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Part Two of Two Episodes: Key Prevention & Treatment Strategies for Osteoporosis

Announcer Introduction:

You're listening to "Boning Up on Osteoporosis" on ReachMD. This program is sponsored by the National Osteoporosis Foundation. Here's your host now.

I'm Dr. Mimi Secor, and today I'm speaking with Dr. Felicia Cosman, Coeditor in Chief of the Osteoporosis International journal and Professor of Clinical Medicine at Columbia University Medical Center in New York about the top research in osteoporosis over the past decade.

So, Dr. Cosman, let's talk about research in pathophysiology. What were some of the major papers in this area?

Dr. Cosman:

This has had a lot of advances over the decade, and one of the key areas that we've been looking at is the importance of muscle mass to fracture risk. There have been several key papers in Osteoporosis International that have looked at the relationship between muscle loss, called sarcopenia, and bone loss. A comprehensive review by Hirschfeld and colleagues in 2017 coined the term 'osteosarcopenia' to discuss the concurrent phenomena of loss of bone and muscle mass. We know that losing bone and muscle with age are both universal phenomena. With muscle loss, the average loss is about 1% per year after age 40, but the rates of both bone and muscle loss are dependent on genetic factors and hormonal factors, mechanical influences, and nutritional factors as well. A meta-analysis that was published by Wong and colleagues in 2018 evaluated the prevalence of sarcopenia and its relationship with fracture incidents.

Specific definitions of sarcopenia have differed across different societies, but sarcopenia is usually diagnosed after a loss of significant lean mass as well as a loss of muscle strength, such as grip strength, for example, or a loss of muscle function, such as gait speed or inability to rise from a chair unaided. Sarcopenia is associated with recurrent falls, which is an obvious major risk factor for osteoporotic fracture. And the prevalence of sarcopenia in patients who suffer fractures is particularly high in men and much higher in elderly patients with fracture compared to age-matched individuals who have not had fractures. Muscle loss also is accelerated after a fracture occurs at least in part because of reduced physical activity, and this maybe is one of the reasons that there is a very high imminent risk of fracture after the first fracture event.

Another really important paper was by Beaudart and colleagues in 2017, which evaluated the impact of nutrition and physical activity on sarcopenia. The authors found that physical activity could improve muscle mass, muscle strength, and physical function in individuals who were age 60 and older. The impact of nutrition on sarcopenia was not as substantial, but most of the patients studied here were healthy, and the authors suggested that nutritional factors would likely play a bigger role in the frail, elderly, and in patients with more comorbidities and known nutritional deficiencies, so that's an area where more research needs to be done.

Another key area of interest was the relationship between diabetes and osteoporosis, and this was reviewed by Ferrari and colleagues in 2018. We've known for a long time that type 1 diabetes is associated with a high risk, about a 3-fold increased risk for many fractures, but over the last decade, we've seen that type 2 diabetes is also associated with an increased risk of fracture, the magnitude not quite as large as what we see for type 1. This is really important because as the incidence of type 2 diabetes is increasing, we're going to see a greater and greater impact on fracture risk. The duration of diabetes is one of the predictors of risk, and fall risk is also increased in diabetes, and several of the diabetes medicines are implicated in producing adverse effects on the skeleton. We know that there are differences in the underlying causes of elevated fracture risk in type 1 versus type 2, but both types of diabetes should prompt physicians to evaluate these patients and treat them when appropriate.

Another key paper was Maurel and colleagues in 2012. They distinguished light drinking, such as 1 alcoholic beverage daily for women, versus heavy drinking, more than 2 drinks daily for women and 4 or more for men. And although they didn't find any adverse effects for light alcohol ingestion on bone, for heavy drinking, fracture risk is elevated. We know that heavy alcohol ingestion impairs the formation and the function of the cells that make bone, called the osteoblasts, and they stimulate activity of the bone-degrading cell, the osteoclast, so this results in reduced bone formation and increased bone breakdown. Furthermore, there are effects beyond those on bone that are associated with heavy drinking that include increased risk of falls, for example, and tobacco use, poor nutrition, all of which can increase the risk of fracture further.

One other area I'd like to mention is that many medicines have adverse effects on the skeleton as unwanted side effects. A number of papers in OI have looked at various medicines and their impact on bone health. One of the most important is what has been found with the proton pump inhibitor class of medicines because these are so prevalent and used, of course, to treat gastroesophageal reflux disease and peptic ulcer disease. And there were 2 papers that looked at this in OI that were highly cited. In 2019, Poly and colleagues performed a meta-analysis of all the literature evaluating proton pump inhibitor use and hip fracture occurrence over a 30-year period—so a very long study, 1990–2018. This was 24 studies, over 2.1 million patients and over 319,000 hip fractures that were included, and they found that proton pump inhibitor use was associated with a 20% greater risk of hip fracture and up to a 30% greater risk for those on higher doses. This attributable risk is modest to moderate in degree—not dramatic, but certainly present—but because the use of these agents is so common, it's important from a public health perspective. In the second paper, Zhao and colleagues in 2016 evaluated the risk of all fractures, including hip fracture, and found a similar, perhaps slightly higher increase in risk of both vertebral and nonvertebral fractures associated with proton pump inhibitors.

