Updated Recommendations for the Diagnosis and Management of Osteoporosis: A Local Perspective

The Osteoporosis Working Group
King Faisal Specialist Hospital and Research Centre

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Postmenopausal osteoporosis and osteoporosis in elderly men are major health problems, with a significant medical and economic burden. Although osteopenia and osteoporosis are more common locally than in the West, fracture rates are generally less than in Western countries. Vitamin D deficiency is common in the region and contributes adversely to bone health. Vitamin D deficiency should be suspected and treated in all subjects with osteopenia or osteoporosis. The use of risk factors to determine fracture risk has been adopted by the World Health Organization and many international societies. Absolute fracture risk methodology improves the use of resources by targeting subjects at higher risk of fractures for screening and management. The King Faisal Specialist Hospital Osteoporosis Working Group recommends screening for women 65 years and older and for men 70 years and older. Younger subjects with clinical risk factors and persons with clinical evidence of osteoporosis or diseases leading to osteoporosis should also be screened. These guidelines provide recommendations for treatment for postmenopausal women and men older than 50 years presenting with osteoporotic fractures for persons having osteoporosis—after excluding secondary causes—or for persons having low bone mass and a high risk for fracture. The Working Group has suggested an algorithm to use at King Faisal Specialist Hospital that is based on the availability, cost, and level of evidence of various therapeutic modalities. Adequate calcium and vitamin D supplement are recommended for all. Weekly alendronate (in the absence of contraindications) is recommended as first-line therapy. Alternatives to alendronate are raloxifene or strontium ranelate. Second-line therapies are zoledronic acid intravenously once yearly, when oral therapy is not feasible or complicated by side effects, or teriparatide in established osteoporosis with fractures.

The Osteoporosis Working Group of King Faisal Specialist Hospital and Research Centre (KFSHRC) met on a number of occasions, to review and update the previous recommendations and guidelines for the diagnosis and management of osteoporosis. The Osteoporosis Working Group realizes that since the publication of the previous recommendations in 2004,1 numerous developments have occurred in the diagnostic strategies and in the management of this common health problem. It also realizes the importance of taking local data into account—whenever possible—when making recommendations for practicing physicians in a certain region. Therefore, the members of the Osteoporosis Working Group reviewed and discussed extensive data related to local osteoporosis prevalence and fracture rates, local refer-
ences for bone mineral density (BMD) measurements, the relationship of vitamin D to bone density and osteopenia, fracture risk factors and a recently developed absolute fracture risk estimate tool (FRAX), newer international guidelines that incorporate the new risk factor tool, studies evaluating the efficacy of available pharmacological therapies, newer therapies, and many other topics related to this subject.

Postmenopausal osteoporosis continues to be an important subject for clinicians and epidemiologists, as the incidence of osteoporotic fractures continues to increase and the burden of such fractures on the health economy is expected to rise to astonishing figures. In Asia, the projected number of hip fractures is 3 million in the year 2050. The price of prevention and treatment could also be high. Therefore, recommendations and guidelines for detection, screening, prevention and management of osteoporosis are obviously needed.

What is new in this report?

• A review of local data, especially in relation to population specific BMD values and the correlation of BMD and risk factors to fracture risk.

• An emphasis on the role of vitamin D deficiency and the need for correction.

• A re-emphasis on the role of clinical risk factors in choosing patients for treatment.

• A review of new international guidelines.

• A review of newer therapies.

• Pre-menopausal, adolescence and post-transplant osteoporosis in addition to osteoporosis in chronic renal failure patients, are addressed.

Definition

Osteoporosis is a progressive, systemic skeletal disorder characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. A fragility fracture is one that occurs as a result of either an injury that is insufficient to fracture normal bone, or no identifiable trauma. Postmenopausal osteoporosis is a function of bone mass achieved at maturity and subsequent bone loss that is accentuated in the early postmenopausal period, and is influenced by certain risk factors.

Previously emphasis was on the mineral content and bone mass (as measured by BMD), whereas the current understanding of osteoporosis puts an equal importance on bone quality and the architecture of the bone that includes, among others, the intrinsic properties of the bone represented by the collagen content and mineralization, and the micro- and macro-architecture of the bone represented by the porosity of cortical bone and the thickness and connectivity of trabeculae. Other mechanical factors may also play a role in the tendency of a long bone to fracture. At this time, however, BMD remains the best available clinical tool in determining bone strength.

The Burden of Osteoporosis In The Region

Today, osteoporosis is a major public health problem that has both a medical and economic impact especially in developed countries. Fractures caused by either osteoporosis or low bone mass can lead to chronic pain, disability and even death, as well as psychological symptoms, including depression. Each year broken bones due to low bone mass or osteoporosis cause over 432,000 hospital admissions, almost 2.5 million medical office visits, and about 180,000 nursing home admissions in the USA.

The osteoporosis problem will soon be of greater importance in developing countries since there is an increase in life expectancy. According to WHO estimates, hip fractures will increase from about 600,000 in 1990 to over 3 million in Asia by year 2020.

Regional Bone Mineral Density Data

Osteopenia and osteoporosis are more common in our local population than in Western countries. In a study of 483 postmenopausal Saudi women 52-62 years of age, Al Desouki found the rate of osteopenia and osteoporosis to be 34% and 24%, respectively. In a study by Al Ghannam et al of 321 healthy Saudi women, the prevalence of osteoporosis was 1.0%, 5.6%, and 28% for age groups 31-40 years, 41-50 years, and >50 years.
In the same study, the prevalence of osteopenia in the respective age groups was 18%, 18.4%, and 38% (Figure 1). Severe vitamin D deficiency was present in 52% of the subjects. BMD in healthy Saudi females was significantly lower than in their counterparts in the United States.

In an effort to create a local BMD reference range, studies were undertaken in different regional countries and mainly in female populations. Most studies found lower BMD than the standard established for the US/European reference data, except the Kuwait study, where the BMD reference range was similar. In Saudi Arabia, Ardawi et al studied a group of 1980 Saudi males and females aged 20 to 79 years. The prevalence of osteoporosis in women was 44.5% using the manufacturer’s reference values compared to only 28.2% when the Saudi reference values were used. On the other hand, more Saudi men were diagnosed with osteoporosis when local reference values were used (Table 1). These studies suggest that the age-related reference data are different in local populations from that used previously by manufacturers of bone densitometers. We therefore recommend the use of the Saudi reference range in BMD studies of Saudi patients in Saudi Arabia.

Local Fracture Data

Local and regional information about osteoporosis and fracture rates is sparse. In a study from Lebanon, Baddourah et al found the lifetime risk for all fractures to be 9.3% in males, and 16.7% in females. This rate is higher than other Asian countries, but less than Europe. Based on a study of Saudi patients >40 years of age who were admitted to local acute care hospitals in Riyadh with proximal femur fractures, Al-Nuaim et al estimated the incidence of proximal femur fractures per 100 000 population as shown in Table 2. These data indicate lower fracture rates than what has been reported from the West. This might be related to genetic factors that may influence bone quality, or more likely cultural and lifestyle differences. Unfortunately, there is no real fracture registry in most regional countries.

The Role of Vitamin D Deficiency

An acceptable international definition of vitamin D deficiency is a value below 50 nmol/L (20 ng/mL). Vitamin D insufficiency is defined as a value of 50-70 nmol/L and a desirable level is above 70 nmol/L. Local studies are needed to verify these values. Hypovitaminosis D is highly prevalent in the regional countries. Several studies showed widespread vitamin

### Table 1. Prevalence of osteopenia and osteoporosis in Saudi population (>50 years) and in US/European population (from reference 14, with permission).

|                | Women |          | Men |          |
|----------------|-------|----------|-----|----------|
|                | US/European reference | Saudi reference | US/European reference | Saudi reference |
| Spine L2-L4    |       |          |     |          |
| Osteopenia     | 39.1  | 42.2     | 32.8| 19.1     |
| Osteoporosis   | 47.7  | 30.5     | 38.3| 49.6     |
| Femoral neck (total) |       |          |     |          |
| Osteopenia     | 57    | 58.6     | 32.3| 56.7     |
| Osteoporosis   | 7.8   | 4.7      | 6.3 | 1.2      |
| Either spine or femur |       |          |     |          |
| Osteopenia     | 41.4  | 43.4     | 46.5| 54.1     |
| Osteoporosis   | 44.5  | 28.2     | 33.2| 37.8     |

Data are percentages.

### Table 2. Proximal femur annual fracture rates per 100 000 population in Saudi subjects seen in Riyadh region (from Nuaim et al with permission).

| Age group (years) | Female | Male |
|-------------------|--------|------|
| 40-49             | 4.5    | 7    |
| 50-59             | 14.6   | 22   |
| 60-69             | 79     | 36   |
| >70               | 394    | 251  |

Values are rates per 100 000 population.
D deficiency. In one study from Lebanon,\textsuperscript{17} 72.8% of the population was affected by vitamin D insufficiency (defined by a 25(OH)D value below 15 ng/mL or 37 nmol/L), with women being at higher risk than men (83.9% vs. 48.5%). Moreover, inadequate vitamin D intake, urban dwelling, veil wearing and high parity were predictors of low vitamin D in the same study. Another study in schoolchildren 10 to 16 years old showed that 52% of the children were vitamin D insufficient (below 20 ng/mL or 50 nmol/L). The proportion of vitamin D insufficiency was 65% in the winter and 40% at the end of the summer. Girls, especially those with a lower (socio-economic status) were at particular risk.\textsuperscript{18} Studies from Saudi Arabia confirmed the widespread vitamin D deficiency among different groups of the population. Fonesca et al found a normal range of vitamin D levels only in 3 of 31 relatively healthy Saudi women with median level of 6 ng/mL or 15 nmol/L. In this study the low level of vitamin D correlated with urban dwelling and low sun exposure.

