Review

Management of osteoporosis
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Abstract

Osteoporosis or osteopenia occurs in about 44 million Americans, resulting in 1.5 million fragility fractures per year. The consequences of these fractures include pain, disability, depression, loss of independence, and increased mortality. The burden to the healthcare system, in terms of cost and resources, is tremendous, with an estimated direct annual USA healthcare expenditure of about $17 billion. With longer life expectancy and the aging of the baby-boomer generation, the number of men and women with osteoporosis or low bone density is expected to rise to over 61 million by 2020. Osteoporosis is a silent disease that causes no symptoms until a fracture occurs. Any fragility fracture greatly increases the risk of future fractures. Most patients with osteoporosis are not being diagnosed or treated. Even those with previous fractures, who are at extremely high risk of future fractures, are often not being treated. It is preferable to diagnose osteoporosis by bone density testing of high risk individuals before the first fracture occurs. If osteoporosis or low bone density is identified, evaluation for contributing factors should be considered. Patients on long-term glucocorticoid therapy are at especially high risk for developing osteoporosis, and may sustain fractures at a lower bone density than those not taking glucocorticoids. All patients should be counseled on the importance of regular weight-bearing exercise and adequate daily intake of calcium and vitamin D. Exposure to medications that cause drowsiness or hypotension should be minimized. Non-pharmacologic therapy to reduce the non-skeletal risk factors for fracture should be considered. These include fall prevention through balance training and muscle strengthening, removal of fall hazards at home, and wearing hip protectors if the risk of falling remains high. Pharmacologic therapy can stabilize or increase bone density in most patients, and reduce fracture risk by about 50%. By selecting high risk patients for bone density testing it is possible to diagnose this disease before the first fracture occurs, and initiate appropriate treatment to reduce the risk of future fractures.

Background

Osteoporosis is a silent disease that causes no symptoms until a fracture occurs. It is a major public health concern, with about 44 million American men and women, or 55% of the population age 50 and over, having osteoporosis or low bone density that can lead to fractures [1]. About 80% of osteoporosis occurs in women and 20% in men. The prevalence is increasing, with over 61 million expected to have osteoporosis or low bone density by 2020. About 30% of Caucasian women age 50 and over have

osteoporosis, when defined as a T-score of less than -2.5 at the spine, hip, or mid-forearm [2]. In men age 50 and older, the prevalence of osteoporosis is about 19% [3]. There are about 1.5 million fragility fractures in the USA each year, with 700,000 vertebral fractures, 300,000 hip fractures, 250,000 wrist fractures, and 250,000 at other skeletal sites. The lifetime risk of fracture is substantial. Population data from Rochester, Minnesota, estimate that at the age of 50, a Caucasian woman has about a 40% lifetime risk and a Caucasian man a 13% lifetime risk of fracture of fracture at hip, spine, or distal forearm [4]. In Malmö, Sweden, the lifetime risk of fracture of the hip, spine, forearm or proximal humerus at age 50 was reported to be 46% in women and 22% in men [5]. The Dubbo study found that at the age 60 there was a residual lifetime fracture risk of 56% for women and 29% for men, assuming average life expectancy [6]. A woman's risk of hip fracture is equal to her combined risk of breast, uterine, and ovarian cancer [7]. Fractures of the spine and hip are associated with an increased risk of chronic pain, deformity, depression, disability, and death. About 50% of those with a hip fracture will be permanently unable to walk without assistance and 25% will require long-term care [8]. The mortality rate five years after a fracture of the hip or a clinical vertebral fracture is about 20% greater than expected [9], with men having higher mortality rates than women, even when standardized for age [10]. The direct cost of osteoporotic fractures in the USA was about $17 billion per year in 2001 [11], extrapolated from 1995 figures using the Medical Index of the Consumer Price Index, with this value expected to rise greatly in future years.

Bone density and bone strength

Osteoporosis is defined as "a skeletal disease characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength primarily reflects the integration of bone density and quality." [12] Bone mineral density (BMD) correlates very well with fracture risk, with the relative risk of fracture approximately doubling (range 1.6–2.6) for every standard deviation decrease in BMD, depending on the skeletal site measured and the type of fracture [13]. Many devices and technologies are available for measuring BMD. Dual-energy X-ray absorptiometry (DXA) is the method used to diagnose osteoporosis according to criteria established by the World Health Organization [14] [Table 1].

