



# BONE HEALTH UPDATE 2005

CLINICAL VIEWPOINTS ON OSTEOPOROSIS

## Practical Guide to Preventing, Recognizing, and Managing Osteoporosis



DIAGNOSIS



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# Practical Guide to Preventing, Recognizing, and Managing Osteoporosis

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## Target Audience

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This booklet is directed at primary care physicians, providing them with the tools they need to prevent, recognize, and manage osteoporosis.

## Learning objectives

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Upon reading this booklet, you will be able to:

- Recognize and appreciate the incidence and burden of osteoporosis
- Identify the risk factors for the development of osteoporosis
- Assess patients for their risk of developing osteoporosis
- Educate patients on prevention strategies
- Make therapeutic decisions based on the latest clinical trial findings

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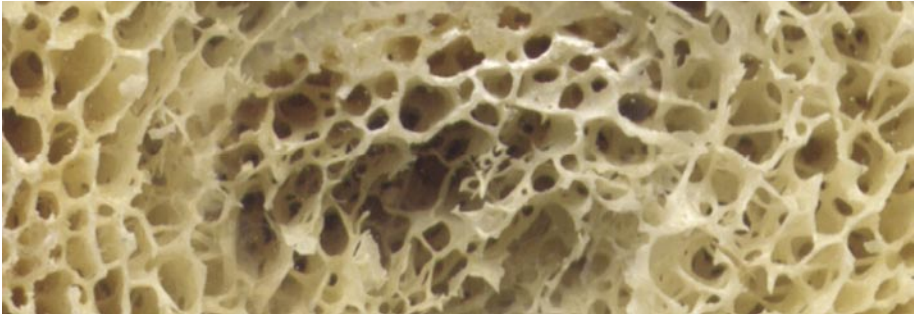
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# OSTEOPOROSIS – AN OVERVIEW

Osteoporosis and its consequences comprise a significant source of mortality, morbidity, and medical expenditures in the United States. As the population ages, the burden of this condition continues to increase, putting an even greater strain on an already overstretched health care system. Public health initiatives increasingly emphasize preventive measures, including early risk assessment, lifestyle changes, calcium supplementation, and pharmacologic interventions. As outlined in this booklet, the growing body of research into osteoporosis sheds light on the most appropriate diagnostic, monitoring, and management tools tailored to meet the needs of patients.

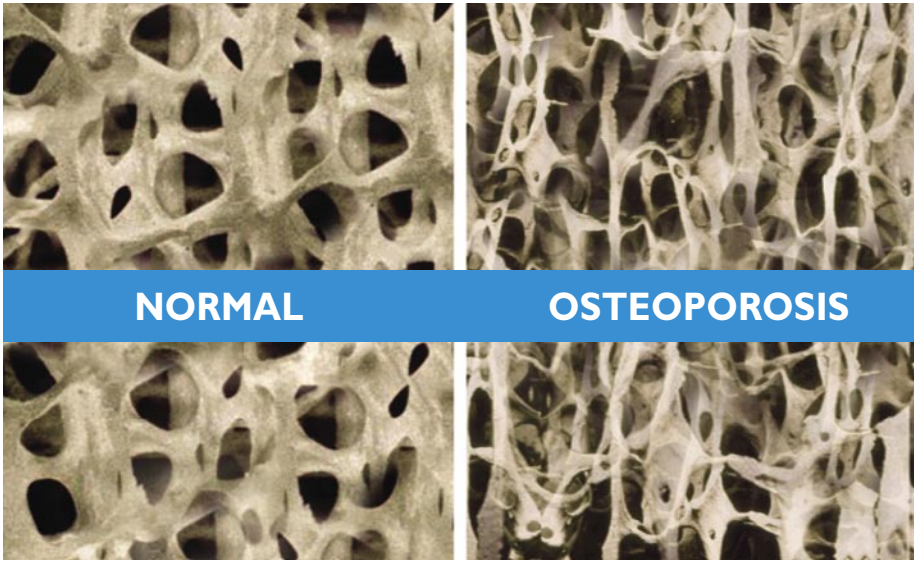


## A GROWING PROBLEM

- 44 million Americans ages 50 years and older have osteopenia or osteoporosis.<sup>1</sup>
- 10 million already have osteoporosis and 34 million have osteopenia.<sup>1</sup>
- Half of all Caucasian women have osteopenia by the end of their first postmenopausal decade.<sup>2,3</sup>
- Over 1.5 million fractures can be attributed to osteoporosis annually, 20% of these being hip fractures.<sup>1</sup> One out of every two Caucasian women will experience an osteoporotic fracture at some point in her lifetime.<sup>4</sup>
- Hip fractures result in 10% to 20% excess mortality within 1 year. Additionally, one-third of patients with a hip fracture will fracture the opposite hip. Up to 25% of hip fracture patients may require long-term nursing home care, and only 40% fully regain their prefracture level of independence.<sup>4</sup>
- The estimated direct expenditures for osteoporosis and related fractures was \$17 billion in 2001.<sup>1</sup>

**THE BASICS OF PATHOPHYSIOLOGY**

Bone metabolism is a complex process dependent on a number of factors. These include genetic and external factors such as diet and physical activity.<sup>5</sup> Once linear growth is completed, bone is continually replenished by a process known as remodeling, whereby bone is built and resorbed and rebuilt again. The maintenance formation of healthy bone is dependent on this process, allowing the body to repair microfractures caused by day-to-day stress on bones. When the balance between bone removal is greater than bone replacement, bone loss occurs. Advancing age and menopause contribute to this imbalance. Among the consequences are reduced bone mass, disruption of skeletal microarchitecture, and an increase in fracture risk.<sup>4</sup>



*Normal Bone vs. Osteoporotic Bone*

## BONE REMODELING

- In normal bone remodeling, resorption and formation are balanced and maintain the honeycomb structure of trabecular plates and rods.
- Osteoclasts remove bone and leave cavities that are filled with new bone by osteoblasts.
- During the development of osteoporosis, osteoclasts remove too much old bone from trabecular plates, penetrating them and causing perforations. As the bone turnover rate increases, so does the number of perforations.
- These perforations gradually expand ultimately converting trabecular plates into trabecular rods.
- As osteoporosis progresses, the osteoclasts continue to penetrate and remove more old bone from the rods' sites, eventually bisecting them.
- Eventually, the bisected rods are completely eroded by continued osteoclastic resorption.
- The result is a system of poorly interconnected rods lacking in structural integrity and strength.

Mineral metabolism is dependent on the proper functioning of a number of systemic or circulating hormones that respond to changes in serum calcium and phosphorus levels. Lowered serum concentrations of these minerals lead to their removal from the bone to serve vital functions in other parts of the body. The bone can be weakened if too much calcium and phosphorus is withdrawn.<sup>5</sup>

## Regulatory hormones and their functions<sup>5</sup>

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- **Calcium-regulating hormones**

- Parathyroid hormone maintains serum calcium levels and stimulates both resorption and formation of bone.
- Calcitriol, derived from vitamin D, stimulates the intestines to absorb sufficient calcium and phosphorus and also directly affects bone.
- Calcitonin inhibits bone breakdown and may protect against excessively high levels of calcium in the blood.

- **Sex hormones**

- Estrogen increases bone growth in childhood and early puberty. At the end of puberty, high concentrations of estrogen close the growth plates at the ends of long bone stopping further growth. It also acts on bone cells to inhibit bone breakdown.
- Testosterone has direct effects on bone and also stimulates muscle growth, which in turn places increased stress on bones and leads to bone formation. Testosterone is converted into estrogen in fat cells.

- **Other systemic hormones**

- Growth hormone (GH) is essential for growth and accelerates skeletal growth at puberty. It stimulates the production of insulin-like growth factor-I (IGF-I). The GH/IGF-I axis stimulates bone formation, resulting in an increase in bone mass.
- Thyroid hormone increases bone remodeling.
- Cortisol in small amounts is important in bone development; however excessive amounts inhibit bone growth in children, and stimulate bone loss in adults.

## Key risk factors

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Taking a comprehensive patient history is a critical step in identifying those at risk for osteoporosis. A number of risk factors for osteoporosis have been identified. Most of these are predictors of low bone density, such as female sex, age, estrogen deficiency, and Caucasian or Asian race.<sup>5</sup> Red flags include a history of fractures related to mild or moderate trauma, family history of osteoporosis, low body weight, late onset of sexual development, use of glucocorticoids, high levels of calcium or alkaline phosphatase in otherwise healthy patients, hyperparathyroidism, hyperthyroidism, or treatment with high doses of thyroid hormone.<sup>5</sup>

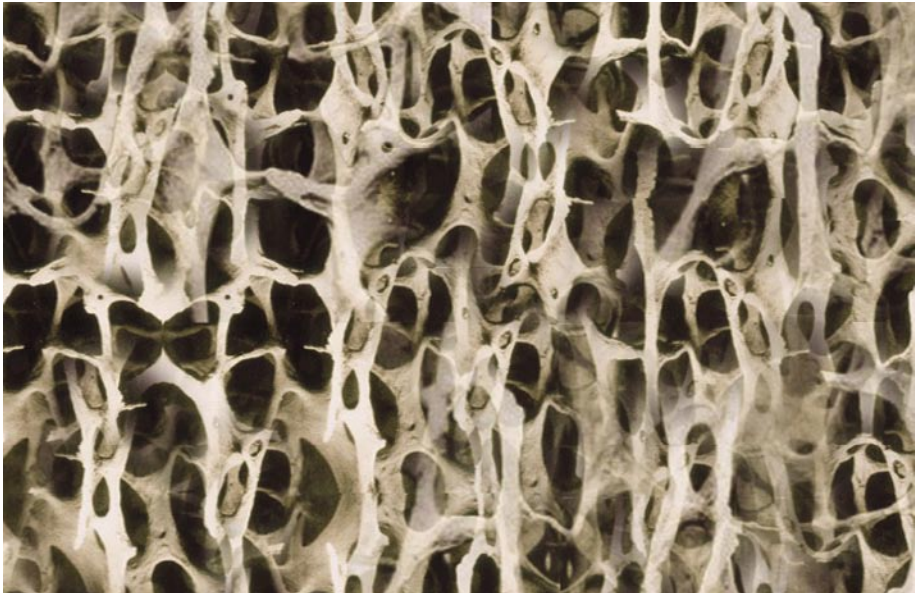
Sedentary lifestyle, cigarette smoking, and excessive alcohol intake are also associated with an increased risk of osteoporosis.<sup>5</sup>

Postmenopausal women represent the highest at-risk group because decreased levels of estrogen lead to accelerated bone loss.