In 100 Saudi mothers and their newborns, Taha et al found that 59 mothers and 70 newborns had levels below 10 ng/mL or 25 nmol/L.\textsuperscript{19,20} These and other studies emphasize the need for urgent measures such as vitamin D supplementation in some food items like milk. The major causes of vitamin D deficiency in the local population are most probably low intake and inadequate supplements in addition to low sun exposure.\textsuperscript{21,22} Another possible contributing cause may be related to accelerated metabolism of vitamin D seen in certain ethnic groups.\textsuperscript{23}

The effect of vitamin D on bone health has been well established. Bone density in a large population of postmenopausal women with osteoporosis correlated inversely with vitamin D levels.\textsuperscript{24} It has also been shown that lower vitamin D levels may contribute to the frequently encountered, severe bone manifestations, seen with primary hyperparathyroidism in Saudi Arabia and other countries with widespread vitamin D deficiency.\textsuperscript{25} Vitamin D deficiency should therefore be suspected and adequately treated in all patients with osteopenia and osteoporosis in our region. In severe cases of vitamin D deficiency, large loading doses of a few hundred thousand units of cholecalciferol or ergocalciferol are usually given by IM route (200 000-300 000 units IM bolus) or preferably by oral route at intervals (50 000 weekly for a few weeks). Maintenance doses higher than the usually recommended dose of 400 units daily may be needed (800-1000 units daily). Malabsorption such as in celiac disease can be found even without frank GI symptoms and should be suspected and ruled out in unexplained severe cases.

### Evaluation/Diagnosis

Optimal evaluation consists of establishing the diagnosis of osteoporosis on the basis of bone mass assessment, establishing the fracture risk, and determining the need for therapy. Bone strength is related to the density and quality of bone. There is at present no accurate measure for bone quality. BMD is considered a surrogate measure of bone strength. Dual-energy X-ray absorptiometry (DXA) is the preferred technique to measure BMD, and is the technique used at most centers. Quantitative ultrasound is useful for screening for osteoporosis.

The hip is the preferred site for BMD measurement due to the high predictive value of hip BMD for fracture risk, particularly in the elderly.\textsuperscript{26} BMD measurement at the spine predicts spine fracture better than measurements at other sites. However, spine changes may affect BMD measurement. The World Health Organization (WHO) has established the following operational definition for osteoporosis based on BMD as measured by DXA, commonly expressed as a T-score (Table 3).

A history and a physical examination to evaluate fracture risk should include assessment for loss of height and change in posture. Laboratory evaluation for secondary causes of osteoporosis should be considered when osteoporosis is diagnosed. Serum calcium, phosphorus, alkaline phosphatase, creatinine, vitamin D, complete blood count and thyroid stimulating hormone (TSH) levels are usually sufficient baseline tests.

### Table 3. World Health Organization definition of osteoporosis.

| Definition          | Criteria                                      |
|---------------------|-----------------------------------------------|
| Normal              | BMD within -1 SD of reference mean for young adults |
| Low bone mass (osteopenia) | BMD within -1.0 and -2.5 SD lower than reference mean for young adults |
| Osteoporosis        | BMD less than -2.5 SD lower than reference mean for young adults |
| Severe              | Osteoporosis as defined above with one or more fragility fractures |

BMD= bone mineral density, SD= standard deviation
Further laboratory tests can be done as clinically appropriate, such as parathyroid hormone level, urine free cortisol, liver function tests, or serum immune electrophoresis. Biochemical indices of skeletal turnover could potentially be helpful in the diagnosis and monitoring of therapy. However, as their role has not been fully elucidated, they are not yet recommended in routine clinical management. The drop of bone resorption markers in response to antiresorptive therapy occurs before a significant change in BMD. This may explain the decrease in fracture rates seen early with such therapy, before changes in BMD.27

Using Risk Factors in Selecting Patients for Diagnosis and Therapy: The Fracture Risk Assessment Tool

The osteoporosis working group has previously advocated the use of risk factors in selecting patients for diagnostic tests and for treatment of osteoporosis. In their previously published recommendations, a fracture index tool was suggested using a few important and easily assessed risk factors.1,28 The argument made by the group was that a mere BMD assessment is likely to result in overtreatment in a local population, with evidence of lower BMD values but fewer fractures than in a Western population.

The concept of using risk factors to determine those at higher fracture risk has recently been adopted by the WHO and many international societies. A group of international experts, under a project by the WHO, has developed a tool to assess the absolute risk for fracture based on known risk factors. These estimates were based on different ethnic groups and populations across the world.29

Absolute fracture risk methodology provides a markedly improved method to assure that people with the highest fracture risk get treated. In addition, absolute fracture risk calculations help to resolve many of the questions about management for people with low bone mass (osteopenia). With the Fracture Risk Assessment (FRAX) tool, these individuals and their clinicians have information from absolute fracture risk methodology to determine when it is medically appropriate to treat and when it is not necessary to treat based on the likelihood of fracture in such patient.

The 10 risk factors used in the FRAX are:

1. Age
2. Sex
3. Low BMI
4. Previous low trauma fracture
5. Parental history of hip fracture
6. Ever steroid exposure
7. Secondary causes of osteoporosis (rheumatoid arthritis)
8. Current cigarette smoking
9. High alcohol intake (>3 units/day)
10. Femoral neck BMD

For the FRAX estimate to work, a threshold for treatment based on the absolute risk has to be adopted in each population, country or region.30 The threshold at which treatment is recommended would have to be decided based on the health economics of preventing fracture in each population. This in turn is decided by the fracture rates and the cost-effectiveness of treatment to prevent hip or other major fractures and the priorities of the health care in that population. For the US this was estimated to be a 10-year risk of 3% for hip fractures and 20% for other fractures. A risk higher than 3% for hip fracture based on the FRAX would justify treatment in an osteoporotic or even osteopenic subject in the US.30

The pitfalls for the use of FRAX in our local population are:

- The database for the FRAX does not include our region; such local databases are essentially lacking.
- The tool was not verified in local studies.
- Some of the risk factors included are not well defined such as the “ever use of steroids”
- The risk for falling due to muscle weakness or visual impairment is not included as a risk factor, though was found to be quite important by other studies.

Nevertheless, the use of risk factors in choosing high risk population for further diagnostic tests and management is extremely important for cost effective management in our region.

Using Risk Factors in the Local Population

One important issue is whether generally used risk factors for osteoporosis or fractures are valid for a specific population. There are very few studies done in the region to address this question. One of these studies was performed in Turkey, to assess the risk variables for osteoporosis. The study was conducted on 126 postmenopausal healthy women as a control group and 225 postmenopausal osteoporotic women. The study suggested that low levels of dietary calcium intake, physical activity, education, and a longer duration of menopause are independent predictors of the risk of low bone density in that population.31 In another study carried out in
Qatar on healthy females age 20 to 70 years, risk factors for osteoporosis were not different from known factors in Western studies, such as female sex, age, early menopause and excessive smoking. However, the study suggested other locally important risk factors like a high number of pregnancies, prolonged lactation and vitamin D deficiency.\textsuperscript{32}

The Correlation of BMD to Fractures and Use of Local versus International Databases for BMD and Risk Factors

The only correlation study we are aware of for BMD versus fractures in the region was recently published.\textsuperscript{33} The study aimed at estimating the prevalence of vertebral fractures in the Lebanese elderly, determining the BMD-fracture relationship, and assessing the effect of database selection on osteoporosis prevalence and fracture risk assessment. The prevalence of vertebral fractures was estimated at 19.9\% in women and at 12.0\% in men. The prevalence of osteoporosis by DXA using total hip was 33.0\% in women and 22.7\% in men. The NHANES database (The US National Health and Nutritional Examination Survey) provided a higher sensitivity for vertebral fracture than a local population-specific database. The relative risk of vertebral fracture per one standard deviation decrease in BMD remained unchanged across the two databases. This would support the notion that the use of an international database of risk factors in predicting fractures in a local population may be valid. However, this is not verified in the Gulf region.

Screening for Osteoporosis in Postmenopausal Women and Elderly Men

Some international guidelines for osteoporosis screening recommend BMD testing for all women age 65 years or older, and for postmenopausal women under age 65 years (especially 60-64 years) who have one or more additional high-risk factors for osteoporosis.\textsuperscript{36,34} More liberal recommendations were made by other societies. However, as BMD is generally lower in Saudi women compared to their Western counterparts, they may develop osteoporosis and fractures at an earlier age. It is also relevant that physical activity and therefore the risk of falling may be less in local females older than 65 years due to different cultural habits. Thus, it is reasonable to start screening postmenopausal Saudi women at an earlier age than that recommended for Western women. We stress that BMD measurement should only be done if it will influence the management decision.

