**SPEAKER:** All right, so osteoporosis. Many of you have probably heard about osteoporosis. It's a systemic skeletal disease characterized by what's been described as low bone mass and basically an architectural deterioration of the bone. And what this ultimately leads to is an increase in bone fragility and an increased fracture risk.

So not everybody fractures. And we don't understand why some people can have really bad bone quality, but don't fracture. And there are other situations where the opposite is true, where you can actually get fractures, despite measures that we would do in the clinic that actually look OK.

This is photographs of bone-- of normal bone and osteoporotic bone here, so just to give you an idea of what this actually looks like. So normal bone-- you have what are called trabeculae. These are very nice sort of structures. You can think of this like a building.

You have all of this-- basically reinforcements and mineral that's actually been arranged in very nice bars that provide strength to this. This is a vertebrae. And then in other situations such as osteoporosis, you get thinning of these spicules of bone. So you end up with a situation where you just have more space.

And as you can imagine, this is much more fragile. So osteoporosis is extremely common. It affects 200 million women worldwide. One third of these women are ages 60 to 70. And 2/3 of these women are actually aged 80 or older. And 30% of women over the age of 50 have had one or more vertebral fractures.

And in many of these cases, these women don't actually know that they've already had a vertebral fracture. This is something that would be identified incidentally, either because of other types of imaging or clinically in retrospect. What's important to keep in mind is that 20% of men over the age of 50 will also have an osteoporosis-related fracture in their remaining lifetime.

And this is an aspect which we have never really focused a lot on for osteoporosis is that men are also very severely affected. So why should we care about these fractures? It turns out that once you have a fracture, this is associated with significant disability.

It portends a relatively poor prognosis. So one year after a hip fracture, this is what happens. So 20% of women will pass away. Permanent disability occurs in 30%. 40% have difficulty with walking and walking independently. And when we talk about walking independently, this is like requiring a walker or a cane.

And 80% have difficulty carrying out at least one activity that is part of independent activity of daily living. So as you can tell from this, having a hip fracture is not a good thing. But it's not just hip fractures. Osteoporosis actually affects the entire skeleton.

And every year we see about one and a half million fractures related to osteoporosis and bone loss. This includes everything from the spine, which is about 46%. That's the most common site, to the hip, which is about 20%. And then to the wrist, which is about 15%.

And so you can tell here. These are all major joints or major portions of the body that are important for activities of daily living. So osteoporosis is also just a very-- has a very significant clinical burden. So if you look at osteoporosis-- and we've talked about this-- 1.5 million fractures that are associated with annual incidents across all ages.

And this is how it compares to other diseases that are obviously very important for women and men. So heart attack-- 500,000, stroke, and breast cancer. So being able to address osteoporotic fractures is actually a critical health care issue that really needs to be addressed. So some of you may have heard about different types of treatments for osteoporosis.

So risk factors for osteoporosis. And there are these relative risk factors that we have that we can use to try to predict the risk of somebody having an osteoporotic fracture. So these are major factors here and what we call moderate factors. And so as you can tell, age and menopausal status is actually very important.

There are other aspects, such as a prior history of fragility fracture, or a hip fracture, and parents sort of indicating that there could be a genetic component to this and other types of measures. But the main ones that we use clinically are the ones in red, so age, menopausal status, the bone density scans or a DEXA scan, calcium intake.

So basically, a low calcium diet as well as smoking and alcohol excess. And since the original sort of description of these factors and the incorporation of these factors into the clinical assessment of osteoporosis, a number of other factors, including those in white here, have slowly started to make it into different types of calculations that we can use to try to predict fracture risk.

I'm not going to go through that today, but there are now all of these other methods to really try to improve our ability to predict whether somebody is going to have a fracture. So as I've mentioned before, hip fractures are associated with an increased risk of death.

And so this is just to give you a rough idea of what we're talking about. So in women who have a hip fracture-- time after the fracture-- you can see that there's a very significant decline in survival. It's much worse in men, which is a very interesting statistic. It's not entirely clear why that's the case.

And this here are sort of the calculated values of people, just in terms of mortality from other causes in people who have not had a hip fracture. So as you can tell, just the presence of a hip fracture alone is also poor predictor of long-term outcome. Hip fractures clearly-- the incidence of hip fractures clearly goes up after menopause.

So you can see if you have women who are in their 50s and then you see this huge increase in vertebral fractures as well as hip fractures, it's not-- it's interesting that you see this increase in risk fractures up until age 60, but then it sort of levels off. We're not entirely sure what causes that, because you would have expected everything to go up.

But this is one of those interesting factors is that we're not entirely sure why some sites tend to be of higher risk than others. And also, again, to emphasize that osteoporotic fractures also occur in men, and that this is a major issue, including vertebral fractures as well as hip fractures, and an increase in risk factors, which does continue to go up over time.

