2015 Guidelines for Osteoporosis in Saudi Arabia: Recommendations from the Saudi Osteoporosis Society

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BACKGROUND AND OBJECTIVES: To provide guidelines for medical professionals in Saudi Arabia regarding osteoporosis.

DESIGN AND SETTINGS: A panel of 14 local experts in osteoporosis assembled to provide consensus based on the strength of evidence and expert opinions on osteoporosis treatment.

PATIENTS AND METHODS: The Saudi Osteoporosis Society (SOS) formed a panel of experts who performed an extensive published studies search to formulate recommendations regarding prevention, diagnosis, and treatment of osteoporosis in Saudi Arabia. Both local and international published studies were utilized whenever available.

RESULTS: Dual x-ray absorptiometry (DXA) scanning is still the golden standard for assessing bone mineral density (BMD). In the absence of local, country-specific fracture risk assessment tool (FRAX), the SOS recommends using the USA (White) version of the FRAX tool. All women above 60 years of age should be evaluated for BMD. This is because the panel recognized that osteoporosis and osteoporotic fractures occur at a younger age in Saudi Arabia. Hormone replacement therapy (HRT) is not recommended for treating postmenopausal women with osteoporosis. BMD evaluation should be performed 1–2 years after initiating intervention, and the assessment of bone turnover biomarkers should be performed whenever available to determine the efficacy of intervention.

CONCLUSION: All Saudi women above the age of 60 years must undergo a BMD assessment using DXA. Therapy decisions should be formulated with the use of the USA (White) version of the FRAX tool.
The National Institute of Health in the United States Consensus Development Conference has redefined osteoporosis as a skeletal disorder characterized by compromised bone strength that increases the risk of fracture. Bone strength primarily reflects the integration of bone density and bone quality. An osteoporotic fracture occurs when a traumatic force is applied on an osteoporotic bone. Thus, osteoporosis is a significant risk factor for fractures. Osteoporosis, once thought to be a natural part of aging among women, is no longer considered age or gender dependent. It is largely preventable due to the remarkable progress in the scientific understanding of its causes, diagnosis, and treatment.

Optimization of bone health is a process that must be met regardless of age and gender. Factors that influence positive bone health are essential to prevent osteoporosis and its devastating complications. Osteoporosis is widely recognized as a major public health concern. Because individual clinicians cannot systemically collect all the evidence bearing on osteoporosis, they require summaries of the current international guidelines as recommended by the International Osteoporosis Foundation (IOF). Nation-specific guidelines are requested to take into consideration the specificities of each and every health care environment. These guidelines are unfortunately unavailable in Saudi Arabia where genetic background, customs, diet, and geographical location have been identified as predisposing factors for osteoporosis not found in other ethnic groups. To fill this gap, the current document was provided to help guide physicians on the proper approach to patients with osteoporosis.

Patients and Methods
The development of the present recommendations was done following Best Practice Guidelines by an expert panel consisting of members from the Saudi Osteoporosis Society (SOS). Panel members included various medical disciplines such as, endocrinology, rheumatology, gynecology, orthopedic surgery, family

## General Recommendations
- Counsel patients and family on osteoporosis and risk of falls
- Advise on effective and adequate sun exposure
- Advise on dietary vitamin D and calcium intake
- Advise on increased outdoor weight bearing physical activity

## Diagnosis
- Bone mineral density (BMD) by dual x-ray absorptiometry (DXA) using standardized and quality-assured equipment
- Bone turnover biomarkers currently not available in major tertiary hospitals in Saudi Arabia but may aid in risk assessment, decision to treat, and in the follow-up of response to therapy

## Treatment
- Treat all those with the diagnosis of osteoporosis based on the DXA scan.
- Treat all patients with osteopenia and fragility fracture.
- Assess fracture risk and decide on therapy using fracture risk assessment tool (FRAX) in patients with osteopenia without fracture.
- Optimize vitamin D and calcium levels before starting therapy and continue vitamin D and calcium with specific osteoporosis therapy.
- Therapy for osteoporosis should be tailored to each patient.
- Oral bis-phosphonates are the first line of treatment (expert opinion) in the majority of patients
- Treatment should be for 5 years; after appropriate assessment, patients might be considered for drug holidays.

