review article

Redefining Osteoporosis Treatment: Who to Treat and How Long to Treat

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ABSTRACT

Osteoporosis is a common disease that is associated with increased risk of fractures and serious clinical consequences. Bone mineral density (BMD) testing is used to diagnose osteoporosis, estimate the risk of fracture, and monitor changes in BMD over time. Combining clinical risk factors for fracture with BMD is a better predictor of fracture risk than BMD or clinical risk factors alone. Methodologies are being developed to use BMD and validated risk factors to estimate the 10-year probability of fracture, and then combine fracture probability with country-specific economic assumptions to determine cost-effective intervention thresholds. The decision to treat is based on factors that also include availability of therapy, patient preferences, and co-morbidities. All patients benefit from nonpharmacological lifestyle treatments such a weight-bearing exercise, adequate intake of calcium and vitamin D, fall prevention, avoidance of cigarette smoking and bone-toxic drugs, and moderation of alcohol intake. Patients at high risk for fracture should be considered for pharmacological therapy, which can reduce fracture risk by about 50%. **(Arq Bras Endocrinol Metab 2006;50/4:694-704)**

Keywords: Osteoporosis; Treatment; Fracture; Intervention; Bone mineral density; Clinical risk factors

RESUMO

Redefinindo o Tratamento da Osteoporose: Quem Tratar e Até Quando.
Osteoporose é uma doença comum, que está associada a um aumento do risco de fraturas e de importantes conseqüências clínicas. A densidade mineral óssea (DMO) é o método usado para o diagnóstico da osteoporose, estimando o risco de fratura e monitorando as alterações da DMO durante o tempo. A combinação de fatores de risco para fraturas com a densidade mineral óssea é melhor preditor do risco de fratura do que um deles isoladamente. Metodologias estão sendo desenvolvidas para usar a DMO e fatores de risco validados para estimar o risco de fraturas em 10 anos. A decisão de tratar também está baseada em fatores que incluem terapia disponível, preferência do paciente e co-morbidades. Todos os pacientes se beneficiam de medidas não farmacológicas tais como uma ingesta adequada de cálcio e vitamina D, prevenção de queda, evitar tabagismo e drogas de efeito tóxico ao osso. Pacientes de alto risco de fraturas devem ser considerados para o tratamento farmacológico, os quais podem reduzir este risco em 50%. **(Arq Bras Endocrinol Metab 2006;50/4:694-704)**

Descritores: Osteoporose; Tratamento; Fratura; Intervenção; Densidade mineral óssea; Fatores clínicos de risco

OSTEOPOROSIS IS A COMMON AND COSTLY disease that is associated with significant morbidity and mortality. Osteoporosis affects 200 million worldwide, one-third of women aged 60 to 70, and two-thirds of women aged 80 or older (1). Approximately 30% of women over age 50 have one or more vertebral fractures (2). Approximately one in five men over the age of 50 will have an osteoporosis-related fracture in their remaining lifetime (1). In 1995, the annual incidence of osteoporotic fracture in the USA was about 1.5 million. There are about 750,000 vertebral fractures, 250,000 hip fractures, 250,000 wrist fractures and 250,000 other fractures per year in the USA (3).

The prevalence of osteoporosis is expected to increase with the aging of the population. While Europe and North America account for about half of worldwide hip fractures among elderly today, this proportion will fall to about one quarter by 2050. At that time there will be a steep increase in the incidence of hip fractures in Asian and Latin American countries due to the rising population (4). The incident hip fracture rate will increase from 378, 000 to 742,000 in the USA, while increasing from 100,000 to 629,000 in South America and 600,000 to 3.25 million in Asia (4). The total number of hip fractures will increase worldwide from 1.66 million to 6.26 million.

Both vertebral and hip fractures are associated with increased mortality (5), with hip mortalities typically occurring sooner after the fracture, than with vertebral fractures. One year after a hip fracture the death rate is 20% higher than expected, with 40% of survivors unable to walk independently and 80% unable to carry out at least one independent activity of daily living (6). The adverse effects of vertebral fractures on health, function, and quality of life are often underestimated. Vertebral fractures result in loss of height, pain, early satiety, decreased lung capacity, increased risk of falls, sleep disorder, increased dependence, increased functional impairment and decreased appetite (7).

