



## Review Article

# Osteoporosis: A silent disease fraught with fragility fractures in geriatric population

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## ABSTRACT

**Introduction:** As per the Population Census 2011, the elderly (aged 60 years or above) population in India was about 104 million (53 million females and 51 million males). As per United Nation Population Fund and Help Age India report speculated this number to rise to 173 million by 2026. The purpose of this article is to review the available literature regarding the different ways at hand for osteoporosis evaluation and diagnosis, various therapeutic modalities available for treatment and how they can be utilized for prevention of fractures due to insufficiency of bones in consequence of osteoporosis.

**Materials and Methods:** The recommendations and conclusions have been evolved after the thorough review of various literatures on osteoporosis. The evidence based recommendations are based on systemic reviews, meta-analysis and randomized controlled trials (RCTs), wherever available.

**Result:** The evidences and recommendations extracted after extensive review of literature has been provided for diagnosis, assessment of risks for fractures, pharmacological therapies with life style modifications, treatment duration of bisphosphonate therapy.

**Conclusion:** The evidences and recommendations extracted after extensive review of literature helped in formulating guidelines to provide a concised but complete overview of all aspects of osteoporosis that will definitely help all healthcare professionals.

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## 1. Introduction

As per Population Census 2011, the elderly (aged 60 years or above) population in India was about 104 million (53 million females and 51 million males). United Nation Population Fund and Help Age India report speculated this number to rise to 173 million by 2026. Any person attaining the age of 60 years, as per National Policy of Government of India on Older persons, is designated as "senior citizen".<sup>1</sup> It is three times more likely for people above 60 years to be admitted to hospitals, moreover due to multisystem complaints, elderly patients are usually found scattered throughout the general medical wards instead of being confined to Geriatric Medicine wards only.<sup>2-5</sup>

The purpose of this article is to review the available literature regarding different ways at hand for osteoporosis evaluation and diagnosis, various therapeutic modalities of treatment and how they can be utilized for prevention of insufficiency fractures. Another purpose of this article is to disseminate the recommendations and conclusions, which will evolve after the thorough review of various literatures on osteoporosis, to all healthcare professionals. The evidence and recommendations are based on systemic reviews, meta-analysis and randomized controlled trials (RCTs), wherever available.

### 1.1. Osteoporosis: Definition

World Health Organization (WHO) described osteoporosis as a "progressive systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of

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bone tissue with a consequent increase in bone fragility and susceptibility to fractures".<sup>6</sup> Osteoporosis has been implicated in the causation of insufficiency fractures. It has been estimated that more than 1/3<sup>rd</sup> of adult women and 1 in every 5 man will sustain one or more insufficiency fractures in their lifetime.<sup>7</sup> Fragility fractures are common at vertebrae, proximal femur, distal radius, proximal humerus, and pelvis. Major fragility fractures are associated with short survival.<sup>8</sup>

## 1.2. Classification

Osteoporosis is classified as primary and secondary. Primary osteoporosis is commonest and includes postmenopausal osteoporosis (PMO) type-1 affecting females aged 51-70 due to decline in estrogen causing excessive bone resorption with a predominant loss of trabecular bone, and involuntional/ senile osteoporosis type-2 affecting both sexes aged 70 or more due to gradual age related bone loss with a predominant loss of cortical bone.<sup>9,10</sup> Secondary osteoporosis is a manifestation of some underlying disease causing into increased bone loss e.g. endocrinal cause (*Cushing syndrome, hyperparathyroidism*), malignant (*myeloma, metastasis*), non malignant (*rheumatoid arthritis, diabetes*), nutritional (*malnutrition, malabsorption*), drug induced (*glucocorticoids*), disuse induced (*prolonged recumbency, immobilization*).

