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A bone health expert considers recent evidence on osteosarcopenia as a risk factor, consequences of delayed denosumab dosing, bisphosphonates and atypical femur fracture, and the T-score as a treatment target in a romosozumab study

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Increasingly, bone health and fragility fracture prevention is one of the most important aspects of healthy aging that we, as women's health care providers (HCPs), must be sure is part of our thought process in caring for women at midlife and beyond. Virtually all ObGyn HCPs are aware of breast health, both in terms of the clinical breast exam and imaging surveillance. The 5-year relative survival rate for "localized breast cancer" is 99%.¹ Most recent data on hip fracture, however, indicate that it is associated with a mortality in the first year of 21%.² We need to be sure that our patients understand this.

Previously, this column provided an update on osteoporosis. In 2016, I asked to change the focus to "Update on bone health" to highlight that simply relying on dual energy x-ray absorptiometry (DXA) testing of bone mass with arbitrary cutoffs for osteoporosis, osteopenia, and normal bone mass is not adequate for improving overall bone health. The addition of the FRAX fracture

risk assessment tool, now widely employed, as well as the trabecular bone score (TBS), not widely employed, helps to refine the assessment of patients' risk status. Further, issues such as sarcopenia, adequate dietary calcium and vitamin D supplementation, and fall prevention (improving balance, use of nonskid rugs in the bathroom, avoiding black ice when present, having nothing to slip on between the bed and the bathroom in the middle of the night, and so on) also are essential elements of "bone health."

Finally, I cannot stress enough the importance of developing a good relationship with whatever facility one uses for DXA testing in order to maximize use of the reports and potential limitations. In addition, we should identify a metabolic bone specialist for referral of unusual cases or patients who require medications unlikely to be prescribed by us as ObGyns, and develop some familiarity with therapies that may be utilized.

Osteosarcopenia greatly enhances fall and fracture risk

Sepúlveda-Loyola W, Phu S, Bani Hassan E, et al. *The joint occurrence of osteoporosis and sarcopenia (osteosarcopenia): definitions and characteristics. J Am Med Dir Assoc. 2020;21:220-225.*

Tokeshi S, Eguchi Y, Suzuki M, et al. *Relationship between skeletal muscle mass, bone mineral density, and trabecular bone score in osteoporotic vertebral compression fractures. Asian Spine J. 2020 Sep 3. doi: 10.31616/asj.2020.0045.*

Kirk B, Zanker J, Duque G. *Osteosarcopenia: epidemiology, diagnosis, and treatment—facts and numbers. J Cachexia Sarcopenia Muscle. 2020;11:609-618.*

The topic of sarcopenia as defined by the concurrent presence of low muscle mass, physical performance, and strength has been discussed previously in this Update series.³ Now, osteosarcopenia, defined as the concomitant presence of osteoporosis or osteopenia combined with sarcopenia, seems to be an extremely important gauge of fracture risk, especially now as the population's longevity has increased dramatically. This new syndrome is associated with higher disability and rates of fracture and falls in older people compared with either entity (the bone component or the sarcopenia component) alone.^{4,5} In fact, in the 2016 ICD-10-CM, sarcopenia was finally recognized as a disease entity.

Severe sarcopenia is known to increase the risk for falls.⁶ Furthermore, evidence is increasing of cross talk between muscle and bone.⁴ The diagnostic criteria of osteopenia and osteoporosis are well established; however, absolute criteria for sarcopenia lack an international consensus.

Assess for osteopenia/osteoporosis plus sarcopenia to determine those at greatest fracture risk

Sepúlveda-Loyola and colleagues performed a cross-sectional analysis of 253 participants, of which 77% were women, average age 78,

who presented for a “falls and fractures” risk assessment. T-scores were measured by DXA. In addition, the investigators measured components of sarcopenia, including physical performance (evaluated by hand grip strength, gait speed, timed up and go test, and 5-time sit to stand test) and dynamic and static balance. Falls in the previous year were self-reported, with 42% of participants having fallen once and 54%, more than once. **Results.** Participants with osteosarcopenia had a statistically significant increased rate of falls of approximately threefold and an increased rate of fractures that was approximately fourfold when compared with osteopenia or osteoporosis alone.

Another important finding was that, despite the links between osteoporosis, fracture, and poor clinical outcomes, the investigators did not find differences in fracture rates in the osteopenic compared with the osteoporotic classifications. Their findings corroborated those of other studies that reported discrepancies in fractures and bone mineral density (BMD), with osteopenic older adults experiencing fracture rates similar to and in some cases greater than those diagnosed with osteoporosis.⁷

Thus, it appears that the use of T-scores that combine osteopenic and osteoporotic criteria into the osteosarcopenic category may be sufficient to capture individuals at the greatest risk of fracture.