The KFSH task force has found that the recent

### Major Recommendation to Clinicians (From the NOF 2008 Clinician’s Guide)

For postmenopausal women and men age 50 and older:

- Counsel on the risk of osteoporosis and related fractures.
- Check for secondary causes.
- Advise on adequate amounts of calcium (at least 1200 mg/d, including supplements if necessary) and vitamin D (800 to 1000 IU per day of vitamin D3 for individuals at risk of insufficiency).
- Recommend regular weight-bearing and muscle-strengthening exercise to reduce the risk of falls and fractures.
- Advise avoidance of tobacco smoking and excessive alcohol intake.
- In women age 65 and older and men age 70 and older recommend BMD testing.
- In postmenopausal women and men age 50-70, recommend BMD testing when you have concern based on their risk factor profile.
- Recommend BMD testing to those who have suffered a fracture, to determine degree of disease severity.
- Initiate treatment in those with hip or vertebral (clinical or morphometric) fractures.
- Initiate therapy in those with BMD T-scores < -2.5 at the femoral neck, total hip, or spine by DXA, after appropriate evaluation.
- Initiate treatment in postmenopausal women and in men age 50 and older with low bone mass (T-score -1 to -2.5, osteopenia) at the femoral neck, total hip, or spine and 10-year hip fracture probability = 3\% or a 10-yr all major osteoporosis-related fracture probability of = 20\% based on the US-adapted WHO absolute fracture risk model.
- BMD testing performed in DXA centers using accepted quality assurance measures is appropriate for monitoring bone loss (recommendation every 2 years). For patients on pharmacotherapy, it is typically performed two years after initiating therapy and at 2-year intervals thereafter.
National Osteoporosis Foundation (NOF) revised guidelines for screening to be useful. These guidelines recommend screening for the following subjects:

- Women 65 and older and men 70 and older
- Postmenopausal women younger than 65 and men 50-70 with clinical risk factors
- Clinical evidence of osteoporosis-like fracture after age 50, loss of height/kyphosis
- Those with conditions or on medications that lead to osteoporosis when BMD may change the management, as in Cushing syndrome, hyperparathyroidism, prolonged corticosteroid use and prolonged immobilization.
- Those considered for osteoporosis therapy with a pharmacological agent
- For monitoring of therapy (every 2 years if needed).

DEXA remains the gold standard for measurement of BMD, especially as a diagnostic tool. Other tools like ultrasound of the calcaneal bone can be used for general screening. DEXA is also the only tool for which the WHO definition of osteoporosis applies.

Clinical Manifestations and Complications

Osteoporosis is a silent disease, as bone loss occurs without symptoms. Most of the time there are no warning signs until a fragility fracture occurs. Osteoporosis-related fractures may occur in any bone, but are most likely to occur at sites of low bone mass. The most typical sites of osteoporosis-related fractures are the vertebrae, distal radius, proximal femur, and ribs. The morbidity of osteoporosis comes mainly from fractures and their potential complications. Vertebral compression fractures are associated with pain, deformity, disability, and increased mortality. The most serious consequences, however, are those associated with hip fractures. In one study on elderly subjects who sustained hip fractures, the life expectancy was reduced by 1.8 years or 25% compared to a matched population. There was also a significant increase in morbidity and health costs in those who had hip fracture.

Prevention of Osteoporosis

Prevention is the most important measure in addressing low BMDs in the youth and women during reproductive age. Frequent pregnancies and lactation may predispose women in our society to lower BMDs. Thus, proper nutritional and family planning advice are warranted for this group. Another important group to target for prevention is postmenopausal women, and those with conditions predisposing to osteoporosis like amenorrhea.

Initiatives should be directed at the following measures:

- Optimal nutrition in the youth to achieve high peak bone mass, including adequate intake of calcium and vitamin D.
- Regular weight-bearing exercise.
- Identification and treatment of subjects with vitamin D deficiency, especially in children, females in the reproductive age group, and the elderly.
- Avoidance of tobacco smoking and alcohol intake.
- Assessment of every postmenopausal woman for risk of osteoporosis to determine the need for diagnostic tests and prevention/treatment.
- Early treatment of secondary causes of osteoporosis [for example, thyrotoxicosis, smoking, primary hyperparathyroidism, others].
- Prevention and early treatment of osteoporosis of patients who are receiving high-dose steroid therapy, or other drugs that may contribute to osteoporosis.

Osteopenia and Fractures

Although patients with lower BMD are at high risk of fractures, studies have shown that the largest number of osteoporotic fractures occurred among those with osteopenia (BMD -1 to -2.5). This can be explained by the presence of larger number of subjects with osteopenia than with osteoporosis and therefore even with a lower risk for fractures, the number of fractures can be substantial. Also it may reflect the influence of other risk factors. On the other hand, the value of antiresorptive agents for fracture prevention has not in general been proven in osteopenic subjects with no prior fractures, although such treatment might improve or stabilize BMD. Therefore, the use of pharmacological agents like antiresorptives in osteopenic subjects, should be limited to those with history of fractures or to those with multiple risk factors for fractures.

Specific Types of Osteoporosis

Premenopausal osteoporosis

The present evidence does not support screening for osteoporosis in premenopausal women in the general population. Certain premenopausal and perimenopausal women, however, are at a higher risk of accelerated bone loss, but there is no clear strategy to identify
those individuals. There is some evidence to support screening premenopausal or peri-menopausal women who have one of the following:

- Fragility fracture
- Frequent or prolonged use of corticosteroids ≥5 mg of prednisone for 3 months or longer
- Prolonged or recurrent amenorrhea
- Primary hyperparathyroidism
- Rheumatoid arthritis
- Prolonged hyperthyroidism

It is important to realize that premenopausal women who have low BMD have a lower risk for fracture than older subjects with the same BMD. Osteoporosis cannot therefore be diagnosed simply based on low BMD in a premenopausal woman. Many premenopausal women with low BMD had simply not achieved an adequate peak bone mass at a younger age. Common causes of low BMD in this category are low body weight and ovulatory disturbances. Secondary causes have always to be ruled out when osteoporosis is discovered. Workup may include ruling out calcium and metabolic bone diseases including vitamin D deficiency, liver or renal diseases, celiac disease and malabsorption, hypogonadism and other secondary causes of osteoporosis. The use of antiresorptive therapy can be recommended only in very specific cases like those with low BMD and prolonged corticosteroid therapy and in certain cases of primary hyperparathyroidism when surgery is not feasible and treatment is indicated.

Steroid-Induced osteoporosis

The American College of Rheumatology recommends the following interventions for prevention of bone loss and fractures in high-risk patients (postmenopausal women, elderly men) or younger patients with a BMD T-score (spine or hip) of less than -1 who are initiating prednisone at a dose of 5 mg/day or higher (or equivalent dose of a glucocorticoid) for more than three months:

- Calcium and vitamin D supplementation (1000 to 1500 mg/day and 800 IU/day, respectively).
- Bisphosphonate therapy: weekly formulations for patient convenience (alendronate 35 mg/week for prevention, 70 mg/week for treatment; risedronate 35 mg/week for prevention or treatment). The ACR recommends use of bisphosphonates with caution in premenopausal women as bisphosphonates are incorporated into the bone matrix and gradually released over time. Theoretically, there may be a risk of fetal harm when pregnancy follows the completion of therapy.
- Replacement of gonadal steroids in men if deficient.
- Consideration of calcitonin therapy if bisphosphonates are contraindicated or not tolerated. If the patient has fractures that are causing pain, then nasal calcitonin at a dose of 200 IU/day (after appropriate test doses) may be helpful. This regimen will attenuate bone loss and can reduce the pain.

The patient should be followed yearly to determine if bone loss continues. An exercise program should also be initiated, although this may be limited by restrictions from the underlying illness. Other published guidelines largely agree with the recommendations above, except for some minor differences.

A recent study indicated that teriparatide (parathyroid hormone analogue) may increase BMD more effectively when compared to alendronate in the prevention of steroid-induced osteoporosis. Zoledronic acid was also recently approved for prevention of steroid induced osteoporosis. In addition to the above recommendations, the task force made the following recommendations for the prevention of steroid-induced osteoporosis:

- In certain cases zoledronic acid may be considered if oral therapies were not possible and the duration of steroid intake is prolonged or indefinite.
- Women with premature hypogonadism, should be considered for estrogen therapy.

Osteoporosis in solid organ transplantation

Osteoporosis is found in up to half of transplant recipients, whereas incidence of fractures after transplantation ranges from 10% to 65%. The decrease in BMD occurs in the first 3 to 6 months and is probably related to the large doses of glucocorticoids used immediately after grafting. Early bone loss at the lumbar spine is typical of glucocorticoid-induced bone loss, followed few months later by femoral neck site bone loss that may exceed that at the lumbar spine, and most studies do not document recovery of bone mass at the hip. Reports on BMD changes after renal transplantation differ. The rapid and significant early loss in BMD in the first 6 months may be followed by continued loss of approximately 1% yearly, up to 8 years after renal transplantation. In heart and liver transplant recipients, the incidence of new fractures
parallels the timing of the most rapid loss of BMD, with most fractures occurring within the first year after transplantation. After renal transplantation, the incidence of fracture remains elevated, consistent with the persistent decline in BMD.

