Turkish Journal of Internal Medicine
http://www.tjim.org
ISSN: 2687-4245
Review Article

Current Approaches to The Basic Aspects of Osteoporosis

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Abstract

Osteoporosis is a systemic skeletal disorder characterized by an imbalanced bone turnover leading to low bone mass and bone microarchitecture disruption that increase the risk of fractures. It is the most common metabolic bone disorder seen in the World due to prolongation of life. In this review, the basic aspects for the evaluation, diagnosis, treatment and follow-up of osteoporosis is discussed in the view of the literature.

Turk J Int Med 2020;2(3):66-72
DOI: 10.46310/tjim.732932

Keywords: *Osteoporosis, etiology, diagnosis, treatment.*

Introduction

Osteoporosis is the most common metabolic bone disorder encountered in the World with the prolongation of human life and aging. In recent decades, it has become an important public health problem, since almost 50% of women and 22% of men have fractures after the age of 50 years. Besides approximately 9 million osteoporotic fractures are reported annually in the World. Osteoporosis is defined as a systemic skeletal disease characterized by an imbalance in bone turnover that results in low bone mass and disruption of bone microarchitecture with increased bone fragility and fracture risk. Osteoporotic fractures, also known as fragility fractures, are the fractures that occur as a result of a person's fall from his/her height or less than height, without trauma, at or slower than walking speed. The bones with the highest risk of osteoporosis related fractures are the femur, vertebra, wrist, humerus and pelvis. [1,2-4]

Osteoporosis can be seen because of primary and secondary causes (*Table 1*). Being postmenopausal (Type 1) and aging (Type 2) are primary causes. Aging in men, menopause in addition to aging in women increase the frequency of osteoporosis. The female to male ratio in primary osteoporosis is 5.7 to 4.[5] Secondary causes should be screened especially

Received: July 13, 2020; Accepted: July 24, 2020; Published Online: July 29, 2020
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Table 1. *Secondary causes of osteoporosis*

Lifestyle related	**Medications**	**Endocrine diseases**
Inadequate calcium and protein intake	Glucocorticoids	Hypogonadism
Vitamin D deficiency	Anticoagulants (heparin, warfarin)	Glucocorticoid excess
Vitamin A excess	Anticonvulsants	Hyperparathyroidism
Immobilization	Proton pump inhibitors	Hyperthyroidism
Insufficient physical activity	Selective serotonin reuptake inhibitors	Hyperprolactinemia
Very low body mass index	Lithium	Diabetes mellitus
Smoking	Thiazolidinedione	
Alcohol consumption	High dose levothyroxine	**Collagen tissue diseases**
	Aromatase inhibitors	Rheumatoid arthritis
Gastrointestinal diseases	Gonadotropin-releasing hormone	Ankylosing spondylitis
Postgastrectomy syndrome	Medroxyprogesterone	
Primary biliary cirrhosis	Aluminum	**Other**
Inflammatory bowel disease	Cyclosporin A	Kidney failure
Hemochromatosis	Tacrolimus	Chronic obstructive
	Methotrexate	pulmonary disease
Hematological diseases		Homocysistinuria
Multiple myeloma		
Lymphoproliferative diseases		

in premenopausal women and men younger than 50 years of age with osteopenia or osteoporosis. Primary causes may also be accompanied by secondary causes in postmenopausal women and older men, so possible secondary causes should be screened in differential diagnosis at any age.[2,3]