## Pharmacologic Intervention
- Start osteoporosis treatment based on Saudi Food and Drug Authority (SFDA)–approved drugs

## Monitoring Therapy
- BMD to be performed 1–2 years after initiating intervention (preferably 2 years)
- Bone turnover biomarkers should be used whenever available to determine the efficacy of intervention

## Summary of Recommendations
medicine, and, last but not least, clinical pharmacists. A systematic research from several electronic databases (PubMed, Embase, and Web of Science) was conducted covering all relevant aspects of osteoporosis: epidemiology, pathophysiology, risk factors, diagnosis, up-to-date pharmacologic and non-pharmacologic treatments, drug side effects, and established osteoporosis guidelines from other parts of the world including local studies with relevant data until October 2014. Papers were selected on the basis of quality and level of evidence. Level and grading of evidence were adapted from the London College of Physicians as shown in Table 1.

Implications
Osteoporosis is a major threat to human health. Among the industrialized nations in North America, Europe, Japan, and Australia, osteoporosis at the hip/spine affects 49 million adults ranging from 9%–38% in women and 1%–8% in men. Fortunately, though mortality is highest during the year of fracture, the rates of incident osteoporotic fractures appear to be stabilizing globally. Estimated direct costs for the treatment of osteoporotic fractures in the US amount to $17 billion in 2005 and is expected to increase by as much as 50% in 2025. In Europe, the economic burden of incident and prior fragility fractures was €37 billion in 2010. The only study that estimated the cost of hip fracture in Saudi Arabia was published in 2007 from the eastern province. According to the study, the annual direct cost of osteoporotic hip fracture management was estimated at SR 2.09 million (US$557,333) at a rate of SR 48,712 (US$ 12,989.90) per patient. This is not inclusive of the indirect cost of these fractures and other types of fractures.

Epidemiology
Multiple studies in Saudi Arabia have consistently shown that the prevalence of osteoporosis is far more common in the country than its Western counterparts. Worthy to note is that vitamin D deficiency is extremely common among Saudis overall, more in females as well as in children and adolescents. This was attributed to the dressing customs and avoidance of sun exposure. This fact might have confounded studies on osteoporosis in Saudi Arabia.

The largest osteoporosis-related local study was performed in Jeddah in the western part of Saudi Arabia where the reference values of BMD were determined in 1980 randomly selected healthy Saudis of both sexes and compared with US/Northern European and other reference data. Age-related changes in BMD were similar to those described in US/Northern European and Lebanese reference data. Based on the BMD of total femur, the overall prevalence of osteoporosis using the manufacturer’s versus Saudi reference data was 6.3%–7.8% versus 1.2%–4.7% (P < .001), respectively. Saudis (≥50 years) in the lowest quartile of body weight exhibited the higher prevalence of osteoporosis (25.6% in females and 15.5% in males) as compared to that of the highest quartiles (0.0% in females and 0.8% in males). The manufacturer’s reference data overestimated the prevalence of osteoporosis among Saudi females and underestimated the prevalence in Saudi males. Consequently, at a national level, 3 separate studies from different regions were done to determine the prevalence of male osteoporosis and osteopenia (either spine or femur) and revealed a prevalence of 37.8% and 54.1%, respectively, in Jeddah; 37.4% and 33.9%, respectively, in Al Khobar; and 21.4% and 35.7%, respectively, in Riyadh. The studies highlighted the importance of using population-specific reference values for BMD measurements to avoid overdiagnosis and/or underdiagnosis of osteoporosis.

Steroid-Induced Osteoporosis
Steroids adversely affect bones at multiple levels. These

| Level of evidence | Type of evidence | Grade of recommendation |
|-------------------|------------------|------------------------|
| Ia                 | Meta-analysis of randomized controlled trials (RCTs) | A                      |
| Ib                 | At least one RCT | A                      |
| Iia                | At least one well-designed, controlled study but without randomization | B                      |
| Iib                | At least one well-designed, quasi-experimental study (e.g., comparative studies, correlation studies, case studies) | B                      |
| III                | At least one well-designed, non-experimental descriptive study (e.g., comparative studies, correlation studies, case studies) | B                      |
| IV                 | Expert committee reports, opinions, and/or experience of respected authorities | C                      |
original article

drugs directly suppress the function of osteoblasts. Prolonged steroid therapy leads to increased unlined resorption cavities, reduced osteoid, thinned trabeculae, and decreased production of new bone during each remodeling cycle. They also prevent calcium absorption from the gut and increase urinary calcium excretion resulting in negative calcium balance. All patients planned for prolonged steroid use should be fully evaluated for the risk of osteoporosis and should receive calcium and vitamin D supplements. These agents have been recommended for better musculoskeletal health and may reduce the risk of fractures in patients using long-term steroids.22,23 Studies using the bisphosphonates have clearly shown the great efficacy of these agents in reducing the risk of steroid-induced osteoporosis and fractures.24