Dr. Secor:

Now, for many of us, preventing osteoporosis has become a much bigger focal point with our patients. So, has there been much research on this in the past decade?

Dr. Cosman:

Yes, there have been important publications addressing this. One of the most important ways that we can prevent osteoporosis is to try to build as much bone as we can during youth. In childhood and in adolescence, the skeleton is most responsive to the influences of nutrition and physical activity. The NOF position statement on peak bone mass was published in 2015 by Weaver and colleagues and reviewed the world literature on the whole subject of peak bone mass acquisition. We know that generally peak bone mass is achieved by the age of about 20 and that the level that each individual achieves is a complex interplay of genetics. That accounts for maybe 60–80% of the variance. That includes gender, but it also includes these modifiable factors: mean body mass, endocrine factors, physical activity, nutrition, and lifestyle. The paper lays out the research agenda for the next decade and the importance of governmental policies to help implement what we now know about how to acquire the maximum amounts of bone that we can during youth as a protection against the later risk of bone loss and the occurrence of osteoporosis-related fractures.

Dr. Secor:

What about other research studies related to nutrition and physical activity?

Dr. Cosman:

There has been a tremendous controversy about the efficacy and safety of calcium and vitamin D supplementation for both prevention and treatment of osteoporosis over the last decade. One of the most important papers that looks at this was a meta-analysis published by Weaver and colleagues in 2016. And here, calcium and vitamin D supplements were associated with a reduced risk of hip and other fractures. I wouldn't say that the controversy is settled at this time, but most experts believe that calcium and vitamin D intake should be supplemented if the diet is insufficient. And in general, for adults we're talking about a total calcium intake that includes diet and supplements as needed of about 1,200 mg per day and a vitamin D dose that is sufficient to achieve a 25-hydroxy vitamin D level of about 30 ng/mL. In the past we were shooting too high, but our data suggests that 30 would be the target range.

A key factor that we can focus on for both prevention and treatment is exercise. An important paper by Giangregorio in 2014 suggests that exercise should be performed by patients for prevention of more fractures. The authors caution that aerobic exercise has multiple health benefits, but for osteoporosis per se, it's really critical to include resistance training to strengthen the large muscle groups and also balance training to reduce the risk of falls.

Similarly, Zhao and colleagues published in 2015 a large meta-analysis on the effects of differing exercise programs in postmenopausal women and how these exercise regimens affected bone density. Their study showed that resistance training alone could maintain spine and hip BMD, but a combination of resistance training and high-impact weight-bearing aerobic activity could increase BMD more at both

cites.

The optimal exercise prescription for bone health is still being explored. It's likely to vary with patient age, with underlying physical conditioning, as well as with the presence of fractures and other musculoskeletal comorbidities, but this is really an important area that we need to continue to target for bone health across our lifespan.

Dr. Secor:

Thank you. Now, unfortunately, we're almost out of time, Dr. Cosman, but before we close, the last area of research I'd like to focus on is the treatment of bone disease. Can you share what advances have been made regarding medications for osteoporosis?

Dr. Cosman:

Sure. There have been several medications that have been FDA-approved for the treatment of osteoporosis over this last decade, and they include denosumab, abaloparatide and romosozumab, 3 important and potent drugs. I j wanted to highlight papers that look at the issue of when you stop denosumab therapy. These were McClung 2016 and 2017 and Zanchetta 2018. Denosumab is a really potent medicine administered by a subcutaneous injection twice yearly. This medicine reduces the risk of fractures in the spine, hip, and all nonvertebral sites. It progressively increases BMD over a 10-year period.. But it's critical for clinicians to realize that the effects of this medicine resolve when the medicine is stopped. When you discontinue denosumab, there is rapid bone loss, and there can be clinical consequences of this, including multiple vertebral fractures; so it's critical if denosumab is to be discontinued that an alternative potent medicine is initiated to prevent any clinical consequences.

Dr. Secor:

Well, in the past decade we've certainly seen a fair share of research in the prevention, diagnosis, and management of osteoporosis, and I hope to welcome you back in another 10 years, Dr. Cosman, to discuss even more research advances. It was great having you on the program today, Dr. Cosman.

Dr. Cosman:

It was my pleasure. Thanks very much for having me.

Announcer Close:

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