Diagnosis

Although osteoporosis is the most common metabolic bone disease, only approximately 20% can be diagnosed and treated. The purpose of diagnosing osteoporosis is to identify patients at high risk for bone fragility and to start treatment to prevent fractures. To diagnose and treat current cases screening of osteoporosis is important (*Table 2*).[2,3] Detailed history and physical examination, laboratory evaluation, bone mineral density measurement and vertebral imaging are important for the diagnosis of osteoporosis. Medical history should be questioned carefully and main clinical findings should be examined detailly in all cases. Difficulty in walking is seen in hip fractures. Fractures lead to chronic pain, difficulty in mobilization, dependence on someone else and depression. Increase in mortality rates due to fractures is also reported.[2,3] Routine laboratory tests should be evaluated, and other tests for secondary causes should be conducted if necessary (*Table 3*). 25-hydroxy (OH) vitamin D level measurement and exclusion of osteomalacia is important. Bone mineral density (BMD) measurement cannot distinguish osteoporosis from osteomalacia, in both cases BMD is reduced.[2,3] Bone turnover markers are the substances that occur in the blood and urine during the bone cycle. They can be measured in plasma, urine, or serum and their levels reflect osteoblastic (bone formation) or osteoclastic (bone resorption) activity. Although bone turnover markers are thought to be helpful in determining the risk of fracture and monitoring the treatment, they are not routinely used in the diagnosis of osteoporosis. Serum procollagen type I N propeptide (s-PINP) can be used as a bone production marker and serum type I collagen C-terminal telopeptide cross-links (s-CTX) as a bone resorbtion marker if measured by standardized methods.[2-4]

Bone mineral density measurement

The most commonly used gold standard method for measuring bone density is dual energy X ray absorptiometry (DXA) because of its availability for clinical use, easy application and low radiation exposure. This method evaluates the L1 to L4 vertebrae in the spine and the femur. It should not be used in pregnant women as it creates low dose radiation exposure. DXA measures BMD areally and shows the amount of bone mineral in grams per square centimeter (BMD=gr/cm^2). The fracture risk of any region in the skeletal system is determined by the BMD measurement of that region. In a standard patient, lumbar spine and hip measurements are taken with DXA. Radius measurement is rarely used in cases such as primary hyperparathyroidism, morbid obesity and the presence of prosthesis and kyphoscoliosis in

Table 2. *Candidates for screening in terms of osteoporosis*

Women over 65 and men over 70 years of age (regardless of risk factors)
Postmenopausal and perimenopausal women <65 years of age and men aged 50-69, in the presence of one of the risk factors stated below
• Fragility fracture • The presence of fractures in direct radiographs • Glucocorticoid usage (≥5 mg/day prednisolone or equivalent, >3 months) • Smoking • Alcohol consumption • Body mass index <20 kg/m² or major weight loss • Rheumatoid arthritis • A history of disease associated with osteoporosis • Drug usage with high-risk for osteoporosis
Women or men <50 years of age in the presence of one of the risk factors stated below
• Hypogonadism or early menopause • Presence of one of the secondary causes of osteoporosis • Fragility fracture • The presence of fractures in direct radiographs • Glucocorticoid usage (≥5 mg/day prednisolone or equivalent, >3 months) • Smoking • Alcohol consumption • Body mass index <20 kg/m² or major weight loss • Rheumatoid arthritis • A history of disease associated with osteoporosis • Drug usage with high-risk for osteoporosis

which hip or vertebra measurements cannot be made.[2,3,6,7]

DXA measurement gives T- and Z-scores other than BMD values. T-score is the standard deviation of the person's measured bone mass compared to the mean peak bone mass of the young adult reference population of the same sex. Z-score, on the other hand, shows the difference between the bone mineral density of the measured region and average bone density value of the normal population of the same age in terms of standard deviation (SD).

The World Health Organization recommends using the T-score for postmenopausal women and men aged 50 years or older for the diagnosis of osteoporosis, and the Z-score in children, premenopausal women and men younger than 50 years of age.[2,3,6] In postmenopausal women and men aged 50 years or older, T-score greater than or equal to -1.0 SD is normal. Osteopenia is diagnosed if the T-score is between -1 and -2.5 SD, osteoporosis if T-score less than or equal to -2.5 SD, and severe (established) osteoporosis if accompanied by one or more fragility fractures.

