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Review Article

Diagnosis and Treatment of Osteoporosis

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Osteoporosis is common among older adults and results in costly osteoporotic fractures. With the aging of the population, low bone mass states will be an increasing clinical issue for both men and women. Screening for this metabolic bone disorder is warranted in most old adults and clinicians must be diligent in identifying persons at risk. The evaluation should include an assessment of risk factors for falls, a bone density test, and consideration of possible secondary causes of osteoporosis. Several medications are available to improve bone density and decrease fractures. There are a variety of pharmaceutical agents that have been recommended for the treatment of osteopenia and osteoporosis including hormone replacement therapy, selective estrogen receptor modulator therapy, anti-resorptive therapy. In addition patients with osteoporosis who have failed anti-resorptive therapy can have a significant improvement in their bone density with anabolic therapy.

Key Words: Osteoporosis, Diagnosis, Treatment

DIAGNOSIS AND TREATMENT OF OSTEOPOROSIS

Osteoporosis is a common disease characterized by a systemic impairment of bone mass and micro-architecture that results in fragility fractures.[1] The disease is an emerging medical and socioeconomic threat characterized by a systemic impairment of bone mass, strength, and microarchitecture, which increases the propensity of fragility fractures.[1,2] With an aging population, the medical and socioeconomic effects of osteoporosis, particularly postmenopausal osteoporosis, will increase further.[1]

Bone strength is determined by properties that include bone mineral density (BMD), bone geometry (size and shape of bone), degree of mineralization, microarchitecture, and bone turnover.[3] Fractures of the hip and spine may be disabling and are associated with mortality rates that are about 20% greater than that of an age-matched population.[3] A fragility fracture (i.e., a nontraumatic fracture or one that occurs with mild trauma, such as a fall from the standing position) of any type is a sentinel event that increases the risk for future fractures.[3]

To reduce the burden of osteoporotic fractures, high-risk patients must be identified, evaluated for factors contributing to skeletal fragility, and treated to reduce fracture risk.[3] Table 1 lists the risk factors of osteoporosis.

BMD can be assessed with dual X-ray absorptiometry (DXA), and osteoporosis is defined by a T score of less than 2.5 (i.e., more than 2.5 standard deviations below the average of a young adult).[1] The measurement of BMD by DXA is a valid method to diagnose osteoporosis and to predict the risk of fracture.[1,4] Although DXA is widely available and has

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Table 1. Clinical risk factors for osteoporosis and mild-trauma fractures[3,12]

Advanced age
Female sex
Estrogen deficiency (any cause after puberty)
History of fracture as an adult
History of fragility fracture in a first-degree relative
History of glucocorticoid use for more than 3 months
Current cigarette smoking
Low body weight (< 127 lbs)
Poor health/frailty
White race
Asian race
Low calcium intake
Alcoholism
Inadequate physical activity
Dementia; cognitive impairment
Recurrent falls
Impaired neuromuscular function and other parameters of immobility
Impaired eyesight despite optimal correction
Residence in a nursing home
Long-term heparin therapy
Anticonvulsant therapy
Aromatase-inhibitor therapy
Androgen-deprivation therapy

Table 2. Indicators for bone mineral density testing[3]

1. Women aged 65 years and older and men aged 70 and older, regardless of clinical risk factors
2. Younger postmenopausal women and men aged 50 to 69 garnering concern based on clinical risk profile
3. Women in the menopausal transition if there is a specific risk factor associated with increased fracture risk, such as low body weight, prior low trauma fracture, or high-risk medication*
4. Adults older than 50 years who have a fracture
5. Adults with a condition (e.g., rheumatoid arthritis) or taking medication (e.g. glucocorticoids in a daily dose ≥ 5 mg prednisone or equivalent for ≥ 3 months) associated with low bone mass or bone loss
6. Anyone being considered for pharmacologic therapy for osteoporosis
7. Anyone being treated for osteoporosis, to monitor treatment effects
8. Anyone not receiving therapy in whom evidence of bone loss would lead to treatment
9. Postmenopausal women discontinuing estrogen should be considered for bone density testing

*High-risk medications include long-term glucocorticoids, anticonvulsants, aromatase inhibitors, and androgendeprivation therapy

been commonly used for clinical phase-3 studies, it has some limitations.[1]

New decision-making methods, such as the fracture-risk assessment tool (FRAX), have integrated clinical risk factors with DXA-based BMD to predict an individual's 10-year risk of sustaining a hip fracture, as well as the 10-year probability of having a major osteoporotic fracture, defined as a clinical spine, forearm, hip, or shoulder fracture.[1,5]

As an area-based measure of bone mineral density, DXA does not allow assessment of bone geometry, nor does it distinguish between cortical bone, the outer shell, and trabecular bone, the spongy inner part, which are important determinants of bone strength and loss at different rates.[1]

Advances in imaging techniques with high-resolution peripheral CT that yield volumetric bone-density data might allow better prediction of bone strength and thus fracture risk if indices such as intracortical porosity are taken into account.[6]