Many factors contribute to the pathogenesis of osteoporosis after organ transplantation. These include bone disease preceding transplantation, immunosuppressive medications, poor nutrition, immobility, hypogonadism, cachexia (lower body mass index), postmenopausal status and lifestyle factors (smoking and alcohol abuse). The mechanisms of glucocorticoid-induced osteoporosis are multiple. Early on, a phase of rapid bone loss is probably secondary to an increase in bone resorption due to a combination of renal calcium wasting, decreased intestinal absorption of calcium, and hypogonadotropic hypogonadism. In addition, glucocorticoids directly promote osteoclastogenesis (bone resorption). Bone formation is also profoundly inhibited. In addition glucocorticoids can induce a profound myopathy, impairing balance and mobility and increasing fall risk and the potential for fractures.46,67

Prevention and management of transplant-induced osteoporosis

The literature regarding prevention and treatment of transplant-associated bone loss is plagued by relatively small numbers of patients with insufficient power to detect significant differences in BMD, differing immunosuppressant regimens, no randomization, or randomization at varying intervals following transplantation. Moreover, the vast majority of studies are not powered to detect fracture outcomes.48

Because rates of bone loss and fracture incidence are highest immediately after transplantation, preventive and therapeutic measures should be instituted at that time and without delay. In addition, the lack of reliable clinical predictors to identify individual patients who will experience osteoporotic fractures makes all transplant recipients candidates for preventive therapy regardless of their baseline bone density.46

Specific resistance training and exercises were shown to help to restore BMD levels more rapidly with alendronate, than alendronate alone.46 Improving overall fitness is recommended to minimize the risk of falling before and following transplantation.46 Vitamin D and calcium should be given to all patients at recommended daily allowance for calcium (1000–1500 mg/d) and for vitamin D (400–800 IU/d) with 25-hydroxyvitamin D levels monitored to assess the adequacy of replacement.46 Vitamin D and calcium alone are clearly insufficient to prevent transplant-related bone loss or fractures.49,50

There are no specific FDA-approved therapies for posttransplantation osteoporosis. Bisphosphonates are clearly the drugs of choice for steroid-induced osteoporosis and any patient who meets WHO criteria for osteoporosis should receive pharmacologic treatment. Also the recommendations stated above by the American College of Rheumatology for prevention of steroid-induced osteoporosis should be followed. Limited data suggest that pretransplant treatment with bisphosphonates decreases posttransplant fracture risk.

When administered prior to liver transplant, intravenous pamidronate prevented osteoporotic vertebral collapse.51 Similarly, in a prospective, uncontrolled pilot study using intravenous pamidronate in lung transplant recipients, the fracture rate decreased and bone mass preserved at 1-year posttransplantation.52 In a study of renal transplant recipients, repeated doses of intravenous pamidronate preserved vertebral BMD during treatment and 6 months after cessation of treatment.53

In renal transplant recipients, alendronate started immediately after grafting reduced bone loss in a non-randomized study.54 Trials using zoledronic acid has also given positive results.55 Calcitonin seems to be ineffective in preventing early bone loss, but may have some benefit in the later post-transplant period in liver56 and renal57 transplant recipients and can be considered a safe alternative if other agents are contraindicated or poorly tolerated.

Recombinant parathyroid hormone (teriparatide) has also been evaluated recently.58 Its usefulness may be limited because of the secondary hyperparathyroidism commonly observed in long-term transplant recipients.56 Gonadal hormone replacement may be beneficial in premenopausal women and men undergoing solid organ transplantation who may have temporary hypogonadism.59 Testosterone replacement, started 6 months after cardiac transplantation in hypogonadal men who were also receiving calcium and vitamin D, stabilized BMD at the lumbar spine within 24 months.46

In the renal transplant population, bisphosphonates are potentially nephrotoxic. Acute renal failure with acute tubular necrosis in association with several intravenous bisphosphonates has been reported.50,61 There remain significant concerns for the use of bisphosphonates in renal patients with preexisting low bone turnover disease, wherein bisphosphonates could further slow bone turnover and potentially increase fracture rate.62

Studies of oral calcitriol in solid organ transplantation gave mixed results. Spinal bone loss was not prevented with low dose of calcitriol, 0.25 mcg/d or 0.5 mcg/48 h in heart and kidney recipients.50 In a
There are few data to guide duration of therapy in transplant recipients. Treatment duration should be based upon patient factors, such as ability to withdraw glucocorticoids, presence of other risk factors for low bone mass and fracture, and BMD measurements. In some patients, 12 months of therapy may be adequate. 63,64 In conclusion, there is a great need for strategic approaches to osteoporosis in transplantation at KFSHRC. Because bone disease is common, all transplant candidates should be evaluated and treated before transplantation to improve skeletal health. Preventive and therapeutic measures should be instituted at that time and without delay.

Treatment of osteoporosis in adolescents
Throughout childhood and adolescence, the skeleton changes in both size and shape. Bones are growing in length and width, cortical thickness is increasing, and there is a dramatic increase in bone mass as well as a significant increase in bone density. All these processes are influenced by genetic, hormonal and environmental factors. 65 Conditions that result in pubertal retardation in adolescents of both sexes, such as chronic diseases, hypogonadism or anorexia nervosa can lead to osteoporosis. In recent years, the issue of low bone mass/low bone density in children and adolescents has attracted much attention. The interpretation of data in the young is difficult because the "normal" BMD values to be used for comparison are continuously changing with age, and depend on several variables, such as gender, body size, pubertal stage, skeletal maturation and ethnicity. For children these values must be adjusted for age and sex (Z-score). 66

Z-score values below -2 are generally a serious warning, most bone specialists make a diagnosis of osteoporosis in children and adolescents only in the presence of low BMD and at least one fragility fracture. 66 This is more easily accepted in children affected by a chronic disease that is known to cause secondary osteoporosis, but the problem is present, and is even more complex, in adolescents who are apparently healthy, but have a low bone density.

There is still no consensus on the treatment of osteoporosis in the young with the exception of osteogenesis imperfecta. The lack of randomized trials comparing drugs and doses in various conditions makes it impossible to declare one therapeutic regimen superior to another. 66,68,69 Effective control of the underlying disease is the best first-line approach to prevent secondary osteoporosis. Growth retardation, pubertal delay, or hypogonadism must be corrected with appropriate hormonal therapy. The identification of osteoporosis risk factors is very important.

Treatment of osteoporosis in adolescents includes adequate calcium dietary intake and correction of vitamin D deficiency which is a common problem among otherwise healthy young patients. A vitamin D level above 50 nmol/L (20 ng/mL) in children is considered optimal. 66 Physical activity (high-intensity impact activities, such as running, jumping, or basketball for 10 to 20 minutes, at least 3 days per week) proved to be helpful. 67,70

Regarding antiresorptive drugs, only bisphosphonates have been successfully used in children. They are regularly used in children with severe osteogenesis imperfecta or osteoporosis related to cerebral palsy, in which the repeated fractures dramatically affect the quality and expectancy of life. 71 Bisphosphonate treatment in children and adolescents is not currently approved by the FDA. 72 Bisphosphonates have been shown to increase BMD, relieve pain, increase mobility, and reduce fragility fractures in osteogenesis imperfecta, corticosteroid-induced osteoporosis and other secondary osteoporosis (in connective tissue diseases, renal insufficiency, cerebral palsy). Intravenous cyclical pamidronate or oral alendronate have been used most often. 71,74

Use of bisphosphonate therapy in pediatric patients remains controversial because of inadequate long-term efficacy and safety data. For this reason, many experts recommend limiting use of these agents to those children with recurrent extremity fractures, symptomatic vertebral collapse, and reduced bone mass. Current data are inadequate to support the use of bisphosphonates in children to treat reductions in bone mass/density alone. 69 The anabolic agent teraparatide has also been used in some cases to promote bone formation.

Treatment of osteoporosis in chronic renal failure and end-stage renal disease
The diagnosis of osteoporosis in chronic renal failure is not easy to make due to the confounding effects of renal osteodystrophy and superimposed osteomalacia that may also result in fractures and low BMD. 75 In Stage 1 through 3 chronic kidney disease (CKD), the metabolic changes that accompany early CKD are intermittent hyperphosphotemia and a mild increase of parathyroid hormone. 77 Fractures in Stage 1 through 3 CKD are most likely caused by osteoporosis than
CKD-related metabolic bone disease. WHO criteria or low trauma fractures for diagnosis of osteoporosis in stage 1 through 3 CKD can be used once other metabolic and biochemical abnormalities have been corrected. The current FDA recommendation is to avoid oral bisphosphonates in patients with glomerular filtration rates (GFR) below 35 mL/minute. Pooled data of nine clinical trials showed that resirdonate 5 mg/day is safe and effective in osteoporotic women with age-related, mild, moderate or severe renal impairment <30 mL/minute. In all three subgroups, resirdonate preserved BMD and reduced the incidence of vertebral fractures. The average duration of exposure was 2 years.