Non-BMD factors that may alter bone strength include bone turnover, architecture (size and shape, or bone geometry), microarchitecture, damage accumulation, matrix properties, mineralization, and mineral properties. These factors and probably many others that have not yet been well-defined are collectively called "bone quality" or "bone qualities." Accumulating knowledge regarding

Table 1: Classification of Bone Mineral Density (World Health Organization) [14].

Classification	T-score
Normal	-1.0 or greater
Osteopenia	Between -1.0 and -2.5
Osteoporosis	-2.5 or less
Severe Osteoporosis	-2.5 or less with a fragility fracture

The WHO classification is founded on epidemiological data in postmenopausal Caucasian women with BMD measured at the spine, hip, and forearm. The prevalence of osteoporosis in this group is approximately 30%, which roughly corresponds to the lifetime risk of fragility fracture.

bone qualities offers insight into the pathophysiology of osteoporosis and metabolic bone disease, and helps in understanding the mechanisms of action of bone-active drugs. However, with the exception of bone turnover markers and bone geometry, none of these are these presently have clinical applications.

The adult skeleton is in a constant state of remodeling, a process whereby bone and bone matrix (mostly composed of type 1 collagen) is continually being removed by osteoclasts in discrete packets, or bone remodeling units, followed by osteoblast-mediated bone formation and mineralization. With high bone turnover states, such as occurs with estrogen deficiency in the early postmenopausal years, there are more bone remodeling units resulting in a greater number of "stress-risers," or weakened areas of bone. A stress-riser in bone is analogous to a scored line on a sheet of glass, where the glass is more likely to break than in an area that is not scored. Ultimately, thinning and perforation of trabecular structures may occur, as well as impaired mineralization. High bone turnover, which is detected clinically by the finding of elevated markers of bone resorption, has been shown to be an independent risk factor for fracture [15].

Small bones, as in individuals with a small frame or in women compared to men, are weaker than large bones. This is consistent with the engineering concept that a tubular structure, such as a long bone, has a greater ability to resist bending forces as the diameter increases. Longer hip axis length (the distance from the lateral surface of the greater trochanter to the inner surface of the pelvis, along the axis of the femoral neck), larger femoral neck-shaft angle (the angle between the axis of the femoral neck and the femoral shaft), and wider femoral neck diameter (the width of the femoral neck at its narrowest portion) are associated with increased risk of hip fracture [16]. This may explain, in part, the lower risk of hip fracture in Chinese and Japanese women compared to Caucasians, despite similar BMD. A larger vertebral body is less likely

to fracture than a smaller one, even with the same BMD, since a larger cross-sectional area has greater resistance to compressive forces [17].

Bone microarchitecture, best evaluated by bone biopsy, concerns bone properties at the microscopic level, such as the spatial distribution of trabecular rods and plates, trabecular thickness and connectivity, cortical thickness and cortical porosity. The horizontal trabeculae, which stabilize the load-bearing vertical trabeculae, are subject to thinning and perforation in patients with osteoporosis, resulting in loss of bone strength and increased fracture risk [18]. The number, size, and distribution of cortical porosities may play a role in determining bone strength [19].

Damage accumulation, such as the increasing number of microfractures with advancing age, occurs at multiple skeletal sites in some, but perhaps not all individuals [20]. While this has adverse effects on the biomechanical properties of bone, the relationship between microfractures and clinical fractures is not clear, and the significance of increased microdamage accumulation with antiresorptive therapy is not known.

Bone matrix is the noncalcified portion of bone, 90% of which is composed of type 1 collagen. It provides elasticity and flexibility to bone. Inherited and acquired disorders of the collagen fibrils, crosslinking, or non-collagenous proteins may have serious consequences on bone strength and fracture risk. Mild forms of metabolic bone disease with abnormal collagen, such as osteogenesis imperfecta and Ehlers-Danlos syndrome, may sometimes masquerade as postmenopausal osteoporosis.