Diagnosis and approach to patients

The World Health Organization (WHO) operationally defines osteoporosis as bone density 2.5 standard deviations (SD) below the mean for young white adult women. This diagnostic criterion, however, does not apply to premenopausal women and children. The follow-up BMD should not be done before (on average) 1-and-a-half to 2 years after starting any intervention and whenever there is a need for follow-up.25

Newer measures of bone strength, such as ultrasound, have been introduced. Recent prospective studies using quantitative ultrasound (QUS) scanners perform nearly as well as DXA for assessing bone health.26 These techniques, however, cannot be used for diagnosing or following up patients with osteoporosis. Information regarding the efficacy in young premenopausal or early menopausal women is lacking. Clinical trials of pharmacologic therapies have utilized DXA, rather than QUS, for entry criteria in studies, and there is uncertainty whether the results of these trials can be generalized to patients identified by QUS to have a high risk of fracture. Accordingly, DXA scanning is still the gold standard for assessing risk. Results from the various ultrasound devices (at least 6 commercial devices) are available and are not interchangeable.27

The launch of WHO technical report: Assessment of osteoporosis at the primary health care level and the related FRAX tool has been a major milestone toward helping health professionals worldwide to improve the identification of patients at high risk of fracture for treatment.28-32 However, the FRAX assessment does not tell one absolutely whom to treat, which remains a matter of clinical judgment. In many countries, guidelines are provided that are based on the expert opinion and/or on health economic grounds. In the absence of the local data, the committee suggests continuing to use the index on a trial basis using the reliable data from the USA (White) version of the FRAX tool in the index until the local data becomes available. The FRAX tool can be reached through the web page: http://www.shef.ac.uk/FRAX

Recommendations:

In the absence of a local, country-specific FRAX tool for Saudi Arabia, the committee recommends using the USA (White) version of the FRAX tool. This is because the National Health and Nutrition Examination Survey (NAHNES) III data are very accurate and reliable, and studies have shown the USA (White) bone mineral content to be close to the Saudi figures. The committee recognizes that hip fractures data are different between the 2 populations, and these are the basis for establishing FRAX data for any country and not the bone mineral content. Yet, this approach seems to be the best option until local figures are available.

Who should be evaluated?

Until good evidence becomes available to support the cost-effectiveness of routine screening, or the efficacy of early initiation of preventive drugs, an individualized approach is recommended. A bone density measurement should be considered based on certain criteria (see below). The FRAX tool mentioned above uses a combination of risk factor evaluation and bone density measurement to predict the fracture risk and help with treatment decisions. Until assessment by randomized clinical trials is conducted, individual decisions regarding screening could be informed by the preliminary evidence that the risk for fracture increases with age, and with an increased number of additional risk factors.

The guidelines committee endorses the American Association of Clinical Endocrinologist’s33 recommendations that state BMD should be measured in the following settings:

- All women ≥40 years who have sustained low-trauma fragility fracture
- All women >60 years of age in Saudi Arabia (expert opinion). This is because the panel recognizes that osteoporosis and osteoporotic fractures occur at a younger age in Saudi Arabia; hence, early diagnosis is important
- Previous fragility fracture or maternal history of hip fracture
- Premature menopause (age <45)
- Prolonged secondary amenorrhea (>1 year)
- For risk assessment in peri-menopausal and/or postmenopausal women who have risk factors for
fractures and are willing to consider available interventions

- Patients who had x-ray findings suggestive of osteoporosis such as fragility fracture, loss of height, or thoracic kyphosis
- Patients who are beginning to receive a long-term glucocorticoid therapy or other drugs associated with bone loss
- Adults with primary hyperparathyroidism or other diseases or nutritional conditions associated with bone loss in whom the evidence of bone loss would result in adjustment of management
- For establishing skeletal stability and monitoring therapeutic response in patients receiving treatment of osteoporosis (baseline testing should be made before intervention)

What are the available effective medical treatments?
In the past 30 years, major strides have been made in the treatment of osteoporosis. Evidence-based reports systematically reviewing the data from randomized clinical trials, including meta-analyses for each of the major treatments, are available and permit conclusions regarding the role of each modality of osteoporosis therapy. Table 2 shows the different pharmacologic agents (and their characters) for osteoporosis available in Saudi Arabia.

