original article

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

Yousef Al-Saleh,[a] Riad Sulimani,[b] Shaun Sabico,[c] Hussein Raef,[d] Mona Fouda,[b] Fahad Alshahrani,[e] Mohammad Al Shaker,[f] Basma Al Wahabi,[g] Mir Sadat-Ali,[h] Hanan Al Rayes,[g] Salwa Al Aidarous,[i] Siham Saleh,[j] Fakhr Al Ayoubi,[k] Nasser M. Al-Daghri[c]

From the [a]College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; [b]College of Medicine, King Saud University, Riyadh, Saudi Arabia; [c]Biomarkers Research Program and Prince Mutaib Chair for Biomarkers of Osteoporosis, Biochemistry Department, College of Science, King Saud University, Riyadh, Saudi Arabia; [d]Department of Medicine, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia; [e]College of Medicine, King Abdulaziz Medical City, Riyadh, Saudi Arabia; [f]Department of Surgery, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia; [g]Department of Medicine, Prince Sultan Military Medical City, Riyadh, Saudi Arabia; [h]College of Medicine, Dammam University, Dammam, Saudi Arabia; [i]College of Medicine, King Abdulaziz Medical City, Jeddah, Saudi Arabia; [j]Department of Pharmacy, Prince Sultan Cardiac Center, Riyadh, Saudi Arabia; [k]Department of Pharmacy, King Fahad Cardiac Center, King Saud University, Riyadh, Saudi Arabia

Correspondence: Yousef Al-Saleh, MD · Assistant Professor, College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia · T: +966(11)8011111 Ext.13056 F: +966(11)8011111 Ext. 14229 · alaslawi@hotmail.com

Ann Saudi Med 2015; 35(1): 1-12

DOI: 10.5144/0256-4947.2015.1

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.

Summary of Recommendations

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

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.[1] 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.[2,3]

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.[4] 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

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**.[5]

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.[6] Fortunately, though mortality is highest during the year of fracture, the rates of incident osteoporotic fractures appear to be stabilizing globally.[7] 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.[8] In Europe, the economic burden of incident and prior fragility fractures was €37 billion in 2010.[9] The only study that estimated the cost of hip fracture in Saudi Arabia was published in 2007 from the eastern province.[10] 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.[10] This is not inclusive of the indirect cost of the 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.[11-14] Worthy to note is that vitamin D deficiency is extremely common among Saudis overall, more in females as well as in children and adolescents.[15-17] 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.[18] 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;[18] 37.4% and 33.9%, respectively, in Al Khobar,[19] and 21.4% and 35.7%, respectively, in Riyadh.[20] The studies highlighted the importance of using population-specific reference values for BMD measurements to avoid overdiagnosis and/or underdiagnosis of osteoporosis.[18]

Steroid-Induced Osteoporosis

Steroids adversely affect bones at multiple levels.[21] These

Table 1. Guideline strength: level of evidence and grade of recommendation.[4]

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

drugs directly suppress the function of osteoblasts. Prolonged steroid therapy leads to increased unfilled 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 criterion 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[33] 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.[43]

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.[45] 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:

(Please refer to **Table 1** for Guideline Strength).

In postmenopausal women with osteoporosis:

a. Alendronate, residronate, 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) Postmenopausal, men >50 yr (1500 mg/d)	May decrease bone loss	Calcium should be taken with meals for better absorption Calcium should not be taken with iron (absorption may be adversely affected when given concurrently)	Caution in patient with hypercalcemia and patients with history of renal stones
VITAMIN D Premenopausal, men <50 yr and pregnant women (600 IU/d) Postmenopausal, men >50 yr (1000 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
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. 70 mg once weekly	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	Hypocalcemia; inability to remain upright for at least ½ hr after the dose. Should not be prescribed for patients with active esophageal abnormalities or peptic ulcer disease. Risk of atypical fracture, osteonecrosis of the jaw Contraindicated: in pregnancy, women who plan to be pregnant Contraindicated in patients with creatinine clearance below 30 mL/min
INTRAVENOUS ZOLEDRONATE 5 mg once yearly	Reduces risk of vertebral and non-vertebral fractures in established osteoporosis. Decreases hip fractures in patients with hip osteoporosis. Decreases mortality in patients admitted with hip fracture	One infusion per yr over minimum of 15 min. Good hydration before receiving the medication	Hypersensitivity flu-like reaction Risk of atypical fracture, ONJ Contraindicated in pregnancy, women who plan to be pregnant, and in patients with creatinine clearance below 30 mL/min
DENOSUMAB 60 mg every 6 mo	Reduces risk of vertebral and non-vertebral fractures in established osteoporosis. Decreases hip fractures in patients with hip osteoporosis	60 mg denosumab in 1 mL solution in a single-use prefilled syringe or vial Subcutaneous injection every 6 mo	Eczema, cellulitis, low calcium Contraindicated in pregnancy, women who plan to be pregnant Risk of atypical fracture, ONJ, Dose adjustment for renal impairment is not necessary.
RALOXIFEN 60 mg/d	Reduces risk of vertebral fractures in established osteoporosis. Does not decrease hip fractures	Stop in periods of prolonged immobilization (surgery, long flight, cholestyramine intake)	Men and premenopausal women Side Effects: Worsening of hot flashes, leg cramps, increase risk of deep vein thrombosis

ficacious in preventing vertebral fractures and non-vertebral fractures in postmenopausal women with osteoporosis. Oral aendronate or residronate 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 1a]
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 are efficacious in preventing vertebral fractures. [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).[52] 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 nonfatal 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).[53]

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.[54]

Raloxifene is the only SERM that is available in Saudi Arabia and has been approved for the treatment of osteoporosis.[55] 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.[56] The drug is also associated with a 60%-70% reduction in the risk of breast cancer especially those with positive estrogen receptors.[57] It also decreases low-density lipoprotein cholesterol and total cholesterol; high-density lipoprotein cholesterol decreases and triglycerides increases.[58] The post hoc analysis of secondary endpoints from MORE found no overall change in cardiovascular or cerebrovascular risk but a potential benefit in women at an increased baseline cardiovascular 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.[59]

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.[60] 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*).[61]

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.[54] 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.[62,63] 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.[64] 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.[65,66]

Recommendations:

a. Therapy with hPTH should be restricted to patients with multiple fractures and low bone density (T score below – 2.7). [Evidence 1a]
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 1b]
c. In men with severe osteoporosis, hPTH (1–34) increases BMD at the spine. [Evidence 1b]. 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 ≤ -3 corresponding to –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 RANKL 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.[79] 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).[80] 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.[81] Home hazards assessment by occupational therapist (removing any obstacles that may result in falls) and withdrawal of psychotropic medications are very important interventions.[82,83] 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.[34] 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.[84] In addition, there is strong evidence that physical activity early in life contributes to a higher peak bone mass.[85-87] 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.

Acknowledgments

The authors are grateful for the support of the Vice Deanship of Scientific Research Chairs, Prince Mutaib Chair for Biomarkers of Osteoporosis, Biochemistry Department, College of Science in King Saud University, Riyadh, Saudi Arabia.