With the development of a diverse therapeutic menu in osteoporosis, there is an increasing need to develop strategies for fracture risk assessment. Treatment is most cost-effective when targeted to those with the highest level of fracture risk. As Prof. John Kanis has said, "We cannot afford to treat everyone (8)". In the management of individual patients, factors other than cost-effectiveness also play a role in treatment decisions.

ASSESSMENT OF FRACTURE RISK

An evaluation of fracture risk is the first step in determining who needs to be treated. Bone mineral density (BMD) is a robust predictor of fracture risk, with an increase in the relative risk of fracture of approximately 1.5–2.0 for every 1 standard deviation (SD) decrease in BMD (9). In 1994, the World Health Organization (WHO) published criteria for the diagnosis of osteoporosis based on BMD measurement at the spine, hip, or forearm with dual-energy X-ray absorptiometry (DXA) (10). With this classification, a patient with a BMD that is 2.5 SD or more below the mean BMD of a young-adult reference population (T-score= -2.5 or less) has a diagnosis of osteoporosis. When the BMD is between 1.0 and 2.5 SD below that of the reference population (T-score= -1.0 to -2.5), the diagnosis is low bone mass (osteopenia), and when the BMD is 1.0 SD below the mean BMD of the reference population or greater (T-score= -1.0 or higher), the BMD is called normal. Patients with a fragility fracture are classified as osteoporotic (clinical diagnosis) regardless of T-score. Although this was intended to provide only a system for BMD classification, T-scores have been interpreted by some third party payers and others to be intervention thresholds as well.

It has become clear that BMD measurement, while valuable, may not provide sufficient information to identify all patients at high risk of fracture. Recent studies have shown that many or most patients in the community with fractures have a baseline BMD above the WHO diagnostic threshold T-score of -2.5. In the National Osteoporosis Risk Assessment (NORA) study using peripheral bone density measurements (11) and in the Study of Osteoporotic Fractures using central bone density measurements (12), approximately one-half of osteoporotic fractures occurred in women with a T-score above -2.5. Although the relative risk of fractures was greater in women with T scores -2.5 or less compared to women with a higher T-score, there were many more women in the higher T-score range. BMD measurement therefore is highly specific for fracture risk but poorly sensitive. This sensitivity, or gradient of risk, can be improved by the addition of clinical risk factors for fracture that are independent of BMD. The use of clinical risk factors for fracture may be especially useful in world regions where BMD measurement is not easily available. It has been estimated that 11.2 DXA units per million general population are necessary for widespread population screening (13). While the USA has about 35.8 DXA units per million and some other western countries exceed the threshold of 11.2, many other countries have far less. In Brazil there are about 7.0 units per million and in the UK about 3.7 per million (13).

Using meta-analyses of population-based cohorts from Europe, North America, Asia, and Australia, the international validity of candidate risk factors for fracture was examined by a WHO task force at a conference held in Brussels, Belgium, in May 2004. In order for risk factors to be clinically useful in areas where BMD testing is available, they must be independent of BMD and modifiable by pharmaceutical intervention. Those factors that were validated by the WHO included BMD at the femoral neck, age, a prior fragility fracture, glucocorticoid exposure, parental history of hip fracture, current smoking, excessive alcohol intake, and secondary osteoporosis (rheumatoid arthritis). Where BMD testing is not available, low body mass index (BMI) may be considered as a surrogate for BMD. The most important of WHO-validated risk factors are age and prior fragility fracture. For any T-score value, fracture probability increases as age increases (14). A 50-year-old woman with a femoral neck T-score of -2.5 has a 10-year hip fracture probability of approximately 2.5%, while an 80-year-old woman with the same T-score has a 12.5% 10-year probability of hip fracture. Prior fracture is another important risk factor independent of BMD. Observational studies (15), meta-analysis of observational studies (16), and follow-up of placebo groups in clinical trials (17) have shown that a prevalent vertebral fracture greatly increases the risk of subsequent fractures, with about a 5-fold increase of fracture in the year following an acute vertebral fracture. The clinical risk factors for fracture that were validated by the WHO can be used to construct models for estimating the 10-year probability (absolute risk) of hip fracture or any osteoporotic fracture. This, in turn, can be used to calculate country-specific cost-effective intervention thresholds.

