exceed 24 months, and then you also have to follow Tymlos with an anti-resorptive agent, so usually either Reclast infusion or denosumab.

Now, this is the newest agent, and I call it the strongest agent that we have on the market. It's romosozumab or Evenity. It's currently FDA-approved for treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fractures or multiple risk factors for fracture, or poor response or intolerance to other available agents. It is approved for men with osteoporosis at high risk in some countries, but not in the United States as of yet.

OK, so it reduces fractures and increases BMD at the lumbar spine, total hip, more than placebo, more than alendronate, and more than teriparatide in postmenopausal women. In the pivotal frame trial, romosozumab compared to placebo reduced risk of new vertebral fractures by 73% and clinical fractures by 36%. And just like the other anabolic agents, once you stop it, the BMD does tend to go towards pretreatment levels. So we usually follow this up with either denosumab, alendronate, or zoledronic acid to maintain the BMD benefits.

Now, it did receive FDA approval with a boxed warning stating that it may increase risk of MI, stroke, and cardiovascular death. So if you have a patient that experienced a stroke or cardiovascular event in the prior 12 months, this is not a medication you should be using. It may cause hypocalcemia, so you have to check vitamin D and calcium levels. It has been associated with very rare cases of atypical femur fractures and ONJ, and actually, fewer cases than denosumab.

OK, so how do you monitor the treatment response? So DXA is currently the preferred approach. We recommend monitoring every one to three years. Medicare approves monitoring every two years, but if they're on treatment, then you can actually do it every year if you want. But I usually do every two years. And then clinical assessment should be performed to identify new fractures, falls, new or worsening comorbidities. Always make sure the DXA scan is done on the same machine, because otherwise, we won't be able to compare them accurately.

OK, now in 2023, American College of Physicians did release some of their own guidelines. So bisphosphonates are recommended as first-line therapy for postmenopausal women and men with primary osteoporosis. And again, if you're going to use a bisphosphonate, choose something like Fosamax, which will reduce fracture risk in both the hip and the spine, or zoledronic acid. If they have a history of heartburn, celiac disease, malabsorption issues, just go for the zoledronic acid.

The denosumab or Prolia is recommended as second-line for women or men with contraindications to or adverse effects from bisphosphonates. But just remember, if you have a patient, if you have a woman who's 55 years old and she has osteoporosis and was unable to tolerate Fosamax or zoledronic acid, you know, Prolia would be something that she may have to be on lifelong, because it's six months, injections, so every six months, injections.

And if you do decide to stop it, you do have to bridge it with either zoledronic acid or a bisphosphonate, which again, if they were started on Prolia because they have adverse effects from the bisphosphonate, this is definitely a case where you can send the patient to us, and we can see what we can do.

Romosozumab or Evenity, and the recombinant parathyroid hormone, teriparatide or Forteo are recommended conditionally only for women with osteoporosis and very high fracture risk. So Evenity is prescribed for one year. It's an injection every month for 12 months, and then as you know, the Forteo is an injection every day for up to two years and more, and should be followed by a bisphosphonate to mitigate rebound bone loss.

OK, some clinical pearls. So please perform BMD testing in women aged 65 or older and men aged 70 years or older. Maintain serum vitamin D sufficiency. So we want it to be greater than 30 nanograms. And ensure adequate calcium intake. Adding trabecular bone scores to FRAX, which is possible on late model densitometry devices, increases the ability of FRAX to predict fractures. We call it the TBS-adjusted FRAX. Bisphosphonates are first line but ensure that start date is clearly documented. And treatment holiday is recommended after five years, unless high risk of fractures.

Please keep in mind that denosumab or Prolia needs to be continued with no holiday. If there is a plan to stop, they need to start alendronate or zoledronic acid infusions. Anabolic agents, so we talked about Forteo, Tymlos, Evenity, need to be followed by anti-resorptive agents to maintain BMD gains.

Do not use romosozumab in women with a heart attack or stroke in the past 12 months. And most importantly, primary care providers and medical specialists are critical gatekeepers who can identify fractures and initiate proven osteoporosis interventions. Thank you so much for listening to my talk.