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Review Article

Osteoporosis treatment in postmenopausal women with pre-existing fracture

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Abstract

Osteoporotic patients with existing fractures are at substantially higher risk of subsequent fractures than those free of fractures. Given the lack of head-to-head comparison trials, indirect comparison of various antiosteoporosis treatments may be an alternative way to develop a preliminary idea. The objective of this study is to conduct a systematic review of antiosteoporosis treatment clinical trials that have investigated on patients with existing fractures. All the results of randomized placebo-controlled trials of the available antiosteoporosis treatments, including bisphosphonates, selective estrogen receptor modulators, calcitonin, strontium ranelate, and agents derived from parathyroid hormone, on patients with existing fractures were summarized. All the antiosteoporotic agents had significant efficacy in increasing lumbar spine bone mineral density and reduction in the occurrence of any new vertebral fractures. All interventions provided gains in quality-adjusted life-years compared with patients without treatment. The results from an indirect comparison must be interpreted with caution due to heterogeneous study design, discrepancies of disease severity at baseline, and differences in analytical methodologies. The devastating complications subsequent to osteoporotic fractures create medical and financial burdens; therefore, treatment of patients with osteoporotic fractures should be positioned in the top priority in the utilization of medical resources.

Keywords: bone; fracture; osteoporosis; postmenopausal women

Introduction

Osteoporosis is a disease defined by decreased bone mass and alteration of microarchitecture, which results in increased bone fragility and subsequent fracture [1]. With the aging of the world's population, the incidence of osteoporosis will inevitably increase year by year. Osteoporotic fracture leads to debilitating health outcomes and consequently a considerable economic burden on the health care system. In the United States, approximately 10 million Americans are diagnosed with osteoporosis each year, leading to a substantial financial burden of annual direct medical costs estimated at $17 billion–20 billion [2]. In Europe, the estimated costs of treating osteoporotic fractures in women by 2050 will be €76.7 billion [3]. Asia has the highest increment in the elderly population; therefore, osteoporotic fracture should grow to be a noticeable health issue. The incidence rate of hip fractures in Asia could rise to 45% by

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the year 2050 [4]. In Taiwan, the incidences of vertebral fracture in females and males above 65 years of age are approximately 20% and 12.5%, respectively [5]. The annual reported cases of hip fractures in the Taiwanese populations aged 65 years or older increased from 8384 in 1996 to 13,075 in 2002, with overall incidence increment of 30% during 7 years [6].

Advancing age, lack of estrogen, vitamin D and/or calcium deficiency, low body weight or low body mass index (BMI), immobility, current smoking, excessive alcohol consumption, endocrine diseases, the use of certain medications (such as glucocorticoids, gonadotropin-releasing hormone agonists, or chemotherapy-induced early menopause), surgical intervention, and family history have been described as risk factors of osteoporosis [7−15]. Some factors, such as poor postural balance, visual impairment, frailty, or sedation medication, also put patients at a risk of osteoporotic fracture [16].

There is ample evidence suggesting that an existing osteoporosis-induced fracture heralds another impending fracture [17−20], and many subsequent fractures have occurred within 1 year of the original incident [21]. The relative risk of refracture events among patients with prevalent vertebral fracture was reported to be 4.7−7.4 [19,22,23]. Therefore, patients with osteoporosis-related fractures should be treated more vigorously.

Pharmacologic therapies to treat osteoporosis have been extensively explored; however, a comparison of fracture risk reduction among therapies is difficult due to the lack of head-to-head studies. Patients with existing fracture are at substantially higher risk of subsequent fracture than those free of fractures [24]. The objective of this review is to focus on those clinical trials whose participants had a fracture at study entry, and to summarize the results with respect to changes in bone mineral density (BMD), bone turnover markers, fracture risk, quality of life, and cost-effectiveness. Consideration of these results can aid in making the most appropriate judgment when selecting the optimal treatment plan, and in attaining the most beneficial effect in the prevention of subsequent fracture.

For this manuscript, a nonsystematic Pubmed search of published data was performed with the following search terms: osteoporosis and fracture. The search was conducted from 1995 to 2000 and used only articles published in English.

Pharmacologic therapies for osteoporosis

The available antiosteoporosis treatments include bisphosphonates, selective estrogen receptor modulators (SERMs), calcitonin, strontium ranelate, and agents derived from parathyroid hormone (PTH). Fig. 1 illustrates the mechanism of action of these antiosteoporosis medications.