INTERVENTION THRESHOLDS

Patients at high risk of fracture are most likely to benefit from treatment to reduce fracture risk. Treatment is most cost-effective when the expenses associated with fracture are high and the cost of treatment is low. Approaches to identifying patients for treatment vary in different world regions according to fracture incidence, available healthcare resources, economic considerations, political will, and cultural priorities. A "case-finding strategy" is supported by the International Osteoporosis Foundations and is widely used in European Union countries. With this approach, individual patients who are at high risk for fracture by virtue of factors such as previous fragility fracture, glucocorticoid therapy, or family history of osteoporosis, are selected for BMD testing. If a densitometric diagnosis of osteoporosis according to the WHO classification is made, then treatment is recommended. Thus each patient selected for treatment must meet two standards by having both a risk factor for fracture and a T-score in the osteoporosis range. With this method, only patients at high risk for fracture are treated, but many other high-risk patients (e.g., those with fragility fractures and T-scores greater than -2.5) will not be treated. Case-finding strategies distribute limited healthcare resources to those who are very likely to benefit, but may miss many other patients in need of treatment.

The "population-based strategy," used in the USA and Canada, selects at-risk populations (e.g., all women age 65 and older, all younger postmenopausal women with risk factors) for BMD testing. Current treatment guidelines then identify treatment thresholds based on the T-score with or without clinical risk factors for fracture. For example, treatment may be recommended when the T-score is below -2.5 (18) or -2.0 (19) regardless of risk factors; when the T-score is between -1.5 and -2.5 (18) or between -1.5 and -2.0 (19) and risk factors are present; or when a fragility fracture has occurred (18,19). Treatment guidelines differ according to the patient populations addressed, T-score cutoffs used, risk factors considered, the definition of a fragility fracture, and whether a fragility fracture must also be associated with low BMD (20). The guidelines do not tell us how to integrate multiple clinical risk factors or how to integrate clinical risk factors and BMD. The plethora of variable treatment guidelines may sometimes serve to confuse more than enlighten (20) and contribute to their underutilization in clinical practice (21). Population-based strategies identify more patients at high fracture risk for treatment than do case-based strategies, but require more healthcare resources (e.g., BMD testing devices, trained personnel), generate greater costs, and may result in some patients at low risk for fracture being treated.

Methodologies that calculate intervention thresholds based on fracture probability using country-specific incidence rates and numerous economic/disutility assumptions may eventually replace the current polyglot of treatment recommendations that are largely based on T-score. The National Osteoporosis Foundation (NOF) and WHO have published models for applying cost-utility analysis to a combination of BMD and clinical risk factors for fracture to establish cost-effective thresholds for pharmacological

therapy (8,22). Application of such models to clinical practice would allow physicians to more effectively target patients most likely to benefit from pharmacological therapy and help to close the treatment gap — the difference between the number of patients who could benefit from treatment and those who are actually treated. In countries were BMD testing is not available, body mass index (BMI) may be considered as a surrogate for BMD.

GENERAL PRINCIPLES OF OSTEOPOROSIS THERAPY

Prevention of osteoporosis or low BMD is preferred to treatment. Bone microarchitectural changes associated with bone loss are largely irreversible. Although treatment can increase BMD and reduce the risk of fracture, it is unlikely to fully restore the quality and strength of bone to normal. BMD in adults is determined by peak bone mass (PBM), which is the maximum bone mass achieved in life, and the subsequent rate of bone loss. The prevention of osteoporosis or low BMD is directed to maximizing PBM and minimizing the rate of bone loss, with the ultimate goal of maintaining bone strength and preventing fractures. Stabilizing BMD or reducing the rate of bone loss is the primary objective in the prevention of osteoporosis once PBM has been attained. The Surgeon General's report on *Bone Health and Osteoporosis* recommends a "pyramid" approach to the prevention and treatment of osteoporosis, with a foundation of lifestyle changes that include nutrition, physical activity, and fall prevention; a second tier of addressing drugs and diseases associated with bone loss or osteoporosis; and a third tier of pharmacological therapy (23).