Similar data about safety and effectiveness of alendronate has been published. Alendronate 5 mg/day was given for first 2 years and 10 mg/day was given for the third year. It reduced vertebrae fractures in patient with GFR down to 15 mL/min. In one trial, raloxifene also increased BMD at both the hip and spine and reduced the risk of vertebral fractures in CKD with the lowest creatinine clearance of 20 mL/minute. There is also prospective evidence that patients with GFR down to 30 mL/minute gain benefit from oral and intravenous bisphosphonate. Therefore, recommendations for treatment osteoporosis in stages 1 to 3 CKD:

- All patients should receive recommended dose of calcium if no contraindication.
- All patients should receive recommended the dose of vitamin D.
- A vitamin D level should be checked in addition to PTH and other markers like alkaline phosphatase to rule out renal-induced metabolic bone disease.
- In stages 1-3 CKD, oral and intravenous bisphosphonates are probably safe if indicated.

Diagnosis of osteoporosis in Stages 4 through 5 CKD, and in patients on dialysis is complicated by the possible presence of a dynamic bone disease, severe hyperparathyroidism and osteomalacia. They can be associated higher risk for fragility fractures and can mimic osteoporosis. Therefore, the WHO criteria for osteoporosis cannot be used for the diagnosis in CKD when GFR <15 mL/minute or on dialysis, even in the presence of fragility. The diagnosis of osteoporosis in Stages 4 through 5 and in end-stage renal disease (ESRD) can be reliably made only by quantitative bone histomorphometry and/or biochemical markers for bone turnover. Double tetracycline-labeled quantitative histomorphometry can discriminate among the various forms of renal osteodystrophy. Biochemical markers like PTH and bone-specific alkaline phosphatase (BSAP) are helpful. An increase in BSAP makes a dynamic bone disease unlikely and osteomalacia or hyperparathyroid bone disease more likely. A PTH level <150 pg/mL is suggestive of low bone turnover. A PTH level 6 times or higher above the upper limit of normal range is associated with high bone turnover. There are no prospective data showing efficacy for any approval pharmacologic agents to treat patients at Stage 4 through 5 and dialysis. Expert opinion suggests that in stages 4 to 5 CKD with fractures, bisphosphonates can be used only after elimination of CKD-related metabolic bone disease. This may require a transiliac bone biopsy. Half of the usual doses of bisphosphonates can be used and the duration is usually not for more than 3 years due to the risk of bone freeze.

The use of bisphosphonates in dialysis patients with osteoporosis has also never been tested prospectively. Renal excretion is the major route of elimination of these drugs, but intravenous clodronate or ibandronate are removed efficiently from the circulation by dialysis and that the total clearance in hemodialysis patients on a dialysis day is not very different from that in healthy subjects. There is also the risk development or worsening of adynamic bone disease.

Management of Osteoporosis

Important goals in the management of osteoporosis are to prevent fractures, treat pain and discomfort caused by osteoporosis complications, and improve bone density/quality if possible. Non-pharmacologi-
A suggested algorithm to use at KFSHRC based on availability of drugs in the hospital, cost and experience as well as level of evidence is as follows:

- Adequate calcium and vitamin D supplements (cholecalciferol or ergocalciferol) should be provided to all patients.
- Alendronate weekly (if no contraindication) can be used as first-line therapy for treatment of postmenopausal osteoporosis or in elderly males with osteoporosis or for prevention of steroid-induced osteoporosis.
- Alternative choices for alendronate in postmenopausal osteoporosis are raloxifene for prevention of vertebral fractures as evidence for efficacy against non-vertebral fractures is lacking, or strontium ranelate, for which there is evidence of vertebral and non-vertebral anti-fracture effects. A second-line therapy (considering availability in the hospital, cost and the need for IV administration) is zoledronic acid intravenously as 5 mg dose once yearly in cases where prolonged oral therapy is not feasible or complicated by significant GI side effects or after a hip fracture.
- Another second-line therapy is teriparatide (non-formulary medication at KFSHRC) for established osteoporosis with fractures and when there is not an adequate response to bisphosphonates. Treatment should not exceed 2 years and should be initiated after 6 months of alendronate discontinuation. Teriparatide treatment is usually followed by antiresorptive treatment when completed.
- Calcitonin should only be used rarely for vertebral osteoporosis and when pain exists and other agents cannot be used.

Pharmacological measures include:

- Change adjustable lifestyle risk factors
- Prevent falls
- Maintain or improve mobility
- Increase weight-bearing exercises

In general, there is no cure for osteoporosis, but certain medications may prevent and/or treat osteoporosis. Drugs for osteoporosis primarily reduce bone turnover by inhibiting osteoclast activity. Although they may lead to an early increase in bone mass, the drugs mainly prevent further loss of bone. Agents that primarily increase bone formation (PTH analogs), have also become available and an agent with dual action of antiresorption and bone formation was also recently introduced (strontium ranelate). Newer therapies are being developed to decrease bone resorption or increase bone formation at targeted molecular levels.

Pharmacotherapy of Osteoporosis

The most commonly used agents in Europe and the US are listed and briefly discussed. The majority of these agents have been shown to reduce the risk of vertebral fractures. Some have been shown to also reduce the risk of nonvertebral fractures and in some cases specifically at the hip site (Appendix 7). Newer therapies targeting specific molecular sites, calcitonin and Vitamin D derivatives and some other agents are also discussed.

Selective estrogen-receptor modulators

Selective estrogen-receptor modulators (SERMs) are non-steroidal agents that bind to the estrogen receptor and act as estrogen agonists or antagonists, depending on the target tissue. The concept of SERMs was triggered by the observation that tamoxifen, an estrogen antagonist in breast tissue, is a partial agonist on bone, reducing the rate of bone loss in postmenopausal women. Raloxifene is the only available SERM at present, but several others are in clinical development. Raloxifene prevents bone loss and reduces the risk of vertebral fractures by 30% to 50% in postmenopausal women with low bone mass, with or without prior vertebral fractures as shown in the MORE (Multiple Outcomes of Raloxifene Evaluation) trial. There was no significant reduction of non-vertebral fractures, although in women with severe vertebral fractures at baseline, a post-hoc analysis showed a significant reduction of non-vertebral fractures. Adverse events rarely included deep venous thromboembolism. There was a significant decrease in the risk of invasive breast cancer that has been subsequently confirmed. The concern about increase in cardiovascular events simi-
lar to that of conjugated estrogen was addressed in a trial and showed a neutral effect, but it did show an increased risk for venous thromboembolism and gallbladder disease.

**Bisphosphonates**

Bisphosphonates have a strong affinity for bone apatite, which is the basis for their clinical use. They are potent inhibitors of bone resorption and produce their effect by reducing the recruitment and activity of osteoclasts and increasing their apoptosis. Oral bioavailability of bisphosphonates is low, between 1% to 3% of the dose ingested, and is impaired by food, calcium, iron, coffee, tea, and orange juice. About 50% of the absorbed bisphosphonate deposits in bone and the remainder is excreted in urine. Their half-life in bone is very prolonged. Alendronate 70 mg once weekly and risedronate 35 mg once weekly are commonly used bisphosphonates.

In the FIT (Fracture Intervention Trial), alendronate reduced the incidence of vertebral, wrist, and hip fractures by approximately half in women with prevalent vertebral fractures. In women without prevalent vertebral fractures, there was no significant decrease in clinical fractures in the overall population, but the reduction was significant in the one-third of patients that had a baseline hip BMD T-score lower than –2.5 SD. Risedronate has been shown in women with prevalent vertebral fractures to reduce the incidence of vertebral and non-vertebral fractures by 40% to 50% and 30% to 36%, respectively. In a large population of elderly women, risedronate decreased significantly the risk of hip fractures (by 30%), an effect that was greater in osteoporotic women aged 70-79 years (40% reduction). Risedronate given daily (2.5 mg) reduces the risk of vertebral fractures by 50% to 60%, whereas an effect on non-vertebral fractures was only demonstrated in a post hoc analysis of women with a baseline of BMD T-score below –3 SD. Comparative and pooled (bridging) studies have shown that oral ibandronate 150 mg once monthly or intravenous ibandronate 3 mg every 3 months are equivalent or superior to daily ibandronate in increasing BMD and decreasing biochemical markers of bone turnover, giving rise to their approval for the treatment of postmenopausal osteoporosis.

The efficacy of yearly infusions of zoledronate 5 mg over three years was assessed in postmenopausal women in a placebo controlled fashion (HORIZON study [Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly]). Zoledronate was found to reduce the incidence of vertebral fractures by 70% and that of hip fractures by 40%. Intravenous zoledronate has also been shown to decrease the risk of mortality when given shortly after a first hip fracture. The overall safety profile of bisphosphonates is favorable. Oral bisphosphonates are associated with mild gastrointestinal disturbances, and rarely cause esophagitis and ulcer. A recent study also showed an increase in esophageal cancer among chronic users. Intravenous zoledronate can induce a transient acute phase reaction with fever, bone and muscle pain that ameliorates or disappears after subsequent courses. Osteonecrosis of the jaw has been described in cancer patients receiving high doses of intravenous pamidronate or zoledronate. Atrial fibrillation was noted to occur in a higher frequency after intravenous zoledronate, but a cause-effect relationship was not established and it was not seen in another study.