The Bisphosphonates
The potent bisphosphonates alendronate and risedronate are one of the first-line agents to treat postmenopausal osteoporosis. Randomized placebo-controlled trials (RCTs) of alendronate and risedronate analyzed by a systematic review and meta-analysis have revealed that all of these bisphosphonates increase BMD at the spine and hip in early as well as in late postmenopausal women in a dose-dependent manner.\(^{34-36}\) Alendronate and risedronate reduce the risk of subsequent non-vertebral fractures in women with osteoporosis and adults with glucocorticoid-induced osteoporosis. The data with alendronate in particular is overwhelming.\(^{37-40}\) In Saudi Arabia, the 70 mg formulation of alendronate is available. It has been found to have the same degree of improvement in BMD, and the suppression of markers of bone turnover in the urine as the 10 mg daily dose, with much less side effects on the gastrointestinal tract.\(^{41,42}\) As expected, compliance and patients’ preference are much more with the 70 mg once-a-week dose.\(^{45}\)

Intravenous Bisphosphonates
Intravenous (IV) bisphosphonates may play a major role in treating osteoporosis in the future. Uncontrolled studies have reported that on average, spine BMD increased by 9% and femoral neck increased by 3% over a year with pamidronate at a dose of 30 mg every 3 months.\(^{44}\) When given in a dose of 90 mg every 6 months, IV pamidronate increased spine and femoral neck BMD by 14% and 10%, respectively, over a 4-year period, and these changes were greater than occurred with once daily oral alendronate.\(^{43}\) IV zoledronate increased BMD in women with postmenopausal osteoporosis.\(^{46}\) After 1 year of treatment in a variety of regimens (0.25 mg q3 months, 0.5 mg q3 months, 1 mg q3 months, 2 g q 6 months, or 5 mg once yearly), spine and femoral neck BMDs were 5% and 3% higher, respectively, in women who received zoledronate compared to placebo. The HORIZON study (a landmark study) showed that infusing zoledronic acid at a dose of 5 mg once yearly during a 3-year period significantly reduced the risk of vertebral, hip, and other fractures. However, this drug was associated with a slightly significant risk of serious atrial fibrillation and renal impairment in at-risk patients than placebo.\(^{47}\)

Some Important Adverse Effects of Anti-Resorptives
In 2003, the first reports describing osteonecrosis of the jaw (ONJ) in patients receiving anti-resorptives including bisphosphonates and denosumab (see below) were published. These cases occurred in patients with cancer receiving high-dose IV bisphosphonate.\(^{48}\) Subtrochanteric and diaphyseal femur fractures have also been associated with long-term bisphosphonate use and could be a consequence of excessive suppression of bone turnover or subsequent use of steroids or proton pump inhibitors with bisphosphonates.\(^{49,50}\) Despite the accumulating evidence of risk, data gathered both from the European Society on Economic and Clinical Aspects of Osteoporosis and Osteoarthritis and the IOF 2012 statement indicated that bisphosphonates have established fracture efficacy up to 3 years, and alendronate and risedronate up to 4–5 years.\(^{51}\) Therapy should be withheld after maximum of 5 years except in very high-risk patients. BMD should be repeated 1-and-a-half to 2 years after withdrawal. Therapy with another agent should be instituted if there is significant deterioration or in case an osteoporotic fracture occurred at any time.

Recommendations:
(See Table 1 for Guideline Strength).

In postmenopausal women with osteoporosis:
- Alendronate, risedronate, and zoledronate are ef-
Table 2. Pharmacological aspects of various agents for osteoporosis.