## Signs and symptoms

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Osteoporosis is regarded as a silent disease because frequently there are no symptoms until a fracture occurs. Physical examination may reveal tenderness or pain over the site of a silent fracture. Exaggerated thoracic kyphosis, commonly called a “dowager’s hump,” is a classic sign and can be associated with loss of height of two inches or more.<sup>6</sup> Balance problems may manifest themselves due to a forward-leaning shift in gravity. Gait changes or increased difficulty in performing daily activities can also alert the clinician to the potential presence of osteoporosis.



*Osteoporotic Bone Structure*

## SIGNS AND SYMPTOMS

- Back pain
- Fractures
- Height loss
- Skeletal deformity (e.g., kyphosis)
- Neck strain (due to exaggerated cervical lordosis)
- Midabdominal pain (due to the ribs resting on the iliac crest)
- Alteration in bowel function (caused by compression of abdominal contents)
- Limited respiratory capacity (caused by advanced kyphosis)

## Risk assessment

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According to a recent report by the US Surgeon General, bone mineral density (BMD) testing is the gold standard for identifying osteoporosis and fracture risk. However, population-wide testing is not cost-effective or practical for assessing the risk of bone disease.<sup>5</sup> The report recommends initial assessment of other risk factors to identify a subset of at-risk individuals. A number of risk assessment tools or clinical prediction rules are in development. The aim of these tools is to arrive at a more individualized approach to diagnosis and treatment. The ideal tool would be easily administered and interpreted. Key features of several tools under development are outlined in Table I.

Table I. Risk assessment tools.

| TOOL  | DESCRIPTION  |
|---|--|
| Osteoporosis Risk Assessment Instrument <sup>7</sup>        | <ul style="list-style-type: none"> <li>• Scores based on age, weight, and current estrogen use</li> <li>• Sensitivity 93% (identifies 93% of people with low BMD)</li> <li>• Specificity 39% (61% of people identified do not have low BMD)</li> </ul> |
| Simple Calculated Osteoporosis Risk Estimation <sup>8</sup> | <ul style="list-style-type: none"> <li>• Based on age, race, weight, estrogen use, rheumatoid arthritis, fracture history</li> <li>• Sensitivity 91%</li> <li>• Specificity 40%</li> </ul>   |
| Osteoporosis Self-Assessment Tool <sup>7,9,10</sup>         | <ul style="list-style-type: none"> <li>• Based on age and weight</li> <li>• Sensitivity 92%</li> <li>• Specificity 46%</li> </ul>  |
| Dubbo Osteoporosis Epidemiology Study <sup>11</sup>         | <ul style="list-style-type: none"> <li>• Based on age, body weight, fracture history</li> <li>• Predicts low BMD, but not fractures</li> </ul>   |
| National Osteoporosis Foundation Guidelines                 | <ul style="list-style-type: none"> <li>• Based on age, weight, current cigarette smoking status, family history of fracture, personal fracture history (no scoring system established)</li> </ul>  |

The pivotal National Osteoporosis Risk Assessment (NORA) study was a large epidemiologic trial including more than 200,000 postmenopausal women; of that group 57,000 had T scores between -1 and -2.5 by peripheral BMD testing. This group was then evaluated with respect to 32 risk factors to determine which were the most powerful predictors of short-term (one year) fracture events.

Investigators found that, in this group of women with reduced bone mineral density, four specific risk factors could capture approximately 75% of women who were likely to fracture. These factors included prior fracture, T score lower than -1.8, fair or poor health and poor mobility. Authors of the study believe this classification system can be used in clinical practice to guide assessment and treatment decisions.<sup>12</sup>

## Diagnostic testing

Bone density testing is the most widely accepted tool to establish or confirm a diagnosis of osteoporosis and predict future fracture risk.<sup>5</sup> BMD has an inverse relationship to the risk of fracture: the lower the BMD, the greater the fracture risk. BMD correlates with the load-bearing capacity of the bone.<sup>13,4</sup>

Dual-energy x-ray absorptiometry (DXA) and quantitative computed tomography (CT) measure BMD at central sites, including the hip and spine. DXA, which can distinguish between different types of bone tissue, is more widely used. Peripheral sites include the heel and wrist. Techniques include single-energy x-ray absorptiometry, peripheral DXA, CT, radiographic absorptiometry, ultrasonometry, and single-photon absorptiometry.

BMD is expressed as a relationship to two norms: the expected BMD for the patient's age and sex (Z-score) or for "young normal" adults of the same sex (T-score). Patient scores are expressed as the number of standard deviations (SDs) from normal scores. Z scores are not used to diagnose osteoporosis because a reduction in bone mass usually occurs with increasing age. The World Health Organization has established definitions based on bone mass measurement at the spine, hip, or wrist in white postmenopausal women (see Table 2).<sup>14</sup>

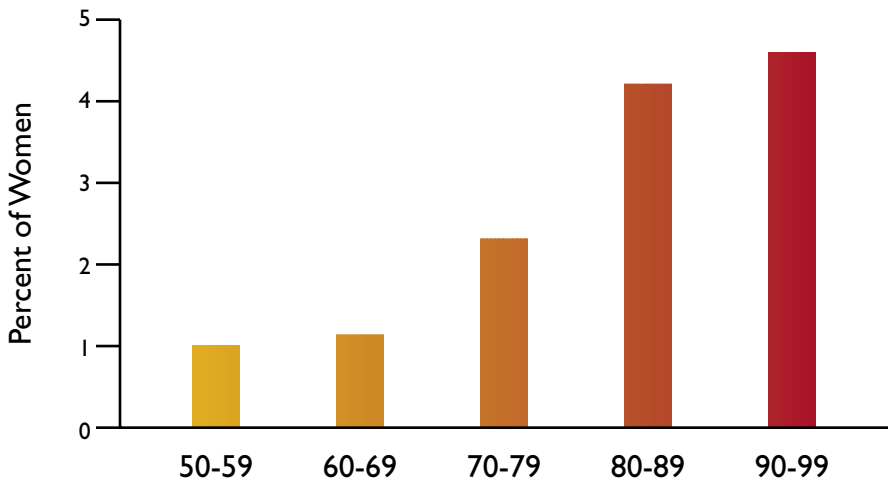
Table 2. WHO definitions based on bone mass measurements.

|                                   |   |
|-----------------------------------|---|
| <b>NORMAL</b>                     | Within 1 SD of a "young normal adult" (T score >-1.0)                                     |
| <b>LOW BONE MASS (OSTEOPENIA)</b> | Between 1 and 2.5 SD below that of a "young normal adult" (T score between -1.0 and -2.5) |
| <b>OSTEOPOROSIS</b>               | > 2.5 SD below that of a "young normal adult" (T score <-2.5)*                            |

*\*Women in this group who have already experienced one or more fractures are deemed to have severe or "established" osteoporosis.*

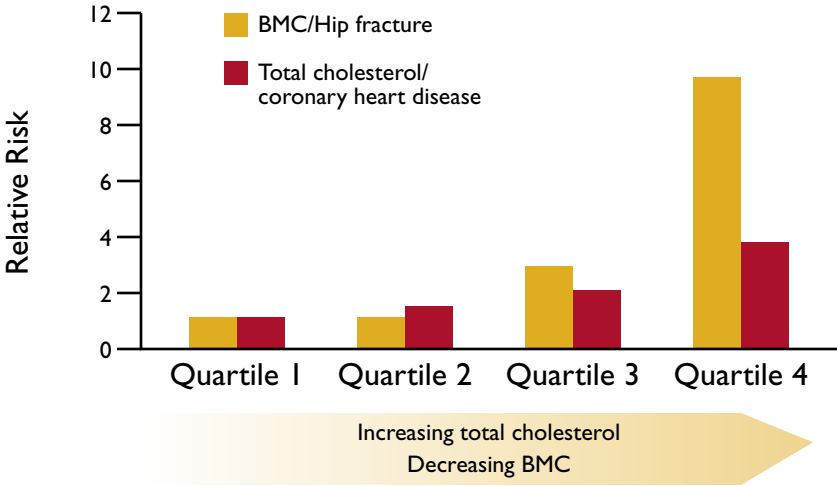
The Surgeon General's report recommends administering a BMD test in all women ages 65 years and older. As shown in Figure 1, a 90-year-old woman with a T score of -2 has a 4.6 fold higher risk of hip fracture than a 50-year old woman with the same T score, highlighting the fact that age is an important and independent determinant of fracture risk.<sup>14</sup> The report also recommends BMD testing in all patients aged 50 years and older who suffer a minor fracture.<sup>5</sup> The report also recommends screening high-risk patients for early signs of bone loss. These comprise patients aged 50 years and less who have had multiple fractures, those who take potentially bone-thinning medications such as glucocorticosteroids and those who have hormonal, kidney, or other diseases that can increase the risk of osteoporosis.<sup>5</sup>

Figure 1. 5-year hip fracture rates for women with T score of -2 without previous hip fracture by age.<sup>15</sup>



A strong correlation exists between decreases in bone density and increases in fracture risk.<sup>15</sup> In fact, the association between low bone mass and fracture is stronger than that between systolic blood pressure and stroke, or that between serum cholesterol and coronary events.<sup>15</sup> Figure 2 shows the increasing risk of hip fractures in the upper quartiles of forearm bone mineral content (BMC) in a cohort of 399 women aged 40 to 70 years, followed for up to 10 years. This is compared with the increased risk of coronary heart disease by quartiles of total cholesterol levels in the Multiple Risk Factor Intervention Trial (MRFIT), which included 316,099 white men followed for an average of 12 years.<sup>16</sup> This comparison shows that bone mineral content is an excellent predictor of fracture risk, as good if not better than the predictive ability of total cholesterol for heart disease.