REFERENCES

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis and therapy. JAMA 2001;285: 785–95.
2. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 2014; 25(10): 2359–81.
3. Balasubramanian A, Tosi LL, Lane JM, Dirschi DR, Ho PR, O'Malley CD. Declining rates of osteoporosis management following fragility fractures in the U.S., 2000 through 2009. J Bone Joint Surg Am 2014; 96: e52.
4. Cauley JA, Chalhoub D, Kassem Am, Fuleihan Gel-H. Geographic and ethnic disparities in osteoporotic fractures. Nat Rev Endocrinol 2014; 10:338–51.
5. Glucocorticoid-induced osteoporosis: guidelines for prevention and treatment. London: Royal College of Physicians, 2002. https://www.nos.org.uk/netcommunity/document.doc?id=423
6. Wade SW, Strader C, Fitzpatrick LA, Anthony MS, O'Malley CD. Estimating prevalence of osteoporosis: examples from industrialized countries. Arch Osteoporos 2014; 9: 182.
7. Sattui SE, Saag KG. Fracture mortality: associations with epidemiology and osteoporosis treatment. Nat Rev Endocrinol 2014; 10: 592–602.
8. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res 2007; 22: 465–75.
9. Svedboum A, Hernlund E, Ivergard M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: a compendium of country-specific reports. Arch Osteoporos 2013; 8: 137.
10. Bubshait D, Sadat-Ali M. Economic implications of osteoporosis-related femoral fractures in Saudi Arabian society. Calcif Tissue Int 2007;81(6):455–8.
11. Ghannam NN, Hammami MM, Bakheet SM, Khan BA. Bone mineral density of spine and femur in healthy Saudi females: relation to vitamin D status, pregnancy and lactation. Calcif Tissue Int 1999;65: 23–8.
12. El-Desouki MI. Osteoporosis in postmenopausal Saudi women using dual x-ray bone densitometry. Saudi Med J 2003;24:953–6.
13. Sadat-Ali M, Al-Habdan IM, Al-Mulhim FA, El-Hassan AY. Bone mineral density among postmenopausal Saudi women. Saudi Med J 2004; 25(11):1623–5.
14. El-Desouki M. Bone mineral density of the spine and femur in the normal Saudi population. Saudi Med J 1995;16:30–5.
15. Al-Daghri NM, Al-Attas OS, Alokail MS, Alkharfy KM, El-Kholie E, Yousef M, et al. Increased vitamin D supplementation recommended during summer season in the gulf region: a counterintuitive seasonal effect in vitamin D levels in adult, overweight and obese Middle Eastern residents. Clin Endocrinol (Oxf) 2012; 76: 346–50.
16. Al-Musharaf S, Al-Othman A, Al-Daghri NM, Krishnaswamy S, Yusuf DS, Alkharfy KM, et al. Vitamin D deficiency and calcium intake in reference to increased body mass index in children and adolescents. Eur J Pediatr 2012; 171: 1081–6.
17. Al-Turki HA, Sadat-Ali M, Al-Elq AH, Al-Mulhim FA, Al-Ali AK. 25-Hydroxyvitamin D levels among healthy Saudi Arabian Women. Saudi Med J 2008;29 (12):1765–8.
18. Ardawi MS, Maimany AA, Bahksh TM, Nasrat HA, Milaat WA, Al-Raddadi RM. Bone mineral density of the spine and femur in healthy Saudis. Osteoporos Int 2005;16:43-55.
19. El-Desouki MI, Sulimani RA. High Prevalence of Osteoporosis In Saudi Men. Saudi Med J 2007;28(5):774–7.
20. Sadat-Ali M, Al Elq A. Osteoporosis among male Saudi Arabs: a pilot study. Ann Saudi Med 2006;26(6):450–4.
21. Seibel MJ, Cooper MS, Zhou H. Glucocorticoid-induced osteoporosis: mechanisms, management and future perspectives. Lancet Diabetes Endocrinol 2013; 1: 59–70.
22. Rozzoli R, Stevenson JC, Bauer JM, van Loon LJ, Walrand S, Kanis JA, et al. The role of dietary protein and vitamin D in maintaining musculoskeletal health in postmenopausal women: a consensus statement from the European society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Maturitas 2014;79:122–32.
23. Aspray TJ, Bowring C, Fraser W, Gittoes N, Javaid MK, Macdonald H, et al. National osteoporosis society vitamin D guideline summary. Age Ageing 2014;43:592–5.
24. Saag K, Shane E, Boonen S, Marin F, Donley DW, Taylor KA, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. New Engl J Med 2007;357:2028–39.
25. Ito M, Nishida A, Kono J, Kono M, Uetani M, Hayashi K. Which bone densitometry and which skeletal site are clinically useful for monitoring bone mass? Osteoporos Int 2003; 14:959–64.
26. Pisani P, Renna MD, Conversano F, Casciaro E, Muratore M, Quarta E, et al. Screening and early diagnosis of osteoporosis through X-ray and ultrasound based techniques. World J Radiol 2013;5:398–410.