Bisphosphonates

Bisphosphonates currently approved for the prevention and treatment of osteoporosis is a class of pyrophosphate

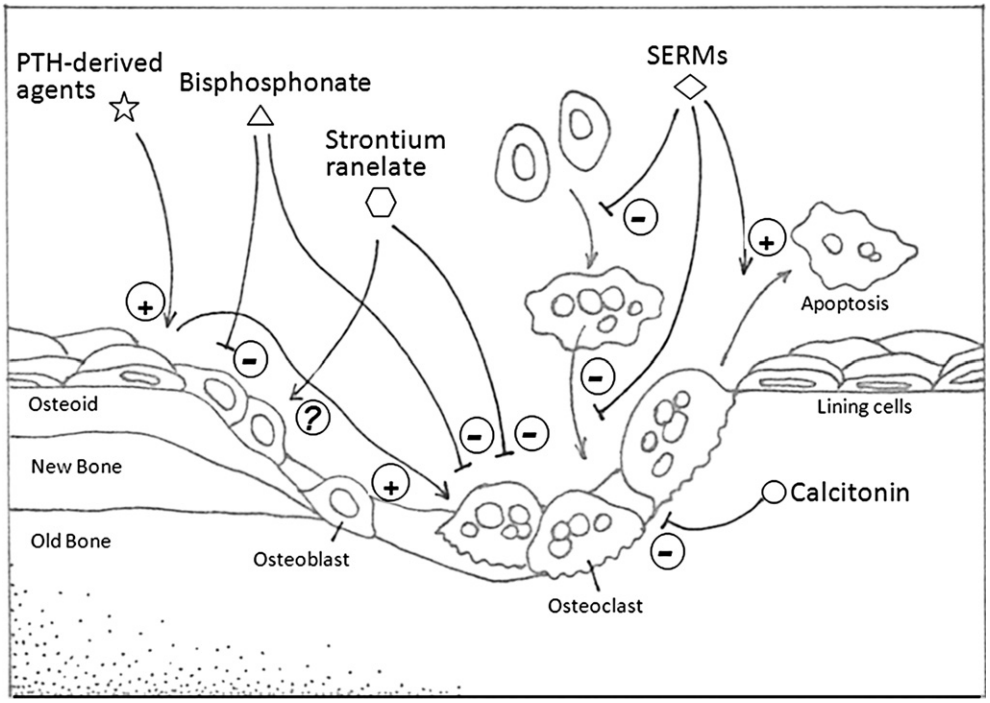

Fig. 1. Mechanisms of action of antiosteoporosis treatments. Bone mass and bone quality are maintained by a continuous renewal of the matrix, a process called bone remodeling. Bone remodeling is regulated by two cell types: osteoclasts, which resorb the calcified bone matrix, and osteoblasts, which are responsible for new bone matrix synthesis. Osteoporosis is a disease characterized by reduced bone strength which results from an imbalance in bone resorption relative to bone formation. Bisphosphonates, selective estrogen receptor modulators (SERMs), and calcitonin are classical inhibitors of bone resorption that restore skeletal balance by reducing bone turnover. The exact mechanism of action of strontium is not known but anti-resorptive effects have been shown. Agents derived from parathyroid hormone (PTH) lead to anabolic effects on the skeleton if administered intermittently and at low dose. The main anabolic actions of PTH involve having mitogenic properties for osteoblastic cells and decreasing osteoblastic apoptosis.

analogues with a nitrogen-containing component [25]. A number of bisphosphonates have been synthesized, and the presence of a nitrogen moiety is directly related to the potency of the bisphosphonate agent [26]. Bisphosphonates have a strong affinity for hydroxyapatite crystals in bone and inhibit osteoclast activity and recruitment via blocking the enzyme farnesyl diphosphate synthase in the mevalonate pathway [26].

SERMs

SERMs are nonsteroidal agents that bind on the estrogen receptor (ER) [27]. Unlike estrogens, which are uniformly agonists, and anti-estrogens, which are uniformly antagonists, the SERMs exert selective agonist or antagonist effects on various estrogen target tissues [28]. A given target tissue has its own distinct ER expression. The underlying mechanisms of the unique pharmacology of SERMs are mainly based on the bulky side-chain which leads to a differential ER conformation on ligand binding or a differential interaction between coregulator proteins and ER [28,29].

Calcitonin

Calcitonin is an endogenous polypeptide hormone produced in humans primarily by the parafollicular cells of the thyroid [30]. The physiologic function of calcitonin is mainly to reduce blood calcium via the metabolic pathway in bone, intestines, and kidney. In bone, calcitonin inhibits resorption activity by decreasing osteoclast formation and suppressing osteoclast attachment [31].

Strontium ranelate

Strontium ranelate is a combination of an organic moiety (ranelic acid) and two atoms of stable nonradioactive strontium [32]. Nonclinical *in vitro* data indicate that strontium increased bone formation in certain preosteoblastic cell systems, and inhibited the bone resorption activity of osteoclasts [33]. However, strontium's mechanism of action is not known. Available in vivo studies in ovariectomized animals provide weak support only in terms of efficacy for the intended clinical use [34]. It has been demonstrated that strontium is predominately distributed into calcified tissues [35].