LIFESTYLE

Nutrition

Good nutrition from infancy through adolescence, with particular attention to adequate daily intake of calcium and vitamin D, is a key component for the attainment of maximum PBM. Nutritional disorders known to impair bone accretion in adolescence include anorexia nervosa (24), inflammatory bowel disease, celiac disease, and cystic fibrosis (25). In reviews of 19 placebo-controlled studies looking at the relationship between calcium intake and bone loss, 16 showed that calcium prevented or slowed bone loss (26,27). In a recent meta-analysis of randomized trials in postmenopausal women, representing 1,806 participants, it was found that calcium was more effective than placebo in reducing rates of bone loss after two or more years of treatment (28). The recommended daily intake of elemental calcium for postmenopausal women is 1200 mg (23), which is much more than the average daily intake in this population (29-31). Vitamin D is important for absorption of calcium and mineralization of bone (32), as well as for optimal muscle function and balance (33). Vitamin D deficiency or insufficiency, defined as a blood level less than 20 or 30 ng/ml, respectively, is common, especially in the frail elderly (34). While it is often difficult to distinguish the effects of calcium and vitamin D in clinical trials, some studies have shown an increase in BMD and reduction in fracture risk in elderly patients supplemented with calcium and vitamin D (35,36). Recommended daily intakes of vitamin D may not be adequate to attain optimal blood levels in all patients. When it is necessary to determine adequacy of vitamin D with certainty, serum 25-OH-vitamin D, not 1,25-dihydroxyvitamin D, should be measured. A recent report from the Women's Health Initiative (WHI) demonstrated that calcium and vitamin D supplementation increased hip BMD in the entire cohort of postmenopausal women, and reduced the risk of hip fracture in those who were adherent to therapy, taking estrogen, or age 60 and older (37). Adequacy of calcium and vitamin D should be assured in all patients, especially those with osteoporosis.

Physical activity

Observational, retrospective, and prospective randomized studies have shown beneficial effects of exercise on bone accumulation during growth, with particular benefit from high impact exercise (38,39). Excessive exercise can be harmful to skeletal health, as seen in adolescents and young-adults with female athlete triad (disordered eating, amenorrhea, and osteoporosis) (40). Weight-bearing exercise is associated with small but significant improvement in BMD in premenopausal and postmenopausal women (41) and in men (42). The Surgeon General recommends a "minimum of 30 minutes of physical activity (such as brisk walking) on most, if not all, days of the week" (43).

Other lifestyle factors

Cigarette smoking and excess alcohol intake should be discouraged during childhood due to well known adverse effects on multiple organ systems (23). Meta-analyses have shown that cigarette smoking is associat-

ed with reduced BMD (44) and increased risk of fracture (45). Every effort should be made to discourage initiation or continuation of cigarette smoking. Excess alcohol is detrimental to skeletal health for many reasons (46), although moderate alcohol drinking has been associated with higher bone mass in some studies (47,48). Administration of drugs that are known to be harmful to skeletal health, such as glucocorticoids and anticonvulsants, should be avoided or minimized in dose and duration.

Falls

The vast majority of hip fractures, most other nonvertebral fractures, and some vertebral fractures, occur as a result of a fall. A fracture occurs when the force applied to the bone exceeds the strength of the bone. Prevention of falling is a key component of a fracture prevention program. Weight-bearing exercise with special attention to quadriceps muscle strengthening should be encouraged. Patients can do balance-training independently, with the help of a physical therapist, or through instructional classes in activities such as Yoga or Tai-Chi. Vitamin D supplementation may increase muscle strength, improve balance, and reduce the risk of falls. Hip protectors, if worn regularly, may reduce the risk of hip fractures in patients who are at high risk of falling.

DRUGS AND DISEASES ASSOCIATED WITH BONE LOSS OR OSTEOPOROSIS

Patients with low BMD or osteoporosis may have factors other than hormone deficiency or aging that contribute to poor skeletal health. Drugs commonly associated with osteoporosis include glucocorticoids, anticonvulsants, aromatase inhibitors, androgen deprivation agents, and excess thyroid medication. Endocrine diseases such a hyperthyroidism, hyperparathyroidism, and Cushing's syndrome may cause osteoporosis. Common nutritional disorders to be considered include malabsorption due to celiac disease, bariatric surgery, or alcoholism. Osteomalacia due to vitamin D deficiency is becoming more common, even in sunny climates. Multiple myeloma may masquerade as postmenopausal osteoporosis. Rheumatoid arthritis and other chronic inflammatory conditions, as well as the drugs used for their treatment, may cause osteoporosis. Clinicians should have a high index of suspicion for factors contributing to low BMD in all patients. A thorough medical history and a few cost-effective laboratory tests (e.g., serum calcium, 24-hour urine for calcium, parathyroid hormone level, thyroid stimulating hormone level in women on thyroid replacement therapy) will identify many patients with secondary causes of osteoporosis (49).

