

## Pharmacological and Non-pharmacological Means for Prevention of Fractures among Elderly

### Abstract

Fractures are major cause of morbidity, mortality, and healthcare and social services expenditure in elderly. Fractures often have multifactorial etiologies and the condition emerges due to the interaction between the different predisposing and precipitating factors. One of the most common causes leading to fractures after minimal trauma in older people is osteoporosis. The objective of this article is to describe the clinical concept and summarize the evidence and to explain the future directions for research, focusing on specific issues related to prevent fracture in the elderly. This study reviewed the scientific literature addressing strategies for primary and secondary prevention of fractures among elderly in the context of pharmacological and non-pharmacological means. A growing body of scientific evidence supports the use of both non-pharmacological and pharmacological interventions for the prevention of fracture. Research on these interventions has yielded positive outcomes in fracture rates. The bisphosphonates and vitamin D and calcium supplements are the preferred therapy for prevention of osteoporotic fractures. Weight-bearing exercise and reducing home hazards have beneficial effects in reducing the incidence of falls and consequently reduce fractures. Prevention of fractures in elderly consists of therapy and prevention of osteoporosis, fall prevention, and using injury-site protection by high-risk elderly patients. Special consideration needs to be taken to reduce home hazard, and falls prevention education can be recommended to the elderly with history of fall or mobility limitations. Future research to prevent fractures in elderly population should not only concentrate on improving bone density and strength but also need to be focused on falls reduction strategies.

**Keywords:** *Accidental falls, elderly, exercises, fracture, hip protectors, home hazards, lifestyle, osteoporosis, prevention*

### Introduction

Fractures represent one of the most important causes of morbidity, mortality and healthcare and social services expenditure in elderly. The incidence of fractures of pelvis, hip, vertebrae, humerus, radius, and ankle increase with advance age. A fracture of elderly person often has multifactorial etiologies, and the condition emerges due to the interaction between the different predisposing and precipitating factors. One of the most common causes leading to fracture after minimal trauma in older people is osteoporosis. Evidence indicates that both pharmacological and non-pharmacological intervention methods have shown benefit in reducing the incidence of fractures in the elderly population and improving daily life activities and quality of life in survivors. Falls are one of the main causes

of injury in people age 65 and older and are responsible for 56% of hospitalization for trauma and for 6% of urgent hospitalization in these age group; 5%–10% of them have fractures.<sup>[1,2]</sup> Current evidence suggests that both falls and risk of falls are prevented in community settings by individuals regularly carrying out specific physical activities and improving the safety of their homes. Nevertheless, a decrease in fracture rate has been recently observed, owing to several factors including awareness about osteoporosis and the danger of falls. Many improvements have been introduced in the care of these patients, including improved surgical devices, earlier mobilization, prophylactic administration of anti-osteoporosis, and increased rate of admission into rehabilitation unit. In this article, we present an evaluation of current literature relating to the prevention of fractures among elderly in the context of pharmacological and non-pharmacological means.

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### Materials and Methods

This article was designed to review previous studies and summarize the current knowledge and controversies related to primary and secondary prevention of fractures among elderly in the context of pharmacological and non-pharmacological means. Searches were performed on MEDLINE, Cochrane Library, and Google Scholar databases from their inception to July 2017. The search was updated in June 2018. No date restrictions were placed on the search. We used the key words “Elderly, accidental falls, fracture, hip protectors, exercises, osteoporosis, prevention, lifestyle, home hazards.” Studies were selected based on the following inclusion criteria: papers in English language and published in peer-reviewed journal were considered. Review articles, clinical trial, cross-sectional study, meta-analyses, letter, editorial, textbook chapters, case reports, practice guidelines, and biomechanical studies were gathered to augment overall knowledge and to identify research articles or data not obtained using the search engines. Studies dealing with fractures or fractures prevention in elderly subjects were considered. Studies dealing with surgical complications, mortality rate, surgical method, and fracture in young or children are excluded. From the search results, articles with irrelevant titles were discounted, with the remaining abstracts examined for relevance. Reference listings of the remaining articles were also searched and scrutinized for relevance.