Figure 2. Predictive validity of BMC for hip fracture. <sup>16,15</sup>



### Future directions in diagnosis

There are still some limitations with regard to the use of BMD testing. Better criteria are needed to identify which patients to test, how to interpret initial results and follow-up testing, and how to communicate the results to patients.<sup>15</sup> More information is needed on how to develop prevention and treatment strategies based on a combination of BMD data and the overall risk profile. Of major concern is the variability across BMD machines and the technologists who perform the tests, as well as the physicians who interpret the results. There may also be variation between the density of bone sites within individual patients, thus testing of multiple sites may add to the reliability of the diagnosis.<sup>15</sup>

New approaches to supplement the information from BMD testing include the use of biochemical markers of bone turnover. Specific blood and urine markers that reflect overall bone turnover include the resorption markers (N-telopeptide of type I collagen, C-telopeptide of type I collagen, free and total pyridinolines, and free and total deoxypyridinolines). Formation markers include bone specific alkaline phosphatase, aminoterminal propeptide of type I collagen, and carboxyterminal propeptide of type I collagen and osteocalcin.<sup>15</sup> These markers may eventually prove to be independent predictors of fracture risk and rate of bone loss. Serial measurements of bone markers may also prove useful in monitoring response to treatment. However, as yet, these measures carry too much variability to be reliable independent markers.<sup>15</sup>

# MANAGEMENT

There are two primary goals of osteoporosis management.

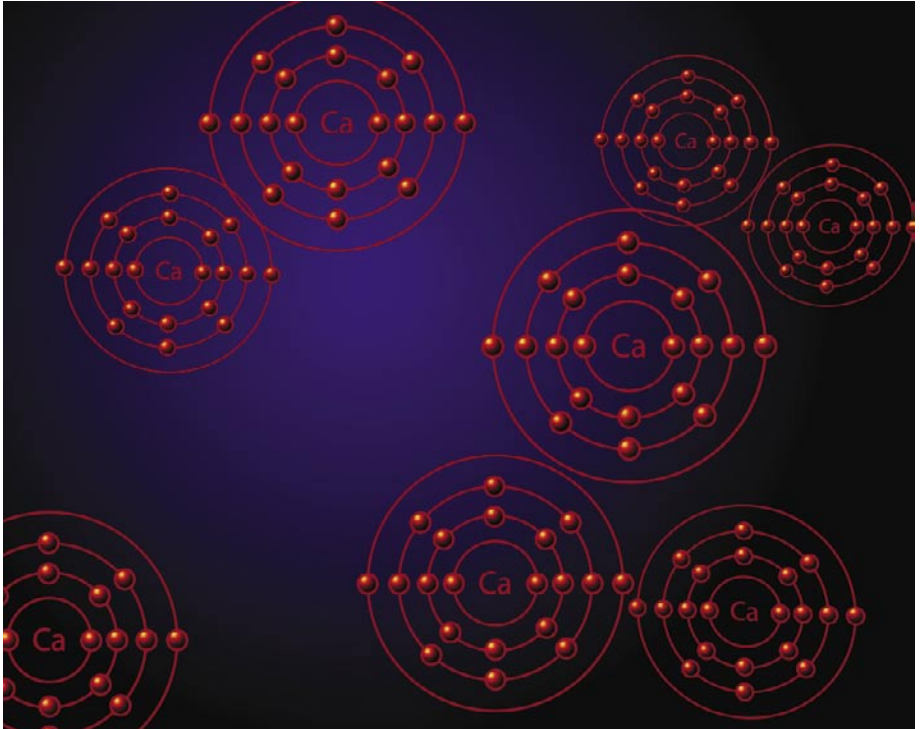
1. to increase or stabilize bone mass.
2. to reduce fractures and the pain, disability, and mortality associated with them.<sup>17</sup>

Clinicians can choose from a variety of treatment strategies for osteoporosis. Non-pharmacologic options include calcium and vitamin D supplementation. Pharmacologic options include hormone replacement therapy (HRT), calcitonin, selective estrogen receptor modulators (SERMs), bisphosphonates, and parathyroid hormone (PTH).

## CALCIUM AND VITAMIN D SUPPLEMENTATION

The Surgeon General's report recommends bone-strengthening interventions such as increased calcium and vitamin D intake and increased weight-bearing exercise.<sup>5</sup>

Calcium is essential for the achievement of optimum bone mass and is important in skeletal development in childhood and in maintaining bone density in adults.

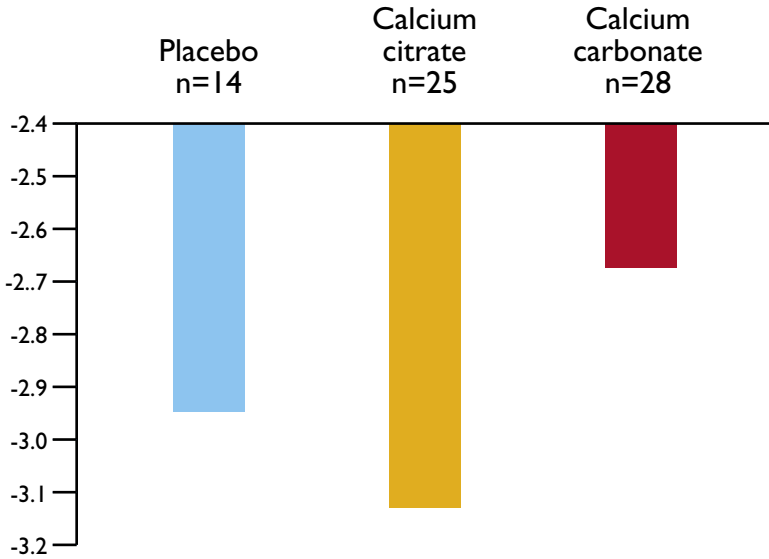


*Calcium is essential for the achievement of optimum bone mass.*

The major functions of vitamin D are to maintain serum calcium, allowing signal transduction and normal neuromuscular activity. Deficiency leads to impaired calcium absorption, secondary hyperparathyroidism, decreased bone mineral density and may result in myopathy, balance, and neuromuscular coordination difficulties, thus increasing the risk of falls. Deficiency may occur secondary to inadequate sunlight exposure, aging, and inadequate dietary intake. Normal 25-hydroxyvitamin D levels are greater than 20 ng/mL. Patients with deficiency have levels less than 20 ng/mL and those with severe deficiency (osteomalacia) have less than five ng/mL. There is growing evidence that, while the lower limit of the normal range is 20 ng/ml, this may be sub-optimal and target values of > 30 ng/ml may be more appropriate.

The benefits of calcium alone in postmenopausal women are modest. A double-blind, placebo-controlled randomized trial evaluated the effect of two forms of calcium on bone loss in the spine and femoral neck in women who had been postmenopausal for five years or less.<sup>18</sup> After two years, all groups experienced significant decreases in BMD. Moreover, there were no significant differences in bone loss in either of the calcium groups compared with placebo (Figure 3)<sup>18</sup> A meta-analysis showed small positive effect on BMD with calcium supplementation alone. There was a trend towards vertebral fracture reduction. No conclusions could be drawn about non-vertebral fractures.<sup>19</sup> Therefore, antiresorptive therapy in addition to calcium supplementation may be necessary to prevent bone loss in most early postmenopausal women.

Figure 3. Lack of effect of calcium supplementation alone in preventing bone loss in postmenopausal women.<sup>18</sup>



Supplementation with vitamin D3 and calcium has been shown to reduce the risk of hip fractures and other non-vertebral fractures in healthy patients.<sup>19</sup> In a study of 3270 healthy elderly women, participants were randomized to receive tricalcium phosphate (containing 1.2 g of elemental calcium) and 20 micrograms (800 IU) of vitamin D3 or a double placebo.<sup>19</sup> After 18 months of treatment, hip fractures were reduced by 43% (P=0.043) and non-vertebral fractures were reduced by 32% (P=0.015) among women treated with vitamin D3 and calcium. In addition, the bone density of the proximal femur increased 2.7% in the vitamin D3/calcium group and decreased 4.6% in the placebo group (P<0.001).<sup>19</sup>

Another study examined the effect of vitamin D (1200 mg) plus calcium (800 IU cholecalciferol) on the risk of falling. A single intervention with vitamin D plus calcium over a three-month period reduced the risk of falling by 49% compared with calcium alone. Over this short-term intervention, recurrent fallers seem to benefit most by the treatment. The impact of vitamin D on falls might be explained by the observed improvement in musculoskeletal function.<sup>20</sup>

A healthy, well-balanced diet rich in calcium and vitamin D should be encouraged in all patients. Women ages 65 years and older have a 50% reduction in intestinal calcium absorption compared with adolescents. Additionally, the production of vitamin D metabolites, which control the absorption of calcium, is decreased. Thus, adequate intake in this group is imperative.

Postmenopausal women should receive 1500 mg of calcium per day. Dietary analysis indicates that women who do not eat dairy products ingest approximately 500 mg per day from other sources. Non-dairy sources of calcium include canned mackerel and sardines, collard greens, baked or broiled salmon, instant oatmeal, rhubarb, soybeans, almonds, orange juice and broccoli. There are a number oral calcium preparations that can supplement dietary intake. The choice of supplement should be guided by such factors as availability, purity, absorbability, and tolerance. Supplements that list ingredients, such as unrefined oyster shells, bone meal, or dolomite, have the most additives and are not the first choice.

Unfortunately, few food sources contain naturally occurring vitamin D. Eggs, fish oil, vitamin-D fortified milk, butter, salmon, herring, and liver are sources of ergocalciferol vitamin D. Patients at risk for osteoporosis benefit from vitamin D supplementation at 400 IU per day.