## 1.3. Risk factors for osteoporosis/fractures

1. Age is directly proportional to osteoporosis and fracture risk irrespective of (BMD).<sup>11</sup>
2. Smoking is strongly linked with osteoporosis and so with fracture risk.<sup>12</sup>
3. Low body mass index (BMI) is implicated as an important risk factor for hip fracture.<sup>13</sup>
4. Personal history of previous fractures at a characteristic location for osteoporosis is predictive of BMD independent doubled risk of fractures in future.<sup>14</sup>
5. Positive family history of osteoporosis and hip fracture is a BMD independent risk.<sup>15</sup>
6. Excessive alcohol - 3 or more units increases the risk. 2 units daily carry no risk.<sup>16</sup>
7. Estrogen deficiency at an early age: The deficiency of estrogen at an early age i.e. before 45 years of age increases the risk of osteoporosis and fractures.<sup>17</sup>
8. Sedentary life style increases the risk of osteoporosis and fractures.<sup>18</sup>
9. Excessive sports in female athlete increases osteoporosis risk as excessive sports may result into "athlete triad" (secondary amenorrhea/anorexia nervosa/osteoporosis).<sup>19</sup>
10. Drugs like Glucocorticoids/anticonvulsants/anticoagulants etc cause osteoporosis.<sup>20</sup>
11. Occupational risk: Certain occupations like astronautics may cause osteoporosis.<sup>21</sup>
12. Environmental risk factors: Though environment around the patients doesn't contribute in causation of osteoporosis but it is definitely implicated in causation of osteoporotic fractures e.g. lack of assistive devices like hand rails, slippery floor, loose throw rugs in the rooms, dark corners and stair cases, obstacles in walking area etc.<sup>22</sup>
13. Personal deficiencies like poor eye sight, poor proprioception, impaired mobility, weak muscles etc are implicated in causation of osteoporotic fractures.<sup>22</sup>
14. Bone mineral density (BMD) though used to diagnose osteoporosis but its values of T-score are also predictive of future fracture risks. For each SD decrease in BMD, the fracture risk enhances by about 2 fold.<sup>23</sup>

## 1.4. Diagnostic tools

A) Bone mineral density (BMD) measurement is considered "gold standard" for diagnosis of osteoporosis and assessment of fracture risk as BMD is inversely proportional to fracture risk. BMD is measured at the cancellous rich sites like vertebra, femoral neck, and distal radius. BMD, (expressed in terms of Z-score and T-score), declines in proportion to the loss of bone mass with advancing age which consequentially increases fragility fracture risk.<sup>24</sup> BMD of a patient is reported as standard deviation above or below the mean BMD of the reference population (age, sex, and ethnicity matched for Z-score and young adult same sex for T-score).

Based on the BMD values of T-score, world health organization (W.H. O) has defined the quality status of bones (Table-1) into four definitions.<sup>25</sup>

The various modalities for BMD evaluation include-SXA (single energy X-ray absorptiometry scan), Central DEXA (dual energy X-ray absorptiometry) approved by W.H. O as standard tool for both axial and peripheral sites, peripheral p-DEXA, Q-CT (quantitative computed tomography), QUS (quantitative ultrasonometry), and MRI.

As recommended by WHO and International Osteoporosis Foundation, femoral neck is the preferred site for DEXA due to its high predictive value for risk of fragility fracture.<sup>26</sup> Though the spine is often used for DEXA but it is not suitable for diagnosis in elderly patients because of the prevalent degenerative changes in spine which increases the BMD artefactually, however spine is a preferred site for assessment of treatment efficacy during the follow up phase.<sup>27</sup> The BMD cutoff values are considered similar for both men and women as evidences are available regarding the similar risk of fracture in either sex for any given age and values of BMD.<sup>28</sup> Use of BMD

**Table 1:** WHO definition of osteoporosis based on BMD §<sup>25</sup>

<b>Classification/ Definition</b>	<b>Bone Mineral Density (BMD)</b>	<b>T-score</b>
Normal	Within 1SD of the mean level for a young adult reference population	T-score at -1 or and above
Osteopenia	Between 1 and 2.5 SD below that of the mean level for a young adult reference population	T-score between -1 and -2.5
Osteoporosis	2.5 SD or more below that of the mean level for a young adult reference population	T-score at or below -2.5
Established Osteoporosis (Severe)	2.5 SD or more below that of the mean level for a young adult reference population fractures	T-score at or below -2.5 With one or more Fractures

value at both femoral neck and spine are advocated by some and the osteoporosis is defined by the lower T-score value among the two sites, however use of multiple site T-score values doesn't improve fracture risk prediction<sup>29</sup> and there is no recommendation for use of multiple sites for diagnosis of osteoporosis, however if, due to some technical reasons BMD evaluation at proximal femur is not possible, assess BMD at spine and if both proximal femur and spine can't be assessed, assess BMD at distal radius.