And I will point out this, which is a very important curve here, is that all of a sudden, things start going down. And the reason they go down is because the men pass away. So this is unfortunately a result of-- this is part of the statistic that if a man has a osteoporotic-related fracture, that their chances of survival is actually extremely low.

All right, so contributors to osteoporotic fractures. We've talked a little bit about some of these. Certainly, hormones, nutrition, genetics, and lifestyle are major factors. And the main part of this is actually contributing to what we call peak bone mass. So peak bone mass occurs usually in the 20s or 30s.

And really, whatever we can do to try to maximize peak bone mass. Good exercise, especially for young women and young men, is really important. It's good nutrition during the developmental phase. Certainly, post-menopausal bone loss as well as age-related bone loss in general all contribute to this process of low bone mass.

And low bone mass is really one of those critical factors that contribute to fractures. So if you have a low bone mass and then you fall, or that there's other skeletal factors such as a propensity to fall, muscle skeletal diseases, autoimmune diseases, things like that, that contributes to your risk as well as this concept of poor bone quality. So we'll talk a little bit about this in a moment.

But bone density scans-- when we do a bone density scan, what we're doing is-- for those that have had that experience, you know that what you do is you lie on a table. They use X-rays. And they basically measure the amount of mineral inside either the hip, or the spine, and sometimes the wrists. But what that tells you is essentially how much cement is there inside the bones.

How much mineral is actually present? It doesn't tell you anything about how it's arranged. And as you can tell from-- like if we use the analogy of buildings, in architecture you can have a very nice building, which has very fine structures in it that doesn't really have that much cement, but can be incredibly strong, versus a building where you just toss in a whole bunch of cement.

And that can be equally as strong, but not as elegant. That's the factor that we're talking about with architecture. And this is a factor that is very, very difficult to assess. So we are not able to tell you what the architecture of a bone looks like at this moment.

But we can tell you how much mineral is actually in there. Oh, yeah. So bone density scans as we were talking about-- these are the common sites. It's usually the spine, the hip, the forearm, the calcaneus, which is the heel, as well as full body. Quantitative CT scans happens to be done usually at the spine, hip, and the forearm.

This is a technique that uses CT scanning to try to look at bone strength and bone architecture, but is not commonly accepted yet, partly because of the higher radiation doses and partly because there's no good standardization. Ultrasound-- which is great, because this can be done very quickly and can be done outside of typical radiology settings.

And then high-resolution pQCT, which is a high-resolution CT scan for looking at architecture. And this is only really available as a research scan at the moment, so the hope is that one of these days it'll be something that can be moved into the clinical realm.

So we're going to touch a little bit upon different types of therapies and the medications that are used for that. But to understand that, it's often helpful to get a good view of what exactly happens in the bone. And so to very briefly review, in the bone what we're interested in are actually these bone marrow precursors.

And so they're sets of cells called mesenchymal cells, which actually contribute to the bone formation as well as hematopoietic cells. And traditionally, we think of hematopoietic cells as the cells that help make the bone marrow, the red blood cells, white blood cells, and things like that.

But the hematopoietic cells create a cell constant called an osteoclast. And these are cells that are capable of resorbing bone. The mesenchymal cells contribute to a cell type called the osteoblast. And the osteoblast actually makes the bone. So we have osteoblasts that lay down your bone mineral and osteoclasts that resorb bone mineral.

And the reason this becomes really important is that the normal process is a balanced cycle. You have bone that is constantly being laid down. You have bone that is constantly being resorbed. And this is how the skeleton heals itself. It says, OK, you have a microfracture.

You have some sort of events that happen to the bone. The osteoclasts come in. They resorb that. They sort of-- if any of you have had your house worked on for the stucco, you have to clean out the crack, and then put in new glue, and then paint it all over. That's what this does.

An osteoclast cleans out that fracture, resorbs all of that damaged bone. And then osteoblasts come in and lay down new bone. And that's the healing process. So this typical process occurs very slowly. Tip-- what we say is that approximately every 10 years you get a new skeleton, so that's the normal process of recycling.

And it's a critical balance that needs to occur. The problem in osteoporosis is that either you get a loss of the ability to put down new bone, or you get a gain of the ability to resorb bone. And so now, you have this imbalance where the net result is that you get a loss of bone.

So what can we do about patients with osteoporosis? Well, there are non-pharmacologic approaches to preventing and managing osteoporosis. That includes everything from adequate intake of dietary calcium and protein. And I should add on here vitamin D. Sorry. I accidentally left that off. Regular physical activity, specifically weight-bearing activity.

So one of the things about runners like marathon runners is that they tend to have osteoporosis. As you can imagine, there's a good reason for that is that if you're running a lot, you don't want to be having to push along a lot of extra weight. Things like minimizing alcohol and smoking and minimizing the risk of a fall.

