Osteoporosis has become an influential disease entity of the 21st century. Its pathophysiology is intricate, and its diagnosis relies heavily on measurement of bone mineral density.

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Osteoporosis affects 1.4 million Canadians, and in 1988, there were 15,000 hip fractures in women and men. It is estimated there will be 28,000 hip fractures in the year 2021, with 12% to 20% of victims dying from related complications. It also is predicted that 32% of women and 17% of men living to the age of 90 will suffer a hip fracture.

In order for osteoporosis to be symptomatic, a fracture must occur. Overall, about one-half of osteoporotic fractures are vertebral, one-quarter are hip fractures, and one-quarter are Colles’ fractures.

The medical press, the lay press and mail boxes continue to be filled with information on osteoporosis. How will this article add to your education on this ubiquitous topic? First of all, the author recommends an Internet site that focuses on guidelines on the investigation, prevention, and treatment of osteoporosis (www.guidelines.gov/index.asp. Search “osteoporosis”). Secondly, this article will highlight and offer an updated or new angle on specific issues on osteoporosis, with the “teaching points” for each.

The objective of this article is to address the following issues: osteoporosis and society; a working pathogenetic understanding of osteoporosis; bone...
Osteoporosis

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mineral density (BMD) and other baseline investigations; non-pharmacological preventative and treatment measures; the role of estrogens and related compounds, androgens, bisphosphonates, and calcitonin in the management of osteoporosis; and glucocorticoid-induced osteoporosis.

Osteoporosis and Society

Osteoporosis is an old disease. In its series on “Images in Clinical Medicine” in 1995, The New England Journal of Medicine, displayed an image of a 45-year-old female skeleton from the early Bronze Age (between 2200 and 1600 BC), whose BMD was deemed osteoporotic when compared with her 14 other female grave companions of a similar age.3

Is osteoporosis primarily a consequence of aging? How many 95 year olds have the bone density of 35 year olds? Why didn’t Osler, in his 1892 Textbook of the Principles and Practice of Medicine, make any index reference to osteoporosis?4 Was it naiveté on his behalf (unlikely), or was it that the average life expectancy for that era denied its inclusion? Over 100 years later, if one examines Harrison’s 1998 edition of Principles of Internal Medicine, seven full-text pages appear on osteoporosis.5 Will we all develop osteoporosis like we all develop osteoarthritis? Can we eradicate osteoporosis? Currently, the answer is “no.” Our reality check weighs in at how society may best manage osteoporosis with its limited resources.

According to 1998 American figures, $13.8 billion was put forward for treatment of osteoporotic related fractures.6 With baby boomers predictably having decreased bone density as they get older, and with the average life expectancy creeping upwards, demographics dictate a corresponding monumental monetary increase for the management of osteoporosis.

As a responsible society, we must look beyond the immediate benefits of new treatments for osteoporosis. Baby boomers who live longer as a result of advances in osteoporotic therapeutics will, nonetheless, still be subject to other age-related diseases, such as ischemic heart disease, diabetes mellitus and Alzheimer’s disease. Therefore, society must be held responsible, both ethically and economically, as to how it delivers advances in the management of osteoporosis to its citizens.

Teaching Points:

1. Osteoporosis is primarily a part of the natural aging process.

D ecreased bone mass can occur because peak bone mass is low, bone resorption is excessive, or bone formation during remodeling is decreased.
2. Society’s approach to osteoporosis must advance with strategic planning.

**A Working Understanding of the Pathogenesis of Osteoporosis**

One accepted definition of osteoporosis encompasses histological terms: “A disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and an increase in fracture risk.”

The different pathogenetic factors involved in osteoporosis weave a complex web. The two specific distinguishing characteristics of osteoporosis—low bone mass and disruption of bony microarchitecture—result from the interplay of numerous factors. Genetic factors, systemic hormones (e.g., calcitonin, parathyroid hormone, vitamin D hormone system, estrogens, androgens, progestins, thyroid hormones, glucocorticoids, growth hormone and insulin-like growth factor), local cytokines (e.g., Interleukins-1 and 6, and tumor necrosis factor-alpha), prostaglandins and local growth factors (e.g., transforming growth factor-beta) all play a role.

Decreased bone mass can occur because peak bone mass is low, bone resorption is excessive, or bone formation during remodeling is decreased. Regarding disturbances in normal microarchitecture, osteoporotic bone has fewer and thinner bony spicules than normal bone, and the horizontal “struts” do not join up to any other structure, resulting in no structural support.

In addition to the abnormal biochemical and visible histological features of osteoporosis, fractures are due to poor posture, decreased muscle strength and the frequency and type of falls.

**Teaching Points:**

1. The litany of potential pathogenetic factors, which may change with time, attests to the complex nature of osteoporosis.

2. The pathogenesis of osteoporosis involves the interplay of basic science, aging and the propensity of patients to fall.

**BMD and Baseline Investigations**

Currently, dual-energy x-ray absorptiometry (DEXA) is the accepted method for measuring BMD. It measures bone density at two sites—the lumbar spine (L1 to L4) and the hip, more specifically, the femoral neck, greater trochanter and Ward’s triangle.