### Overview of common fractures in elderly

Worldwide, osteoporosis causes more than 9 million fractures annually, of which 1.6 million were at the hip, 1.7 million at the forearm, and 1.4 million were clinical vertebral fractures.<sup>[3]</sup> Estimates indicate that 50% of women and 20% of men over 50 years of age will experience an osteoporosis-related fracture.<sup>[4]</sup> The incidence varies substantially from one population to another. In the United States, the number of osteoporosis-related fractures was estimated to exceed 2 million in 2005. Nonvertebral fractures were estimated to account for 73% of the total number of fractures. Women age 65 years and older accounted for 74% of all fractures.<sup>[5]</sup> In the European Union, approximately 3.5 million new fragility fractures occur annually, comprising 620,000 hip fractures, 520,000 vertebral fractures, 560,000 forearm fractures, and 1,800,000 other fractures (i.e., fractures of the pelvis, rib, humerus, tibia, fibula, clavicle, scapula, sternum, and other femoral fractures).<sup>[6]</sup> In African and Asian countries lying somewhere between. However, with the rapid increase in the ageing population and increased longevity, it has been estimated that more than 50% of hip fractures will be concentrated in Asia.

### Assessment of fracture risk factors in elderly

Bone mineral density (BMD) is the standard measure for the diagnosis of osteoporosis and the assessment

of fracture risk. Several additional clinical factors have been identified which contribute significantly to risk of fracture independently of BMD. These include age, sex, race, height, weight, body mass index, prior fragility fracture, smoking, excess alcohol, family history of hip fracture, rheumatoid arthritis, and the use of oral glucocorticoids.<sup>[7]</sup> These risk factors in conjunction with BMD can be integrated to provide estimates of fracture probability using web-based algorithm design called FRAX (Fracture Risk Assessment Tool). FRAX calculates the 10-year probability of a major osteoporotic-related fracture in the proximal part of the humerus, the wrist, or the hip or spine. In addition, BMD considers only the density of the bone and fails in measuring bone microarchitecture. Recently, a new tool to assess osteoporosis and fracture risk, called Trabecular Bone Score (TBS), has been developed. TBS is a texture parameter related to bone microarchitecture that may provide skeletal information that is not captured from the standard BMD measurement. TBS has been shown to have predictive value for fracture independent of fracture probabilities using the FRAX.<sup>[8,9]</sup> However, some other factors, including risk of falls and poor vision, causes of secondary osteoporosis such as hypogonadism, or other risks associated with bone quality, such as chronic kidney disease, may increase fracture risk.<sup>[10]</sup> Cognitive impairment, stroke, and lack of urine control were reported to be associated with increased risk of severe fall-related fractures.<sup>[10]</sup> Measurements of biochemical bone marker levels can also be used to assess fracture risk and help select patients for therapy.<sup>[11]</sup> Vitamin D deficiency has been associated with increased fall rates and fractures.<sup>[12]</sup> Therefore, vitamin D levels' estimation can also be used to assess fracture risk. Other measurements such as serum calcium, creatinine, alkaline phosphatase, liver enzymes and complete blood count, serum protein electrophoresis, thyroid function tests, and parathyroid hormone level are useful for identifying some forms of metabolic bone diseases and exclude severe underlying illnesses.

Many drugs commonly used by elderly people have been reported to be associated with increased risk of fall-related fractures. These include antihypertensive agents, diuretics,  $\beta$ -blockers, sedatives and hypnotics, neuroleptics and antipsychotics, antidepressants, narcotics, and nonsteroidal anti-inflammatory drugs.<sup>[13]</sup> However, the risks and benefits need to be fully considered when initiating these medications in those at risk of falls. Reducing medication use can dramatically decrease falls. In one study, withdrawal of psychotropic medications resulted in a 66% reduction in the rate of falls.<sup>[14,15]</sup>

### Pharmacologic fracture prevention in elderly

#### Calcium and vitamin D

Calcium and vitamin D have long been recognized as important and required to protect bone and prevent