B) Biochemical bone markers are proteins and peptides released by osteoblasts and osteoclasts during their physiological activities of bone turnover (remodeling), detectable in serum and urine and have been classified as bone formation markers and bone resorption markers. Though these biochemical indices may aid in the diagnosis of osteoporosis and fracture risk but their role have been found more pertinent in the monitoring of treatment.<sup>30</sup>

C) Routine laboratory tests like serum calcium, serum phosphorus, serum alkaline phosphatase, and others are of no consequence in establishing the diagnosis of primary type-1 and type-2 osteoporosis, however, serum and urinary investigations are helpful for the diagnosis of secondary osteoporosis due to some underlying disease.

D) Conventional radiography (X-ray) doesn't show any evidence of osteoporosis until 30%-40% of bone mass is lost. However, conventional radiographs have a role in vertebral fracture assessment majority of which remain undiagnosed<sup>31</sup> because of usually being asymptomatic even if they are moderate or severe in nature but they are strong predictive risk factors for future fractures not only at spine but at other locations as well<sup>32</sup>, and therefore lateral radiographs of dorsolumbar spine should be obtained in high risk patients or if patient gives history of non vertebral fracture after 50 years of age or loss of height of  $\geq 4\text{cm}$ .<sup>33</sup>

### 1.5. Treatment of osteoporosis

The treatment aim is- to prevent fragility fractures by restoring maximum possible BMD, to minimize further bone loss and risk of fractures, and all that can be achieved by two means viz- life style modifications and pharmacotherapy.

#### A) Life style modifications:

#### 1. Balanced diet with an adequate amount of calcium and vitamin D

Increased calcium through diet or supplements enhances BMD to some extent<sup>34</sup> but evidence is lacking that calcium alone reduces fracture risk.<sup>35</sup> However, combination of calcium and vitamin D has been found to reduce the risk of fractures as shown by controlled clinical trials.<sup>3</sup> As per recommendations of Institute of Medicine (IOM) supported by National Osteoporosis Foundation (NOF) women aged 51 and above and men 71 and above should consume 1200mg calcium per day while men aged 50-70 should take 1000mg calcium per day.<sup>36</sup> Calcium in excess of 1200-1500mg/day may increase the risk of nephrolithiasis, cardiovascular disease, and stroke however, scientific literature is controversial over this issue.

Scientific Advisory Committee on Nutrition (SACN) recommended 400IU of vitamin D daily for adults of all ages<sup>37</sup> however, as per another meta-analysis fracture protective daily dose of vitamin D was found to be  $\geq 800$  IU<sup>38</sup> and this amount of dose has also been found helpful in preventing falls.<sup>39</sup> Post menopausal females and men  $>50$  years should be given 800 IU daily and as per certain studies intermittent large doses  $\geq 100,000$  IU are not recommended.<sup>40,41</sup>

#### 2. Cessation of smoking

Smoking is strongly associated with osteoporosis and is harmful to overall health.<sup>3,12-42</sup>

#### 3. Moderation of alcohol intake

Alcohol in moderation poses no negative impact rather may enhance BMD with low risk of fracture, alcohol more than 2 units/day for females and 3 or more units/day for males affect BMD negatively and increases risk of falling and fracture.<sup>3,4,16-42</sup>

#### 4. Regular weight bearing exercises and strategies for fall prevention

Weight bearing and muscle strengthening exercises lower the risk of falling and fractures by improving agility, strength, posture, and balance.<sup>43</sup> The recommended exercises include walking, jogging, Tai Chi, stair climbing, dancing, and mild to moderate impact aerobics to improve coordination and balance as bones and muscles work antigravity while feet and legs bear the body weight, they have been found to decrease the risk of fall upto 25% and

exert beneficial impact on BMD.

Periodic ophthalmic and ENT checkup for optimization of any visual and hearing impairment may help in lowering fall incidences.

Certain fall prevention safety measures must be undertaken at home like avoidance of loose throw rugs, dark corners/staircases, slippery tiles in wash rooms, moreover grab bars in the bathing area and near the toilet seats may help in reducing falls.<sup>22</sup> Hip fracture risk in elderly people may be reduced by using hip protectors<sup>44</sup> but they are usually not well accepted by elderly people.