Mineralization is responsible for stiffness, or mechanical rigidity, of bone. Too much (osteopetrosis) or too little (osteomalacia) bone mineral can have adverse effects on bone strength. Mineralization takes place in two phases: the primary, or active bone formation phase, occurring over a period of months, and the secondary, or slow phase, which takes years. The second phase, which may be responsible for as much as 50% of bone mineralization, is incomplete in high bone turnover states. The rapid increase in BMD over the first 6–12 months of bisphosphonate therapy is due to "filling of the remodeling space" associated with the first phase of mineralization, while the slower increase in BMD over the following years is due to increased secondary mineralization allowed by the reduced rate of bone turnover [21]. Even the size and distribution of hydroxyapatite crystals may affect the mechanical properties of bone, with animal studies suggesting that a mix of small and large crystals are stronger than only large crystals or only small crystals [22].

Clinical risk factors

Consideration of risk factors can provide helpful information for patient management. It is enlightening to distinguish risk factors for osteoporosis from risk factors for fracture, risk factors for hip fracture from risk factors for vertebral fracture, and skeletal risk factors for fracture from non-skeletal ones, since the clinical implications will vary accordingly. For example, risk factors for osteoporosis, such as advanced age, small stature, or family history, are commonly used in selecting patients for bone density testing, and may determine whether the test is covered by insurance. Clinical risk factors for osteoporosis are not a substitute for bone density testing, and in fact cannot accurately predict which individual patients have low bone density [23]. Risk factors for fracture, which overlap risk factors for osteoporosis but are not totally the same, can help determine which patients require medical intervention. Skeletal risk factors for fracture, such as low bone density or high bone turnover, may be treated with pharmacologic agents. Non-skeletal risk factors for fracture, such as poor balance and high risk for falling, require other types of intervention, such as balance training and hip protectors. Advancing age is a risk factor for osteoporosis and fractures for which there is no antidote. Good nutrition, regular weight-bearing exercise, and avoidance of cigarette smoking, alcohol excess and bone-toxic drugs can maximize the genetic potential for skeletal integrity. Validated risk factors for fracture also vary according to the type of fracture, with many more risk factors identified for hip fracture than for vertebral fracture. A list of common skeletal and nonskeletal risk factors for hip fracture is in Table 2. The best validated risk factors for vertebral fracture are low BMD, advancing age, and previous fracture.

Table 2: Selected Skeletal and Nonskeletal Risk Factors for Hip Fracture [15,48].

Skeletal	Nonskeletal
Low BMD	Advanced age
Previous fracture	Mother with hip fracture
High bone turnover	Anticonvulsant therapy
Small stature	Frailty

Identification of skeletal and nonskeletal risk factors can help to customize therapy to address the issues of most importance in preventing fractures.

Long-term glucocorticoid therapy

A meta-analysis of 66 BMD studies and 23 fracture studies showed that oral glucocorticoid treatment with more than prednisolone 5 mg per day or equivalent leads to a decrease in BMD and increased risk of fracture [24]. The increase in fracture risk begins within 3–6 months of starting glucocorticoids, decreases soon after stopping, and is

independent of age, sex, or underlying disease. Analysis of the United Kingdom General Practice Research Database (UK GPRD) of 244,235 patients on oral glucocorticoid therapy showed that a low dose (less than 2.5 mg per day) was associated with an increased risk of vertebral and non-vertebral fractures, and doses greater than 2.5 mg per day were associated with increased risk of vertebral, nonvertebral, and hip fractures [25]. Fracture risk was dose-dependent, increasing dramatically as the dose increased. The fracture risk associated with glucocorticoid therapy appears to be related to average daily dose rather than cumulative dose, suggesting that the adverse skeletal effects are acute rather than chronic [26]. Some [27], but not all [28], studies have shown that patients on glucocorticoid therapy fracture at a higher BMD than patients not on glucocorticoid therapy, suggesting problems with bone quality that are independent of BMD, and that perhaps treatment thresholds should be more aggressive for glucocorticoid patients. A UK GPRD study of 170,818 patients on inhaled glucocorticoids showed increased risk of vertebral, nonvertebral, and hip fractures compared to controls, but suggested that the risk increase may have been due to the underlying respiratory disease rather than the inhaled glucocorticoids [29]. A meta-analysis of 27 studies showed that inhaled glucocorticoids (triamcinolone, budesonide, beclomethasone) in doses over 1.5 mg per day (0.75 mg per day for fluticasone propionate) may be associated with a significant reduction in bone density [30]. In a 2-year randomized placebo-controlled trial of inhaled fluticasone in asthma patients, there was no significant change in BMD with doses of 0.176 mg per day [31]. There is no convincing evidence that intranasal glucocorticoids in normally prescribed doses have any clinically significant adverse effect on skeletal integrity [32], although some studies have demonstrated suppression of the hypothalamic-pituitary-adrenal axis [33]. Further study is needed to define the impact of intranasal glucocorticoid formulation, dose, and combination with oral or inhaled glucocorticoids on the development of bone disease. The prevalence of glucocorticoid-induced osteoporosis is often difficult to determine due to the confounding effects of comorbidities and polypharmacy. A study of general practice patients in Iceland showed that 26% of those treated with oral glucocorticoids for more than 3 months were diagnosed with osteoporosis, and 20% had a history of fragility fractures [34]. The pathophysiology of glucocorticoid-induced osteoporosis is multifactorial, and includes 1.) impairment of osteoblast, osteocyte, and osteoclast function, leading to decreased bone turnover and reduced microfracture repair; 2.) disordered calcium metabolism, with reduced intestinal absorption, increased renal excretion, and possible secondary hyperparathyroidism; and 3.) decreased synthesis of sex hormones [35].