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osteoporotic fractures. Several evidence-based reviews have investigated the efficacy of vitamin D and calcium supplementation on bone loss and fracture reduction in elderly. A recent Cochrane review suggests that there is high-quality evidence that calcium combined with vitamin D results in small and significant reductions in the risk of hip fracture (16%), vertebral fracture (14%), any non-vertebral fracture (11%).<sup>[16]</sup> Similarly, another Cochrane review demonstrated that vitamin D supplementation alone is unlikely to be effective in preventing hip fracture (11 trials, 27,693 participants; risk ratio (RR) 1.12, 95% confidence interval (CI) 0.98–1.29) or any new fracture (15 trials, 28,271 participants; RR 1.03, 95% CI 0.96–1.11).<sup>[17]</sup> Treatment with calcium at a dosage of 1200 mg or more has been shown to be more effective than with doses less than 1200 mg in fracture prevention, and with vitamin D doses of 800 IU or more than with doses less than 800 IU.<sup>[18]</sup> However, it is clear from these studies that the concomitant use of calcium and vitamin D supplementation is recommended in elderly, particularly in those at risk of marginal and low vitamin D status. It is generally recommended to intake 800 IU/day of vitamin D and 1000 mg of calcium per day.<sup>[19]</sup> Nevertheless, the risks associated with calcium supplements are not uncommon in elderly patients. Recent scientific evidence, however, suggests that elevated consumption of calcium supplements may raise the risk for cardiovascular disease (CVD) and can be connected with accelerated deposit of calcium in blood-vessel walls. However, the purported CVD risk associated with total calcium intake may depend on the source of calcium intake.<sup>[20]</sup> Intake of calcium from food sources has not been shown to increase CVD risk, whereas a signal for increased risk of myocardial infarction (MI) among calcium supplement users has been reported. Food remains the best source of calcium; however, calcium supplements should be considered when dietary intake of calcium is inadequate.<sup>[21]</sup>

### Bisphosphonates

Bisphosphonates are potent inhibitors of osteoclasts, have an established role in improving the bone density, and prevent osteoporotic fractures. More recently, evidence shows that bisphosphonates decrease the risk of overall osteoporotic fracture [odds ratio (OR) 0.62;  $P < 0.001$ ], vertebral fracture (OR 0.55;  $P < 0.001$ ), and non-vertebral fracture (OR 0.73;  $P < 0.001$ ) in postmenopausal women with osteoporosis.<sup>[22]</sup> This finding is similar to the results of the meta-analysis studies conducted by Zhou *et al.*, which found that the relative risk reduction in vertebral fractures ranged from 0.55 to 0.61.<sup>[23]</sup> One large randomized study evaluated in a 2008 Cochrane review suggests 10 mg bisphosphonates per day, both clinically important and statistically significant reductions in vertebral, non-vertebral, hip, and wrist fractures.<sup>[24]</sup>

### Calcitonin

Calcitonin is a potent osteoclast inhibitor through receptors, and it has been approved for the treatment of osteoporosis

and other diseases involving accelerated bone turnover. Several studies have shown its effects to reduce bone turnover, stabilize or increase bone density, preserve or improve microarchitecture, and improve mineralization.<sup>[25,26]</sup> The effects of calcitonin on fracture prevention rate are controversial. The most relevant clinical trial to evaluate the effect of calcitonin in the prevention of fractures was the Prevent Recurrence of Osteoporotic Fractures (PROOF) study, a 5-year double-blind, randomized, placebo-controlled trial showing that salmon calcitonin nasal spray at a dosage of 200 IU/day can reduce the risk of vertebral osteoporotic fractures by 33% [relative risk (RR) = 0.67; 95% CI 0.47–0.97;  $P = 0.03$ ].<sup>[27]</sup> However, the 100 and 400 IU/day dosages did not significantly reduce vertebral fracture risk. Effects on nonvertebral fractures were not significant (RR = 0.80; 95% CI 0.59–1.09;  $P = 0.16$ ).<sup>[26]</sup> However, more studies are necessary to confirm these results. Nevertheless, few safety concerns have been raised for calcitonin. In 2012, the European Medicines Agency suspended calcitonin nasal spray from the market and limited the duration of use of other calcitonin products due to a putative association with cancer. Current understanding of the biology and mechanism of action of salmon calcitonin does not support a role as an oncogenor tumor-accelerating agent. Such evidence is lacking in preclinical carcinogenicity, genotoxicity, and mutagenicity studies and, in general, biological plausibility. Consideration of all the available data suggests that the association between calcitonin and cancer is weak.<sup>[28]</sup> Further studies are necessary to conclude a causal association between calcitonin and cancer.