The measurement is compared to two standards: young, sex- and race-matched adults to provide a measure of peak bone mass (T-score), and race-, sex- and age-matched controls (Z-score). For a given BMD, the T-score is the number of standard deviations (SD) below the mean of young adult controls, while the Z-score provides the mean of age-matched controls. Using World Health Organization (WHO) definitions, osteopenia is present when the T-score at either the hip or spine is less than -1.00, whereas osteoporosis is defined as a T-score of at least -2.5, and severe osteoporosis is a T-score below -2.5 with fractures.
Osteoporosis

Teaching Points:
1. Measurement of BMD by DEXA is the cornerstone investigation test in the diagnosis and monitoring of osteoporosis.
2. Other baseline investigations will be dictated by the clinical examination, but there are minimal recommendations.

Current BMD measurement standards relate to women, and consequently, when we use such standards for children and men, there are inherent inaccuracies.

The indications for BMD are by no means absolute, but guidelines put forward by the Osteoporosis Society of Canada are helpful (Table 1).

The presence of spinal osteoarthritis, scoliosis and fractures may lead to inaccuracies in BMD measurements. The frequency of measurements, especially with respect to efficacy of treatment, is not entirely clear, but often, should be carried out every one to two years. Access to BMD measurement centers and waiting times also will influence the frequency of measurement.

The baseline screening investigation is dictated by the patient’s clinical history and physical examination. Minimal testing in most patients includes a complete blood count, erythrocyte sedimentation rate (ESR), calcium, alkaline phosphatase, creatinine, serum protein electrophoresis and thyrotropin (TSH).

### Table 1

**Recommended Indications for Bone Mineral Density Measurements by the Osteoporotic Society of Canada**

1. Menopausal women to aid decision making with respect to hormone replacement therapy (HRT).
2. Hypogonadism in either sex.
3. For monitoring the effectiveness of osteoporosis therapy.
4. Vertebral fractures or radiologic evidence of osteopenia.
5. Primary Hyperparathyroidism.
6. A strong family history of osteoporosis or the presence of other risk factors.
7. Prolonged treatment (greater than three months) with supraphysiologic doses of glucocorticoids (greater than 7.5 mg/day of prednisone or its equivalent).

Adapted from reference 8

Non-Pharmacological Preventative and Treatment Measures

After osteoporosis is diagnosed or there is a decision to attempt to prevent it, non-drug therapies should be discussed with all patients.

It is recommended to put patients on an optimal diet, with adequate levels of calcium and vitamin D, to avoid malnutrition. Post-menopausal women and older men should take 1 g to 1.5 g of elemental calcium in divided doses, and vitamin D should total 800 IU per day.

Patients should perform weight-bearing exercise for at least 30 minutes three times weekly, and this may include walking. Such exercise ben-
efits both premenopausal and post-menopausal women. The beneficial effect on BMD is small in older women, except when exercise is vigorous, and most of the benefit probably results from increased muscular strength. Younger women also should recognize that excessive exercise may lead to amenorrhea and osteoporosis. Adapting the patient’s home environment to prevent falls is also advised.

A further non-pharmacological modality is smoking cessation, as smoking cigarettes accelerates bone loss. Smoking one pack per day throughout adulthood, decreases BMD by 5% to 10%. In post-menopausal women, smoking may negate the beneficial effects of estrogen therapy, as smoking may accelerate the metabolism of estrogen.

Teaching Points:

1. It is imperative that you discuss non-pharmacological treatment measures for the prevention and treatment of osteoporosis with your patients.
2. Attention to a nutritious diet with adequate calcium and vitamin D, weight-bearing exercise and smoking cessation are all important non-pharmacological treatment measures.

The Use of Estrogens and Related Compounds

Simply stated, estrogen inhibits bone resorption, therefore, following menopause, there is increased bone resorption and rapid bone loss, which slows with time after menopause.

Barring contraindication, estrogen is the treatment of choice to prevent osteoporosis in perimenopausal women. Established osteoporosis in this group of patients may be treated with estrogen or alendronate, a bisphosphonate. Women wishing for cardiovascular, metabolic, or symptomatic benefits of estrogen are likely to choose estrogen, and those women with contraindications, such as thromboembolic disease and concern about possible breast cancer, are more likely to take alendronate.

Using 0.625 mg of conjugated estrogens decreases bone loss and the risk of fracture, whereas transdermal estrogen has similar effects on bone, but does not have the same beneficial effects on serum lipid values as oral estrogen.

It is obligatory for women with an intact uterus to be prescribed intermittent or continuous progestin therapy as a preventative measure for endometrial hyperplasia and cancer.