PHARMACOLOGICAL THERAPY FOR OSTEOPOROSIS

We are fortunate to have a diverse menu of therapeutic options for patients with osteoporosis, including both antiresorptive (anti-catabolic) and anabolic agents (50). In a chronic asymptomatic illness such as osteoporosis, pharmacological therapy should be individualized for each patient based on approved indications, medical needs, and medication preferences. Important attributes of osteoporosis medications include efficacy (fracture risk reduction), side effects, convenience, cost, time on market, drug interactions, dosing interval, and nonskeletal benefits and risks. Registered medications for osteoporosis prevention include estrogen, the selective estrogen receptor modulator (SERM) raloxifene, and three bisphosphonates: alendronate, ibandronate, and risedronate. Registered medications for osteoporosis treatment include raloxifene, the three bisphosphonates, nasal calcitonin, teriparatide, and strontium ranelate (51,52).

All of the registered agents have been shown to reduce the risk of vertebral fractures. Alendronate and risedronate reduced the risk of hip fractures in randomized placebo-controlled clinical trials. Estrogen reduced the risk of vertebral and hip fractures in the Women's Health Initiative (WHI). In the USA, alendronate is indicated for the reduction of hip fracture, while risedronate is indicated for reduction of a composite endpoint of nonvertebral fracture including hip fracture. Alendronate has been shown in meta-analyses to reduce nonvertebral fracture risk. In post-hoc analyses of high-risk subsets of clinical trial cohorts, ibandronate and raloxifene reduced the risk of nonvertebral fractures. Calcitonin has not been demonstrated to reduce either hip or nonvertebral fracture. Teriparatide is indicated for both men and women at high risk of fracture. Only teriparatide and alendronate are indicated in men.

All three bisphosphonates are effective when given daily. Alendronate and risedronate may be given weekly and ibandronate may be given monthly by mouth or every 3 months by intravenous (IV) injection. Raloxifene, nasal calcitonin, teriparatide, and strontium ranelate require daily dosing. The dosing regimen for bisphosphonates requires a 30 minute

post dose fast for alendronate and risedronate and a 60 minute post dose fast for ibandronate. All three bisphosphonates have been noted to have problems with gastrointestinal tolerability in clinical practice. Rarely, bisphosphonates have been associated with a syndrome of myalgias and arthralgias, which may recur on rechallenge. Bisphosphonates, particularly IV bisphosphonates, have been associated with osteonecrosis of the jaw, largely in cancer patients such as those with multiple myeloma, who have poor dental hygiene and have had chemotherapy, irradiation, or glucocorticoid use. Raloxifene and estrogen share increased incidence of venous thromboembolic events. Raloxifene also has increased incidence of leg cramps and vasomotor symptoms while estrogen reduces vasomotor symptoms. Estrogen is associated with uterine hyperplasia unless combined with progesterone. Endometrial hyperplasia is not seen with raloxifene. Estrogen in WHI when combined with progesterone increased risk of breast cancer and increased risk of cardiovascular events. Raloxifene showed no increased risk of cardiovascular events and in a subset of high-risk women showed a significant decrease. Raloxifene at 8 years showed no increased risk of breast cancer and in fact showed a significant reduction in risk of invasive breast cancer. The single available anabolic agent, teriparitide, has been associated with osteosarcoma in rodent models. The osteosarcoma did not occur when the rodents had exposure of less than 70% of their lifespan. As a result, teriparitide is not indicated in pediatric populations, individuals with high bone turnover such as Paget's disease of bone, or patients at high risk of osteosarcoma, such as history of spinal irradiation. Teriparatide is also associated with transient hypercalcemia 4–6 hours after injection and elevation of uric acid not associated with clinical gout.

Convenience with osteoporosis medications relates to dosing intervals, post-dose fast, and availability of IV vs. oral vs. nasal medications (51,52). No significant drug interactions have been noted with osteoporosis medications. Nonskeletal benefits of osteoporosis therapies include reports of analgesia seen with nasal calcitonin, decreases in new and worsening back pain seen with teriparatide, and reduction in breast cancer risk seen in one study with raloxifene, which awaits confirmation in future studies.