27. Najeh CF, HansD, Li J, Fan B, Fuerst T, He YQ, Tsuda-Futami E, et al. Comparison of six calcaneal quantitative ultrasound devices: precision and hip fractures. Osteoporos Int 2000;11:1051–62.
28. Kanis JA, McCloskey EV, Johansson H, Oden A, Strom O, Bogstrom F. Development and use of FRAX in osteoporosis. Osteoporos Int 2010;21:S407–13.
29. McCloskey EV, Johansson H, Oden A, Kanis JA. From relative risk to absolute fracture risk calculation: the FRAX algorithm. Curr Osteoporos Rep 2009;7:77–83.
30. McCloskey E, Kanis JA. FRAX updates 2012. Curr Opin Rheumatol 2012;24: 554–60.
31. Kanis JA, Hans D, Cooper C, Baim S, Bilezikian JP, Binkley N, et al. Interpretation and use of FRAX in clinical practice. Osteoporos Int 2011;22:2395–411.
32. McCloskey E, Johansson H, Oden A, Kanis JA. Fracture risk assessment. Clin Biochem 2012;45:887–93.
33. American Association of Clinical Endocrinologists 2001 Medical Guidelines for Clinical Practice for the Prevention and Management of Postmenopausal Osteoporosis. Endocr Pract 2001; 7(4):293–312.
34. Herd RJM, Balena R, Blake GM, Ryan PJ, Fogelman I. The prevention of early postmenopausal bone loss by cyclic etidronate therapy: a 2 years, double blind, placebo-controlled study. Am J Med 1997;103:92–9.
35. Harris ST, Watts NB, Genant HK. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. JAMA 1999;282(14):1344–52.
36. McClung MR, Geusens P, Miller PD. Effect of risedronate on the risk of hip fracture in elderly women. N Engl J Med 2001;344(5):333–40.
37. Hosking D, Chilvers CED, Christiansen C. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. N Engl J Med 1998;338:485–92.
38. McClung MR, Clemmesen B, Daifotis A. Alendronate prevents postmenopausal bone loss in women without osteoporosis. A double blind, randomised, controlled trial. Ann Intern Med 1998;128:253–61.
39. Cumming SR, Black DM, Thompson DE. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures. Results from the fracture intervention trial. JAMA 1998;280:2077–82.
40. Pols HA, Felsenberg D, Hanley DA. Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. Fosamax International Trial Study Group. Osteoporos Int 1999;9(5):461–8.
41. Delmas PD. The use of bisphosphonates in the treatment of osteoporosis. Curr Opin Rheumatol 2005;17:462–6.
42. Cryer B, Miller P, Petruschke RA, Chen E, Geba GP, Papp AE. Upper gastrointestinal tolerability of once weekly alendronate 70 mg with concomitant non-steroidal anti-inflammatory drug use. Aliment Pharmacol Ther 2005;21:599–607.
43. Kendler D, Kung AW, Fuleihan Gel-H, Gonzalez JG, Gaines KA, Verbruggen N. Patients with osteoporosis prefer once weekly to once daily dosing with alendronate. Maturitas 2004;48(3):243–51.
44. Calderari F, Burckhardt P. Treatment of osteoporosis with intravenous pamidronate: a retrospective analysis. J Bone Miner Res 1999;14(Suppl 1):S276.
45. Wimalawansa SJ. Intermittent, intravenous pamidronate therapy: highly effective treatment for postmenopausal osteoporosis. J Bone Miner Res 2001;16(Suppl 1): S405.
46. Reid IR, Brown JP, Burckhardt P, Horowitz Z, Richardson P, Trechsel U, et al. Intravenous zoledronic acid in postmenopausal women with low bone mineral density. N Engl J Med 2002;346(9):653–61.
47. Reid IR, Black DM, Eastell R, Bucci-Rechtweg C, Su G, Hue TF, Mesenbrink P, et al. Reduction in the risk of clinical fractures after a single dose of zoledronic acid 5 mg. J Clin Endocrinol Metab 2013;98(2):557–63.
48. Bamias K, Kastritis E, Bamia C, Moulopoulos LA, Melakopoulos I, Bozas G, et al. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. J Clin Oncol 2005;23: 8580–7.
49. Abrahamsen B, Eiken P, Eastell R. Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. J Bone Miner Res 2009; 24:1095–102.
50. Gedmintas L, Solomon DH, Kim SC. Bisphosphonates and risk of subtrochanteric, femoral shaft and atypical femur fracture: A systematic review and meta-analysis. J Bone Miner Res 2013; 28:1729–37.
51. Cooper C, Reginster JY, Cortet B, Diaz-Curiel M, Lorenc RS, Kanis JA, et al. Long-term treatment of osteoporosis in postmenopausal women: a review from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the International Osteoporosis Foundation. Curr Med Res Opin 2012;28: 475–91.
52. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized con-