Diagnosis
Bone density testing
A clinical diagnosis of osteoporosis may be made in the presence of a fragility fracture, provided other causes of fracture have been ruled-out. A fragility fracture is any fracture occurring after trivial trauma, such as falling from the standing position, coughing, bending, or reaching. Most fractures in adults, except those from major trauma, such as auto accident or falling off a ladder, are fragility fractures. The preferable method of diagnosing osteoporosis is by bone density testing, before the first fracture has occurred. The WHO criteria may be used to classify BMD, expressed as T-score, as normal, osteopenia, or osteoporosis.

A T-score is the standard deviation (SD) variance of the patient's BMD compared to a healthy young-adult reference population. It is calculated according to the following formula, with BMD and SD expressed as g/cm^2:

$$\text{T-score} = \frac{\left(\text{Patient's BMD}\right) - \left(\text{Mean Young-Adult BMD}\right)}{\left(1 \text{ SD of Young-Adult BMD}\right)}$$

This formula shows that the T-score is dependent on factors other than the patient's BMD, and that a change in the mean or SD of the reference population can result in a different T-score. For example, if the mean young-adult BMD in the reference population is higher, the T-score will decrease, and if the SD is lower, the T-score will increase. This is a clinically import concept, since the reference population may vary according to the manufacturer of the instrument, the software version installed, or the region of interest being measured. For this reason, comparison of serial DXA studies should always be done with absolute BMD values in g/cm^2, and not with T-scores.

A Z-score is the standard deviation (SD) variance of the patient's BMD compared to an age- and sex-matched reference population, and should <u>not</u> be used to diagnose osteoporosis. It is calculated according to the same formula as the T-score, except that the reference population is age- and ethnicity-matched instead of young-adult matched.

The WHO classification system was originally devised as a public health tool for evaluating the prevalence of osteoporosis in populations of postmenopausal women. It was not intended for use in the diagnosis of osteoporosis in individual patients. However, in the absence of a better yardstick, it quickly came to be used in that fashion. The T-score cut-off of -2.5 for diagnosing osteoporosis was selected because it identified approximately 30% of postmenopausal Caucasian women as having osteoporosis, which is roughly the same as the lifetime risk of clinical

fragility fractures in this population. The WHO criteria apply to BMD measurement by DXA of the spine, hip and forearm in postmenopausal women and in men age 65 and older [36]. At the present time, the WHO criteria should not be used with BMD measurement devices other than DXA, nor for measurement at skeletal sites other than spine, hip, and forearm. Perhaps in the future, with standardization of reference databases, and acquisition of device-specific data on prevalence of osteoporosis and fracture risk, the diagnosis of osteoporosis will be made with devices other than DXA.

Who should be tested?

Bone density testing should be considered in anyone at risk for osteoporosis, or being monitored for treatment of osteoporosis, provided that the results of the test are likely to play a role in patient management decisions. Of all the published guidelines of indications for bone density testing, the most comprehensive are those of the International Society for Clinical Densitometry (ISCD) [36], listed in Table 3.

Table 3: Indications for Bone Density Testing [36] (Official Position of the International Society for Clinical Densitometry).