So we do occasionally use hip protectors. Many patients don't like those, because they're basically pads that go underneath the pants to protect the hip. But they are actually incredibly effective and not that expensive. So the drugs for treating osteoporosis really falls down into these two groups.

So as I've mentioned before, we had those groups of cells that resorb bone and groups of cells that build up bone. We only have one medication called parathyroid hormone, or teriparatide. That increases bone formation. There's decreased bone turnover, so to try to decrease that resorption of bone. And this is actually where most of the drugs are.

So there's hormone therapy, which had gone out of favor for a period of time and is now slowly coming back for a number of reasons. But hormone replacement therapy is one of them. Raloxifene, which is a selective estrogen receptor modulator, often used in breast cancer, but also very effective in preventing bone loss.

Calcitonin-- which has sort of fallen out of favor. This is the medication that was used many, many years ago as one of the first medications that was used for treatment of osteoporosis, but actually has recently been associated with an increased risk of cancer or cause cancer.

And so that has actually fallen out of favor. And then the most common ones are bisphosphonates such as alendronate and risedronate. And more commonly, more recently is zoledronic acid, which is an infusion form instead of a tablet. Strontium has been used in the past in Europe primarily, although there is now a black box warning for the use of strontium.

This was available as a nutritional supplement over the counter. And then there are these newer medications that are just coming out called RANKL inhibitors. The main one is denosumab. And this is an injectable that's done every six months. So as you can tell from this, the majority of our therapies are really trying to block the bone loss process.

We don't have much in the way of actually building back bone. And so really when we think about osteoporosis, the goal has to be prevention-- is really trying not to lose bone in the first place. All right. So the goals for our group really has been to say, OK, well, from a research standpoint, is there anything that we can do to enhance growth of bone and repair of bone?

How can we identify new drug targets? And can we use human diseases to study bone and really try to identify what's going on? All right. So the important aspect related to the osteoporosis, particularly from a case management standpoint is, what do you do about these patients? How do you triage care for osteoporosis?

So there's obviously lots and lots of people with osteoporosis and at risk of osteoporosis. So general practice is actually a really, really important component. And they are usually the first line of defense. We refer osteoporosis to routine osteoporosis, meaning osteoporosis that occurs on the physiologic basis, typically related to menopause.

And these are patients that have no fractures, no height loss. This would be something not particularly complicated and generally very responsive to standard treatments, so treatments like the bisphosphonates, the anti-resorptives. If they work, totally good. We can leave these patients in the general practice arena.

What is important from a case management standpoint is, when do you think about specialty clinics? And these are patients that have early onset fragility fractures. So a young woman who is pregnant and has a fracture-- that's unusual. They will heal, which is the good part.

But really, how do you manage that? And so the other example would be somebody who is in their 20s or 30s, where you would not normally expect a fragility fracture. And they're doing an activity, or they're just sitting there and then something breaks, right?

That's clearly not right. And that type of early onset fragility fracture is really important to be seen in a subspecialty clinic. High frequency of fractures-- so patients who had more than a couple of fractures a year, particularly if they're fragility factors. Not I went skiing five times this year, then I hit a tree.

Not that type of frequency of fractures. That's probably not endocrinology. That might be neurology or psychiatry. But that's a little bit different. But you often have a pretty good idea. It's just like, oh, they just fractured again, and they were just walking on the street or on the sidewalk.

So there's something clearly going on. Genetic disorders-- so patients with osteogenesis imperfecta. You often hear about these. These are typically pediatric patients who have an abnormality in the bone formation, unusual bone densities on the bone density scan.

So T-score is less than minus 3. So really, sort of on the far end. And what has been very interesting is that if you look at bone density reports, they will say that, well, if your bone density is above minus 2.5, you're probably OK. You don't really have osteoporosis.

But we have one condition of plus 2.5. So if that patient actually has a bone density that is two and a half standard deviations above the average, that is not normal either, OK? That is probably not osteoporosis, because those patients are usually not fracturing. But that is not a normal value.

And those patients should be seeing a subspecialty clinic. Failure to respond to standard therapies and then complicated patients. So these are the patients where some of you may run into, specifically transplant patients, renal failure patients, patients who are undergoing gender transitions, radiation therapy, cancer.

These types of situations where many of the medications may actually induce bone loss, or be associated with bone loss, or even the process themselves. So for example, gender transitions. We have no idea what happens to male to female gender transitions.

And it turns out, some of the preliminary studies both done at UCSF and elsewhere is that many of those patients actually develop osteoporosis. So high levels of estrogen are not necessarily protected in those particular situations. And it might be because of the aromatase inhibitors that are used as part of the gender transitions.