#### B) *Pharmacotherapy:*

The aim of pharmacotherapy is to alter the bone turnover balance either by enhancing the bone formation or by minimizing the bone resorption. The pharmacological agents available include osteoblastic agents like parathyroid hormone (PTH), anabolic steroids, fluoride, and strontium ranelate, and the antiresorptive agents like Bisphosphonates HRT, SERM (raloxifene), calcitonin, denosumab (RANKL inhibitor) etc. Among the lot bisphosphonates are FDA approved and are considered the “gold standard/1<sup>st</sup> line therapeutic agent” for prevention and treatment, but in case they are not tolerated or contraindicated, PTH and denosumab are considered, rest are less preferred. Drug interventions are based on high level evidences.

##### A) *Bisphosphonates*

Bisphosphonates inhibit bone resorption and are analogues of inorganic pyrophosphate. 1<sup>st</sup> generation bisphosphonates etidronate, medronate, clodronate and 2<sup>nd</sup> generation pamidronate are not approved by FDA for osteoporosis. FDA approved bisphosphonates for prevention and treatment of osteoporosis include 2<sup>nd</sup> generation risedronate, alendronate, ibendronate and 3<sup>rd</sup> generation zoledronic acid.

1. Risedronate is given 5mg tablet/day or 35mg tablet/week orally, or 75mg tablets on two consecutive days per month, or 150mg tablet once a month for the treatment of postmenopausal osteoporosis, male osteoporosis, and glucocorticoids induced osteoporosis.<sup>45</sup> It has been found to reduce vertebral fractures by 41%-49% and non vertebral fractures by 36% over a period of 3 years.<sup>46</sup> Must be taken after an overnight fast, first thing in the morning with 8 oz (240ml) plain water (no other liquid), patient must remain upright (sitting/standing) and wait at least 30 min before taking the first drink, food, or other medication.
2. Alendronate is given 10mg tablet/day or 70mg tablet/week orally for the treatment of postmenopausal osteoporosis, male osteoporosis, and glucocorticoids induced osteoporosis. For prevention dose is 5mg tablet/day or 35mg tablet /week. It has been found to decrease vertebral and hip fractures by 50% over a period of 3 years.<sup>47</sup> Must be taken after an overnight

fast, first thing in the morning with 8 oz (240ml) plain water (no other liquid), patient must remain upright (sitting/standing) and wait at least 30 min before taking the first drink, food, or other medication.

3. Ibendronate is given 150mg tablet once a month orally, or 3mg/3ml by intravenous injection over 15-30 seconds every three months (serum creatinine should be checked before each injection) for the treatment of postmenopausal osteoporosis, male osteoporosis, and glucocorticoids induced osteoporosis. Oral preparation is also approved for prevention. It has been found to reduce vertebral fractures by 50% over 3 years however, its effect on non vertebral fracture has not been documented.<sup>48</sup> Must be taken after an overnight fast, first thing in the morning with 8 oz (240ml) plain water (no other liquid), patient must remain upright (sitting/standing) and wait at least 60 min before taking the first drink/food/other medication.
4. Zoledronic acid is given 5mg once a year by intravenous infusion (creatinine clearance should be estimated before administration) over a period of 15 minutes for the treatment of postmenopausal osteoporosis, male osteoporosis, and glucocorticoids induced osteoporosis and once every 2 years for prevention. Patient needs to be well hydrated and pre-treated with acetaminophen to thwart the risk of acute phase reaction (fever, headache, arthralgia, or myalgia). It has been found to reduce vertebral fractures by 70%, hip fractures by 41%, and non vertebral fractures by 25% over a period of 3 years.<sup>49</sup> It may cause renal failure and atrial fibrillation a serious complication. It is contraindicated if creatinine clearance is less than 35 ml/min or in cases of acute renal impairment.

#### Bisphosphonate safety profile

All oral bisphosphonates may cause gastrointestinal side effects like oesophagitis and gastritis, may affect renal functions, may cause osteonecrosis of jaw (ONJ) after prolonged use and this risk is more if treatment exceeds 5 years duration,<sup>50</sup> may cause low trauma atypical femur fractures, usually bilateral, after long term use usually >5 years often preceded by pain in thigh or groin region arousing suspicion of such fractures that need investigation like bilateral X-ray femur or by MRI or radionuclide bone scan if need be in cases of high clinical suspicion<sup>51</sup> and if detected surgical fixation may be required in some while some may be managed conservatively and the bisphosphonate therapy should be discontinued.