Table 3. *Evaluation of osteoporosis*

History	Age, gender, complaints, personal and family histories, osteoporosis and fracture-related conditions, concomitant diseases, drugs used, smoking, alcohol, nutrition and exercise habits
Clinical symptoms and findings	Back pain due to vertebral fractures, shortened height, spinal kyphosis, scoliosis, postural problems due to kyphosis and scoliosis, restrictive lung and heart function disorders, sleep disorders
Physical examination	Height, weight, body mass index, presence of kyphosis or scoliosis, findings related to secondary causes (Cushing, hyperthyroidism, arthritis etc.)
Laboratory tests	Serum calcium, phosphorus, 25OH vitamin D, parathormone, alkaline phosphatase, thyroid stimulating hormone, creatinine, alanine and aspartate aminotransferases and calcium in 24-hour urine
Imagings	Dual energy X ray absorptiometry (DXA), vertebral thoracolumbar X ray graphies

According to Z-score, premenopausal women, men younger than 50 years old, and children diagnosed as having a lower bone mass than expected according to their chronological age if Z-score is less than or equal to -2 SD and normal bone mass according to chronological age if Z-score is higher than -2 SD.[2,3] BMD values of DXA measurements are also used in treatment follow-up, but not T- or Z-scores, to evaluate the effectiveness of osteoporosis treatment.

Vertebral Imaging

Vertebral imaging is also important in the diagnosis and follow-up of osteoporosis. Lateral thoracolumbar vertebra X-ray radiography should be performed and evaluated in patients with osteoporosis and having high risk of fracture.[2,5] The main groups in which vertebral imaging is recommended are;

- Women aged ≥70 years and men ≥80 years with a total hip, femoral neck or vertebra T-score of ≤-1.0 SD,
- Women aged 65-69 years and men 70-79 years with a total hip, femoral neck or vertebra T-score of ≤-1.5 SD,
- Postmenopausal women and men ≥50 years with specific risk factors like;
  - Recently used or ongoing glucocorticoid therapy,
  - History of fragility fracture,
  - At least 2 cm shorter than the previous height during follow-up,
  - Height shortened by at least 4 cm according to height in twenties.

Vertebral fractures can be evaluated by visual semi-quantitative methods like thoracolumbar X ray graphies in which the area between the thoracic 4th vertebra and the lumbar 4th vertebra is examined. Fractures in vertebras can be wedge, concave or crushed collapse nature. Height of the vertebra is an important evaluation parameter as

Table 4. *FDA approved treatment options, their recomended dosages, mode of administrations, main side effects and usages in postmenopausal and male osteoporosis*

Drug	Recomended dose and route of administration	Main side effects	Usage in osteoporosis	
			Postmenopausal	Male
Bisphosphonates				
Alendronate	10 mg/day or 70 mg/week, oral	dyspepsia, abdominal pain, musculoskeletal pain	+	+
Ibandronate	2.5 mg/day or 150 mg/month, oral or 3 mg/3 months, intravenous	dyspepsia, abdominal pain, musculoskeletal pain, back pain, headache	+	-
Risedronate	5 mg/day or 35 mg/week or 150 mg/month, oral	rash, abdominal pain, dyspepsia, diarrhea, arthralgia	+	+
Zoledronate	5 mg/year, intravenous	fever, myalgia, hypotension, fatigue, nausea, vomiting, inflammation in the eyes, abdominal pain	+	+
Selective estrogen receptor modulators				
Raloxifene	60 mg/day, oral	arthralgia, leg cramps, flu-like syndrome, peripheral edema, hot flashes, venous thromboembolism	+	-
Calcitonin				
Calcitonin	100 IU/alternate day, subcutaneous or intramuscular or 200 IU/day, intranasal applying to 1 nostril alternatingly	injection site reaction, nausea, vomiting, abdominal pain, flushing, rhinitis, nasal irritation, dry nose, dizziness	+	-
Parathyroid hormone analog				
Teriparatide	20 mcg/day, subcutaneous	transient hypercalcemia, nausea, rhinitis, arthralgia, pain	+	+
Monoclonal antibody				
Denosumab	60 mg/6 month, subcutaneous	dermatitis, rash, bone and muscle pain, urinary infection	+	+