1. All women aged 65 and older.
2. Postmenopausal women under age 65 with risk factors for osteoporosis.
3. Adults with a fragility fracture.
4. Adults with a disease or condition associated with low bone mass or bone loss.
5. Adults taking medication associated with low bone mass or bone loss.
6. Anyone being treated for low bone mass, to monitor treatment effect.
7. Anyone not receiving therapy, in whom evidence of bone loss would lead to treatment.

Women discontinuing estrogen should be considered for bone density testing/bone mass measurement according to the indications listed above. These indications provide a framework for selecting patients for bone density testing. In order to determine if the test is covered by insurance, it is important to be familiar with local requirements.

Evaluation of low bone density

It is prudent to have a high index of suspicion for contributing factors in every patient with low density. A T-score of -2.5 or below is not always osteoporosis. It could be metabolic bone disease, such as osteomalacia, or a localized bone disorder, such as a bone cyst in the measured skeletal site. A postmenopausal woman with osteoporosis does not always have postmenopausal osteoporosis. She could have malabsorption due to undiagnosed celiac disease, or possibly multiple myeloma. Table 4 lists diseases, conditions, and medications commonly associated with low bone density. In every patient with low BMD, it is reasonable to consider measuring a complete blood count,

serum calcium, phosphorous, creatinine, alkaline phosphatase, liver enzymes, and thyroid stimulating hormone. Tests that are often helpful include a 24-hour urine for calcium, celiac antibodies, and in older patients, a serum and urine protein electrophoresis. In selected patients, a serum intact parathyroid hormone level, urinary free cortisol (or other tests to rule out Cushing's syndrome), or additional studies may be helpful.

Prevention and treatment
Nonpharmacologic therapy

Nonpharmacologic therapy can be divided into the categories of nutrition, lifestyle, and fall prevention. These represent the foundation for the management of osteoporosis, without which patients are unlikely to achieve the full benefit of pharmacologic therapy. Calcium and vitamin D supplementation have been shown to increase BMD [37] and reduce the risk of fractures [38] in prospective trials. The average American diet is deficient in calcium, and many Americans have an insufficient daily intake of vitamin D. The National Osteoporosis Foundation recommends that all adults have a daily intake of at least 1200 mg elemental calcium with diet plus supplements, and 400–800 IU vitamin D per day for patients at risk of deficiency [39].

Lifestyle intervention for osteoporosis includes regular weight-bearing exercise and avoidance of unhealthy behavior, such as cigarette smoking and excess alcohol intake. Patients with low BMD and high risk for falling may benefit from additional measures, such as muscle strengthening, fall prevention, balance training, Tai Chi, extra care with the dosing of certain drugs (e.g., sedatives, hypnotics, antihypertensives, anticonvulsants), nightlights, handrails, grab-bars, removal of slippery carpets and dangerous obstacles at home, correction of impaired eyesight and hearing, and the wearing of hip protectors.

The decision to treat

Since the goal of treatment is to prevent fractures, selection of patients for drug treatment should be based on level of fracture risk. Current guidelines for initiation of pharmacologic therapy [Table 5] are based on T-score or T-score plus clinical risk factors. While these guidelines are a helpful for appropriate patient populations, over-reliance on T-scores alone may underestimate or overestimate absolute fracture risk and lead to inappropriate therapy. For example, a healthy 30 year-old premenopausal woman with a T-score (or Z-score) of -2.1 probably has a low 5–10 year absolute fracture risk and would probably not benefit from pharmacologic therapy, while an elderly man or woman with a T-score of -1.4 and a history of fragility fracture is at high risk for future fracture and could expect a significant reduction in fracture risk with therapy. Efforts are currently underway to develop a standardized

Table 4: Causes of Low Bone Mineral Density.

Inherited	Nutritional	Endocrine	Drugs	Other
Osteogenesis imperfecta	Malabsorption	Hypogonadism	Glucocorticoids	Multiple myeloma
Homocystinuria	Chronic liver disease	Hyperthyroidism	Anticonvulsants	Rheumatoid arthritis
Marfan's syndrome	Alcoholism	Hyperparathyroidism	Long-term heparin	Systemic mastocytosis
Hypophosphatasia	Calcium deficient diet	Cushing's syndrome	Excess thyroid	Immobilization
	Vitamin D deficiency	Eating disorder	GnRH agonists	

Low BMD may be the result of many medical disorders. There should be a high index of suspicion in all patients with low BMD for these types of contributing factors.