| Drug/Dose          | Effect                                      | Instructions                                                                 | Side effects and contraindications                                                                 |
|--------------------|---------------------------------------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| **CALCIUM**        |                                             |                                                                              |                                                                                                   |
| Premenopausal, men <50 yr and pregnant women (1000 mg/d) | May decrease bone loss                                                       | Calcium should be taken with meals for better absorption                                        | Caution in patient with hypercalcemia and patients with history of renal stones                     |
| Postmenopausal, men >50 yr (1500 mg/d) |                                             |                                                                              |                                                                                                   |
| **VITAMIN D**      |                                             |                                                                              |                                                                                                   |
| Premenopausal, men <50 yr and pregnant women (600 IU/d) | Doses are for persons with normal Vit D levels Maintains BMD Active 1, 25 dihydroxyvitamin D should not be used | Expose to sun for 10-15 min 2-3 times/wk                                                         | As above                                                                                           |
| Postmenopausal, men >50 yr (1000 IU/d) |                                             |                                                                              |                                                                                                   |
| **ALENDRONATE**    |                                             |                                                                              |                                                                                                   |
| This medicine should be taken as soon as patient wakes up in the morning, before eating, or drinking anything. Tablet should be swallowed as a whole with a large glass (8 ounces) of plain water only (not mineral water, coffee, juice, or any other liquid). Patient should not lie down on their back, eat, or drink for at least 30 min after taking alendronate. | Reduces risk of vertebral and non-vertebral fractures in established osteoporosis. It decreases hip fractures only in those patients with osteoporosis at the hip (not osteopenia) | See above                                                                                           |
| 70 mg once weekly |                                             |                                                                              |                                                                                                   |
| **INTRAVENOUS ZOLEDRONATE** |                                             |                                                                              |                                                                                                   |
| 5 mg once yearly   |                                             |                                                                              |                                                                                                   |
| **DENOSUMAB**      |                                             |                                                                              |                                                                                                   |
| 60 mg every 6 mo   |                                             |                                                                              |                                                                                                   |
| **RALOXIFEN**      |                                             |                                                                              |                                                                                                   |
| 60 mg/d            |                                             |                                                                              |                                                                                                   |
ficacious in preventing vertebral fractures and non-vertebral fractures in postmenopausal women with osteoporosis. Oral alendronate or risedronate are the first-line agents to treat established osteoporosis especially when the hip is affected. [Evidence Ia]

b. Alendronate, risedronate, and zoledronate increase BMD significantly at both spine and hip [Evidence Ia]

c. These drugs prevent spine fractures and hip fractures (in those who are osteoporotic at the hip). [Evidence Ia]

d. After 6 years of therapy with alendronate, only morphometric vertebral fractures (picked on x-ray) are reduced. All other types of fractures are not reduced. The risk of long bone atypical fractures also increased. For these reasons, therapy with bisphosphonates should be limited for 5 years (see below). Only high-risk patients with no other alternative option should continue therapy beyond 5 years.

In Men with Osteoporosis:

a. Alendronate and zoledronate are efficacious in preventing vertebral fractures and increases BMD at the spine and femoral neck [Evidence Ia]

b. Hip fracture data are lacking for both.

In Glucocorticoid-Induced Osteoporosis:

a. In postmenopausal women on steroids, alendronate, risedronate, and zoledronate are efficacious in preventing vertebral fractures [Evidence Ia]

b. In men on steroids, alendronate, risedronate, and zoledronate increase BMD at the spine and maintain or increase BMD at the hip. [Evidence Ia]

c. In men and women on steroids, alendronate, risedronate, and zoledronate increase BMD at the spine and maintain or increase BMD at the hip. [Evidence Ia]

d. Therapy with bisphosphonate should be for 5 years after which they should be stopped except in high-risk patients. Bone density should be measured in 1-and-a-half to 2 years, and risk should be assessed again. High-risk patients, those with fracture but not on treatment/therapy and those in whom BMD deteriorates, should receive an alternative therapy or should be put back on bisphosphonate if the alternative therapy is not suitable/unavailable. [Evidence IV]

Hormone Replacement Therapy

The women’s health initiatives have dramatically changed the view toward a routine recommendation to most postmenopausal women of using hormone replacement therapy (HRT). It was the first randomized controlled trial to show that HRT reduces the fracture risk. Even though women were not selected on the basis of low BMD, HRT reduced the risk of hip and vertebral fractures by 34% and reduced the overall fracture risk by 24%. HRT increased the risk of non-fatal myocardial infarction or death due to cardiac disease by 29%, and there were 7 more cardiac events per year for every 10 000 women treated with HRT. In addition, HRT increased the risk of stroke by 41% (risk of venous thromboembolism increased by 111%, absolute risk of pulmonary embolism per 10 000 person-years attributable to HRT increased by 8 events, and risk of all venous thromboembolic disease increased by 18 events).