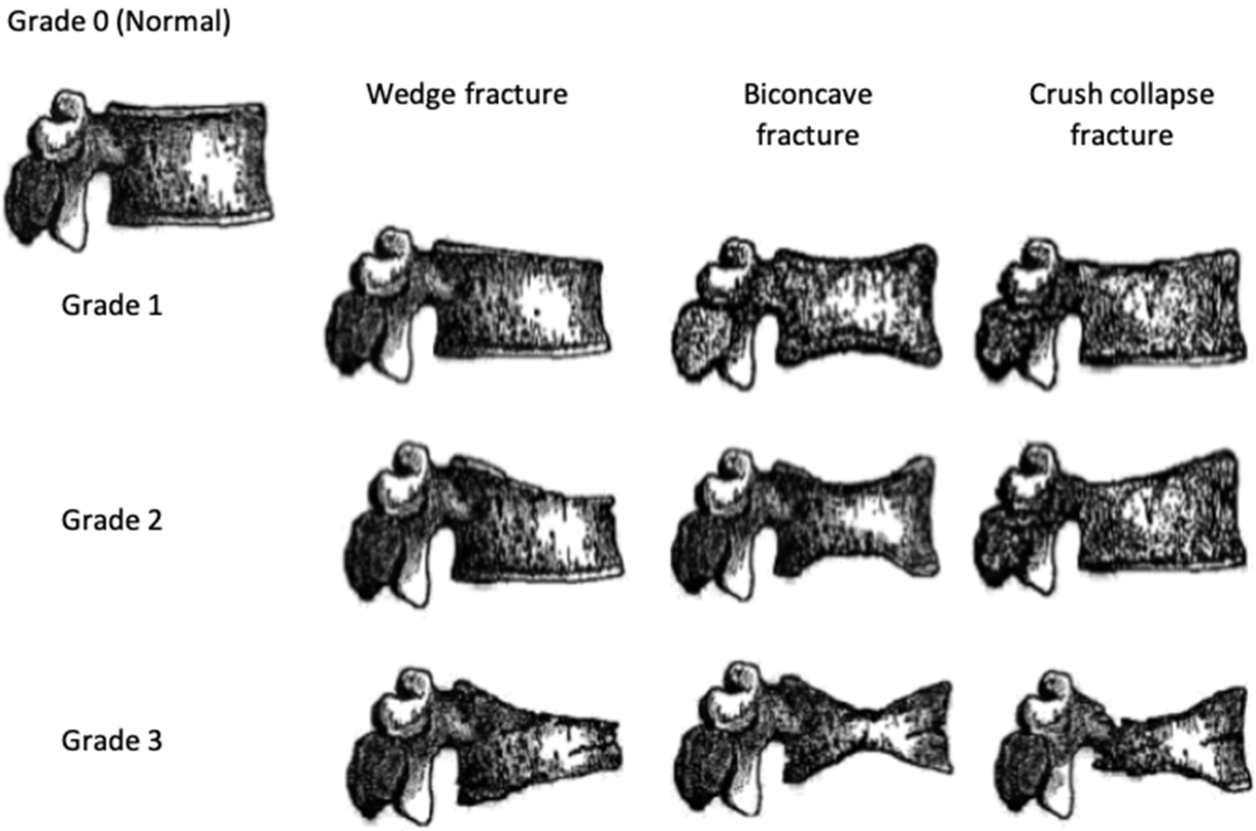

Figure 1. *Evaluation of vertebral fractures*[9]

well as type of the fracture. The vertebra is stated to be normal (Grade 0) if there is no vertebral height loss, mild (Grade 1) if <25% loss, moderate (Grade 2) if 26-40% loss, and severe (Grade 3) if more than 40% loss (Figure 1).[8,9] Women and men with vertebral fractures have an increased risk of developing new vertebral and femur fractures. Presence of a vertebral fracture in women increases the risk of a new vertebral fracture 5 times and a new hip fracture 2 times compared to ones without vertebral fracture.[2,10,11]