Table 5: Indications for Pharmacologic Therapy.

National Osteoporosis Foundation [39]
    Initiate therapy to reduce fracture risk in women with:
        1. BMD T-scores below -2.0 by central DXA with no risk factors
        2. BMD T-scores below -1.5 by central DXA with one or more risk factors
        3. A prior vertebral or hip fracture
American Association of Clinical Endocrinologists [47]
    The following women may benefit from pharmacologic treatment of osteoporosis:
        1. Women with postmenopausal osteoporosis (Women with low-trauma fractures and low BMD and women with BMD T-scores of -2.5 and below)
        2. Women with borderline low BMD (e.g., T-scores of -1.5 and below) if risk factors are present
        3. Women in whom nonpharmacologic preventive measures are ineffective (bone loss continues or low trauma fractures occur)

These recommendations are very similar, with the main difference being the T-score cut-off for treatment in patients with no other risk factors.

Table 6: Nonskeletal Effects of Pharmacologic Therapy.

Medication	Pros	Con
Estrogen	Relieves Menopausal symptoms, Cholesterol, LDL, HDL	Uterine Bleeding, Thromboembolic Disorders, Stroke, Coronary Artery Disease, Estrogen Sensitive Tumors, Triglyceride, Breast Tenderness, Fluid Retention
Alendronate/Risedronate	Weekly Dosing	Complicated Administration, GI Effects
Raloxifene	Cholesterol, LDL, Reduced Breast Cancer Risk?, Cardiovascular?	Hot Flashes, Thromboembolic Disorders, Leg Cramps
Nasal Calcitonin	Ease of Administration, Analgesic Effect	Nasal Irritation
Teriparatide	Analgesic Effect?	Osteosarcoma in Rats, Injectable, Refrigeration, Hypercalcemia

The selection of the best pharmacologic agent for an individual patient requires a thorough understanding of patient factors and all drug effects, both skeletal and nonskeletal.

methodology for calculating and expressing absolute fracture risk, which is arguably the best way of establishing therapeutic thresholds. Personal issues and non-skeletal effects of medications are also important to consider in the decision to treat and drug selection [Table 6]

Pharmacologic therapy
The medications that are FDA-approved for the management of osteoporosis may be divided into antiresorptive agents (estrogen, alendronate, risedronate, and calci-

tonin) and anabolic agents, of which there is now only one-teriparatide. These agents can be expected to stabilize or increase BMD [Table 7] and reduce fracture risk by approximately 50% in most patients. All of the FDA-approved medications have been shown to reduce the risk of vertebral fractures, while only estrogen, alendronate, and risedronate have reduced the risk of hip fractures in prospective clinical trials. [Table 8]

Table 7: Bone Density Response to Therapy.

Generic Name	Brand Name	Spine	Hip
Estrogen	Various	↑	↑
Alendronate	Fosamax	↑	↑
Risedronate	Actonel	↑	↑
Ibandronate	Boniva	↑	↑
Calcitonin	Miacalcin	-	-
Raloxifene	Evista	↑	↑
Teriparatide	Forteo	↑	↑

This table illustrates direction of change in bone mineral density (BMD) with each type of drug. This does not represent a comparison of the magnitude of BMD change with different drugs. All of the medications that are currently approved by the FDA, with the exception of salmon calcitonin, have been shown to increase BMD at both the spine and hip.

Table 8: Fracture Risk Reduction in Response to Therapy.

Generic Name	Brand Name	Spine Fracture	Non-Vertebral Fracture	Hip Fracture
Estrogen	Various	✓	✓	✓
Alendronate	Fosamax	✓	✓	✓
Risedronate	Actonel	✓	✓	✓
Ibandronate	Boniva	✓		
Calcitonin	Miacalcin	✓		
Raloxifene	Evista	✓		
Teriparatide	Forteo	✓	✓	

This table illustrates the direction of change in fracture risk with each type of drug. This does not represent a comparison of the magnitude of fracture risk reduction with different drugs. While all FDA-approved medications have been shown to reduce the risk of spine fracture, only estrogen, alendronate, and risedronate have reduced the risk of hip fracture in randomized placebo-controlled trials.