Recommendations:

a. HRT is not a first-line preventive therapy in postmenopausal women with low bone density. When used for the prevention of postmenopausal osteoporosis, the risks of HRT may outweigh the benefits [Evidence Ib]

b. HRT is not recommended for treating postmenopausal women with osteoporosis. With a prolonged use of HRT taken only for the treatment of postmenopausal osteoporosis, the substantial risks of cardiovascular disease, stroke, venous thromboembolism, and invasive breast cancer may lead to an unfavorable risk–benefit ratio [Evidence Ia]

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) are non-hormonal agents that bind to estrogen receptors with an affinity equivalent to that of estradiol, but they have estrogen agonist effects in some tissues and antagonist effects in others. The structure of any ligand is an important factor in determining the conformational changes that occur in the estrogen receptor when the ligand binds to it. Each ligand seems to produce a different final shape in the estrogen receptor, and this shape determines interactions with protein cofactors and DNA response elements that ultimately translate into tissue-specific estrogen agonist or antagonist effects.

Raloxifene is the only SERM that is available in Saudi Arabia and has been approved for the treatment of osteoporosis. It is taken as a single tablet (60 mg/d) without regard to meals, calcium, and vitamin D supplements or time of the day. It has no estrogen-agonistic effects in the breast and uterus. RCTs on the effects of
Raloxifene have shown increases in bone density, but less than those reported with bisphosphonates or estrogen. **Skeletal effects:** Data from the Multiple Outcomes of Raloxifene Evaluation (MORE) suggest a sustained vertebral anti-fracture efficacy. The drug is also associated with a 60%-70% reduction in the risk of breast cancer especially those with positive estrogen receptors. It also decreases low-density lipoprotein cholesterol and total cholesterol; high-density lipoprotein cholesterol decreases and triglycerides increases. The post hoc analysis of secondary endpoints from MORE found no overall change in cardiovascular or cerebrovascular risk. These risks were not primary outcomes and, therefore, the results were looked at in other trials wherein the researchers found that among 10,101 postmenopausal women who were followed for median of 5.6 years, raloxifene reduced the risk of invasive breast cancer and clinical vertebral fracture but increased the risk of fatal stroke and venous thromboembolism. There was no alteration in risk for coronary events.

**Recommendations:**

a. Raloxifene increases BMD at the spine and hip; however, it is efficacious in preventing only vertebral fractures in postmenopausal women with osteoporosis. [Evidence Ia]
b. In postmenopausal women with osteoporosis, raloxifene decreases the incidence of estrogen-receptor–positive invasive breast cancer; however, it is not recommended for preventing or treating breast cancer. [Evidence Ib]
c. Raloxifene has no beneficial effect on vasomotor symptoms and may increase their incidence. [Evidence Ib]
d. In the majority of patients with osteoporosis, raloxifene should be used as a second-line therapy, especially, in younger patients who are not at high risk for hip fractures. [Evidence Ib]

**Calcitonin**
Calcitonin is a naturally occurring peptide hormone. Only 1 study—Prevent Recurrence of Osteoporotic Fractures study—had a sample size that was enough to detect significance and was designed to detect a change in fracture rates. In this investigation, a daily dose of 200 IU of nasal salmon calcitonin significantly reduced vertebral fractures by 33%-36%. Although this study was a prospective RCT, its results were classified as Level 2 evidence because of concerns about the absence of a dose response (no significant fracture reduction with the daily dose of 400 IU) and a high drop-out rate.

Note: As of March 5, 2013, the US Food and Drug Administration (FDA) panel has ordered to STOP marketing Salmon Calcitonin after the evidence of increased malignancy among patients treated for osteoporosis ([http://www.medscape.com/viewarticle/780323](http://www.medscape.com/viewarticle/780323)).

**Recommendations:**
Nasal and subcutaneous calcitonin should not be used to treat osteoporosis.

**Recombinant Human Parathyroid Hormone (hPTH)**
Although continuous exposure to parathyroid hormone (PTH) decreases bone mass, its intermittent administration leads to the opposite effect and improves bone density through increasing bone formation. Thus, it is the only bone-forming agent that is approved for the treatment of osteoporosis. Recombinant human parathyroid hormone (hPTH) or teriparatide (trade name: Forteo) was reported as a clinical treatment for osteoporosis in 1980; however, animal studies were conducted back in early 1930s. The use of large amounts of this agent for prolonged duration was found to result in osteosarcoma in rat studies. The synthetic N-terminal fragment (1-34) has been used almost exclusively in clinical trials. It also showed efficacy in the treatment of steroid-induced osteoporosis and osteoporosis in men.

