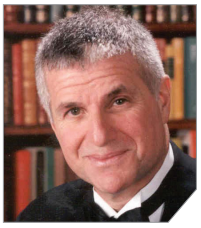

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How muscle mass, strength, and performance are playing a recognized role in bone health, plus when to measure BMD in premenopausal women

Recently, the National Osteoporosis Foundation (NOF) changed its name to the Bone Health and Osteoporosis Foundation (BHOF). Several years ago, in 2016 at my urging, this column was renamed from "Update on osteoporosis" to "Update on bone health." I believe we were on the leading edge of this movement. As expressed in last year's Update, our patients' bone health must be emphasized more than it has been in the past.[1]

Consider that localized breast cancer carries a 5-year survival rate of 99%.[2] Most of my patients are keenly aware that periodic competent breast imaging is the key to the earliest possible diagnosis. By contrast, in this country a hip fracture carries a mortality in the first year of 21%![3] Furthermore, approximately one-third of women who fracture their hip do *not* have osteoporosis.[4] While the risk of hip fracture is greatest in women with osteoporosis, it is not absent in those without the condition. Finally, the role of muscle mass, strength, and performance in bone health is a rapidly emerging topic and one that constitutes the core of this year's Update.

Muscle mass and strength play key role in bone health

de Villiers TJ, Goldstein SR. Update on bone health: the International Menopause Society white paper 2021. Climacteric. 2021;24:498-504. doi:10.1080/13697137.2021.1950967.

Recently, de Villiers and Goldstein offered an overview of osteoporosis.[5] What is worthy of reporting here is the role of muscle in bone health.

The bone-muscle relationship

Most clinicians know that osteoporosis and osteopenia are well-defined conditions with known risks associated with fracture. According to a review of PubMed, the first article with the keyword "osteoporosis" was published in 1894; through May 2020, 93,335 articles used that keyword. "Osteoporosis" is derived from the Greek *osteon* (bone) and *poros* (little hole). Thus, osteoporosis means "porous bone."

Sarcopenia is characterized by progressive and generalized loss of skeletal muscle mass, strength, and function, and the

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The morbidity and mortality from fragility fractures are well known. Initially, diagnosis of risk seemed to be mainly T-scores on bone mineral density (BMD) testing (normal, osteopenic, osteoporosis). The FRAX fracture risk assessment tool, which includes a number of variables, further refined risk assessment. Increasingly, there is evidence of crosstalk between muscle and bone. Sarcopenia, the loss of skeletal muscle mass, strength, and performance, appears to play an important role as well for fracture risk. Simple tools to evaluate a patient's muscle status exist. At the very least, resistance and balance exercises should be part of all clinicians' patient counseling for bone health.

condition is associated with a risk of adverse outcomes that include physical disabilities, poor quality of life, and death.[6,7] "Sarcopenia" has its roots in the Greek words *sarx* (flesh) and *penia* (loss), and the term was coined in 1989.[8] A PubMed review that included "sarcopenia" as the keyword revealed that the first article was published in 1993, with 12,068 articles published through May 2020.

Notably, muscle accounts for about 60% of the body's protein. Muscle mass decreases with age, but younger patients with malnutrition, cachexia, or inflammatory diseases are also prone to decreased muscle mass. While osteoporosis has a well-accepted definition based on dual-energy x-ray absorptiometry (DXA) measurements, sarcopenia has no universally accepted definition, consensus diagnostic criteria, or treatment guidelines. In 2016, however, the International Classification of Diseases, Tenth Revision, Clinical Modification (CD-10-CM) finally recognized sarcopenia as a disease entity.