The parathyroid hormone analogs

Intermittent administration of PTH (for example, with daily subcutaneous injections) results in an increase of the number and activity of osteoblasts, leading to an increase in bone mass and in an improvement in skeletal architecture at both cancellous and cortical skeletal sites. The 1-34 N-terminal fragment (teriparatide) is used for the management of osteoporosis. Treatment with teriparatide has been shown to reduce significantly the risk of vertebral fractures and to reduce non-vertebral but not hip fractures. The recommended dose is 20 µg of teriparatide daily, given as a subcutaneous injection. The effect was initially seen in patients with severe osteoporosis and established vertebral fractures. Efficacy was later shown with osteoporosis even without fractures.

The most common reported adverse events in patients treated with teriparatide are nausea, pain in the limbs, headache and dizziness. In normocalcemic patients, slight and transient elevations of serum calcium concentrations have been observed following the injection of teriparatide. The change is small and routine monitoring of serum calcium during therapy is not required. Teriparatide may cause small increases in urine calcium excretion, but the incidence of hypercalciuria does not differ from that in placebo-treated patients. However, these agents should be used with caution in patients with active or recent urolithiasis. Isolated episodes of transient orthostatic hypotension. Isolated episodes of transient orthostatic hypotension are also reported. The use teriparatide is contraindicated in conditions with increased bone turnover (for example, pre-existing hypercalcemia, metabolic bone diseases other than primary osteoporosis, including hyperparathyroidism and Paget disease of bone, unexplained elevation of alkaline phosphatase, prior external beam or
implant radiation therapy to the skeleton or in patients with skeletal malignancies or bone metastasis). Severe renal impairment is also a contraindication.

**Strontium ranelate**

Strontium ranelate is a recently approved agent in Europe, for the treatment of postmenopausal osteoporosis, to reduce the risk of vertebral and hip fractures. There is some evidence that strontium ranelate both inhibits bone resorption and stimulates bone formation, suggesting that the agent may uncouple the bone remodelling process. Studies conducted up to 5 years have shown fracture efficacy of strontium ranelate, at spinal and non-vertebral sites, in a wide range of patients.\(^\text{102,103}\) Modest reduction in hip fracture rates has also been shown in women over the age of 74 years with low bone density at the femoral neck.\(^\text{104}\)

The recommended daily dose is a one 2-gram sachet once daily by mouth. The absorption of strontium ranelate is reduced by food, milk and its derivative products and the drug should be administered, therefore, between meals. Ideally, it should be taken at bedtime, preferably two hours after eating. Strontium ranelate is not recommended for patients with severe renal impairment (creatinine clearance below 30 mL/min).

The most common adverse events are nausea and diarrhea, which are generally reported at the beginning of treatment and usually disappear after the third month of treatment. An increase in the incidence of venous thromboembolism (relative risk 1.42) has been reported when pooling all phase III studies in osteoporosis. Therefore, strontium ranelate should be used with caution in patients at increased risk of venous thromboembolism, including those with a past history. Hypersensitivity reactions have also been reported rarely with this agent. The effects of the major pharmacological interventions on vertebral and hip fracture risk are summarized in Table 7 of the appendix.

**Combination and Sequential Treatments**

The combination of two inhibitors of bone resorption may result in a further decrease in bone resorption and a greater increase in BMD. Whether this results in a better effect on fracture risk, however, has not been adequately addressed or proven. If low doses of hormone replacement treatment (HRT) are used for a limited period of time for the management of climacteric symptoms, concomitant use of bisphosphonates may provide an appropriate reduction in bone turnover that may not be achieved with low doses of HRT alone.\(^\text{105}\)

Patients pre-treated with inhibitors of bone resorption, who have not achieved a full therapeutic response, are good candidates for treatment with anabolic agents. The increase in bone turnover that follows the introduction of teriparatide in patients treated with an anti-resorptive agent is similar to that observed in treatment-naive patients as is the pattern of response in BMD, with the exception of a six-month delay in the increase in spinal and hip BMD in patients previously exposed to alendronate.

An important question is whether the combination of an anti-resorptive agent and an anabolic drug, such as teriparatide, would provide a therapeutic advantage. In a published study, there was no evidence of synergy between teriparatide and alendronate, and the changes in the density and cortical volume suggested that the concurrent use of alendronate may reduce the anabolic effects of teriparatide.\(^\text{106}\) The apparent absence of synergistic effect of teriparatide and alendronate should not obscure the potential benefit of using an inhibitor of resorption after treatment with teriparatide. Indeed, there are data that suggest that the administration of an inhibitor of resorption (bisphosphonate or SERM) after treatment with teriparatide maintains or even potentiates the skeletal benefit observed during teriparatide treatment.\(^\text{107}\)

**Other Pharmacological Interventions**

**Calcitonin**

Calcitonin is a hormone that inhibits osteoclastic bone resorption. Salmon calcitonin is approximately 40-50 times more potent than human calcitonin, and the majority of clinical trials have been performed with salmon calcitonin. For clinical use it can be administrated either by injection or nasal application, which provides a biological activity of 25% to 50% compared with the injectable formulation. Calcitonin modestly increases bone mineral density at the lumbar spine and forearm. It may reduce the risk of vertebral fracture; however, the magnitude of the impact on these fractures remains questionable. Overall there seems to be no effect on non-vertebral fractures.\(^\text{112}\) Because of its cost and limited and modest effect, routine use is not recommended. The analgesic properties may, however, be an interesting option for acute pain following a spinal fracture.

**Hormone replacement therapy**

Estrogens reduce the accelerated bone turnover induced by menopause and prevent bone loss at all skeletal sites regardless of age and duration of therapy. Results from observational studies and randomized placebo controlled trials have shown that estrogen decreases the
risk of vertebral and non-vertebral fractures (including hip fracture) by about 30%, regardless of baseline BMD. When HRT is stopped, bone loss resumes at the same rate as after the menopause, although fracture protection may persist arguably for several years.\textsuperscript{109}

The results of the Women’s Health Initiative (WHI)\textsuperscript{108} suggests, however, that the long-term risks of HRT outweigh the benefits. In this large cohort of postmenopausal women in their 60s, the combined use of conjugated estrogen and medroxyprogesterone acetate was associated with a 30% increased risk of coronary heart disease (CHD), and breast cancer and with a 40% increase in stroke. There was also a slight increase in the risk of dementia. In hysterectomized women receiving conjugated estrogen alone, there was also a significant increase in stroke, but not of CHD and breast cancer, suggesting a deleterious effect of medroxyprogesterone acetate. Whether the benefits of HRT would outweigh the risks with other estrogen and progestin and in younger postmenopausal women is debated, but so far there is no placebo-controlled study showing the long-term safety of such alternatives. In many countries HRT is only recommended for climacteric symptoms, at a dose as small as possible and for a limited period of time. Thus, HRT is no longer recommended as a first line treatment for the prevention and treatment of osteoporosis.

Vitamin D derivatives
Both alfacalcidol (25 OH vitamin D3) and calcitriol (1,25 (OH)2 Vitamin D3) are used by some for the treatment of osteoporosis. Several but not all studies show decreases in vertebral fracture risk.\textsuperscript{107,108} The effects on bone mineral density have been less extensively studied. A few reports have suggested that alfacalcidol and calcitriol exert a direct action on muscle strength and decreases the likelihood of falling in elderly subjects.\textsuperscript{110,111} The major problem with the use of the vitamin D derivatives is the risk of hypercalcaemia and hypercalciuria. Most guidelines recommend against using active vitamin D (one alpha or calcitriol) in the treatment of osteoporosis without clear indication of renal failure or vitamin D synthesis defects or other clear indications.

Newer therapies
Newer therapies continue to be developed and introduced for the management of osteoporosis. They can be divided into drugs with improved formulation and potency such as zoledronic acid with once yearly intravenous administration and ibandronate with once monthly oral administration or quarterly intravenous administration. These drugs could provide better adherence and compliance to therapy. Drugs with newer therapy targets that improve bone formation include teriparatide and strontium ranelate. They appear to have a dual action of improving bone formation and slowing down bone resorption. Other therapies under evaluation have a specific molecular target resulting in decreasing bone resorption or enhancing bone formation. Osteoclasts are bone-forming cells that control the differentiation of osteoclasts into active cells, through a certain molecule called RANK ligand (RANKL) that binds to the RANK receptors on osteoblasts. Osteoprotegrin (OPG) is also secreted from osteoblasts and block the RANKL-RANK interaction, therefore decreasing osteoclasts differentiation.

Denosumab, a new drug under evaluation, acts as an anti-RANKL blocking osteoblast differentiation and slowing bone resorption similar to the OPG. Other drugs under investigation are the cathepsin K inhibitors, that inhibit cathepsin K, which is an enzyme secreted by osteoclasts to increase bone resorption. Newer bone forming agents are also in development. The action of osteoblasts is regulated by special proteins called Wnt that interact with special receptors on the surface of osteoblasts called LRP5 and LRP6. This interaction stimulates the activity of osteoblasts in bone formation through intracellular factors like axin and B-catenin. Sclerostin is a factor that blocks the interaction of Wnt with LRP receptors, slowing bone formation. A new drug under testing is an antisclerostin antibody that would therefore increase bone forming activities of the osteoblast.\textsuperscript{113} These and other drugs under investigation, could present a new front for the management of osteoporosis in the near future.