1. Diagnosis

Osteoporosis may be diagnosed in postmenopausal women and men 50 years and older when the lowest T-score of the lumbar spine, femoral neck, total hip, or 33% (one-third) radius (a region of interest in the distal radius that is defined by each DXA manufacturer) is -2.5 or less according to WHO criteria.[3] This cut-off was selected because it identifies approximately 30% of postmenopausal women as having osteoporosis by measurement of BMD at the lumbar spine, hip, and forearm, which approximates the lifetime risk for fracture at these skeletal sites.[3] Table 2 lists indicators for BMD testing. A presumptive diagnosis of osteoporosis may also be made in

Table 3. Potentially helpful findings on physical examination for osteoporosis[3]

1. Loss of height may be associated with vertebral fracture
2. Low body weight is an independent risk factor for fracture
3. Weight loss may be due to hyperthyroidism or malnutrition
4. Fast heart rate may be due to hyperthyroidism or anemia
5. Fast respiratory rate may be due to asthma
6. Kyphos may be the result of vertebral fractures or upper back muscle weakness
7. Poor gait, muscle strength, balance may increase the risk for falls and fractures
8. Paralysis or immobility may result in bone loss, increased risk for falls, or both
9. Joint laxity could be due to Marfan syndrome, osteogenesis imperfect, or Ehlers-Danlos syndrome
10. Inflammatory arthritis is associated with osteoporosis and use of glucocorticoids
11. Osteoarthritis or lower limb injury may result in decreased load-bearing capability and bone loss
12. Blue sclera, poor tooth development, hearing loss, and fracture deformities are associated with osteogenesis imperfecta
13. Poor dental hygiene is a risk factor for osteonecrosis of the jaw with bisphosphonate therapy
14. Thyromegaly, thyroid nodules, and proptosis suggest hyperthyroidism
15. Urticaria pigmentosa suggests systemic mastocytosis
16. Kyphosis or shortened distance between lowest ribs and iliac crest suggests vertebral fractures
17. Abdominal tenderness may be due to inflammatory bowel disease
18. Stretch marks, buffalo hump, and bruising suggest glucocorticoid excess
19. Signs of venous thrombosis suggest that treatment with estrogen or raloxifene may be contraindicated
20. Small testicles in men suggest hypogonadism

the presence of a fragility (low-trauma) fracture, regardless of BMD.[3]

In premenopausal women and men younger than 50 years, Z-scores (the SD difference between a subject's BMD and an age-, sex- and ethnicity-matched reference population)—not T-scores—should be used, and the WHO diagnostic criteria should not be applied.[3] Table 3 shows potentially helpful findings on physical examination for osteoporosis.

2. The goals of treatment

The primary goal of treatment is to reduce the risk for fractures.[3] Fractures occur when a force applied to a bone exceeds its strength; fracture risk is reduced by improving bone strength and preventing falls.[3]

Bone strength cannot be directly measured in vivo; therefore, surrogate markers of bone strength, such as BMD and markers of bone turnover, are used to assess skeletal health at baseline and to monitor the effectiveness of treatment.[3] BMD is typically measured about 1 to 2 years after starting therapy, with the goal of maintaining or increasing BMD.[3]

Essential care for skeletal health includes regular physical activity and adequate intake of calcium and vitamin D.[3] Pharmacologic agents have been proven to reduce fracture risk.[3]

Periodic reevaluation of the risk for falls is appropriate because risk may increase with advancing age.[3] Reduction of fall risk with such measures as quadriceps strengthening and balance training is important in osteoporosis treatment, especially in frail, elderly patients.[3]

3. Current therapies

The aim of therapy is usually prevention of further fractures. In addition to lifestyle modifications (cessation of smoking, reduction of alcohol consumption, and increased physical activity), vitamin D and calcium supplementation are recommended as baseline treatment in every patient with osteoporosis.[1] Use of vitamin D has produced a renaissance because vitamin-D deficiency is highly prevalent and associated with various adverse extraskeletal effects, including cardiovascular and metabolic diseases, malignancies, and a high propensity to falls.[1,7] A

Table 4. Established treatments for osteoporosis[1]

	Dose	Interval	Route	Side-effects
Bisphosphonates				Osteonecrosis of the jaw,subtrochanteric femur fractures
Alendronate	70 mg	Weekly	Oral	Esophageal irritation
Risedronate	35 mg or 150 mg	Weekly or monthly	Oral	Esophageal irritation
Ibandronate	150 mg	Monthly	Oral	Esophageal irritation
Ibandronate	3 mg	Every 3 months	IV	Acute-phase reaction
Zoledronic acid	5 mg	Yearly	IV	Acute-phase reaction, hypocalcaemia, potential renal toxic effects
Raloxifene	60 mg	Daily	Oral	Thromboembolic disease
Strontium ranelate	2 g	Daily	Oral	Thromboembolic disease; drugrash with eosinophilia systemicsyndrome, abdominal discomfort
Teriparatide	20 μg	Daily	SC	Hypercalcaemia, nausea, diarrhea
PTH (1-84)	100 μg	Daily	SC	Hypercalcaemia, nausea, diarrhea