Currently, the most widely accepted definition comes from the European Working Group on Sarcopenia in Older People, which labeled presarcopenia as low muscle mass without impact on muscle strength or performance; sarcopenia as low muscle mass with either low muscle strength or low physical performance; and severe sarcopenia has all 3 criteria being present.[9]

When osteosarcopenia (osteoporosis or osteopenia combined with sarcopenia) exists, it can result in a threefold increase in risk of falls and a fourfold increase in fracture risk compared with women who have osteopenia or osteoporosis alone.[10]

FAST TRACK

When osteosarcopenia exists, it can result in a threefold increase in risk of falls and a fourfold increase in fracture risk compared with women who have osteopenia or osteoporosis alone

Denosumab decreased falls risk, improved sarcopenia measures vs comparator antiresorptives

El Miedany Y, El Gaafary M, Toth M, et al; Egyptian Academy of Bone Health, Metabolic Bone Diseases. Is there a potential dual effect of denosumab for treatment of osteoporosis and sarcopenia? Clin Rheumatol. 2021;40:4225-4232. doi: 10.1007/s10067-021-05757-w.

Osteosarcopenia, the combination of osteoporosis or osteopenia with sarcopenia, has been shown to increase the overall rate of falls and fracture when compared with fall and fracture rates in women with osteopenia or osteoporosis alone.[10] A study by El Miedany and colleagues examined whether denosumab treatment had a possible dual therapeutic effect on osteoporosis and sarcopenia.[11]

Study details

The investigators looked at 135 patients diagnosed with postmenopausal osteoporosis and who were prescribed denosumab and compared them with a control group of 272 patients stratified into 2 subgroups: 136 were prescribed alendronate and 136 were prescribed zoledronate.

Assessments were performed for all participants for BMD (DXA), fall risk (falls

risk assessment score [FRAS]), fracture risk (FRAX assessment tool), and sarcopenia measures. Reassessments were conducted after 5 years of denosumab or alendronate therapy, 3 years of zoledronate therapy, and 1 year after stopping the osteoporosis therapy.

The FRAS uses the clinical variables of history of falls in the last 12 months, impaired sight, weak hand grip, history of loss of balance in the last 12 months, and slowing of the walking speed/change in gait to yield a percent chance of sustaining a fall.[12] Sarcopenic measures include grip strength, timed up and go (TUG) mobility test, and gait speed. There were no significant demographic differences between the 3 groups.

Denosumab reduced risk of falls and positively affected muscle strength

On completion of the 5-year denosumab therapy, falls risk was significantly decreased (P = .001) and significant improvements were seen in all sarcopenia measures (P = .01). One year after denosumab was discontinued, a significant worsening of both falls risk and sarcopenia measures (P = .01) occurred. This was in contrast to results in both control groups (alendronate and zoledronate), in which there was an improvement, although less robust in gait speed and the TUG test (P = .05) but no improvement in risk of falls. Thus, the results of this study showed that denosumab not only improved bone mass but also reduced falls risk.

Compared with bisphosphonates, denosumab showed the highest significant positive effect on both physical performance and skeletal muscle strength. This is evidenced by improvement of the gait speed, TUG test, and 4-m walk test (P<.001) in the denosumab group versus in the alendronate and zoledronate group (P<.05).

These results agree with the outcomes of the FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis 6 months) trial, which revealed that not only did denosumab treatment reduce the risk of vertebral, nonvertebral, and hip fracture over 36 months, but also that the denosumab-treated group had fewer falls (4.5%) compared with the other groups (5.7%) (P = .02).[13]

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These data highlight that osteoporosis and sarcopenia may share similar underlying risk factors and that muscle-bone interactions are important to minimize the risk of falls, fractures, and hospitalizations. While all 3 antiresorptives (denosumab, alendronate, zoledronate) improved measures of BMD and sarcopenia, only denosumab resulted in a reduction in the FRAS risk of falls score.

FAST TRACK

Compared with bisphosphonates, denosumab showed the highest significant positive effect on both physical performance and skeletal muscle strength

Estrogen's role in bone health and its therapeutic potential in osteosarcopenia

Mandelli A, Tacconi E, Levinger I, et al. The role of estrogens in osteosarcopenia: from biology to potential dual therapeutic effects. Climacteric. 2021;1-7. doi: 10.1080/13697137.2021.1965118.