trolled trial. JAMA 2002;288(3):321–33.
53. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3 years randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (More) Investigators. JAMA 1999;282:637–45.
54. Brown JP, Josse RG. Scientific Advisory Council of the Osteoporosis Society of Canada. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. CMAJ 2002;167(10 suppl)S1–S34 .
55. Khan A, Fortier M, Menopause and Osteoporosis Working Group, Fortier M, Reid R, Abramson BL, et al, Osteoporosis in menopause. J Obstet Gynaecol Can 2014; 36:839–40.
56. Eastell R, Adachi J, Harper K, Sarkar S, Delmas PD, Ensrud K. The effects of raloxifene on incident vertebral fractures in postmenopausal women with osteoporosis: 4-year results from the MORE trial. J Bone Miner Res 2000;15(Suppl 229):F418.
57. Cauley J, Norton L, Lippman M, Eckert S, Krueger KA, Purdie DW, et al. Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Breast Cancer Res Treat 2001;65:125–34.
58. Barrett-Connor E, Grady D, Sashegyi A, Anderson PW, Cox DA, Hoszowski K, et al. Raloxifene and Cardivascular events in osteoporotic postmenopausal women: four years results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. JAMA 2002;287(7):847–57.
59. Barrett-Connor E, Mosca L, Collins P, Geiger MJ, Grady D, Kornitzer M, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med 2006;13: 355(2):125–37.
60. Overgaard K, Hansen MA, Jensen SB, Christiansen C. Effect of salcatonin given intranasally on bone mass and fracture rates in established osteoporosis: a dose response study. BMJ 1992;305:556–61.
61. FDA Panel Says to Stop Salmon Calcitonin. Downloaded March 23, 2014. http://www.medscape.com/viewarticle/780323.
62. Kurland ES, Cosman F, McMahon DJ, Rosen CJ, Lindsay R, Bilezikian JP. Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effects of bone mineral density and bone markers. J Clin Endocrinol Metab 2000;85:3069–70.
63. Orwoll E, Scheele WH, Calancy AD, Adami S, Syveren U, Diez-Perez A. Recombinant human parathyroid hormone (1-34) therapy reduces the incidence of moderate-severe vertebral fractures in men with low bone density. J Bone Miner Res 2001;16(suppl):S 162.
64. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effects of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434–41.
65. Hodsman AB, Fraher LJ, Watson PH, Ostbye T, Sitt LW, Adachi JD, et al. A randomized controlled trial to compare the efficacy of cyclical parathyroid hormone versus cyclical parathyroid hormone and sequential calcitonin to improve bone mass in postmenopausal women with osteoporosis. J Clin Endocrinol Metab 1997;82:620–8.
66. Fujita T, Inoue T, Morii H, Morita R, Norimatsu H, Orimo H, et al. Effect of an intermittent weekly dose of human parathyroid hormone (1-34) on osteoporosis: a randomized double-masked prospective study using three dose levels. Osteoporos Int 1999;9:296–306.
67. Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector T, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 2004; 350:459–68.
68. Reginster JY, Seeman E, De Vernejoul MC. Strontium ranelate reduces the risk of non-vertebral fracture in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) Study. J Clin Endocrinol Metab 2005;90(5):2816–22
69. Reginster JY. Strontium ranelate: an anti-osteoporotic treatment demonstrated vertebral and non-vertebral anti-fracture efficacy over 5 years in postmenopausal osteoporotic women. Oral communication, the 6th European congress on clinical and economic aspects of osteoporosis and osteoarthritis (ECCEO 6, Vienna, Austria, March 2006).
70. Kaufman JM, Audran M, Bianchi G, Braga V, Diaz-Curiel M, Goemaere S, et al. Efficacy and safety of strontium ranelate in the treatment of osteoporosis in men. J Clin Endocrinol Metab 2013;98(2): 592–601.