### Teriparatide

Teriparatide is a potent anabolic agent used to treat osteoporosis in women or men with a high risk for bone fracture. They act by directly stimulating bone formation and improving bone mass quantity and quality. High-quality evidence showed that treatment with teriparatide increases in BMD and low incidences of new vertebral and nonvertebral fractures.<sup>[29]</sup> However, the high costs and subcutaneous administration of teriparatide make it less attractive for some elderly people with osteoporosis, although it is an effective alternative for those who have severe osteoporosis, cannot tolerate oral bisphosphonates, or who have failed other therapies.<sup>[30]</sup>

### Estrogen

Multiple studies have shown that estrogen replacement therapy has a beneficial effect on the reduction of fractures in patients with osteoporosis. In a meta-analysis of 21 studies, estrogen therapy replacement was shown to reduce nonvertebral fractures by 27%,<sup>[31]</sup> and in another meta-analysis of 13 studies, there was a significant reduction 33% of vertebral fractures.<sup>[32]</sup> However, there is some evidence that estrogen when given together with calcium and vitamin D will be more effective in reduction of osteoporotic fractures.<sup>[33]</sup>



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### Selective estrogen receptor modulators

Selective estrogen receptor modulators (SERMs) have a beneficial effect on bone. These SERMs inhibited bone turnover and prevented bone loss caused by estrogen deficiency. Raloxifene, second-generation SERM, has been approved for the prevention and treatment of post-menopausal osteoporosis. A systemic review that included 15 studies reported a statistically significant increase in BMD of the lumbar spine, but not the hip region, a low incidence of vertebral fracture, decrease in markers of bone turnover, and improved hip structural geometry.<sup>[34]</sup> For lasofoxifene, another SERM, the randomized, double-blind, placebo-controlled study Postmenopausal Evaluation and Risk Reduction with Lasofoxifene (PEARL) clinical trial for vertebral fracture risk in postmenopausal women showed a 42% reduction compared with placebo ( $P < 0.01$ ), and 24% reductions in the absolute incidence of nonvertebral fracture.<sup>[35]</sup> In a 3-year randomized, double-blind, placebo-controlled study ( $N = 7,492$ ), bazedoxifene 20 mg and bazedoxifene 40 mg significantly ( $P < 0.05$ ) reduced the risk of new vertebral fractures by 42%, compared with placebo in postmenopausal women with osteoporosis.<sup>[36]</sup> In a second 2-year extension of the 3-year in a same study, the relative risk reductions were 36.5% ( $P < 0.001$ ). Bazedoxifene had no effect on the overall incidence of nonvertebral fractures (12.0%; placebo, 10.8%).<sup>[36]</sup>

### Denosumab

A new therapeutic advance in the treatment of postmenopausal osteoporosis is denosumab. Denosumab is a human monoclonal antibody which reduces the risk of fracture by inhibiting osteoclast formation, decreasing bone resorption, and increasing BMD. In a large randomized, placebo-controlled trial, denosumab has been reducing the risk of vertebral fractures by 68% for 3 years. The risk of hip fractures was diminished by 40% and nonvertebral fractures by 20% in postmenopausal women.<sup>[37]</sup>