IV=intravenous, SC=subcutaneous

meta-analysis raised concerns that calcium supplementation could be associated with an increased risk of cardiovascular events.[8] Also, concurrent vitamin-D deficiency could be present, which itself increases the risk of cardiovascular events.[1,7]

The Women's Health Initiative showed that calcium in combination with vitamin D had no effect on the risk of coronary heart disease, which is reassuring in this regard.[1,9] Nonetheless, the American Society for Bone and Mineral Research has issued a statement and recommends the use of combined vitamin D and calcium supplementation instead of calcium-only supplementation and the preference for an increased dietary uptake of calcium over calcium supplements.[1]

Osteoporosis therapies fall into two classes, anti-resorptive drugs, which slow bone resorption, and anabolic drugs, which stimulate bone formation.[1] Drugs used for osteoporosis are summarized in Table 4. Although these drugs are effective, most have limitations and side-effects that affect long-term administration and adherence.[10] For a more detailed overview of the different treatments for osteoporosis, we recommend a recent review.[11]

4. Recent developments in bone biology

In the past decade, the pathogenesis of osteoporosis has been linked to tissue, cellular, and molecular processes.[1] Master signals that integrate various endocrine, neuroendocrine, inflammatory, and mechanical stimuli have been defined.[1] At the cellular level, communication and coupling between the main bone-cell types, the bone-forming osteoblasts and the bone-degrading osteoclasts, constitute the smallest functional unit.[1]

1) Osteoclasts and bone resorption

Osteoclasts originate from hemopoietic stem cells and are closely related to monocytes and macrophages.[1] Differentiation from osteoclast precursor to fully activated multinucleated osteoclast depends essentially on receptor activator NF-κB ligand

Table 5. Clinical development of novel treatments for osteoporosis[1]

	Target (function)	Drug class	Phase	Route
Antiresorptive drugs				
Denosumab	RANK ligand (stem-cell factor for osteoclasts)	Antibody against RANKL	3 (complete)	SC
Odanacatib	Cathepsin K (osteoclastic enzyme that degrades collagens)	Cathepsin K inhibitor	3	PO
Saracatinib	c-src kinase (enzyme involved in osteoclast activation)	c-src inhibitor	3	PO
Anabolic drugs				
MK-5442	CaSR (triggers PTH release if inhibited)	Calcilytic drug	2	PO
AMG 785	Sclerostin (inhibitor of the Wnt/â-catenin pathway)	Antibody against sclerostin	2	SC
BHQ 880	Dickkopf-1 (inhibitor of the Wnt/â-catenin pathway)	Antibody against dickkopf-1	1,2	SC

SC=subcutaneous, PO=per oral

(RANKL), a member of the tumor necrosis factor (TNF) family, and the permissive role of macrophage-colony stimulating factor (M-CSF).[1] RANKL, abundantly expressed by bone-forming osteoblasts, bone-marrow stromal cells, and T and B lymphocytes, activates its receptor, RANK, expressed on osteoclasts.[1]

2) Osteoblasts and bone formation

The osteoblast is a unique bone-forming cell derived from mesenchymal stem cells.[1] The rate of bone formation is determined by the speed and effectiveness of precursor cells differentiating into mature osteoblasts that secrete a matrix that can be mineralized and by their life spans.[1]

3) Osteocytes

Osteocytes account for more than 90% of all bone cells and are found scattered throughout the mineralized matrix.[1] They are terminally differentiated osteoblasts and share morphological similarities with neural cells.[1] Their long dendritic processes form a sensory network, whereby they can sense and communicate mechanical stress within the bone.[1]

5. Novel targets for treatment of osteoporosis

A summary of novel treatments for osteoporosis is shown in Table 5.

CONCLUSION

With multiple novel antiosteoporotic compounds in advanced clinical trials, the number of available drugs will increase considerably in the coming years.[1] Present antiresorptive treatments are effective, but some are limited by side effects, concurrent comorbidities, and inadequate long-term compliance.[1] Many of the new drugs combine efficacy with convenient administration that might translate into better adherence.[1] With novel drugs on the brink of clinical approval, treatment of osteoporosis might become increasingly complex, especially for the general practitioner.[1] Thus, successful integration of these novel compounds into an evidence-based oncept of osteoporosis therapy requires simple and applicable tools for clinical decision making.[1]

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Peer Reviewers' Commentary

With novel drugs on the brink of clinical approval, treatment of osteoporosis might become increasingly complex, especially for the general practitioner. Thus, successful integration of these novel compounds into an evidence-based concept of osteoporosis therapy requires simple and applicable tools for clinical decision making. In this review article the reader's understanding of the osteoporosis treatment drugs were easy to summarize, it reflects the latest knowledge in primary care is thought to be very helpful.

(정리: 편집위원회)