## Hormone replacement therapy—weighing the risks

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Until recently, hormone replacement therapy (HRT) was widely accepted as first-line treatment for both the prevention and treatment of osteoporosis. Emerging evidence suggests, however, that although HRT prevents bone loss and decreased bone mass, there is no definitive evidence supporting its use as a treatment for established osteoporosis.<sup>6</sup> In addition, the Women's Health Initiative, a randomized controlled primary prevention trial of HRT in 16,308 postmenopausal women 50 to 79 years, was discontinued after 5.2 years primarily because of an unacceptable incidence of breast cancer in women in the HRT group.<sup>21</sup> In this study, women in the active treatment group received conjugated equine estrogens, 0.625 mg per day and medroxyprogesterone acetate 2.5 mg per day. Although protective for hip fractures and all fractures combined, HRT was associated with coronary heart disease (n=286); breast cancer (n=290); stroke (n=212); and pulmonary embolism (n=101).<sup>21</sup>

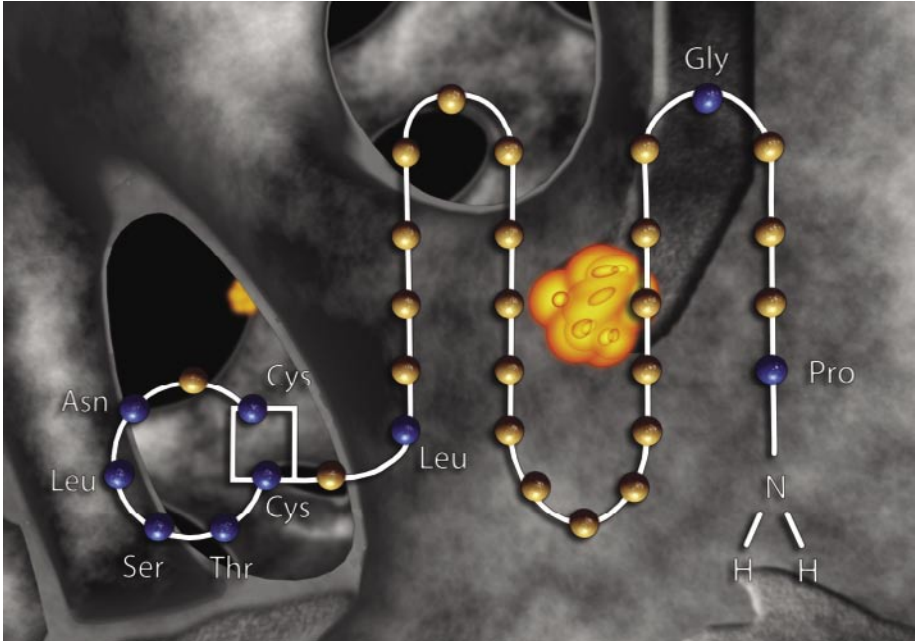
According to the Surgeon General's Report, HRT should only be considered for women at significant risk of osteoporosis who cannot take non-estrogen medications.<sup>5</sup> It has been suggested that there may be some benefit in using HRT in the short-term, then terminating therapy to avoid the adverse outcomes. However, trial results do not support this suggestion. Two randomized studies reported that bone

loss resumes when hormones are discontinued.<sup>22,23</sup> This finding is borne out in long-term observational studies suggesting that even those patients who take HRT in the long term and then terminate therapy do not have a lower fracture risk many years later.<sup>24,25</sup> Interestingly, another study found a higher rate of fractures in patients who discontinued HRT than in those who had never taken it.<sup>26</sup>

In short, clinicians are faced with balancing the positive effects of estrogen without engendering any of the potential adverse effects. Unless there is an overriding need (eg, a high fracture risk patient who cannot tolerate other forms of therapy) it is recommended that HRT be avoided.

## Calcitonin

Calcitonin is a polypeptide hormone produced by the thyroid gland. Normally secreted in response to elevated calcium levels, calcitonin lowers serum calcium levels by decreasing bone resorption and increasing urinary calcium excretion. Calcitonin slows bone loss by directly inhibiting osteoclasts, which have abundant calcitonin receptors.<sup>27</sup> When calcitonin binds to its receptor on osteoclasts, it rapidly inhibits the action of these bone-resorbing cells. Calcitonin does not appear to affect osteoblast activity.<sup>27</sup>



*Calcitonin slows bone loss by directly inhibiting osteoclasts.*

In addition to its effects on bone resorption, calcitonin also seems to have analgesic properties, in part due to the release of endogenous opioids.<sup>27</sup> Therefore, calcitonin may be particularly useful for patients with severe pain from recent compression fractures. Calcitonin may be genetically engineered from human calcitonin or derived from salmon. Because it is broken down in the gastrointestinal (GI) tract, calcitonin cannot be taken orally. Injectable calcitonin is well absorbed, but this method of administration is often inconvenient for patients.<sup>27</sup> Calcitonin nasal spray is an effective and convenient option, although low-grade problems with nasal dryness and irritation can occur.

In the Prevent Recurrence of Osteoporotic Fractures (PROOF) study, 1255 osteoporotic postmenopausal women were treated with nasal calcitonin (100 IU, 200 IU or 400 IU per day) or placebo for up to five years.<sup>27</sup> The percentage change in BMD during five years barely exceeded 1% with nasal calcitonin. The mean changes of lumbar spine BMD were not statistically different from placebo. There was no significant difference in BMD at the hip.

Urinary NTx (cross-linked N-telopeptides of type I collagen) reduction was significant in the 100 IU group at one year and up to three years in the 400 IU group, but not in the 200 IU group, which is the FDA-approved dose.<sup>27</sup>

In the PROOF trial, the only significant reduction in five-year incidence of spine and femur fractures occurred at the 200 IU dose.<sup>27</sup> Notably, the dose at which fracture risk was decreased (200 IU) is not the same dose at which bone turnover was affected.

Nasal calcitonin is indicated for female patients at least five years postmenopausal with low bone mass who cannot tolerate estrogens or in whom estrogens are contraindicated.

## Selective estrogen receptor modulators

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Selective estrogen receptor modulators (SERMs) are the newest class of drugs used for the treatment of osteoporosis. SERMs have different effects on specific estrogen receptors throughout the body.<sup>28</sup> SERMs provide some of the benefits of estrogen (increase in BMD and decrease in lipids) without some of the negative side effects (breast tenderness, menstrual abnormalities, and breast cancer).<sup>29</sup> Newer SERMs have been tailored to provide the specific bone-preserving effects of estrogen. Raloxifene hydrochloride is a SERM that preserves bone density but is not associated with increased risk of breast cancer.<sup>30</sup>



*SERMs mimic the bone preserving and antiresorptive effects of estrogen.*

Raloxifene is the first SERM approved for the prevention and treatment of postmenopausal osteoporosis.

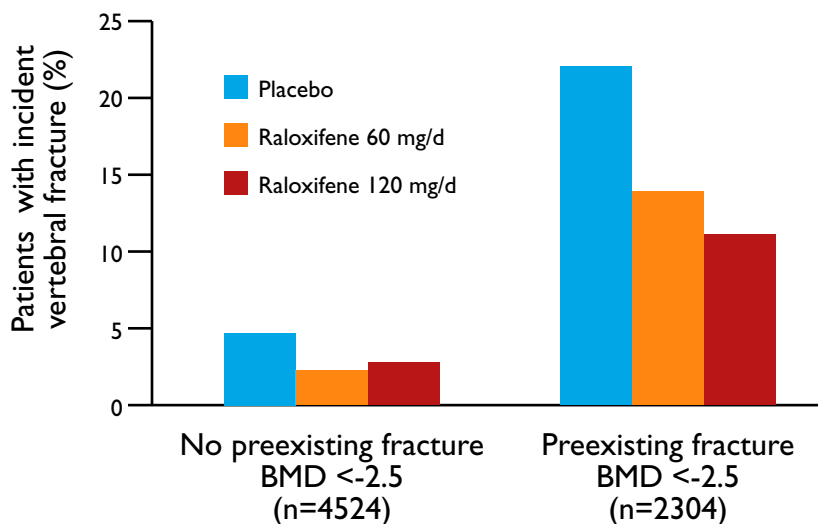
#### **MORE STUDY DESIGN<sup>29</sup>**

- Double-blind, placebo-controlled.
- Evaluated the effect of raloxifene on the risk of vertebral fractures.
- 7705 osteoporotic women (hip or spine T-score < -2.5 and/or prevalent vertebral fracture) were randomized to placebo, 60 mg or 120 mg of raloxifene and received 500 mg supplemental calcium and 400 IU vitamin D daily.

In the Multiple Outcomes of Raloxifene Evaluation (MORE) study, the frequency of vertebral fracture was reduced both in women who did and did not have prevalent fracture (Figure 4).<sup>29</sup> The risk of non-vertebral fracture for raloxifene vs. placebo did not differ significantly (RR, 0.9; 95% CI, 0.8-1.1 for both raloxifene groups combined). Compared with placebo, raloxifene increased bone mineral density in the femoral neck by 2.1 % (60 mg) and 2.4% (120 mg) and in the spine by 2.6% (60 mg) and 2.7% (120 mg) (P<0.001 for all comparisons).<sup>29</sup>

In the MORE trial, there was no difference in the proportion of women reporting non-traumatic, non-spine fractures among those receiving raloxifene (6.3%) vs. placebo (6.8%); RR: 0.92; 95% CI (0.77-1.1).<sup>29</sup> There was also no significant difference in the percentage of women with hip fractures for the group receiving raloxifene vs. placebo.<sup>29</sup>

Figure 4. Positive effect of raloxifene on radiographic vertebral fractures.<sup>29</sup>



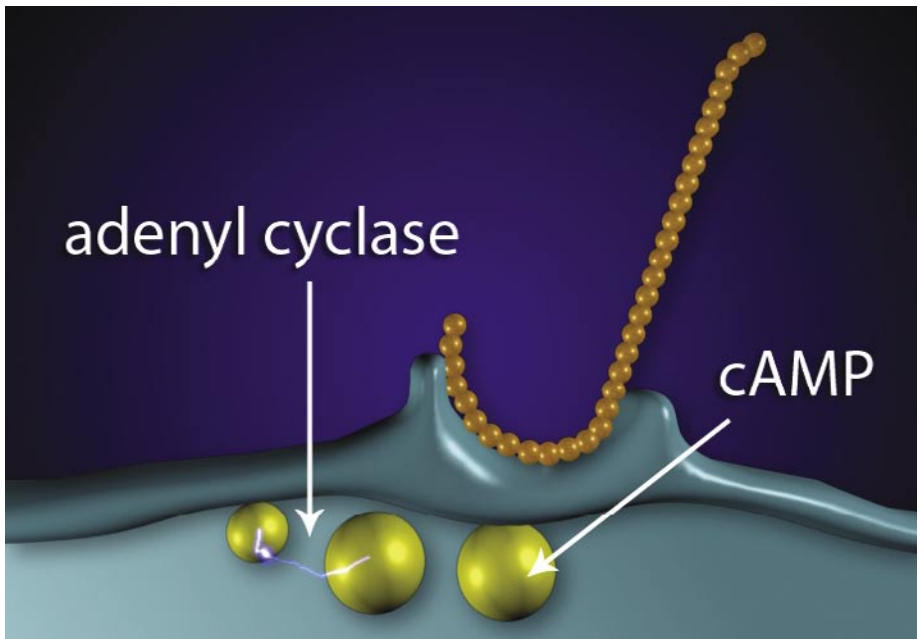
In a meta-analysis of seven placebo-controlled trials, raloxifene was found to reduce vertebral fracture risk by 40% ( $P<0.01$ ).<sup>31</sup> Raloxifene has a modest (8%) and non-significant effect on non-vertebral fracture risk ( $P=0.27$ ). Clinical trials show that raloxifene treatment, compared with placebo, results in a significant improvement in BMD at many sites, including total body, lumbar spine, combined forearm, and combined hip. Raloxifene treatment is associated with some adverse events, including a 46% increase in hot flashes ( $P<0.01$ ) and a 64% increase in leg cramps ( $P=0.15$ ).<sup>31</sup> Overall, this meta-analysis concluded that raloxifene reduces vertebral fractures, but has little effect on non-vertebral fractures.<sup>31</sup>

The overall benefits of raloxifene include improved bone mass, reduction of vertebral fractures, no breast tenderness, bleeding, or spotting, and the potential for reduced risk of breast cancer.<sup>30,31</sup> Raloxifene does not relieve vasomotor symptoms, and may increase hot flashes. In addition, raloxifene decreases low density lipoproteins.<sup>31</sup>

Another SERM, tamoxifen, is not approved for use in osteoporosis. However, clinical trials in breast cancer patients demonstrated that tamoxifen maintains or improves BMD in postmenopausal women but causes bone loss in premenopausal women.<sup>32</sup> Newer SERMs, currently being studied, may offer additional benefits to raloxifene.