#### Bisphosphonate contraindications

All bisphosphonates oral or intravenous are contraindicated in hypocalcaemia, hypersensitivity to bisphosphonates, oesophageal stricture/achalasia that delays oesophageal emptying, severe renal impairment (GFR  $\geq$  30-35 ml/min), inability to sit or stand upright for

at least 30-60 min, and pregnancy/lactation.

#### Duration of bisphosphonate therapy and drug holiday

The rare complications like atypical femoral fractures and osteonecrosis of jaw after prolonged use (> 5years) of bisphosphonates resulted into debates regarding its optimum duration. It is observed that bisphosphonates are retained in bone for variable periods and so its beneficial effects may persist for some time even if treatment is discontinued. In case of alendronate treatment withdrawal results in decrease in BMD after 2-3 years<sup>52</sup> and after 1-2 years in case of ibendronate and risedronate<sup>53</sup> while in case of zolidronic acid withdrawal after 3 years of treatment resulted into minimal decrease in BMD without treatment for next 3 years.<sup>54</sup> As most studies are limited to 3 years the recommendations for prolonged use and drug holiday are based on limited evidences available from studies on treatment extensions in postmenopausal females.<sup>55</sup> In case of treatment discontinuation, the fracture risk need to be reassessed if a new fracture occurs irrespective of its timing and if there is no new fracture event, the fracture risk should be reassessed after 18 months to 3 years.

Based on these evidences, treatment with alendronate, risedronate or ibendronate should be reviewed after 5 years of continuous treatment and after 3 years in case of zolidronic acid. Fracture risk in such treated patients is reassessed by BMD of femoral neck through FRAX<sup>56</sup> to decide about the discontinuation of treatment for some time however, if T-score of hip BMD is  $\geq -2.5$ , treatment should be continued irrespective of the FRAX derived probability of fracture. Continuation of treatment beyond 3-5 yrs (3 for intravenous, 5 for oral agents) as per above evidences may be recommended for patients aged 75 or more, previous hip/vertebra fracture, new fracture despite regular treatment, patient on oral  $\geq 7.5$ mg prednisolone/day.

#### B) Teriparatide (recombinant human parathyroid hormone (PTH) 1-34)

Approved by FDA for osteoporosis in postmenopausal females, men and glucocorticoids induced osteoporosis. It minimizes the vertebral fracture risk by 65% and non-vertebral fractures by 53% after 18 months of treatment.<sup>5</sup>

As both osteoblasts and osteoclasts respond to PTH, it has a dual mode of action. It behaves as an osteoclastic agent enhancing the bone resorption when its levels are continuously elevated, while it behaves as an osteoblastic agent with an anabolic effect most marked in cancellous bone when it is administered intermittently.

Dosage: Daily subcutaneous injection of 20 $\mu$ g into thigh or abdominal wall for 18 to 24 months, available as a prefilled syringe with dosage for a month. ? Nausea, dizziness, and leg cramps are common side effects. Bone malignancy/metastasis and hypercalcemia are contraindications. Transient elevation of serum calcium may occur so calcium intake should be restricted. Whenever treatment is stopped, bone loss resumes rapidly, alternative

therapy is usually required to protect BMD.

#### C) Denosumab (RANKL/RANKL inhibitor)

It is a fully humanized monoclonal antibody against Receptor Activator of Nuclear factor Kappa B Ligand (RANKL) and is FDA approved drug for postmenopausal osteoporosis as it minimizes risk of vertebral fractures by 68% and hip fractures by 40% over 3 years.<sup>57</sup> It is also useful in enhancing BMD in men on treatment for prostate carcinoma with gonadotropin reducing hormone drugs that may result in enhanced risk of fragility fractures. Dosage: 60mg every 6months by subcutaneous injection. It may cause hypocalcemia, skin infection (cellulitis) and skin rash, osteonecrosis of jaw when used at high doses, and rarely atypical fracture femur. Calcium levels before each dose should be assessed and adequate calcium and vitamin D should be taken to avoid hypocalcemia. Whenever treatment is stopped, bone loss resumes rapidly, alternative therapy is usually required to protect BMD.