Antiresorptive therapies such as estrogen, raloxifene, bisphosphonates, or calcitonin are anticatabolic. The fracture reduction by antiresorptive therapy is likely due to increased bone strength resulting from filling in of the remodeling space and increased secondary mineralization. Anabolic therapy with teriparatide initially increases formation (modeling), then increases bone turnover (remodeling) with formation increasing greater than resorption (51,52). Fracture reduction by anabolic therapy is likely due to increased bone strength from the addition of new bone (increased bone size and / or improved architecture).

CASE SCENARIOS

Case No. 1: Management of low BMD in a premenopausal woman

A healthy 37-year premenopausal woman requests a bone density test after her mother falls and fractures her hip. A DXA study shows L1-L4 T-score of -1.7 and Z-score of -1.5. The left femoral neck T-score is -1.2 and Z-score is -1.1. She now asks what this means and how it should be treated. What do you tell her?

The WHO classification of BMD applies to postmenopausal women and men age 50 and older, but not to healthy premenopausal woman, men under age 50, and children. Z-scores, not T-scores, are preferred for reporting BMD in this patient. The normal range is defined as a Z-score between -2.0 and +2.0, which encompasses about 95% of this population. A Z-score of -2.0 or below in a premenopausal woman can be described as "below the expected range for age". In the case presented, the lowest relevant Z-score is -1.5, which is less than average for the age- and sex-matched population, but within the expected range. Most healthy premenopausal women with less than average BMD have less than average PBM, which is primarily genetically determined. It is likely that bone turnover and changes in BMD over time are similar for this patient compared to women the same age with average BMD, and that fracture risk is not significantly different than normal. Therefore, the diagnosis in this patient is normal (but less than average) BMD and average fracture risk for age. Pharmacological therapy is rarely indicated in premenopausal women with low BMD and is not indicated in this patient with normal BMD. She should be advised to have a healthy lifestyle that includes regular weight-bearing exercise, adequate daily intake of calcium and vitamin D, and avoid cigarette smoking and excess alcohol. If there is clinical concern regarding unrecognized factors that may be contributing to less than average BMD, than some simple laboratory studies may be considered. A repeat DXA study at the time of menopause may be helpful to establish a baseline for postmenopausal management.

Case No. 2: Acute vertebral fracture in a patient with osteopenia

A 62-year-old woman who is a cigarette smoker develops sudden severe mid-back pain while lifting her grandson. Spine X-ray shows a deformity of T11 compatible with a severe wedge fracture, at the same level where she has spinous process tenderness on physical exam. A DXA study shows L1-L4 T-score of -1.5 and left femoral neck T-score of -1.3. What is the diagnosis and how should she be treated?

The presence of a fragility fracture is sufficient to make a clinical diagnosis of osteoporosis, independently of BMD. The finding that her T-score is not in the range classified as osteoporosis (-2.5 or less) by the WHO is not surprising. Studies have shown that about one-half of patients with fragility fractures have T-scores higher than -2.5. Despite fracture risk being lower with higher T-scores, there are so many more women with T-scores higher than -2.5 than below that the total number of women with fractures is higher. The presence of a recent vertebral fracture is a strong risk factor for future fractures of all types. A thorough medical history, evaluation for contributing factors, and aggressive treatment is indicated. She should be advised on the importance of regular weight-bearing exercise, adequate daily intake of calcium and vitamin D, stopping cigarette smoking, and avoiding excess alcohol intake. Finally, pharmacological therapy is indicated. Bisphosphonates, raloxifene, calcitonin, strontium, teriparatide, and estrogen have all been shown to reduce vertebral fracture risk by approximately 50%, with some of these proven to reduce nonvertebral fracture risk as well. The choice of drug should be based on factors that include cost, affordability, patient preferences, and likelihood of long-term adherence to therapy.

Case No. 3: BMD loss in a patient treated with an oral bisphosphonate

A 59 year-old woman falls and fractures her wrist. A DXA study shows L1-L4 T-score of -2.7. She is then started on an oral bisphosphonate. Two years later, a follow-up DXA shows a loss of BMD at the spine and hip. What should be done next?