Osteosarcopenia is a particular term used to describe the coexistence of 2 pathologies, osteopenia/osteoporosis and sarcopenia.[14] Sarcopenia is characterized by a loss of muscle mass, strength, and performance. Numerous studies indicate that higher lean body mass is related to increased BMD and reduced fracture risk, especially in postmenopausal women.[15]

Menopause, muscle, and estrogen's physiologic effects

Estrogens play a critical role in maintaining bone and muscle mass in women. Women

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Estrogens play a crucial role in maintaining bone and skeletal muscle health in women. Estrogen therapy is an accepted treatment for osteoporosis, whereas its effects on sarcopenia, although promising, indicate that additional studies are required before it can be recommended solely for that purpose. Given the well-described benefits of exercise on muscle and bone health, postmenopausal women should be encouraged to engage in regular physical exercise as a preventive or disease-modifying treatment for osteosarcopenia.

experience a decline in musculoskeletal quantity and quality at the onset of menopause.[16] Muscle mass and strength decrease rapidly after menopause, which suggests that degradation of muscle protein begins to exert a more significant effect due to a decrease in protein synthesis. Indeed, a reduced response to anabolic stimuli has been shown in postmenopausal women.[17] Normalization of the protein synthesis response after restoring estrogen levels with estrogen therapy supports this hypothesis.[18]

In a meta-analysis to identify the role of estrogen therapy on muscle strength, the authors concluded that estrogens benefit muscle strength not by increasing the skeletal mass but by improving muscle quality and its ability to generate force.[19] In addition, however, it has been demonstrated that exercise prevents and delays the onset of osteosarcopenia.[20]

When should bone mass be measured in premenopausal women?

FAST TRACK

BMD testing is only indicated in younger women in settings in which the result may influence management decisions

Conradie M, de Villiers T. Premenopausal osteoporosis. Climacteric. 2021:1-14. doi: 10.1080/13697137.2021.1926974.

Most women's clinicians are somewhat well acquainted with the increasing importance of preventing, diagnosing, and treating postmenopausal osteoporosis, which predisposes to fragility fracture and the morbidity and even mortality that brings. Increasingly, some younger women are asking for and receiving both bone mass measurements that may be inappropriately ordered and/or wrongly interpreted. Conradie and de Villiers provided an overview of premenopausal osteoporosis, containing important facts that all clinicians who care for women should be aware of.[21]

Indications for testing

BMD testing is only indicated in younger women in settings in which the result may influence management decisions, such as:

- a history of fragility fracture
- diseases associated with low bone mass, such as anorexia nervosa, hypogonadism, hyperparathyroidism, hyperthyroidism, celiac disease, irritable bowel disease, rheumatoid arthritis, lupus, renal disease, Marfan syndrome
- medications, such as glucocorticoids, aromatase inhibitors, premenopausal tamoxifen, excess thyroid hormone replacement, progesterone contraception
- excessive alcohol consumption, heavy smoking, vitamin D deficiency, calcium deficiency, occasionally veganism or vegetarianism.

BMD interpretation in premenopausal women does *not* use the T-scores developed for postmenopausal women in which standard deviations (SD) from the mean for a young reference population are employed. In that population, the normal range is up to -1.0 SD; osteopenia > -1.0 < -2.5 SD; and osteoporosis > -2.5 SD. Instead, in premenopausal patients, Z-scores, which compare the measured bone mass to an age- and gender-matched cohort, are employed. Z-scores > 2 SD below the matched population should be used rather than the T-scores that are already familiar to most clinicians.

Up to 90% of these premenopausal women with such skeletal fragility will display the secondary causes described above. ●

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Very specific indications are required to consider bone mass measurements in premenopausal women. When measurements are indicated, the values are evaluated by Z-scores that compare them to those of matched-aged women and not by T-scores meant for postmenopausal women. When fragility or low-trauma fractures or Z-scores more than 2 SD below their peers are present, secondary causes of premenopausal osteoporosis include a variety of disease states, medications, and lifestyle situations. When such factors are present, many general women's health clinicians may want to refer patients for consultation to a metabolic bone specialist for workup and management.

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