#### D) Hormone replacement therapy (HRT)

Estrogen alone or in combination with progesterone is FDA approved for osteoporosis prevention and treatment in females. It minimizes risk of vertebral and hip fractures by 34% after 5 years of therapy.<sup>58</sup> Dosage: 0.625mg-1.25mg oestrogen  $\pm$  2.5mg medroxyprogesteron tablets orally/day with no recommended duration, however, in view of the unfavorable side effects, HRT should be used in the lowest effective doses for the shortest duration and should be considered mainly for females within first few years of menopause. Whenever treatment is stopped, bone loss resumes rapidly, alternative therapy is usually required to protect BMD. HRT carries risk of recurrence of menstruation (vaginal bleeding), however, this can be overcome to certain extent by using combination therapy, breast tenderness/carcinoma, endometrial carcinoma, ovarian carcinoma, myocardial infarction, congestive heart failure, strokes, deep vein thrombosis, pulmonary embolism, and Nausea/headache/mood swings.

#### E) Raloxifene (SERM)

It is a selective estrogen receptor modulator (SERM) that inhibits bone resorption and acts either as agonist in bones or as antagonist in breast and uterus at specific estrogen receptors preventing bone loss at all skeletal sites and is approved by FDA for prevention and treatment of postmenopausal osteoporosis and has been found to minimize risk of vertebral fractures by 55% but its role in minimizing non-vertebral fractures is not documented.<sup>59</sup> Raloxifene doesn't carry the risk of endometrial, breast, or ovarian carcinoma while sustaining all benefits of HRT. But it carries an enhanced risk of hot flushes, leg cramps, and thromboembolic events and also their effect on BMD enhancement is less vis-à-vis HRT. Dosage: Currently raloxifene is the most favored and approved SERM agent for the treatment of osteoporosis and is given 60mg per day with or without food.

#### F) Calcitonin

It is FDA approved for osteoporosis in 5 years postmenopausal women in whom other treatments may not be suitable. It doesn't enhance BMD in early postmenopausal years. It minimizes risk of vertebral fractures by 30% but not the risk of non-vertebral fractures.<sup>60</sup> It is though much less effective vis-à-vis HRT or bisphosphonates but it is of value in patients with vertebral fractures as it inhibits the prostaglandins and stimulates the  $\beta$ -endorphins resulting into an effective analgesia. Dosage: Available as Salmon calcitonin 10 times more potent than naturally produced human calcitonin. It is given as nasal spray of 200 IU daily in alternate nostrils or as intramuscular injection of 100 IU daily. It may cause nausea, loss of appetite, facial flushing, rhinitis, epistaxis, and allergic reactions, atrophy of nasal mucosa if used in single nostril or for a longer duration. The continued therapy with salmon calcitonin needs periodic evaluation due to possible risk of malignancy however a definitive causal relationship could not be established.

## 2. Conclusion

The selection of a pharmacological agent for treatment of osteoporosis depends upon its efficacy in reducing the risk of fragility fracture across the skeletal sites, its adverse effects, and the cost of the drug as these agents are intended for a long term use. Bisphosphonates like alendronate and risedronate of generic formulations being quite cost effective with broad spectrum anti fracture efficacy have become the first line treatment options in majority patients. Parenteral bisphosphonates and denosumab are also effective and affordable. Raloxifene and HRT are also effective and cheap but carry risk of complications. Teriparatide is costly so restricted for at very high risk patients for spine fracture.

After completion of 5 years therapy with oral bisphosphonates and 3 years therapy with intravenous zoledronic acid, the treatment should be reviewed for discontinuation or continuation of treatment. Treatment with bisphosphonates beyond 3-5 years can be recommended to be continued in patients aged  $\geq 75$  years, in patients with a history of vertebral or hip fracture, in patients sustaining fracture while on treatment, and in patients on concomitant oral glucocorticoid therapy.

In the event of treatment discontinuation, fracture risk should be reassessed after about 18 month to 3 years for need of treatment resumption however, the fracture risk should be reassessed early if a new fracture occurs regardless of when it happened.

No evidence based recommendations are available to guide decisions beyond 10 years of therapy and so such patients should be evaluated on individual basis.

## 3. Source of Funding

None.

## 4. Conflict of Interest

None.

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### Author biography

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