This patient has a diagnostic classification of "severe osteoporosis" based on the history of fragility fracture and T-score of -2.5 or less. The DXA images and BMD values in this patient should be carefully reviewed to assess whether the comparison is valid. If the BMD has decreased more than the least significant change (LSC), calculated after measuring the precision error at that facility, and the analysis is correct (e.g., same skeletal site, same labeling of vertebral levels, same positioning, similar bone area, same scan mode, same instrument), then there is cause for concern. BMD and not T-scores should always be compared, since a change in the reference database used can result in a change in T-score that may not reflect a genuine change in bone density. Stability or increase of BMD is associated with a reduction in fracture risk, while a loss of BMD is cause for concern. Factors that may cause a loss of BMD include poor adherence to therapy, wrong dose or dosing interval, limited or absent weight-bearing, inadequate intake of calcium and vitamin D, significant co-morbidities, malabsorption, and bone-toxic medications (e.g., high dose glucocorticoids, hormone deprivation therapy). The choice of laboratory studies to be done should be individualized to the patient, but may include measuring serum calcium, phosphorous, creatinine, 25-hydroxyvitamin D, celiac antibodies, and parathyroid hormone level. A marker of bone resorption, such as N-telopeptide or C-telopeptide, may be helpful when it is found to be very high or very low. A low value suggests that the patient is taking the medication, and that it is being absorbed, and that it is having the expected effect on reducing bone turnover, or that the patient has low baseline bone turnover. A high value suggests poor adherence to therapy or the presence of other factors that impair drug action. If contributing factors are identified, they should be treated. If none are found, options for management include changing medication, changing dose or dosing interval, or keeping treatment the same and repeating the DXA after one or two more years.

Case No. 4: How long to treat?

A 72 year-old woman with a diagnosis of osteoporosis has been taking an oral bisphosphonate regularly and correctly for 8 years. Her BMD has increased more than the LSC, and the L1-L4 T-score has improved from -2.7 to -1.9. She asks you how long she needs to keep taking the medication. What do you tell her?

Bisphosphonates are known to have a residual beneficial effect on BMD and suppression of bone turnover that varies according to the pharmacological properties of the agent used. This is unlike the bone effects of estrogen, SERMs, or calcitonin, which rapidly diminish with discontinuation. The concept of a "drug holiday" for patients who have been on prolonged bisphosphonate therapy is controversial. It is not clear whether fracture risk persists, or for how long, after discontinuation of bisphosphonate. Therapy with alendronate appears to be safe and effective for as long as 10 years, and risedronate for as long as 8

years. The decision to discontinue or temporarily withhold a bisphosphonate after many years of therapy should probably be based on the estimated fracture risk, expected benefit of the drug for reducing fracture risk, and the safety of continuing therapy. There are insufficient data at this time to provide a definitive answer. A "drug holiday" of 6–12 months could be considered in a reliable patient who is not a high fracture risk, with appropriate monitoring of bone turnover markers and/or BMD. If bone resorption increases or BMD decreases, treatment should be restarted.

Case No. 5: Acute fracture while on bisphosphonate therapy

A 70-year-old Hispanic woman with low BMD and multiple vertebral fractures has been treated with a weekly bisphosphonate, calcium, and vitamin D for two years. She is seen in the office with a new complaint of mid-back pain. Her L1-L4 baseline T-score before treatment was -3.0. A repeat DXA now shows L1-L4 T-score of -3.5 and femoral neck T-score of -3.0. Her physical exam shows significant mid-thoracic spinous process tenderness and X-ray of the spine shows a deformity of T7 with 40% anterior loss of height. Diagnostic workup for secondary osteoporosis was negative, including normal serum protein electrophoresis and a serum 20-hydroxyvitmain D of 25 ng/ml. What do you recommend for her?

Her pain was aggressively treated with opioids. She was initially switched to another oral bisphosphonate but her bone resorption markers (urinary NTX) remained high at 55. Calcium supplementation was increased to 500 mg TID. Her bisphosphonate was stopped and she was started on teriparatide. Her back pain diminished and she had a 6% increase in L1-L4 BMD at 6 months (DXA requested by patient). This case illustrates the potential use of anabolic therapies in patients who are not responding to antiresorptive therapies. It also illustrates the reduction in new and worsening back pain seen in the Fracture Prevention Trial. One hypothesis for pain relief with PTH treatment is stabilization and healing of bone microcracks.

Case No. 6: Early postmenopausal woman with low BMD

A 52-year-old newly postmenopausal white woman who is asymptomatic in terms of vasomotor symptoms is seen for assessment of osteoporosis risk. She has no fractures, height loss, or family history of osteoporosis. She has a strong family history of breast cancer in her mother and older sister who developed breast cancer in her late fifties. She is 62 inches tall and weighs 137 pounds. She had never undergone BMD testing. A DXA showed a T-score of -1.8 at L1-L4 and -1.5 in the femoral neck. Do you recommend treatment with an osteoporosis medication?