### Non-pharmacologic fracture prevention in elderly

#### Hip protectors

Hip protectors are one of multifactorial interventions for fall and fracture prevention in residential, high-risk patients. In a systematic review by Santesso *et al.* which included data of 14 studies (11,808 participants) conducted in nursing or residential care settings, moderate quality evidence for a small reduction in hip fracture risk (RR 0.82, 95% CI 0.67–1.00) was found; the absolute effect is 11 fewer people (95% CI from 20 fewer to 0) per 1000 having a hip fracture when provided with hip protectors.<sup>[38]</sup> However, not all elderly people with a high risk of hip fracture will agree to use hip protectors and in those who do, long-term adherence may decrease. Therefore, adherence is a major problem in assessing the effectiveness of hip protectors in preventing fractures. To increase adherence, it is necessary

to educate older persons who are at risk on the dangers of hip fractures and the value of hip protectors as a preventive device. Moreover, little data are available on the cost-effectiveness of hip protectors. The most commonly reported complications with hip protectors are skin irritation. A Cochrane review of 18 trials found that the incidence of adverse events while wearing hip protectors, including skin irritation, ranged from 0% to 5%.<sup>[39]</sup>

#### Exercise

Physical exercise has demonstrated its beneficial effects in reducing the risk of the number of fall. In a meta-analysis that included data from 25 studies, the investigators revealed that the exercise training programs prevented or reversed almost 1% of bone loss per year in both lumbar spine and femoral neck for both pre- and postmenopausal women.<sup>[40]</sup> Exercise training appears to significantly reduce fear of falling<sup>[41]</sup> and the risk and number of falls.<sup>[42]</sup> The risk and incidence of fractures are also reduced among active people.<sup>[43]</sup> Kujala *et al.* detected a positive association between physical activity and reduced incidence of hip fracture (hazard ratio 0.38, 95% CI 0.16–0.91).<sup>[44]</sup> In a systematic review by Cadore *et al.*, the investigators evaluated the Effects of Different Exercise Interventions on Risk of Falls, Gait Ability, and Balance in Physically Frail Older Adults.<sup>[45]</sup> The investigators found that the mean decrease in the incidence of falls after the physical training period ranged from 22% to 58%, the mean improvement in balance ranged from 5% to 80%, the mean improvement in gait ability ranged from 4% to 50%, and the mean increase in muscle strength ranged from 6% to 60%.<sup>[46]</sup>

Some exercises such as weight-bearing exercise, especially resistance exercise, appear to have the greatest effects on BMD.<sup>[47]</sup> One study revealed that people who did resistance training had increased BMD compared with those who did not do such training. Furthermore, several studies have shown that this type of exercise intervention can improve neuromuscular activity, muscle mass, strength, power, and functional capacity.<sup>[46]</sup> In a study conducted by Fiatarone *et al.*, it was found that the resistance training groups improved their habitual gait velocities and stair-climbing abilities and enhanced the leg muscle strength outcomes ( $P < 0.001$ ).<sup>[48]</sup> Another study revealed statistically significant improvements in the Timed Up and Go test, gait speed, after 12 weeks of resistance training that was performed three times per week.<sup>[49]</sup> Moreover, Tai Chi exercises have also demonstrated improved balance, gait speed, muscle strength, and quality of life in elderly. Recent studies including a systematic review have demonstrated that Tai Chi interventions have beneficial effects in reducing the risk of falls through improving the balance.<sup>[46,50,51]</sup> The mean improvement in balance after Tai Chi exercise has been reported to range from 5% to 80%.<sup>[46]</sup> For the above-mentioned exercises, multicomponent exercise programs appear to be important

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in preventing loss of BMD and reduce the incidence of falls and consequently reduce fractures.

### Lifestyle

Certain lifestyle factors, including nutrition, smoking, and alcohol consumption, are known to play an important role in bone health. In terms of nutrition, accumulating evidence suggests that vegetable and fruit are potentially an efficacious intervention for preventing and reversing bone mass and structural loss in postmenopausal women. According to a recent meta-analysis, increased intake of vegetables, but not fruits, was found to be associated with a lower risk of hip fracture.<sup>[52]</sup> Several biological mechanisms have been proposed to explain this relation, most of them concerned with the possibility of the role of potassium, magnesium, calcium, vitamin K, and antioxidant (e.g., vitamin C, carotene, and carotenoids) content in fruits and vegetables in maintaining bone health; these elements can increase osteoclastogenesis and osteoclastic differentiation or inhibit osteoblastic differentiation.<sup>[53-55]</sup>