71. Kaufman JM, Audran M, Bianchi G, Braga V, Diaz-Curiel M, Goemaere S, et al. Efficacy and safety of strontium ranelate in the treatment of osteoporosis in men. Osteoporos Int 2011;22(Suppl 1): s114–s115.
72. [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/01/news_detail_002005.jsp&mid=WC0b01ac058004d5c1]. Downloaded March 24, 2014
73. Lacey DL, Timms E, Tan HL, Kelley MJ, Dunstan CR, Burgess T, et al. Osteoprotegerin (OPG) ligand is a cytokine that regulates osteoclast differentiation and activation. Cell 1998;93:165–76.
74. Hsu H, Lacey DL, Dunstan CR, Solovyev I, Colombero A, Timms E, et al. Tumour necrosis factor receptor family member RANK mediates osteoclast differentiation and activation induced by osteoprotegerin ligand. Proc Natl Acad Sci USA 1999;96:3540–5.
75. Honore P, Luger NM, Sabino MA, Schwei MJ, Rogers SD, Mach DB, et al. Osteoprotegerin blocks bone cancer induced skeletal destruction, skeletal pain and pain-related neurochemical reorganization of the spinal cord. Nat Med 2000;6:521–8.
76. Min H, Morony S, Sarosi L, Dunstan CR, Capparelli C, Scully S, et al. Osteopprotegerin reverses osteoporosis by inhibiting endosteal osteoclasts and prevenst vascular calcification by blocking a process resembling osteoclastogenesis. J Exp Med 2000;192:463–74.
77. Simonet WS, Lacey DL, Dunstan CR, Kelley M, Chang MS, Luthy R, et al. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. Cell 1997;89:309–19.
78. Orwoll E, Teglbjaerg CS, Langdahl BL, Chapurlat R, Czerwinski E, Kendler DL, et al. A randomized, placebo-controlled study of the effects of denosumab for the treatment of men with low bone mineral density. J Clin Endocrinol Metab 2012;97(9): 3161–9.
79. Deprez X, Fardellone P. Nonpharmacologic prevention of osteoporotic fractures. Joint Bone Spine 2003;70:448–57.
80. Kannus P, Parkkari J, Niemi S. Prevention of hip fracture in elderly people with use of a hip protector. N Engl J Med 2000;343(21):1506–13.
81. Sinaki M, Itoi E, Wahner HW, Wollan P, Gelzzcer R, Mullan BP, et al. Stronger back muscles reduce the incidence of vertebral fractures: a prospective 10 year follow-up of postmenopausal women. Bone 2002;30:836–41.
82. Cumming R, Thomas M, Szonyi G, Salkeld G, O'Neill E, Westbury C, et al. Home visit by occupational therapist for assessment and modification of environmental hazards: a randomized controlled trial of falls prevention. J Am Geriatric Soc 1999;47:1397–1402.
83. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Buchner DM. Psychotropic medication withdrawal and a home based exercise program to prevent falls: result of a randomized controlled trial. J Am Geriatr Soc 1999;47:850–3.
84. Yeap SS, Hew FL, Lee JK, Goh EM, Chee W, Mumtaz M, et al. The Malaysian clinical guidance on the management of postmenopausal osteoporosis, 2012: a summary. Int J Rheum Dis 2013;16:30–40.
85. Whitfield GP, Kohrt WM, Pettee Gabriel KK, Rahbar MH, Kohl HW 3rd. Bone mineral density across a range of physical activity volumes: NHANES 2007-2010. Med Sci Sports Exerc 2014; [Epub ahead of print].
86. Al-Othman A, Al-Musharaf S, Al-Daghri NM, Krishnaswamy S, Yusuf DS, Alkharfy KM, Al-Saleh Y, Al-Attas OS, Alokail MS, Moharram O, Sabico S, Chrousos GP. Effect of physical activity and sun exposure on vitamin D status of Saudi children and adolescents. BMC Pediatr 2012;12:92.
87. Strope MA, Nigh P, Carter MI, Lin N, Jiang J, Hinton PS. Physical activity-associated bone loading during adolescence and young adulthood is positively associated with adult bone mineral density in men. Am J Mens Health 2014; [Epub ahead of print].