This early postmenopausal woman with low BMD (osteopenia) has no clinical risk factors for osteoporotic fracture. According to the treatment guidelines of the National Osteoporosis Foundation no pharmacological intervention would be recommended. With no personal/family history of fracture, her absolute risk for an osteoporotic spine, hip or wrist fracture over the next 5 years is very low (less than 0.12% per year). No treatments have been proven to reduce fracture risk in women in their 50s with osteopenia, although several treatments reduce bone loss. Bisphosphonates would not be recommended based on her low absolute risk and the high number needed to treat to prevent one fracture (about 2000). However, a SERM such as raloxifene may be considered to prevent further bone loss and to decrease her risk of breast cancer with a strong family history. Raloxifene decreased risk of invasive breast cancer by 76% at eight years in the CORE trial. Raloxifene is not currently indicated for prevention of breast cancer. Although a positive effect was seen in CORE, confirmation of this finding is needed in a second randomized controlled trial. Results from two such trials are currently pending. She is a candidate for raloxifene since she no longer is symptomatic with hot flashes and has no history of thromboembolic disorder.

Case No. 7: Glucocorticoid-induced osteoporosis

A 60-year-old man with Crohn's disease has been treated with prednisone 10 mg per day or more for 20 years. He presents to you with chronic back pain. The physical examination shows thoracic kyphosis and spine X-ray reveals multiple vertebral fractures. He has a past history of vertebroplasty at T12. He has had three intestinal surgeries, bruises easily, and is Cushingoid in appearance. His L1-L4 T-score is -1.6 and femoral neck is -1.0. Daily calcium intake is 600 mg at best due to gastrointestinal intolerance. Would you recommend any further diagnostic studies? What osteoporosis medication would you recommend?

This patient has glucocorticoid-induced osteoporosis, the most common cause of secondary osteoporosis. More than one-half of all patients treated chronically with glucocorticoids will develop osteoporosis. Rapid bone loss often occurs in the first six months of treatment. Fractures occur in patients at a higher bone density than in those with postmenopausal osteoporosis. Glucocorticoids have been

shown to cause osteocyte apoptosis and damage to bone microarchitecture. Recommendations for this patient include aggressive therapy with bisphosphonates, adequate calcium intake, and identifying any vitamin D deficiency. Teriparatide is not FDA-approved for treatment of glucocorticoid-induced osteoporosis. The patient was treated with two types of weekly bisphosphonates but could not tolerate them due to gastrointestinal intolerance and exacerbation of his underlying Crohn's disease. Options for therapy include a parenteral bisphosphonate such as ibandronate 3 mg intravenously every 3 months, which was recently approved for the treatment of postmenopausal osteoporosis but not for glucocorticoid-induced osteoporosis, and teriparatide which has demonstrated efficacy in clinical trials for the treatment of glucocorticoid-induced osteoporosis but is not currently approved for this indication. Medications indicated for male osteoporosis include alendronate and teriparatide. Medications indicated for glucocorticoid-induced osteoporosis include risedronate and alendronate.

CONCLUSIONS

The evaluation of skeletal health begins with fracture risk assessment. BMD testing is an excellent predictor of fracture risk, with an approximate 2-fold increase in fracture risk for every 1.0 SD decrease in BMD. DXA at the spine, hip, or forearm is the "gold-standard" technology for measuring BMD for diagnostic classification and monitoring changes in BMD over time. The indications for DXA vary according to affordability and availability, as well as cultural and regulatory issues. Other technologies measuring BMD or other parameters of bone strength are also predictive of fracture risk. Combining clinical risk factors for fracture with BMD is a better predictor of fracture risk than BMD or clinical risk factors alone. All patients should be advised on the importance of non-pharmacological approaches to bone health — regular weight-bearing exercise, adequate daily intake of calcium and vitamin D, fall prevention, avoidance of smoking and medications know to be toxic to bone, and moderation of alcohol intake. All patients with low BMD or fragility fractures should be considered for medical evaluation for factors other than hormone deficiency and aging that may be contributing factors. Patients at high risk for fracture are candidates for pharmacological therapy. Currently available therapy can reduce fracture risk by about 50%.

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