## Parathyroid hormone

The classic action of PTH is catabolic to bone by stimulating bone resorption. However, it has been known for many years that intermittent administration of PTH is anabolic, with bone formation being stimulated to a greater extent than bone resorption.



*Teriparatide binds to osteoblasts and increases intracellular production of cAMP by adenylyl cyclase.*

### FPT DESIGN<sup>33</sup>

- Prospective, randomized, double-blind, placebo-controlled.
- Designed to compare the proportion of patients with new vertebral fractures following three years of treatment with 20 mg/day (n=541) or 40 mg/day (n=552) of teriparatide plus calcium and vitamin D compared with calcium and vitamin D alone (n=544).
- Participants were postmenopausal women with osteoporosis who, at study entry, had a minimum of one moderate or two mild nontraumatic vertebral fractures.
  - A mild vertebral fracture was defined as at least 20% decrease in anterior, central, or posterior vertebral height of the average of the adjacent vertebrae.
  - A moderate fracture was defined as at least a 25% decrease in one of these heights.
  - A nontraumatic fracture was defined as not caused by a wound or injury that is severe enough to cause a fracture in otherwise healthy persons.

In the Fracture Prevention Trial (FPT), which examined the effect of human recombinant PTH(1-34) (teriparatide), there was a 65% to 69% reduction in risk of new incident vertebral fracture with 20 µg/mL and 40 µg/mL teriparatide, respectively ( $P<0.001$  for both). There was no evidence of a difference in efficacy between the two doses. Compared with placebo, teriparatide 20 µg/mL and 40 µg/mL reduced the risk of new non-vertebral fragility fractures by 53% and 54%, respectively. Both reductions were statistically significant. Compared with placebo, teriparatide 20 µg/mL and 40 µg/mL also significantly reduced the risk of multiple vertebral fractures, including multiple moderate or severe fractures.

In a sub-group analysis of the FPT trial, treatment with teriparatide was associated with similar reductions in the relative risk of fracture in each subgroup of age (treatment-by-age interaction,  $P=0.558$ ).<sup>34</sup> However, a greater proportion of women assigned to placebo in the older subgroups (65-75 and >75 years) had a new vertebral fracture.<sup>34</sup> The proportion of women who had new vertebral fractures differed significantly among treatment groups in the <65 and 65-75 years groups ( $P<0.001$ ) but not for the >75 years group ( $P=0.054$ ).

The effects of teriparatide on the relative risk for developing new vertebral fractures did not differ significantly ( $P=0.817$  and  $P=0.615$ , respectively) when compared across bone mineral density tertiles. Teriparatide treatment significantly decreased vertebral fracture risk in patients with a vertebral bone mineral density T score <-33 or between -2.1 and -3.3 ( $P<0.001$  and  $P=0.027$ , respectively) and showed a trend toward reduced fracture risk in the group with a T score > -2.1 ( $P=0.115$ ).

As with all osteoporosis treatments, teriparatide is associated with some adverse events. In the FPT trial, teriparatide, compared with placebo, was associated with significantly more cases of elevated serum creatinine, elevated calcium, nausea (40 µg/mL dose only), headache (40 µg/mL dose only), leg cramps (20 µg/mL dose only), and study withdrawal due to an adverse event (40 µg/mL dose only).<sup>33</sup>

Although originally designed to be three years in duration, the FPT of teriparatide was terminated after 19 months due to the finding that the drug caused an increase in the incidence of osteosarcoma in rats. As a result teriparatide was approved with a black box warning and it is contraindicated in patients who, for a variety of reasons, are at increased baseline risk of developing osteosarcoma.

## Bisphosphonates

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Bisphosphonates slow bone loss by increasing bone formation and decreasing bone turnover. They bind to the bone surface and are taken up by osteoclasts, as these cells endeavor to resorb that bone.<sup>5</sup> Bisphosphonates block the pathway that plays a role in the production of essential lipid compound within osteoclasts. This results in accelerated cell death and decreases the ability of osteoclasts to cause bone loss.<sup>5</sup> Alendronate and risedronate, two bisphosphonates currently approved and readily available for osteoporosis treatment and prevention, are available in a once-daily or once-weekly dose. High-dose, once-weekly bisphosphonates are more convenient for patients than once-daily bisphosphonates and therefore may improve compliance. For bisphosphonates to work most effectively, calcium and vitamin D supplements are also needed.

Ibandronate is another FDA-approved bisphosphonate, however, it is not readily available in the US at this time.

## Alendronate

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Both alendronate and risedronate have been studied in randomized, placebo-controlled trials with trial extensions that exceed three years in duration.

### **FIT DESIGN<sup>35</sup>**

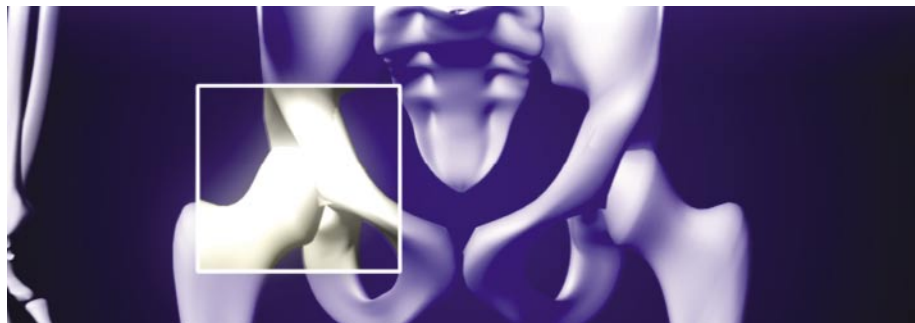
- 2027 women aged 55-81 years with at least one vertebral fracture.
- Participants were randomly assigned to placebo or alendronate and followed for 36 months.

In the Fracture Intervention Trial (FIT) compared with placebo, treatment with alendronate significantly reduced the risk of several types of fracture, including the primary endpoint of new vertebral fractures (Table 3).<sup>35</sup>

Table 3. Alendronate reduces fracture risk in women with existing vertebral fracture.<sup>35</sup>

| FRACTURE TYPE                     | RISK REDUCTION (%) | P VALUE |
|-----------------------------------|--------------------|---------|
| Radiological vertebral            | 48                 | <0.001  |
| Multiple vertebral (radiological) | 87                 | <0.001  |
| Clinical vertebral                | 45                 | 0.003   |
| Any clinical                      | 30                 | <0.001  |
| Nonvertebral                      | 27                 | <0.001  |
| Nonvertebral (osteoporotic)       | 36                 | 0.002   |
| Hip                               | 53                 | 0.005   |
| Wrist                             | 30                 | 0.038   |

The FIT combined analysis included 3658 women ages 55 to 80 years and included women with an existing vertebral fracture or no vertebral fracture. All women had a BMD T score  $<-2.5$  at the femoral neck<sup>36</sup> Following 12 months of therapy, alendronate decreased the incidence of clinical vertebral fractures by 59%. After 18 months of therapy, alendronate decreased the incidence of hip fracture by 63%. After three years of alendronate treatment, there was a significant 51% reduction in fracture risk at the hip. After four years, the risk reduction at the hip was 54%.<sup>36</sup>



*In FIT, alendronate decreased incidence of hip fracture by 63%*

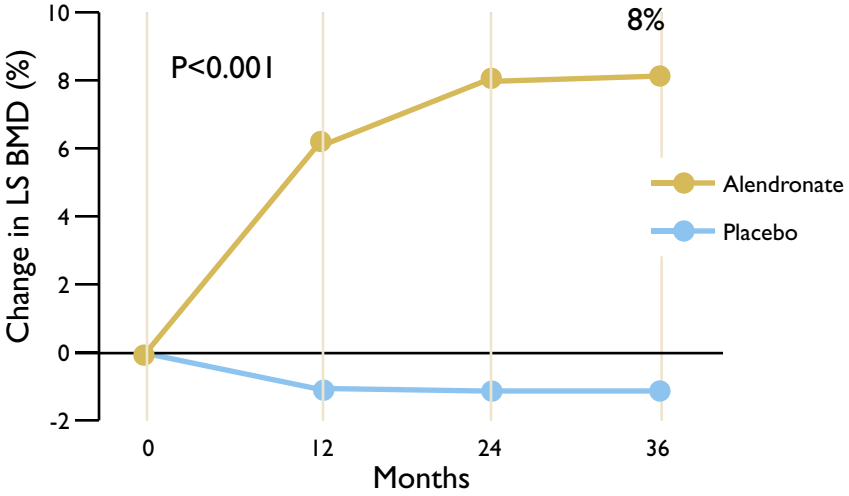
### **ALENDRONATE PHASE III OSTEOPOROSIS TREATMENT STUDY GROUP TRIAL DESIGN<sup>37</sup>**

- 994 women with postmenopausal osteoporosis.
- Participants were randomly assigned to receive placebo or five mg or 10 mg of alendronate daily.
- Approximately 20% of patients were given 20 mg daily for two years followed by five mg for one year. All patients received 500 mg of calcium daily.