Treatment

Non-pharmacological approaches like having calcium-rich diet, exercise, exposure to sunlight for vitamin D production, quitting smoking and alcohol are the main treatment options for osteopenia and osteoporosis as well as measures taken to reduce the risk of trauma or fall.[2,3,12] Exercise in adulthood leads to higher BMD and better neuromuscular function causing lower risk of falls and fractures.[1]

Besides lifestyle changes, pharmacological treatment is given in patients with a vertebral, femoral neck or total hip T-score of -2.5 or below in DXA measurement with or without a concamitant fracture. In patients with osteopenia, drug treatment can be started if 10 years of hip fracture risk is calculated to be ≥3% or 10 years of major osteoporotic fracture risk is ≥20% with the fracture risk assessment (FRAX) tool which is validated in postmenopausal women and men aged >40 years.[2,12]

While making the treatment decision, each patient should be evaluated with her/his own characteristics, and other risk factors should be taken into consideration along with BMD. If there are conditions accompanying that may lead to secondary osteoporosis, they should be treated as well. Otherwise, the treatment efficacy of the drugs used for osteoporosis may be reduced. Testosterone replacement therapy is recommended for young male patients with hypogonadism with a serum total testosterone level below 200 ng/dL. Although estrogen replacement therapy should be given in hypogonad premenopausal women with estrogen deficiency, estrogen replacement is not recommended as the first-line therapy in the prevention or treatment of postmenopausal osteoporosis. In postmenopausal women, estrogen therapy is only recommended if there is a high risk of osteoporosis and other non-estrogen treatments are not suitable for the patient.[2,3,12,13]

There are different pharmacological treatment

options in osteoporosis. The main agents used are calcium, vitamin D, bisphosphonates, estrogen replacement therapy, selective estrogen receptor modulators, calcitonin, teriparatide, denosumab and strontium ranelate. Among them strontium ranelate which has both anabolic and antiresorbtive effects on bone has not been approved by American Food and Drug Administration (FDA) for the treatment of osteoporosis. Oral calcium 1000-1200 mg/day and oral vitamin D 800-1200 IU/day should be given to all patients, depending on their needs. Appropriate anabolic or antiresorptive treatment options should be given to the patient when necessary, taking into account factors such as the gender of the patient, the menopausal status, the effects of the drug and the potential for possible side effects (*Table 4*). Pharmacological treatment other than calcium and vitamin D should not be considered unless there is an ongoing bone loss or recurrent low-traumatic fractures in premenopausal women. If it is absolutely necessary, drug side effects, benefits and risks should be evaluated very well, and possible adverse effects and contraindications of drugs used in childbearing age on mother and baby should be carefully and detailly evaluated.[2,4,12,14,15]

In follow-up, all the patients with osteoporosis should be reassessed clinically to monitor compliance and side effects of drugs. Presence of height loss, new fractures and risk of falls should be evaluated at each visit which may alter patient management. BMD testing can be used for treatment monitoring as well as bone turnover markers if possible. It would be ideal if BMD testing could be done on the same DXA machine.[2,3,15] The fact that consecutive BMD measurement values have not changed or increased indicates that the treatment is effective.[2,3] BMD measurement with DXA should be repeated every 2 years in postmenopausal women and men over 70 years, once a year in patients under treatment, every 6 months in patients receiving teriparatide therapy, every 6 months or a year according to the physician's decision in patients with secondary osteoporosis.[2]

Conclusion

Osteoporosis, although the most common metabolic bone disorder, it is generally underdiagnosed. The purpose of diagnosing osteoporosis is to identify high risk patients and start treatment to prevent fractures. Unfortunately, quite low percentage of the patients are properly diagnosed and treated. For a proper approach, basic aspects for the evaluation, diagnosis, treatment and follow-up of osteoporosis should be known detailly and applied properly to the patients.

Conflict of Interest

The author declared that there is no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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