The Women's Health Initiative was the first large prospective randomized placebo-controlled trial to show reduction of hip fracture, vertebral fracture, and other nonvertebral fractures with conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA) [40] and CEE alone [41]. However, the study was stopped before its planned completion date due to increased risk of adverse events. Considering the small but significant increase in

Table 9: Management of Glucocorticoid-Induced Osteoporosis [42].

Patient beginning therapy with glucocorticoid (prednisone equivalent of ≥5 mg/day with plans for treatment duration of ≥3 months):
  1. Modify lifestyle risk factors for osteoporosis (Smoking cessation or avoidance. Reduction of alcohol consumption if excessive.)
  2. Instruct in weight-bearing physical exercise.
  3. Initiate calcium supplementation.
  4. Initiate supplementation with vitamin D (plain or activated form).
  5. Prescribe bisphosphonate (use with caution in premenopausal women).
Patient receiving long-term glucocorticoid therapy (prednisone equivalent of ≥5 mg/day):
  1. Modify lifestyle risk factors for osteoporosis. (Smoking cessation or avoidance. Reduction of alcohol consumption if excessive.)
  2. Instruct in weight-bearing physical exercise.
  3. Initiate calcium supplementation.
  4. Initiate supplementation with vitamin D (plain or activated form).
  5. Prescribe treatment to replace gonadal sex hormones if deficient or otherwise clinically indicated.
  6. Measure bone mineral density (BMD) at the lumbar spine and/or hip.
     If BMD is not normal (i.e., T-score < -1.0), then prescribe bisphosphonate (use with caution in premenopausal women). Consider calcitonin as second-line agent if patient has contraindication or intolerance to bisphosphonate therapy.
     If BMD is normal, follow-up and repeat BMD measurement annually or biannually.

The devastating effects of glucocorticoids on bone can be largely mitigated by early intervention with bone-protective agents.

the risk of breast cancer, stroke, coronary heart disease, and venous thromboembolic disease with CEE plus MPA, and the increase risk of stroke with CEE alone, it is likely that estrogen will not be used as a drug of first choice for the treatment of osteoporosis, and that its main use will be for the control of menopausal symptoms. The bisphosphonates, alendronate and risedronate, are both proven to reduce the risk of hip fractures, and may be good choices in elderly patients and any patients with high risk of hip fracture. Raloxifene and calcitonin are useful agents where reduction of hip fracture risk is not a primary concern, with the added benefit that raloxifene may reduce the risk of breast cancer and calcitonin may have an analgesic effect in patients with acute painful vertebral fractures. Teriparatide, human recombinant 1–34 parathyroid hormone, is approved for use in women and men at high risk for fracture. Despite its greater expense and the inconvenience of daily subcutaneous injections for a 2-year course of therapy, this agent is a welcome addition to the pharmacologic armamentarium for selected patients. Current evidence suggests that there is no added benefit to combining teriparatide with alendronate, but giving a bisphosphonate following a course of treatment with teriparatide may serve to preserve the bone mass previously gained. Combination therapy in general is discouraged, since there are no studies showing that it offers additional benefit in terms of fracture risk reduction.

Glucocorticoid-induced osteoporosis (GIO)
Long-term term glucocorticoid therapy may have devastating consequences in terms of loss of bone density and increased fracture risk. Any patient being started on oral glucocorticoid therapy with the intent to treat for more than 3 months should be considered for bone density testing and bone-protective medication. Table 9 shows the

guidelines of the American College of Rheumatology for the prevention and treatment of GIO [42].

Monitoring treatment
The ultimate indicator of efficacy for osteoporosis therapy is reduction of fracture risk. In clinical trials, this is done by comparing fractures rates in a group receiving active medication compared to placebo. For individual patients in clinical practice, BMD is normally used as a surrogate measurement of changes in bone strength and fracture risk in response to therapy. An increase or stabilization of BMD is associated with reduction in fracture risk [43], although other measures of bone qualities, particularly changes in bone turnover markers [44], are correlated to changes in fracture risk as well. Patients started on pharmacologic therapy are typically retested in 1–2 years in order to be sure there has been no loss of BMD, and retested at longer intervals once response to therapy has been shown. Patients at very high risk for bone loss, such as those on glucocorticoid therapy, may need to be tested as often as every 6 months, until stability of bone mass has been demonstrated.