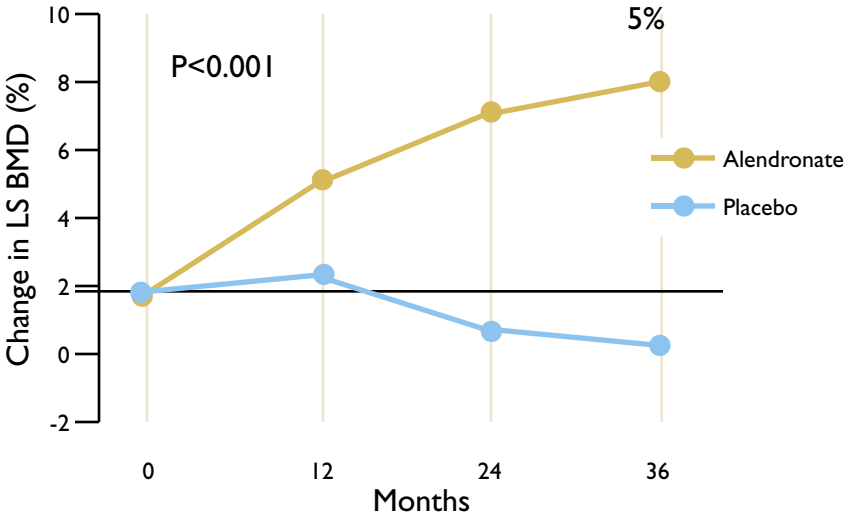
In a study conducted by the Alendronate Phase III Osteoporosis Treatment Study Group, alendronate at 10 mg daily, during a three-year period, demonstrated a graded percent change in lumbar spine BMD exceeding 8% and a graded percent change in BMD at the femoral neck of approximately 5%. By comparison, patients taking placebo lost 1.5% at the femoral neck (Figure 5).<sup>37</sup>

Figure 5. Alendronate improves mean lumbar spine and femoral neck BMD.<sup>37</sup>

### LUMBAR SPINE



### FEMORAL NECK



### VERT STUDY DESIGN<sup>38</sup>

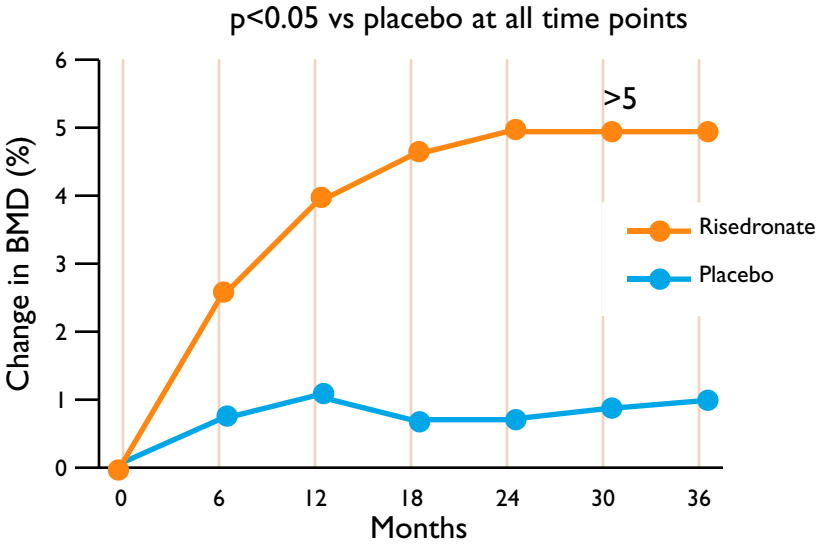
- Double-blind, trial of 2458 postmenopausal women (<85 yrs old) with at least one vertebral fracture.
- Participants were treated with risedronate (2.5 or 5 mg/d) or placebo for three years.

In the Vertebral Efficacy with Risedronate Therapy (VERT) study, risedronate showed a 41% reduction in new vertebral fracture risk and a 39% reduction in non-vertebral fracture risk, compared with placebo.<sup>38</sup> At one year of therapy, vertebral fracture risk was reduced by 65%. It is important to note that the VERT trial used a weaker criteria in defining a new vertebral fracture risk (>15% reduction). The FIT, MORE, and PROOF trials defined new vertebral fracture risk as >20% reduction.

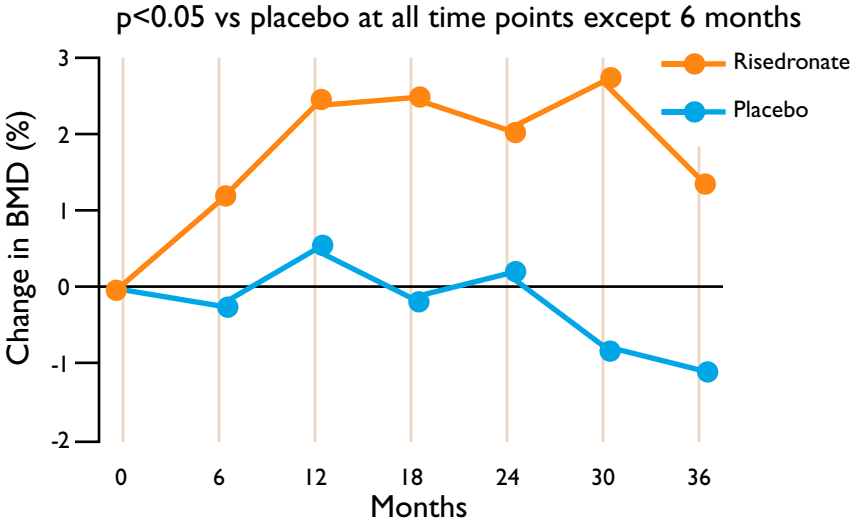
In the VERT trial, patients treated with risedronate had a greater improvement in BMD compared with patients randomized to placebo. The maximum dose studied (risedronate five mg) showed a slightly-greater-than 5% increase in lumbar spine BMD and a 2% increase in femoral neck BMD after three years (Figure 6).<sup>38</sup>

Figure 6. Risedronate at 5 mg increases mean lumbar spine and femoral neck BMD.<sup>38</sup>

### LUMBAR SPINE



### FEMORAL NECK



### HIP STUDY DESIGN<sup>39</sup>

- Assessed the impact of risedronate on hip fracture risk in 9,331 elderly women.
- Two groups were enrolled: one group comprised women ages 70 to 79 years with confirmed osteoporosis (low femoral neck BMD) and >one additional clinical risk factor for hip fracture, the other group comprised women ages 80 years and older who had >one clinical risk factor for hip fracture.
- Patients were treated with oral risedronate (2.5 or 5 mg/d) or placebo for three years
- The primary endpoint was the occurrence of hip fracture.

In the HIP Intervention Program study, there was a 40% reduction in the incidence of hip fractures in osteoporotic women ages 70 to 79 years treated with risedronate five mg/d (RR 0.6, 95% CI 0.4–0.9, P = 0.009).<sup>39</sup> This group included women 70 to 79 years old who had osteoporosis indicated by a T score for bone mineral density at the femoral neck that was more than four standard deviations (SDs) below the mean peak value in the young adult (-4) or lower than -3 plus a nonskeletal risk factor for hip fracture such as poor gait or a propensity to fall.<sup>38</sup> Among women at least 80 years old in HIP, there was no significant reduction in the incidence of hip fracture in the women treated with risedronate five mg/d.<sup>39</sup>

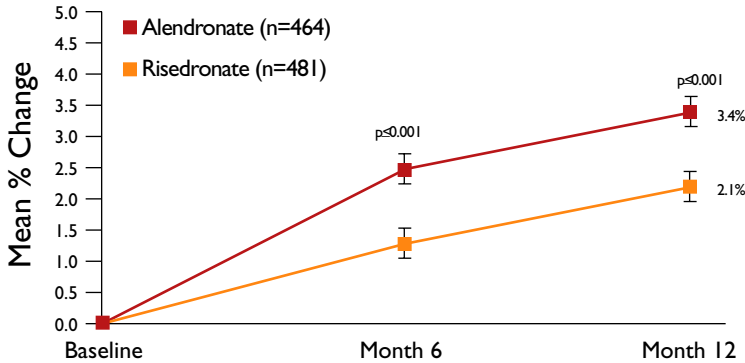
A recent meta-analysis evaluated the findings of eight placebo-controlled trials of risedronate in early postmenopausal women and those with established osteoporosis. Overall, risedronate was shown to reduce vertebral fractures by 36% and non-vertebral fractures by 27%. Compared with placebo, risedronate also showed a greater improvement in BMD.<sup>40</sup>

### FACT DESIGN<sup>41</sup>

- Randomized, double-blind, active-comparator study that evaluated 1053 postmenopausal women at 77 US sites.
- Community-dwelling, ambulatory women who were at least 40 years of age (or at least 25 years of age if surgically menopausal) and postmenopausal for at least six months.
- Patients were required to have osteoporosis, defined as a BMD T-score of at least  $-2.0$  at the hip trochanter, total hip, femoral neck, or lumbar spine.
- Patients were excluded if they were taking or had recently taken any treatments that might influence bone turnover, including bisphosphonates within the year preceding the trial, or for more than two years within the past five years: estrogen or SERMs within the previous six months, or PTH within the previous year.
- As recommended by the prescribing information for alendronate, patients with abnormalities of the esophagus that delay emptying (i.e., stricture, achalasia) were excluded.
- Patients were randomized 1:1 to receive 12 months of therapy with either alendronate 70 mg once weekly plus a risedronate placebo once weekly, or risedronate 35 mg once weekly plus an alendronate placebo once weekly.
- Patients were instructed to take a minimum of 1000 mg of calcium and 400 IU of vitamin D daily.
- A central laboratory evaluated all biochemical data. A quality assurance center evaluated results of DXA data, which were obtained at 0, 6, and 12 months.