Skeletal muscle mass plays a role in vertebral compression fractures

Tokeshi and colleagues conducted retrospective observational study to investigate the relationships between skeletal muscle mass, BMD, and TBS in individuals with osteoporotic vertebral compression fractures.

They evaluated 142 patients with an average age of 75; of these, 30% had radiographically diagnosed vertebral compression

WHAT THIS EVIDENCE MEANS FOR PRACTICE

In the past, our assessment of risk for fragility fracture was based mostly on bone mass measurement by DXA. Scoring systems like the FRAX tool have included other risk factors, such as age, body mass index, previous fracture, family history of hip fracture, smoking, any history of rheumatoid arthritis, use of glucocorticoids, and alcohol consumption. However, sarcopenia is a condition characterized by loss of skeletal muscle mass, strength, and function. While it is a natural part of the aging process, when it is severe and coupled with osteopenia or osteoporosis, it significantly increases the risks of falls as well as fracture. Women's HCPs should increasingly think about the presence of sarcopenia in their patients, especially those with low bone mass (osteopenia or osteoporosis), particularly when making decisions about initiating pharmaceutical intervention. In addition, recommendations for resistive and balance exercises virtually should be universal.

fractures (average age, 79) and 70% had no vertebral compression fractures (average age, 70). Body composition was measured using whole-body DXA; appendicular skeletal muscle mass index was determined as the sum of upper and lower extremities' lean mass (kg/height in m²). TBS was measured using the patented algorithm software on DXA scans for the lumbar vertebrae.

Results. The investigators found that the vertebral compression fracture group was statistically significantly older, had lower femur BMD, and had decreased leg muscle mass. The TBS was not identified as a risk factor.

Certain lifestyle factors add to risk of osteosarcopenia

In an editorial, Kirk and colleagues summarized the epidemiology, diagnosis, and treatment of osteosarcopenia. They concluded that this syndrome can be expected to grow in age-related and disease-related states as a consequence of immunosenescence coinciding with an increase in sedentary lifestyle, obesity, and fat infiltration of muscle and bone.

Increasingly, clinicians should screen for osteosarcopenia via imaging methods (DXA) to quantitate bone mass (as is currently done) and, increasingly, quantify muscle mass. In addition, assessment of muscle strength, easily done by testing grip strength, as well as functional capacity (gait speed), will become increasingly important.

Finally, the authors call for a more comprehensive geriatric assessment that includes medical history and risk factors as well as treatment (including osteoporosis drugs, where indicated), and progressive resistance and balance exercises. Nutritional recommendations, in terms of protein, vitamin D, and calcium, also are necessary. They anticipate that diagnosis and treatment of osteosarcopenia will become part of routine health care in the future.

FAST TRACK

Clinicians should screen for osteosarcopenia via DXA imaging to quantitate bone mass, as is currently done, and, increasingly, quantify muscle mass

The denosumab discontinuation dilemma

Lyu H, Yoshida K, Zhao SS, et al. Delayed denosumab injections and fracture risk among patients with osteoporosis: a population-based cohort study. Ann Intern Med. 2020;173:516-526.

Tripto-Shkolnik L, Fund N, Rouach V, et al. Fracture incidence after denosumab discontinuation: real-world data from a large healthcare provider. Bone. 2020;130:115150.

Denosumab, marketed under the brand name Prolia, is a human monoclonal antibody that blocks the binding of RANK ligand and inhibits development and activity of osteoclast, thus decreasing bone resorption and increasing BMD. In the original pivotal clinical trial of denosumab, almost 7,900 women between the ages of 60 and 90 (average age, 73) with osteoporotic T-scores were enrolled.⁸ The women were randomly assigned to receive 60 mg of denosumab subcutaneously every 6 months or placebo for a

total of 3 years. In that trial, the denosumab-treated group, relative to the placebo group, showed a statistically significant decrease in radiographic vertebral fracture, hip fracture, and nonvertebral fracture.

An open-label extension study looked at denosumab use for a total of 10 years.⁹ That study found that denosumab treatment for up to 10 years was associated with low rates of adverse events, low fracture incidence compared with that observed during the original trial, and continued increases in BMD without plateau. Thus, denosumab appeared to be an extremely safe and effective agent for treating postmenopausal women with osteoporosis.