The pivotal randomized controlled trial of teriparatide evaluated its efficacy in reducing vertebral and non-vertebral fractures in 1637 postmenopausal women with at least 1 vertebral fracture at enrolment. Compared with placebo treatment, teriparatide resulted in dose-dependent increases in BMD at both the lumbar spine (10%-14%) and total hip (3%-4%) after a median of 21 months. This has been confirmed in other smaller studies.

**Recommendations:**

a. Therapy with hPTH should be restricted to patients with multiple fractures and low bone density (T score below – 2.7). [Evidence Ia]
b. hPTH (1–34) is efficacious in preventing both vertebral and non-vertebral fractures (excluding hip fractures) in postmenopausal women with severe osteoporosis and increases BMD at all skeletal sites with the exception of the radius. [Evidence Ib]
c. In men with severe osteoporosis, hPTH (1–34) increases BMD at the spine. [Evidence Ib]. Fracture data are lacking in this population.
d. In postmenopausal women with glucocorticoid-
induced osteoporosis, hPTH (1–34) increase BMD at the spine. [Evidence 1a]
e. Therapy should be for 18 months only after which treatment should be stopped. Patients may continue with anti-resorptive after stopping the drug. [Evidence 1b]
f. Therapy with hPTH should not be combined with anti-resorptive because that will decrease the gain in bone density attained by using hPTH alone. [Evidence 1a]

Strontium Ranelate
This is a divalent cation that can substitute for calcium in hydroxyapatite crystals of bone. It has a particular profile characterized by an inhibition of bone resorption and stimulation of formation. In a randomized controlled trial, SOTI (Spinal Osteoporosis Therapeutic Intervention) (N=1649, mean age 69 years) reported after 3 years that strontium ranelate at 2 g/d increases BMD and reduces the vertebral fracture risk in postmenopausal osteoporotic women.\(^67\) The other landmark study for this agent, the TROPOS (Treatment of Peripheral Osteoporosis), included 5091 postmenopausal women with osteoporosis.\(^68\) It showed that the drug reduced (in the entire sample) the relative risk for all non-vertebral fractures by 16\%(P= .04) and by 19\% for major fragility fractures at these sites (P= .031). Only in a certain subgroup of the study population did the drug remarkably reduce the risk for hip fractures. These were women at very high risk for hip fractures (age ≥74 years and femoral neck BMD T score ≤ -2.4 according to NHANES reference) (n=1977).\(^69\)

Strontium has recently received European approval for the treatment of osteoporosis in men at an increased risk of fracture (previously approved only for postmenopausal women). The decision was based on a recent RCT conducted among 243 male patients followed up for 2 years, which showed improved bone density compared to the placebo group.\(^70,71\)

Note: In June 2014, the SFDA decided to stop the registration of strontium ranelate in Saudi Arabia based on its high cardiovascular risks. This decision came after a subcommittee in the European Medication Agency concluded increased cardiovascular risks with the use of Strontium for Osteoporosis. The drug is still available in the European Union.

The European Medicines Agency (EMA) restricted the use of strontium to patients who cannot be treated with other medicines approved for osteoporosis.\(^72\) http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Protelos_and_Osseor/human_referral_prac).

**Recommendations:**
Strontium ranelate should no longer be used to treat osteoporosis in Saudi Arabia.

**Anti-cytokines: The RANK-RANKL system**
The receptor activator on nuclear factor κB ligand (RANKL) has been identified as an essential cytokine for forming and activating osteoblasts.\(^73\) RANK, a member of the tumor necrosis factor super family, is expressed by osteoblasts with their immature precursors necessary and sufficient for osteoclastogenesis. RANKL activates its receptor, RANK, which is expressed on osteoclasts and their precursors, promoting osteoclast formation and activation, and prolonging osteoclast survival by suppressing apoptosis.\(^74\) RANKL is expressed on bone-forming osteoblasts, which indicates that bone resorption and bone formations are coupled through RANKL. In vitro and in vivo studies suggest that RANKL expression can be blocked by synthetic osteoprotegerin fusion proteins, soluble RANK fusion protein, or RANK antibodies.\(^75,76\)