The primary objective of the FOSAMAX™ ACTONEL® Comparison Trial (FACT) was to evaluate the mean percent change from baseline in hip trochanter BMD after 12 months of treatment. At month 12, alendronate was 67% more effective than risedronate in increasing BMD at the hip trochanter. The mean percent change from baseline was 3.4% with alendronate and 2.1% with risedronate, representing a treatment difference of 1.4% in favor of alendronate (95% CI: 0.8–1.9%,  $P < 0.001$ ). The effect of alendronate became evident by month six ( $P < 0.001$  vs. risedronate) (Figure 5).<sup>41</sup>

Figure 5. Hip Trochanter BMD<sup>41</sup>



A secondary endpoint evaluated in this study was mean percent change from baseline in biochemical markers of bone turnover. NTx was a measured marker of bone resorption and BSAP was a measured marker of bone formation. At all time points (months 3, 6, and 12), alendronate produced significantly ( $P < 0.001$ ) greater decreases in NTx than did risedronate. Differences in favor of alendronate became evident from as early as month 3.<sup>41</sup>

NTx reductions of 53% (alendronate) and 40% (risedronate) were observed at month 12. This represented a treatment difference of 13% (95% CI: -16.6 to -8.5,  $P < 0.001$  vs. risedronate).<sup>41</sup>

Alendronate also produced significantly ( $P < 0.001$ ) greater decreases in BSAP than risedronate at all time points (months 3, 6, and 12). Together, these results indicate an overall reduction in bone turnover from as early as month 3.

Another secondary endpoint of the study was the percentage of patients with upper GI adverse events at 12 months post-treatment. Upper GI adverse experiences were reported by 22.5% of patients in the alendronate group and 20.1% of patients in the risedronate group. These events resulted in discontinuation in a minority of patients: 2.5% in the alendronate group and 3% in the risedronate group. Overall, there were no significant differences between treatment groups in the upper GI adverse experience profile.<sup>41</sup>

In addition, alendronate showed superiority in other secondary endpoints not discussed here.

## CONCLUSIONS FROM FACT

In this head-to-head study, alendronate 70 mg once weekly produced larger increases in BMD and greater reductions in markers of bone turnover than did risedronate 35 mg once weekly.

The superior antiresorptive effect of alendronate was seen as early as three months, as demonstrated by decreases in markers of bone turnover.

These results are consistent with the results of another clinical trial comparing alendronate and risedronate. In this study, alendronate produced a significantly greater mean BMD increase than did risedronate at six months, and it was maintained at 12 months at the trochanter.<sup>42</sup> Significant reductions in BSAP with alendronate compared with risedronate were maintained over the 12 months of treatment. The incidence of upper GI adverse events causing discontinuation was similar in the two treatment groups.

### USING BISPHOSPHONATES

- Absorption is poor with bisphosphonates; therefore they should be taken alone first thing in the morning on an empty stomach with a full glass of water.
- Patients should not eat anything for at least 30 minutes after taking a bisphosphonate.
- To avoid irritation of the esophagus, patients should stay upright for at least 30 minutes after administration.
- Caution should be used when prescribing bisphosphonates for patients with a history of esophageal narrowing or ulcers or chronic stomach ulcers.
- Bisphosphonates are contraindicated in pregnant woman and patients with impaired kidney function (good kidney function is required to clear the drug from the blood).

## Combination therapy

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Researchers have investigated the benefits of combining various therapies for the treatment of osteoporosis. Despite promising initial data on combination therapy and its beneficial effect on BMD, as outlined below, there are some limitations. These include extremely limited data on effect of combination therapy on fracture risk. In addition, combination therapy is more expensive than monotherapy; it may result in over-suppression of bone turnover and theoretically could compromise bone strength by inhibiting repair of microdamage.

## Parathyroid hormone plus hormone replacement therapy

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In a trial of 52 women who had been on HRT for at least two years prior to enrollment, the efficacy of PTH in combination with established HRT in women with osteoporosis was evaluated.<sup>43</sup> Patients were assigned randomly to remain on HRT alone (n=25) or to remain on HRT and also receive daily subcutaneous PTH(1-34) 400 U (25 mcg) per day (n=27) for three years. The lumbar spine BMD in PTH-treated women rose rapidly up to a peak of about 14% after three years. Total body bone mineral density also increased most rapidly within the first six months with a final increase approaching 4%.<sup>43</sup>

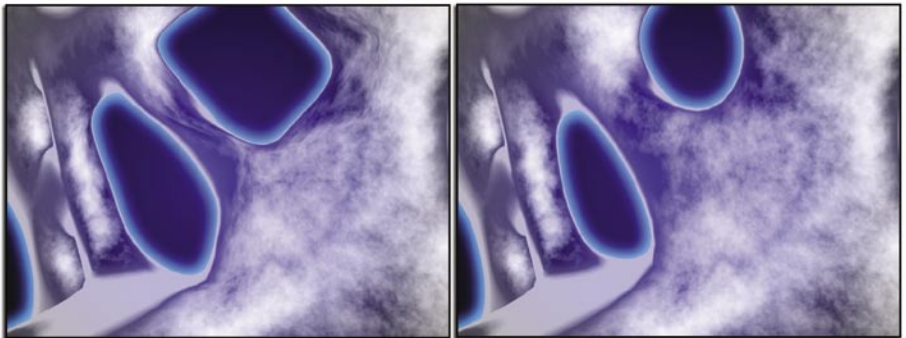
Notably, combination therapy with PTH plus HRT reduced the percentage of women who had vertebral fractures from 37.5% to 8.3% (using a 15% height reduction criterion) and from 25% to 0% (using a 20% height reduction criterion) compared with women receiving HRT alone ( $P<0.02$  for both).<sup>44</sup>

Given the results of this trial, combination therapy with PTH plus HRT appears to be a more effective means of increasing BMD and reducing vertebral fracture compared with HRT alone.

## Raloxifene plus alendronate

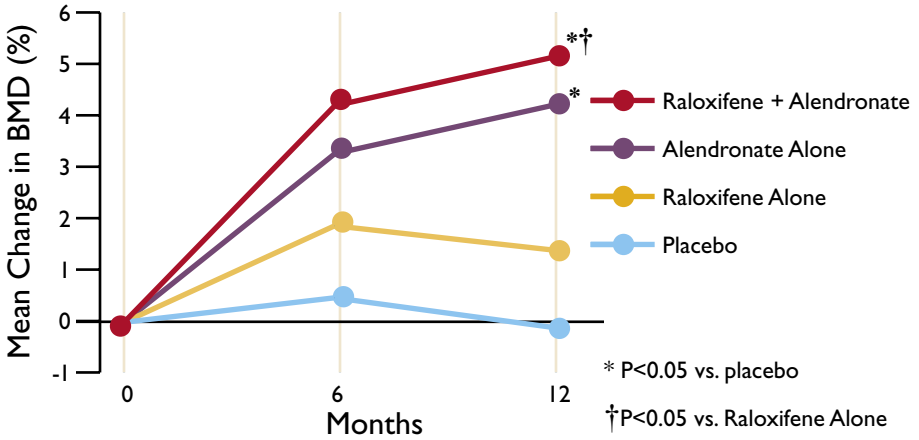
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In a randomized, double-blind, placebo-controlled, clinical trial, 331 postmenopausal women with osteoporosis were randomly assigned to receive raloxifene 60 mg/d, alendronate 10 mg/d, both agents, or neither.<sup>44</sup> The primary endpoint was BMD at 12 months. All changes in BMD and bone markers at 12 months were significantly different between placebo and each of the active treatment groups, and between the raloxifene and raloxifene plus alendronate groups ( $P<0.05$ ) (Figure 9).<sup>44</sup>



*Bisphosphonates increase bone mass and mineralization, thus increasing bone strength and fracture risk.*

Figure 9. Raloxifene plus alendronate—effects on BMD<sup>44</sup>



## Hormone replacement therapy plus alendronate

In a randomized, double-blind, placebo-controlled, clinical trial, 573 postmenopausal women ages 65 years or older were randomly assigned to receive hormone replacement (conjugated equine estrogen, 0.625 mg/d, with or without medroxyprogesterone, 2.5 mg/d), alendronate 10 mg/d, both agents, or neither.<sup>45</sup> All participants received calcium and vitamin D supplements. The primary endpoint was BMD at 3 years. Alendronate was superior to hormone replacement, and combination therapy was superior to either therapy alone. Combination therapy may represent an option for women with more severe disease or for those who have failed to achieve an adequate response to monotherapy.<sup>45</sup>

## Management conclusions

Non-pharmacological interventions include adequate calcium and vitamin D intake, weight-bearing exercise programs, reduction of other risk factors for osteoporotic fractures, and reduction of the risk of falls in the elderly. Calcium and vitamin D supplementation is not sufficient to treat individuals with osteoporosis. Treatment strategies should be individualized to each patient, with choices depending on age, the presence or absence of existing fractures, and BMD measured at the spine and hip.<sup>17</sup>

Results of large placebo controlled trials have shown that alendronate, raloxifene, risedronate, PTH, and nasal calcitonin greatly reduce the risk of vertebral fractures. Furthermore, a large reduction of non-vertebral fractures has been shown for alendronate, risedronate, and PTH. HRT is an option for the prevention of osteoporosis in early postmenopausal women who cannot take non-estrogen agents.<sup>17</sup>

### IN PRACTICE

- Preventing and treating osteoporosis is a partnership between patients and their health care providers.
- The role of primary care physicians is to:
  - promote awareness of the importance of bone health and the factors that influence it;
  - identify those who are at risk of bone disease;
  - suggest lifestyle changes to promote bone health;
  - offer therapeutic interventions to prevent bone loss and fractures.
- Education on the role of nutrition, exercise, and a generally healthy lifestyle should begin in childhood and continue through adolescence and adulthood.
- As people grow older, it is critical they are aware of the importance of maintaining and exceeding (if appropriate), recommended daily doses of both calcium and Vitamin D.
- All people should be encouraged to engage in resistance and weight-bearing exercise.
- Risk factors for bone loss should be assessed in all postmenopausal women and those aged 65 years or older should undergo DXA.
- BMD testing should be considered in men with fragility fractures, patients taking medications that can induce bone loss, and men with multiple risk factors.
- Fall prevention strategies are an integral part of any management program, particularly in the elderly.
- Selection of therapeutic interventions should be tailored to the severity of a patient's bone loss or risk factors and other comorbid conditions.

# OSTEOPOROSIS DICTIONARY

## A

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### **ALENDRONATE**

A bisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. It is used to prevent and treat osteoporosis.

## B

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### **BISPHOSPHONATE**

A class of drugs used to prevent and treat osteoporosis. They slow bone loss by inhibiting osteoclasts.

### **BONE MASS**

The amount of calcium and minerals in the bone .

### **BONE MINERAL DENSITY (BMD)**

Bone mass divided by area.

### **BONE MINERAL DENSITY (BMD) TEST**

A bone mineral density test is an important, non-invasive diagnostic tool that measures the amount of mineral (calcium) in certain bones and is used to estimate the risk of fracture.