Discontinuation of treatment
It is intuitive that pharmacologic therapy should be continued as long as fracture risk is high, and stopped when that is no longer the case. Prolonged therapy adds to patient cost and inconvenience, and possibly increases the risk of drug toxicity due to longer exposure. Clinical trials and knowledge of drug mechanisms of action are helpful in predicting the likely outcome of discontinuation, and suggestive of appropriate measures for follow-up. Discontinuing estrogen, raloxifene, or calcitonin therapy is likely to be associated with rapid loss of therapeutic effect and subsequent bone loss due to sex hormone deficiency and/

or aging. Therefore, patients at high risk for fracture who stop these drugs should probably soon be started on another anti-fracture drug. Bisphosphonates, having a strong affinity for bone and a long bone half-life, have been shown to have persistence of suppression of bone turnover for months to years after cessation of therapy. This suggests that patients who have been taking an oral bisphosphonates for years may continue to benefit from drug effects for a long time after discontinuation, with the duration of persistent effect varying according to the pharmacological properties of the bisphosphonate used. With teriparatide, there is evidence that discontinuation may be quickly followed by bone loss, which can be prevented by initiating bisphosphonate therapy.

Nonresponders

In clinical trials, the overwhelming majority of patients treated for osteoporosis with antiresorptive or anabolic medication stabilize or increase BMD and benefit from a reduction in fracture risk. In clinical practice, approximately 10% of elderly patients treated with a bisphosphonate have been shown to lose BMD [45], defined as a BMD decrease more than the Least Significant Change (LSC) at a 95% level of confidence, a value that can be calculated for each bone densitometry center. Medical evaluation of these BMD losers revealed a previously unrecognized contributing factor, or secondary cause of osteoporosis in about 50%. Although there is no universal consensus on the definition of non-response to therapy, defining nonresponse in terms of BMD loss more than the LSC is a useful tool in clinical practice, and is cause for further medical investigation. Common causes for nonresponse include poor adherence (not taking medication or not taking it correctly), calcium or vitamin D defi-

ciency, and comorbidities (diseases, conditions or medication that impair drug effect or are associated with osteoporosis) [46].

When to refer to an osteoporosis specialist

The care of osteoporosis patients crosses all medical specialty lines. Primary care specialists and most medical subspecialists may justifiably claim the right to manage osteoporosis in their patients, and do it well. In a small percentage of patients with unusual clinical presentations, intolerance to standard medications, or poor response to therapy, additional expertise may be required. Table 10 shows established guidelines for referral to an osteoporosis specialist [47].

Summary

Osteoporosis is a common disorder of low bone strength due to a combination of factors that include low BMD, high bone turnover, altered microarchitecture, geometry, damage accumulation, and mineralization, leading to increased risk of fractures. The consequences of fragility fractures are serious-disability, loss of independence, chronic pain, and increased mortality. Patients on long-term oral glucocorticoid therapy, even at low doses, are at increased risk for fracture. Inhaled glucocorticoids in sufficiently high doses may increase fracture risk. Intranasal glucocorticoids, in doses normally prescribed, do not appear to have clinically significant adverse skeletal effects. BMD testing is the most important clinical tool for diagnosing high risk patients before the first fracture occurs, allowing for timely and appropriate medical intervention to strengthen bones and reduce the risk of fracture.

Table 10: When to Refer to an Osteoporosis Specialist [47].

Referral to an osteoporosis specialist is appropriate when the patient is in any of the following circumstances:
1. Has osteoporosis that is unexpectedly severe or has unusual features at the time of initial assessment
    Has very low BMD (a T-score below -3.0 or a Z-score below -2.0)
    Has osteoporosis despite young age (premenopausal)
    Has fractures despite borderline or normal BMD
2. Has a suspected or known condition that may underlie the osteoporosis (for example, hyperthyroidism, hyperparathyroidism, hypercalciuria, Cushing's syndrome, or hypogonadism)
3. Is a candidate for combination therapy
4. Is intolerant of approved therapies
5. Fails to respond to treatment
    Takes estrogen yet has low baseline BMD
    Is undergoing treatment yet shows an apparent loss of BMD on serial studies
    Has fractures on treatment

Most osteoporosis patients can be successfully managed by the primary care physician, but a small percentage with unusual or difficult problems can benefit from consultation with an osteoporosis specialist. Referral to an osteoporosis specialist is appropriate when the patient is in any of the following circumstances:

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Authors' contributions

The author is solely responsible for all content of this review.

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