Choice of Therapy and Suggested Algorithm at KFSHRC
With the wide availability of different therapies and the development of even more therapies in the future, the choice of therapy may become more difficult for practitioners. However, like many other chronic diseases, alternative therapies provide more flexibility and individualized choices. There are, however, certain criteria and basic rules for the choice of treatment that practicing physician needs to take in account, including the level of evidence for efficacy of a certain agent. Trials on different therapeutic agents have been done. Randomized controlled trials (RCTs) or metaanalyses of a number of RCTs for a specific agent are considered of highest value. Comparison between agents, however, is not possible based on those studies because of different populations and therefore different risks for fractures. Direct
head-to-head comparisons between agents are rare and are very difficult to do, as it would require a very long duration and large number of subjects to show a measurable effect on fracture risk. Therefore, it is our recommendation to seek the best evidence for each agent, especially in terms of efficacy against vertebral, non-vertebral and hip fractures. Appendix 7 summarizes the efficacy of different agents available at KFSHRC.

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Appendices for Prevention and Treatment of Osteoporosis with Therapeutic Agents Available at King Faisal Specialist Hospital and Research Centre

Appendix 1. Recommended daily elemental calcium intake for peri- and postmenopausal women.

Appendix 2. Calcium Supplements Available at KFSHRC.

Appendix 3. Recommended daily intake of Vitamin D.

Appendix 4. Calcium content of foods.

Appendix 5. Agents Approved for the Management of Osteoporosis.

Appendix 6. Adverse effects and drug interactions of the Agents Approved for the Management of Osteoporosis at KFSHRC.

Appendix 7. Effect of agents available at KFSHRC on fracture risk reduction compared with placebo.
Appendices for Prevention and Treatment of Osteoporosis with Therapeutic Agents Available at King Faisal Specialist Hospital and Research Centre (Appendices 1-7).

Appendix 1. Recommended daily elemental calcium intake for peri- and postmenopausal women.

| Source                                    | Aged 31-50 | Aged 51 and older |
|-------------------------------------------|------------|-------------------|
| Institute of Medicine                     | 1000 mg    | 1200 mg           |
| National Institutes of Health             | 1000 mg    | 1000 mg           |
| Premenopausal women aged 25-50            |            |                   |
| Postmenopausal women younger than age 65 and using estrogen therapy | 1000 mg    |                   |
| Postmenopausal women not using estrogen therapy | 1500 mg    |                   |
| All women aged 65 and older               | 1500 mg    |                   |
| Osteoporosis Society of Canada            |            |                   |
| Menopausal women                           | 1500 mg    |                   |

Appendix 2. Calcium (Ca) Supplements Available at KFSHRC.

| Product                                      | Calcium content                  |
|----------------------------------------------|----------------------------------|
| Intravenous                                  |                                  |
| Calcium gluconate 10%                        | 2.3 mmol/10 mL                   |
| Calcium chloride 10%                        | 6.8 mmol/10 mL                   |
| Oral                                         |                                  |
| Calcium carbonate                            | 31.25 mmol/ML (suspension)       |
| Calcium glubionate and calcium lactobionate (Calsyr) | mmol/5 mL (syrup)               |
| Calcium carbonate 420 mg (Titralac)          | 4.2 mmol/tab                      |
| Calcium carbonate 600 mg (as elemental) (Caltrate) | 15 mmol/tab                    |
| Calcium carbonate and calcium lactate-glucunate (Calcium-Sandoz) | 12.5 mmol/ effervescent tab      |

Equivalents: 2 mEq=1 mmol=40 mg elemental calcium

Appendix 3. Recommended daily intake of Vitamin D.

| Category                       | Intake                                      |
|--------------------------------|---------------------------------------------|
| Premature infants              | 10-20 mcg/day (400-800 units), up to 750 mcg/day (30,000 units) |
| Infants and Children           | 5 mcg/day (200 units/day)                   |
| Adults:                        |                                            |
| 18-50 years                    | (400-800 units/day)                         |
| 51-70 years                    | (800 units/day)                             |
| Elderly >70 years              | (800 units/day)                             |

Dietary supplementation (each mcg = 40 USP units). Higher doses may be required in our population especially those with osteopenia, when double the recommended doses may be needed for maintenance. Correction of vitamin D deficiency may require high loading doses orally or IM.
### Appendix 4. Calcium content of foods.

| Food                          | Serving size | Approximate Ca per serving (mg) |
|-------------------------------|--------------|---------------------------------|
| **Milk**                      |              |                                  |
| Whole or skim                 | 1 cup (8 oz) | 290-315                         |
| Chocolate, whole, low-fat     | 1 cup        | 280-285                         |
| Powdered nonfat               | 1 tsp        | 50                              |
| Ice cream, soft, hardened     | 2 cup        | 90-100                          |
| **Cheese**                    |              |                                  |
| American                      | 1 oz         | 175                             |
| Cheddar                       | 1 oz         | 200                             |
| Cottage                       | 2 cup        | 70                              |
| Cream                         | 2 tbsp       | 20-40                           |
| Mozzarella, part-skim         | 1 oz         | 210                             |
| Parmesan                      | 1 tbsp       | 70                              |
| Ricotta, part-skim            | 4 oz         | 335                             |
| **Yogurt**                    |              |                                  |
| Whole-milk, plain            | 1 cup        | 295                             |
| Low-fat, plain, fruit         | 1 cup        | 340-450                         |
| Frozen, flavored              | 1 cup        | 160-240                         |
| **Fish, shellfish**           |              |                                  |
| Sardines in oil (with bones)  | 3 oz         | 370                             |
| Salmon, canned (with bones)   | 3 oz         | 170-210                         |
| **Vegetables, nuts**          |              |                                  |
| Almonds, dry roasted         | 3 cup        | 100                             |
| Beans, kidney                 | 1 cup        | 50                              |
| Beans, baked, canned         | 1 cup        | 130                             |
| Beans, refried, canned       | 1 cup        | 190                             |
| Bok choy, raw                 | 1 cup        | 160-250                         |
| Broccoli, fresh, cooked      | 1 cup        | 120-180                         |
| Cabbage, fresh, cooked       | 1 cup        | 50                              |
| Collards, fresh, cooked      | 1 cup        | 300-350                         |
| Figs, dried                   | 10 figs      | 270                             |
| Soybeans, cooked              | 1 cup        | 175                             |
| Soybean curd (tofu)           | 4 oz         | 30-155                          |
| Turnip greens                 | 1 cup        | 200                             |
| **Fortified foods**           |              |                                  |
| Calcium-fortified milk        | 1 cup        | 500                             |
| Calcium-fortified soy milk    | 1 cup        | 80-300                          |
| product                       |              |                                  |
| Cereal with added calcium     | 1 cup        | 100-1,000                       |
| (without milk)                |              |                                  |
| Fruit juice with added calcium| 1 cup        | 225-300                         |
| Breakfast bars                | 1 bar        | 200-500                         |
### Appendix 5. Agents Approved for the Management of Osteoporosis.

| Agent                                      | Approved Indications                                                                 | Dosage                                                                                           | Availability at KFSHRC                                                                 |
|--------------------------------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| Calcium and vitamin D                      | Prevention and treatment of postmenopausal osteoporosis                                | See Appendices 1, 2 and 3                                                                      | Calcium: see Table 2
|                                            |                                                                                      | Vitamin D3: tablet, 50,000 units                                                                | Vitamin D2: tablet, 400 units, 1000 units,                                               |
| Bisphosphonates alendronate (Fosamax)      | Prevention of postmenopausal osteoporosis                                            | 10 mg orally once a day or 70 mg orally once a week                                            | Tablet, 10 mg, 70 mg                                                                     |
|                                            | Treatment of postmenopausal osteoporosis (women and men)                              |                                                                                                  |                                                                                         |
|                                            | Treatment of glucocorticoid-induced osteoporosis (GIO)                                |                                                                                                  |                                                                                         |
| Zoledronic acid (Aclasta)                  | Treatment of osteoporosis (to reduce the incidence of fractures in postmenopausal     | 5 mg intravenously once yearly                                                                  | Infusion, solution [premixed]: 5 mg (100 mL)                                            |
|                                            | women with osteoporosis or to reduce the incidence of new clinical fractures in       |                                                                                                  |                                                                                         |
|                                            | patients with low-trauma hip fracture)                                              |                                                                                                  |                                                                                         |
|                                            | Approved for GIO and male osteoporosis                                               |                                                                                                  |                                                                                         |
| Selective estrogen receptor modulator      | Prevention and treatment of postmenopausal osteoporosis                               | 60 mg orally once a day                                                                         | Tablet, 60 mg                                                                           |
| raloxifene (Evista)                        |                                                                                      |                                                                                                  |                                                                                         |
| Salmon calcitonin (Miacalcin)              | Treatment of postmenopausal osteoporosis                                              | 200 IU intranasally once a day (alternating nostrils daily)                                      | Spray, nasal: 200 units/metered dose                                                      |
|                                            |                                                                                      | 100 units SC or IM every other day                                                              |                                                                                         |
|                                            |                                                                                      |                                                                                                  |                                                                                         |
| Strontium ranelate (Protelos)              | Treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip     | 2 g orally once a day                                                                           | Granules for oral suspension, 2 g                                                        |
|                                            | fractures                                                                            |                                                                                                  |                                                                                         |
| Estradiol Valerate conjugated estrogen     | Prevention of osteoporosis                                                            | 0.625 mg orally once a day                                                                     | Cream, vaginal: 0.625 mg/g (42.5 g)                                                      |
|                                            | Treatment of moderate to severe vasomotor symptoms associated with menopause         |                                                                                                  | Tablett; 0.3 mg, 0.625 mg, 1.25 mg                                                        |
|                                            | Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated    |                                                                                                  |                                                                                         |
|                                            | with menopause                                                                        |                                                                                                  |                                                                                         |
### Appendix 6. Adverse effects and drug interactions of the Agents Approved for the Management of Osteoporosis at KFSHRC.