## C

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### **CALCITONIN**

A hormone produced in the parafollicular cells of the thyroid that participates in regulating the blood level of calcium and stimulates bone mineralization. A synthetic preparation of the hormone is used in the treatment of certain bone disorders including osteoporosis.

### **CALCIUM**

The most abundant mineral in the body. Calcium is essential for the formation and repair of bone and teeth, but also essential to nerve transmission, muscle contraction, blood clotting and other metabolic activities . Ninety-nine percent of calcium in the body is contained in the bones.

## **CORTICAL BONE**

Cortical bone, also known as compact bone, forms a protective outer shell around every bone in the body and represents nearly 80% of the skeletal mass.

## **CORTICOSTEROIDS**

Steroid hormones produced in the adrenal cortex which influence or control key physiological processes. Excessive levels of corticosteroids, whether endogenous or exogenous, cause rapid and substantial bone loss and increase fracture risk.

## **D**

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### **DUAL-ENERGY X-RAY ABSORPTIMETRY (DXA OR DEXA)**

A diagnostic technique for measuring bone density. Low energy x-rays are passed through the bones to measure the mineral (calcium) content of the bones. The amount of bone loss is calculated from the amount of energy that travels through the bone and is picked up by the detector.

## **E**

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### **ESTROGEN**

A female hormone that promotes the development of secondary sex characteristics. A lack of estrogen in women may accelerate the process of osteoporosis.

### **ESTROGEN REPLACEMENT THERAPY**

Estrogen replacement therapy is the replacement or supplementation of the female hormone, estrogen, to treat the physical, emotional, and health-risk symptoms associated with menopause, including osteoporosis. Estrogen replacement therapy is most commonly used in conjunction with progesterone replacement or supplementation in a therapeutic strategy called hormone replacement therapy. Estrogen and progesterone both reduce the risk of osteoporosis, but hormone replacement therapy is associated with serious health risks.

## **F**

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### **FEMORAL NECK FRACTURES**

Fractures of the short, constricted portion of the thigh bone between the femur head and the trochanters.

## **FRACTURE**

A traumatic injury to the bone in which the continuity of the tissue of the bone is broken. Bone fractures are a common result of osteoporosis.

## **H**

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## **HYDROXYAPATITE**

An inorganic compound composed of calcium, phosphate and hydroxide. It is found in the bones and teeth in a crystallized form that gives these structures rigidity.

## **I**

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## **ISOFLAVONE**

A type of plant estrogen (phytoestrogen) found chiefly in soybeans.

## **K**

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## **KYPHOSIS**

Kyphosis is a curving of the spine that causes a bowing of the back. In adults, kyphosis can be a result of osteoporotic compression fractures. Multiple compression fractures from osteoporosis can be left untreated if there is no neurologic problems or pain, but the osteoporosis needs to be treated to help prevent future fractures. For debilitating deformity or pain, surgery is an option.

## **L**

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## **LOW BONE MASS**

Also referred to as osteopenia. A BMD T-score between  $-1$  and  $-2.5$ .

Low bone mass is a risk factor for osteoporosis and fractures.

Osteoporosis is defined as a T-score less than  $-2.5$

## **N**

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## **NORMAL BONE MASS**

Normal bone density is characterized by a T-score better than  $-1$ .

## O

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### **OOPHORECTORY**

Surgical removal of ovaries resulting in estrogen loss, which is a risk factor for osteoporosis.

### **OSSIFICATION**

The process of forming new bone.

### **OSTEOBLAST**

A cell that makes bone by producing a matrix that then becomes mineralized. Bone mass is maintained by a balance between the activity of osteoblasts that form bone and other cells called osteoclasts that break it down.

### **OSTEOCLAST**

A cell that actively removes old or fatigued bone so that new bone may be replaced by osteoblasts. When osteoclast cells resorb bone faster than the osteoblasts are forming it, then osteoporosis occurs.

### **OSTEOCYTE**

A mature cell found within the bone that helps maintain bone as living tissue.

### **OSTEOGENESIS**

The formation or growth of bone.

**OSTEOPENIA** See *low bone mass*.

### **OSTEOPOROSIS**

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture

## P

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### **PERIPHERAL DUAL ENERGY X-RAY ABSORPTIOMETRY (PDEXA)**

A diagnostic test that measures bone density in distal bones such as the finger, wrist or heel. If results are abnormal, a more specific test, such as a DEXA is required

## PHYTOESTROGENS

Plant derived estrogens that may help reduce the risk of osteoporosis, but data are limited.

## R

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### RALOXIFENE

A selective estrogen receptor modulator (SERM) that helps prevent and treat osteoporosis. It can only be used after menopause. It slows bone loss and slightly increases normal bone growth.

### RESORPTION

The loss of substance or bone by breakdown and assimilation by the action of osteoclasts.

### RISEDRONATE

A bisphosphonate used to prevent and treat osteoporosis in women and may also be used to prevent and treat osteoporosis caused by long-term use of corticosteroids. It inhibits osteoclast-mediated bone resorption.

## S

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### SECONDARY OSTEOPOROSIS

Osteoporosis that is caused by other disease, conditions or drug treatments.

### SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)

A class of drug that acts like estrogen on some tissues, but blocks the effect of estrogen on other tissues. Raloxifene, used to reduce the risk of osteoporosis in menopausal women, is a SERM.

## T

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### TERIPARATIDE

Teriparatide is the amino-terminal portion of human parathyroid hormone (PTH), which is the primary regulator of calcium and phosphate metabolism in bones. Daily injections of teriparatide stimulate new bone formation leading to increased bone mineral density.

## **TRABECULAR BONE**

Lattice-like network of bone spicules located primarily within the vertebral bodies and at the ends of the long bones.

## **T-SCORE**

The results of a bone mineral density test that compares the actual level of bone density to the optimal peak bone density (age 30 in women). It is reported as number of standard deviations below the average. A T-score of greater than -1 is considered normal. A T-score of -1 to -2.5 is considered osteopenia, and a risk for developing osteoporosis. A T-score of less than -2.5 is diagnostic of osteoporosis.

## **U**

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### **ULTRASOUND**

A diagnostic test that is used to measure bone density in the heel using sound waves.

## **V**

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### **VITAMIN D**

A fat-soluble vitamin found in food and also made in the body after exposure to ultraviolet (UV) rays from the sun. Vitamin D is essential for normal bone and tooth development and a key factor in calcium absorption.

## **Z**

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### **Z-SCORE**

The results of a bone mineral density test used to compare results to others of the same age. It is useful to determine if there is something unusual contributing to bone loss. A Z-score of less than -1.5 raises concern of factors other than aging as contributing to bone loss.

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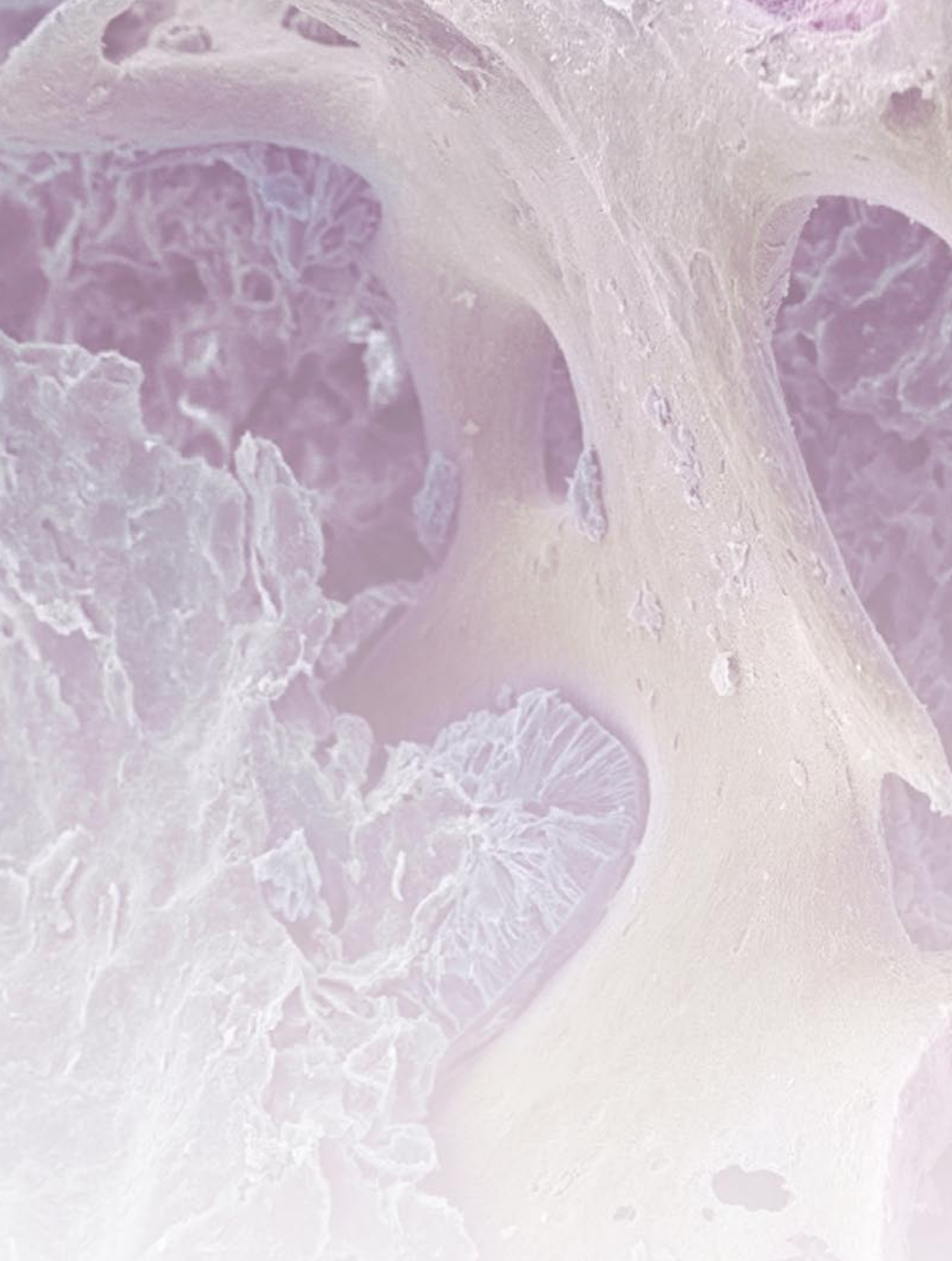
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