Denosumab cessation leads to rebound vertebral fractures

As opposed to bisphosphonates, denosumab does not incorporate into bone matrix, and bone turnover is not suppressed after cessation of its use. Reports have implied that denosumab discontinuation may lead to an increased risk of multiple vertebral fractures.¹⁰ One theory is that unlike atypical femoral fractures that seem to emerge from failure of microdamage repair in cortical bone with long-term antiresorptive treatment, denosumab rebound-associated vertebral fractures seem to originate from the synergy of rapid bone resorption and accelerated microdamage accumulation in trabecular bone triggered by the discontinuation of this highly potent reversible agent.¹¹

Post hoc analysis of the denosumab placebo-controlled trial and its extension reported that the vertebral fracture rate increased after denosumab discontinuation to the level observed in untreated patients.¹² Further, a majority of participants who did sustain vertebral fracture after discontinuing denosumab had multiple vertebral fractures, with the risk being greatest in participants who had a prior vertebral fracture. This caused those authors to suggest that patients who discontinued denosumab should rapidly transition to an alternative antiresorptive treatment.

Effect of dose delays, discontinuation on vertebral fracture rate

Lyu and colleagues recently described their population-based cohort study of the United Kingdom's Health Improvement Network primary care database between 2010 and 2019. They found that delayed administration of a subsequent denosumab dose by more than 16 weeks was associated with an increased risk for vertebral fracture compared with on-time dosing. They noted, however, that the evidence was insufficient to conclude that fracture risk at any other anatomic sites is increased with such a delay.

In a similar study, Tripto-Shkolnik and colleagues examined an Israeli database of 2.3 million members in a state-mandated health organization. They identified osteoporotic patients with at least 2 denosumab prescription dispenses and defined treatment discontinuation as a refill gap of 3 months or more. Fractures were identified by an osteoporosis registry, including fractures that occurred within 1 year from discontinuation in denosumab discontinuers as well as from the second year of treatment forward for persistent users. They identified 1,500 denosumab discontinuers (average age, 72) and 1,610 persistent users (average age also 72). At baseline, the groups were

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Denosumab is an extremely safe and effective treatment for postmenopausal osteoporosis. Discontinuation or even delay in dosing seems to result in a “rebound” effect of increased vertebral fractures and even multiple vertebral fractures, especially in those with history of a previous vertebral fracture. This is extremely important in this era of COVID-19, in which patients—especially elderly patients who are perceived to be at the greatest risk—often delay management of chronic disease to limit their potential exposure to the virus. Further, even in normal, nonpandemic times, clinicians need to make patients receiving denosumab aware of the importance of timely administration of doses as scheduled. If such dosing is not possible, then clinicians and patients need to be aware of the potential need for instituting other antiresorptive therapies. In addition, the need to ostensibly continue denosumab therapy for long periods of time and indefinitely may make it a less desirable choice for younger patients.

comparable in fracture history, smoking, and bone density.

In the discontinuation group, 0.8% had multiple vertebral fractures versus 0.1% in the persistent users ($P = .006$); the overall

rate of fractures per 100 patient-years of follow-up was 3 times higher in the discontinuation group than in the persistent user group, and the rate of vertebral fractures was almost 5 times higher in the discontinuation group.

Atypical femur fracture risk and bisphosphonate use

Black DM, Geiger EJ, Eastell R, et al. Atypical femur fracture risk versus fragility fracture prevention with bisphosphonates. N Engl J Med. 2020;383:743-753.

Since their introduction in the 1990s, bisphosphonates have been the mainstay of osteoporosis treatment. This category of medications inhibits osteoclast-mediated resorption and remodeling of bone. Various large, randomized, controlled trials have established the efficacy of bisphosphonates to increase BMD and decrease the risk of hip and vertebral fracture by as much as 40% to 70%.¹³

However, case reports of unusual fragility fractures in the subtrochanteric region and along the femoral diaphysis in patients treated with bisphosphonates started to appear approximately 15 years ago.¹⁴ Since then, concerns and publicity about these atypical fractures have led to substantial declines in bisphosphonate use clinically.

Bisphosphonate preventive benefits versus atypical fracture risk

Black and colleagues reviewed data on women 50 years and older who were enrolled in the Kaiser Permanente health care system in California. The total cohort included slightly more than 1 million women, of which almost 200,000 (17.9%) used bisphosphonates at any point from 2007–2017.

A total of 277 atypical femur fractures occurred. Among bisphosphonate users, there were 1.74 fractures per 10,000 patient-years. Overall, there were almost 59 fractures per 10,000 person-years. The incidence of atypical fractures was highest in women between the ages of 75 and 84 years, and the incidence diminished after age 85. Rates of atypical fractures increased as the duration of bisphosphonate use increased. In addition, rates of atypical fractures decreased with time since bisphosphonate discontinuation.