| Agent     | Important Drug interaction                                                                                                                                                                                                 | Serious Adverse Reaction                                                                 | Contraindications                                                                                      | Monitoring parameters                               |
|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| Calcium   | Calcium channel blockers effects may be diminished; monitor response. Digitalis: may potentiate digoxin toxicity. Levothyroxine: may decrease T4 absorption; separate dose from levothyroxine by at least 4 hours Polystyrene sulfonate: Potassium-binding ability is reduced; avoid concurrent use. Tetracycline, beta-blockers, iron, quinolone antibiotics, alendronate, sodium fluoride, and zinc absorption is significantly decreased; administer 1-2 hours before any iron supplements and 1-3 hours after meals or other medications. Thiazide diuretics: High doses of calcium with thiazide diuretics may result in milk-alkali syndrome and hypercalcemia; monitor response. | Mild hypercalcemia (calcium: >2.6 mmol/L to ≤2.99 mmol/L) may be asymptomatic or manifest itself as constipation, anorexia, nausea, and vomiting. More severe hypercalcemia (calcium: >2.99 mmol/L) is associated with confusion, delirium, stupor, and coma. | Hypercalcemia, renal calculi                                                                          | Monitor calcium and phosphate level                   |
| Vitamin D | Mineral oil: Absorption of ergocalciferol may be decreased. Thiazide diuretics: Concomitant use may cause hypercalcemia.                                                                                                                                                  | Cardiovascular: Hypertension, vascular calcification. Central nervous system: Mental retardation. Endocrine and metabolic: Acidosis, growth suppression (children), hyperphosphatemia, polydypsia. Gastrointestinal: Anorexia, constipation, nausea, weight loss. Hematologic: Anemia. Neuromuscular and skeletal: Aches, osteoporosis (adults), stiffness, weakness. Renal: Azotemia (reversible) | Hypercalcemia; hypervitaminosis D or abnormal sensitivity to the toxic effects of vitamin D. | Monitor calcium and phosphate level                   |
### Osteoporosis Guidelines

| Pharmacological Agent | Side Effects | Precautions/Contraindications | Monitoring Parameters |
|-----------------------|-------------|-------------------------------|----------------------|
| **Alendronate (Fosamax)** | Bone/joint/muscle pain: Infrequently, severe (and occasionally debilitating) Gastrointestinal mucosa irritation: May cause irritation to upper gastrointestinal mucosa. Esophageitis, esophageal ulcers, esophageal erosions, and esophageal stricture (rare) have been reported Osteonecrosis of the jaw: Bisphosphonate therapy has been associated with osteonecrosis, primarily of the jaw; this has been observed mostly in cancer patients, but also in patients with postmenopausal osteoporosis and other diagnoses | Antacids, Calcium, Liron, and magnesium salts: May decrease the absorption of bisphosphonate derivatives; should be administered at a different time of the day. Antacids containing aluminum, calcium, or magnesium are of specific concern NSAIDs: May enhance the gastrointestinal adverse/toxic effects (increased incidence of GI ulcers) of bisphosphonate derivatives | Measure Alkaline phosphatase, serum calcium and phosphorus, monitor pain and fracture rate and hormonal status (male and female) prior to therapy; bone mineral density (should be done prior to initiation of therapy and after 6-12 months of combined glucocorticoid and alendronate treatment) |
| **Zoledronic acid (Aclasta)** | Osteonecrosis of the jaw: New onset A fib was higher in one study. A flu like symptoms may occur in the few days following IV infusion Hypocalcemia | No in vivo drug interaction studies have been performed for Reclast. Exercise caution when administering zoledronic acid with aminoglycosides, loop diuretics and nephrotoxic drugs | Periodic assessment of renal function in patients with chronic renal impairment. Monitor Ca and P04 |
| **Raloxifene (Evista)** | Cholestyramine reduced raloxifene absorption and clinical efficacy | Cholestyramine reduced raloxifene absorption and clinical efficacy | | |
| **Strontium Ranelate (Protelos)** | Cardiovascular: Incidence of venous thromboembolism (0.7%) Skin and Immunology: severe hypersensitivity syndromes including drug rash with eosinophilia and systemic symptoms Stevens-Johnson syndrome Gastrointestinal: Vomiting, abdominal pain, oral mucosal irritation including stomatitis and/or mouth ulceration Hypersensitivity to the active substance or to any of the excipients. | Food, milk, and calcium-containing compounds may reduce its bioavailability. Antacids containing aluminium or magnesium may reduce Strontium absorption. Such products should be given at least 2 hours apart from, and, in the case of antacids, preferably after, strontium ranelate. Tetracyclines or quinolones may form complex, strontium ranelate should not be given with them | Periodic assessment of renal function in patients with chronic renal impairment. |
| **Salmon calcitonin (Miacalcin)** | Cardiovascular: Myocardial infarction, thrombophlebitis Hematologic: Anemia Immunologic: Anaphylaxis Neurologic: Cerebrovascular accident Respiratory: Bronchoospasm Hypersensitivity to synthetic calcitonin-salmon | Decreases lithium concentrations | Monitor serum electrolyte, calcium, alkaline phosphatase, urinalysis and bone mineral density Nasal formulation: Visualization of nasal mucosa, turbinates, septum, and mucosal blood vessels |
**Hormone Replacement Therapy**

- Enhance the effect of: anticoagulants, corticosteroids, and cyclosporine
- Estrogen may diminish the effect of thyroid products
- CYP1A2 and CYP3A4 inducers may decrease the effect of estrogen

**Cardiovascular:**
- Hypertension, myocardial infarction
- Endocrine metabolic: fluid retention, B, diabetes mellitus, hypercalcemia
- Gastrointestinal: Disorder of gallbladder, pancreatitis
- Hematologic: Venous thromboembolism
- Neurologic: Cerebrovascular accident, dementia, impaired cognition
- Respiratory: Pulmonary embolism
- Other: Breast cancer, cervical cancer, malignant neoplasm of endometrium of corpus uteri, ovarian cancer

**Arterial thromboembolic disease**
- (stroke, myocardial infarction) (active or recent)
- Breast cancer, known, suspected or history of, except in appropriately selected patients being treated for metastatic disease
- Deep vein thrombosis/pulmonary embolism (active or a history of these conditions)
- Estrogen-dependent neoplasia (known or suspected)
- Genital bleeding, undiagnosed abnormal
- Liver dysfunction or disease

**Perform physical examination yearly including:**
- (blood pressure and Papanicolaou smear, breast exam, and mammogram)
- Monitor for signs of endometrial cancer in female with uterus.
- Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding.
- Monitor for loss of vision, sudden onset of proptosis, diplopia, migraine; signs and symptoms of thromboembolic disorders
- Monitor blood sugar, lipid profile thyroid function.

**Assess need for therapy at 3- to 6-month intervals**

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*Before prescribing estrogen therapy to postmenopausal women, all non-estrogen preparations should be considered first. The risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of progesterin when added to estrogen therapy. Estrogens with or without progesterin should be used for shortest duration possible consistent with treatment goals.*
Appendix 7. Effect of agents available at KFSHRC on fracture risk reduction compared with placebo.

| Agent                                      | Vertebral Fracture Risk | Non-vertebral Fracture Risk | Hip Fracture Risk | BMD |
|---------------------------------------------|--------------------------|-----------------------------|-------------------|-----|
| Alendronate                                 | Reduced                  | Reduced                     | Reduced           | ↑   |
| Hormone replacement therapy (estrogen)      | Reduced                  | Reduced                     | Reduced           | ↑   |
| Zoledronic acid                             | Reduced                  | Reduced                     | Reduced           | ↑   |
| Raloxifene (Evista)                         | Reduced                  | No change                   | No change         | ↑   |
| Strontium ranelate (Protelos)               | Reduced                  | Reduced                     | Reduced           | ↑   |
| Salmon calcitonin (Miacalcin)               | Reduced                  | No change                   | NA               | ↑   |
| Calcium                                     | No change                | No change                   | No change         | ↑   |
| Vitamin D                                   | Reduced/no changes       | Reduced/no changes          | Reduced/no change | ↑   |