Alcohol consumption is considered a critical modifiable factor that affects bone health. Available evidence from a systemic review found a lower risk of hip fracture among persons consuming up to 0.5 to 1 drinks per day, and persons consuming more than 2 drinks per day had a higher risk of hip fracture.<sup>[56]</sup> Another study found that women consuming 1.8 drinks or more per day had a higher risk of wrist fracture compared with abstainers.<sup>[57]</sup> The link between vertebral osteoporotic fractures and alcohol has been reported in one study; the investigators found increased odds of fracture among men who consumed more than 0.3 drinks per day compared with abstainers [adjusted OR 4.61 (1.19–17.90)].<sup>[58]</sup>

In several meta-analyses, smoking has been recognized as a risk factor for low BMD and increased risk of fracture.<sup>[59-62]</sup> It is hard to determine whether a decrease in bone density and increased risk of fracture are due to smoking itself or to other risk factors common among smokers. However, several biological effects of smoking on bone have been suggested. For example, smoking decreased intestinal calcium absorption and increased metabolism or decreased production of oestrogen, which may be affect indirectly on bone strength.<sup>[63]</sup> Furthermore, smoking may contribute to impaired physical balance and to increased risk of falling. However, a healthier lifestyle advocated reducing the risk of fractures.

### Home hazards

Environmental hazards potentially include poor stairway design and disrepair, inadequate lighting, clutter, slippery floors, unsecured mats and rugs, and unstable furniture and obstructed walkways, among many others. In one-half to two-thirds of falls, the environment factors are considered the major risk factor.<sup>[64]</sup> Many older people

attribute their falls to trips or slips inside the home or immediate home surroundings.<sup>[65]</sup> Unsecured mats and rugs, and unstable furniture are among the home hazard most frequently mentioned in the literature as unsafe and potentially increasing fall risk.<sup>[66]</sup> Numerous studies have found that floor mats in hallways, bathmats, loose rugs/mats, and flooring were among the most common home hazard associated with falls resulting in hip fractures.<sup>[66,67]</sup> However, the existence of home hazards alone is insufficient to cause falls, and the interaction between a history of falls mobility limitations, and their home hazards appears to be more important.<sup>[68]</sup> Patients and their families should be advised to eliminate home hazards such as loose or frayed rugs and unstable furniture. Furthermore, adequate lighting, bathroom grab rails, raised toilet seat, secure stairway banisters, raising or lowering bed, and an easily accessible alarm system needed to be considered particularly in older person with previous history of fall or functional disabilities.

### Patients' education

Falls prevention education has been demonstrated to have beneficial effects on the lower fall risk and fall incidence rates. A recent randomized trial of elderly patients on hospital rehabilitation wards found that patients' education program consists of multimedia information (DVD and workbook) about falls and falls prevention, and tailored follow-up by a trained health professional significantly reduced falls and injurious falls.<sup>[69,70]</sup> The intervention reduced falls on hospital rehabilitation wards by 40% and injury resulting from falls by 35%.<sup>[68]</sup> Feedback from 473 patients who received the education identified that patients found the education enjoyable and stated that the education helps raise their awareness, knowledge, and confidence to actively engage in falls prevention strategies.<sup>[71]</sup> Therefore, falls prevention education can be recommended to elderly pateints. However, future research may need to be done to explore the cost-effectiveness of patient education for the prevention of falls.

### Conclusions

Prevention of fractures in elderly consists of therapy and prevention of osteoporosis, fall prevention, and using injury-site protection by high-risk elderly patients; concerning therapy and prevention of osteoporosis, maximizing peak bone mass, preventing bone loss by regular exercise, in particular weight-bearing and resistance exercise, calcium, and vitamin D, and use of evidence-based anti-osteoporotic drugs to treatment of established osteoporosis. For fall prevention, regular strength and balance training, reducing psychotropic medication, smoking cessation, avoiding excessive alcohol intake, and increased intake of vegetables. Hip protectors need to be considered for those at high risk of hip fracture and to reduce recurrent fracture. Special consideration can be taken to reduce home hazard, and falls prevention

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education can be recommended to the elderly with history of fall or mobility limitations.

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