**Denosumab**
This is a fully human monoclonal antibody against the RANK ligand and inhibits osteoclast-mediated bone resorption in the way mentioned above. It is an extremely potent anti-resorptive drug. The landmark study for denosumab is the FREEDOM trial (Fracture Reduction Evaluation of Denosumab) in osteoporosis every 6 months.\(^77\) The study included 7868 women who received subcutaneous denosumab every 6 months and demonstrated reduction in the risk of vertebral, non-vertebral, and hip fractures versus placebo. As of September 2012, denosumab (Prolia) distributed by AMGEN has been approved by US FDA as a treatment for bone loss in men with osteoporosis at high risk for fracture, secondary to the findings of Orwoll and colleagues that 1-year denosumab therapy among men was well tolerated and resulted in a reduction in bone resorption with subsequent increase in BMD in all assessed skeletal sites.\(^78\)

**Summary Statements** (see also Table 2):
1. Denosumab suppresses bone resorption markers and reduces vertebral, non-vertebral, and hip fractures. [Evidence 1a]
2. Denosumab is approved for the treatment of postmenopausal and male osteoporosis. [Evidence 1a]
3. Cases of ONJ have been reported.

**Selection of Therapy**
The selection of any of these agents used for osteo-
Porosis should be individualized based on the patient characteristics, efficacy, and health economics. There is no agent that is suitable for all patients, and clinical judgment should always be exercised. Referral for expert opinion is warranted in difficult or complicated patients, patients who continue to fracture despite being on therapy, patients who develop an adverse effect to a certain medication and in any time at the physician discretion.

**Fall Prevention and Hip Protectors**

Non-pharmacologic interventions directed at preventing falls and reducing their effect on fractures have been promising. These include studies to improve strength and balance in the elderly, as well as using hip protectors to absorb or deflect the impact of a fall. Deprez et al emphasized the importance of falls as a risk factor for non-vertebral and mainly hip fractures. The study concludes that falls occur at least once a year in 30% of individuals older than 65 years and in 50% of those older than 80 years of age with a 5%-6% fracture incidence. They considered environmental risk factors (inappropriate clothing, obstacles at home, slippery shower, the use of psychotropic agents with long half-life, etc.) or patient-related factors (lower limb weakness, neurological disturbances, etc.) and reviewed many clinical tools that could be used to evaluate the risk of falls.

A recent RCT involving 1801 frail, elderly adults demonstrated that an anatomically designed external hip protector reduces the risk of hip fracture by 60% relative hazard of 0.4 (95% CI 0.2-0.8). The main interventions likely to be beneficial are muscle strengthening and balance retraining. One study has shown that the benefits from 2 years of back exercise course continued even 8 years after cessation. Home hazards assessment by occupational therapist (removing any obstacles that may result in falls) and withdrawal of psychotropic medications are very important interventions. Smoking cessation should be considered, although the effect on long-term outcomes has not been rigorously studied.

How should the response to treatment be monitored?

Several approaches have been introduced for the monitoring of patients receiving therapies for osteoporosis. The goals of monitoring are to increase compliance to treatment regimens and determine treatment responses. Many patients do not continue prescribed therapy or do not adhere to a treatment protocol, even when enrolled in formal clinical trials. The best tests for monitoring treatment response would reflect the largest changes with the least error, and these assessment tools are not readily available. The Fracture Intervention Trial (FIT) reveals an additional problem with monitoring. In this study, the larger the bone loss in the first year, the greater the gain the next year, for both the placebo and active treatment groups. Thus in most instances, repeating bone mass measurement at an interval shorter than 2 years after initiating therapy may not be helpful for physicians’ decision-making about treatment efficacy. Although this holds true, many experts in the field prefer to repeat DEXA after 1 year of starting therapy.

**Universal Recommendations**

There are several interventions recommended for the general population, which includes vitamin D and calcium correction for maintaining muscle and bone strength, diet, and exercise. Calcium is the single most important nutrient for attaining peak bone mass and for preventing and treating osteoporosis. Factors contributing to low calcium intakes are restriction of dairy products, low level of fruit and vegetable consumption, and a high intake of low-calcium beverages such as sodas. For the general population, the recommended dietary allowance for calcium among older adults (>50 years) is 1200 mg/d and 600 IU/d of vitamin D. In addition, there is strong evidence that physical activity early in life contributes to a higher peak bone mass. It has been the observations of many experts in the field in Saudi Arabia that the fracture rate among elderly Saudi females especially that of the hip joint is much less than what is observed in Western countries. This observation can partially be explained by the lower exercise and motility rate of our elderly females compared to their Western counterparts.

In conclusion, the present recommendations of the SOS has focused on the evaluation and treatment of osteoporosis for Saudi adults. Separate recommendations for vitamin D and calcium as well as osteoporosis for children and adolescents are warranted.

**Conflicts of interest**

None.

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