The rate of atypical fractures in women who had never received bisphosphonate therapy was 0.1 per 10,000 person-years. The number of fractures prevented for each fracture type far outweighed bisphosphonate-associated atypical fractures at all time points along the 10 years of study. In White women, for instance, at 3 years there were 541 clinical fractures prevented and 149 hip fractures prevented, while 2 bisphosphonate-associated atypical fractures occurred, all per 10,000 women.

Interestingly, in the Asian population at the same time point, 330 clinical fractures were prevented and 91 hip fractures were prevented, but 8 atypical fractures of the femur

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Many patients and even clinicians have moved away from the use of bisphosphonates to reduce fragility fracture risk because of fears of atypical femur fractures. With bisphosphonate use, the reduction in hip fracture as well as other fractures far overshadows the small but real complication of atypical femur fracture. The Asian population seems to have 4 to 6 times the risk for these atypical femur fractures. Thus, bisphosphonate therapy, especially now that it is available in generic formulations, should remain an important option for appropriate patients.

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occurred, per 10,000 women. The authors further referenced an earlier Kaiser study that showed that 49% of 142 atypical femur fractures occurred in Asian patients who comprised only 10% of the study population.¹⁵

The authors concluded that the risk of atypical femur fracture increases with

longer duration of bisphosphate use and rapidly decreases after bisphosphate discontinuation. Asian women have a higher risk than White women. With bisphosphonate treatment, the absolute risk of atypical femur fracture is very low compared with the reduction in the risk of hip and other fractures.

Romozumab increases BMD gains and improves T-scores

Cosman F, Lewiecki EM, Ebeling PR, et al. T-score as an indicator of fracture risk during treatment with romozumab or alendronate in the ARCH trial. J Bone Miner Res. 2020;35:1333-1342

Romozumab (Evenity) is a monoclonal antibody that binds and inhibits sclerostin, thus having the dual effect of increasing bone formation and decreasing bone resorption.¹⁶ It is administered for 1 year as monthly doses of 210 mg subcutaneously. Previous studies have shown that romozumab produces large increases in lumbar spine and total hip BMD,¹⁷ reduces the risk of new vertebral and clinical fractures compared with placebo,¹⁶ and reduces the risk of vertebral, clinical, nonvertebral, and hip fractures compared with alendronate over a median treatment period of 33 months (the ARCH study).¹⁸

According to the package insert, romozumab is indicated “for the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.”

Should T-score be a therapeutic target?

Cosman and colleagues performed a post hoc analysis of the ARCH trial specifically to evaluate mean BMD and corresponding mean T-score changes (and the relationships between T-scores) after 1 year of

romozumab or alendronate therapy and subsequent fracture incidence. The study is quite detailed with much numerical data and statistical analysis.

Basically, the ARCH trial randomly assigned patients with osteoporosis to receive either monthly subcutaneous romozumab 210 mg or weekly oral alendronate 70 mg for 12 months. After the double-blind portion of the trial, all patients received open label weekly oral alendronate 70 mg through the end of study (24 months), although they were still blinded to the initial treatment assignment. In addition, patients received daily calcium and vitamin D supplements.

The data analysis found that 1 year of romozumab led to larger BMD gains than alendronate therapy. Also, the T-score achieved with either therapy was directly related to subsequent fracture risk. The authors thus proposed that these data support the use of the T-score as a therapeutic target for patients with osteoporosis.

It is important to note that in the original ARCH study, the participants' average age was 71 years and approximately one-third were older than 75. The average T-score was -2.7 at both the lumbar spine and femoral neck. Approximately 20% of patients had a pre-existing vertebral fracture, and approximately 20% had a previous nonvertebral fracture.

The authors of the current study, furthermore, found that mean BMD gains after 1 year of romozumab treatment were more than twice those seen with alendronate

FAST TRACK

One year of romozumab led to larger BMD gains than alendronate, and the T-score achieved with either therapy was directly related to subsequent fracture risk

at the total hip, femoral neck, and lumbar spine. These BMD changes resulted in a larger proportion of patients who achieved T-scores above the osteoporosis level at each of the skeletal sites after 1 year of therapy. Fewer fractures occurred during the second year and the entire open label period among patients who had received romosozumab first compared with those who received alendronate. ●

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Women's HCPs need to be aware of romosozumab even if they are not the ones primarily to prescribe it. Perhaps familiarity with the drug will allow some clinicians to begin to implement this treatment into their care for elderly patients with osteoporosis, especially those with pre-existing fractures. It may be useful to monitor patients' total hip T-score while on treatment if osteoporosis treatment goals have been achieved to minimize future fracture risk.

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