Raloxifene, a tissue selective estrogen receptor modulator (SERM), has been approved for the prevention and treatment of osteoporosis. Studies have shown that it increases BMD and reduces low-density lipoprotein (LDL) cholesterol concentration.
It is recommended to put patients on an optimal diet, with adequate levels of calcium and vitamin D, to avoid malnutrition. Post-menopausal women and older men should take 1 g to 1.5 g of elemental calcium in divided doses, and vitamin D should total 800 IU per day.

but not to the same degree as estrogen. To its advantage, raloxifene does not stimulate endometrial hyperplasia or vaginal bleeding, and may help prevent the development of breast cancer.15

Teaching Points:
1. Estrogen replacement remains a cornerstone therapy for a large number of perimenopausal women for both the prevention and the treatment of established osteoporosis.
2. Raloxifene, a tissue SERM, although less effective than estrogen, has been approved for prevention and treatment of osteoporosis. It does not adversely affect the uterus and may help to prevent breast cancer.

The Use of Androgens
A deficiency in androgen results in increased bone turnover, similar to what estrogen loss causes in women. In one study, testosterone replacement resulted in an average increase of 39% in the first year of 72 hypogonadal men. The increase was greatest in those men whose bone density was lowest at baseline.16

There is no evidence, however, for improvement
in bone density when testosterone is given to eugonadal males.

**Teaching Points:**
1. Androgen replacement is an effective therapy for osteoporosis in hypogonadal males.
2. Androgens have no role in the treatment of osteoporosis for eugonadal males.

**The Role of Bisphosphonates**

Bisphosphonates are stable analogues of pyrophosphate, and through its net effect on osteoclasts or their precursors, decreases bone resorption.

Etidronate, the longest studied bisphosphonate, given in cycles of 400 mg per day followed by 11 weeks of supplemental calcium per day, is approved for the prevention of post-menopausal osteoporosis.17

Alendronate, a more potent bisphosphonate, has been approved at a dose of 10 mg per day in the treatment of established osteoporosis in post-menopausal women and is a very reasonable alternative for patients who are unable to take estrogen. At 5 mg per day, it has been approved for the prevention of osteoporosis.18

More recently, risedronate (5 mg per day) has been found to be effective in reducing the risk of clinical fractures in women with post-menopausal osteoporosis.19

Etidronate is the least expensive of the three options, but it is the least potent and there are concerns about its long-term effects on bone. Both alendronate and risedronate are more expensive. Alendronate has the added concern of possibly causing pill-induced esophagitis, requiring the patient to be upright when taking it one-half hour before breakfast with a full glass of water.

**Teaching Points:**
1. Alendronate is a reasonable alternative to estrogen in the prevention and treatment of post-menopausal osteoporosis.
2. Choosing which bisphosphonate to use should be based on a function of potency, potential adverse effects, cost and patient convenience.

**Calcitonin Usage**

On a practical level, calcitonin, which rapidly inhibits the action of osteoclasts, used intranasally at 200 IU per day, would be the third choice in the treatment of osteoporosis, after considering the use of estrogens and bisphosphonates. The Prevent Recurrence of Osteoporotic Fractures (PROOF) study showed that salmon calcitonin reduces vertebral fractures by 36% in women who have experi-
enced one to five previous fractures. Subcutaneous calcitonin given in doses up to 100 IU daily increases BMD and may be used as first-line therapy in patients who have substantial pain from an acute osteoporotic fracture. Because of its expense and the route of delivery, subcutaneous calcitonin is seldom used as a means of prevention.

**Teaching Points:**
1. Intranasal calcitonin would be the third choice for treatment of post-menopausal osteoporosis, following estrogens and bisphosphonates.
2. Subcutaneous calcitonin may be utilized for very painful acute osteoporotic fractures.

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**Corticosteroid-Induced Osteoporosis**

Glucocorticoids decrease intestinal calcium absorption and increase urinary calcium excretion. Calcium supplementation of 1 g per day, and vitamin D, 400 to 800 IU/day have been shown to attenuate the bone loss in patients on glucocorticoids.

As glucocorticoids reduce the production of sex steroids, the use of estrogens in females and testosterone in hypogonadal males on glucocorticoids is recommended.

The bisphosphonates, alendronate, etidronate, and risedronate all have literature support for their usage in glucocorticoid-induced osteoporosis. This may relate to the prevention of osteocyte and...
osteoblast apoptosis.

Similarly, calcitonin, administered intranasally or subcutaneously, may be used in the treatment of glucocorticoid-induced osteoporosis.28,29

Unless a contraindication exists, calcium and vitamin D would be advisable for patients on prolonged corticosteroids, and the use of more aggressive therapies will relate to the initial BMD scores, changes in BMD scores and the previous occurrence of osteoporotic fracture(s).

Teaching Points:
1. The treatment and prevention of glucocorticoid-induced osteoporosis includes calcium and vitamin D supplementation.

2. More aggressive therapies in the way of estrogens, androgen, bisphosphonates and calcitonin, will be used, depending on the initial BMD scores, changes in BMD and a history of previous osteoporotic fractures.

Summary
Osteoporosis will become an influential disease entity of the 21st century, primarily due to the prolongation of life expectancy. Its pathophysiology is intricate, owing to the number of potential pathogenetic-related factors. Its diagnosis relies heavily on measurement of BMD. Treatments available include calcium, vitamin D, estrogens, androgens, bisphosphonates.
nates, calcitonin and SERM. Given limited societal resources, our future endeavors for the management of osteoporosis, must be made with strategic, accountable planning.

References