Teriparatide

Teriparatide ($^{1\text{-}34}$PTH) is a recombinant formulation compromising the first 34 N-terminal amino acids of PTH that increases bone mass and improves bone microstructure via a daily subcutaneous administration. PTH-stimulates bone formation and resorption and can increase or decrease bone mass, depending on the mode and dose of administration [36]. Continuous administration can lead to deleterious consequences for the skeleton. However, intermittent low dose administration of PTH results in an increase in the number and activity of osteoblasts, leading to an increase in bone mass and an improvement in skeletal architecture [37].

Review of antiosteoporosis treatment trials

Table 1 [14,16,29,30,33–35,37] is a summary of the clinical trials that have included postmenopausal women with preexisting fracture as a subpopulation.

Bisphosphonates

Alendronate

The Fracture Intervention Trial (FIT) was a randomized, double-masked, placebo-controlled trial testing the hypothesis that alendronate reduces fracture rates in women with osteoporosis [38]. The FIT had two arms: the vertebral fracture arm and the clinical fracture arm. The vertebral fracture arm included 2027 women with osteoporosis and at least one preexisting vertebral fracture. Baseline vertebral fractures were defined as any of the ratios of vertebral heights being more than 3 standard deviations (SDs) below the mean population norm for that vertebral level. A new morphometric vertebral fracture was defined as a decrease of 20% and greater than 4 mm in any vertebral height from baseline to end of the study.

Risedronate

The Vertebral Efficacy with Risedronate Therapy (VERT) trial was a randomized, double blind, placebo-controlled trial testing the efficacy and safety of risedronate in postmenopausal women with established osteoporosis [24,39]. The VERT Multinational study (VERT-MN) enrolled 1226 postmenopausal women at 80 centers in Europe and Australia; the patients were required to have two or more prevalent vertebral fractures [24]. The VERT North American Study (VERT-NA) included 2458 women younger than 85 years with at least one vertebral fracture at baseline and who were enrolled from 110 centers in North America [40]. Both trials had extension studies with an additional 2 years of treatment to determine the long-term efficacy and safety of risedronate.

Patients in the VERT-MN study were randomized to receive risedronate 2.5 or 5 mg/day or a placebo; the 2.5 mg group was discontinued by protocol amendment after 2 years. The identification of prevalent or incident fractures was based on quantitative and semiquantitative assessments [41,42]. An incident new vertebral fracture was defined quantitatively as a loss of 15% or more in the anterior, posterior, or middle vertebral height in a vertebra that was normal at baseline, and semiquantitatively as a change from grade 0 (normal) to grades 1 (mild), 2 (moderate), or 3 (severe). A worsening vertebral fracture was recorded if there was a change of 4 mm or more in vertebral height or a change in grade in a previously fractured vertebra.

Ibandronate

The oral iBandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE) was a multinational, double-blind, placebo-controlled, randomized trial composed of 2946 postmenopausal women with one to four prevalent vertebral fractures and a BMD T-score less than −2.0 in at least one vertebra [43]. Participants were randomly assigned to

Table 1
Antiosteoporosis treatment among patients with osteoporosis and prevalent fractures.

Agent	Trial (duration)	Number of patients	Study population			Primary endpoint	Reference
			Age and postmenopausal duration (years)	Criteria: Prevalent fracture [BMD (T-score)]	Patient population by region		
Bisphosphonates							
Alendronate	FIT-VFA (3 y)	2027	55−81	≥1 vertebral FX (FN ≤ −2.1)	USA 97% Caucasian, 1% Asian, and 1% African-American	New morphometric vertebral FX	29
Risedronate	VERT-NA (3 y)	2458	≤ 85 & menopause ≥5	≥2 vertebral FX or ≥1 vertebral FX [LS ≤ −2 (≤ 0.84 g/cm)]	North America	New vertebral FX	30
	VERT-MN (3 y)	1226	≤ 85 & menopause ≥5	≥2 vertebral FX	Europe and Australia	New vertebral FX	16
Ibandronate	BONE (3 y)	2946	55-80 & menopause ≥5	1−4 vertebral FX (LS ≤ −2.0)	North America & Europe	New morphometric vertebral FX	33
Raloxifene	MORE (4 y)	2304	Menopause ≥2	≥2 moderate vertebral FX or ≥1 moderate or severe vertebral FX or ≥2 mild vertebral FX (LS or FN ≤ −2.5)	96% white	Incident vertebral FX	14
Calcitonin	PROOF (5 y)	1255	Menopause ≥1	1-5 TS or LS vertebral compression FX (LS ≤ −2.0)	USA and UK	New vertebral FX	34
Strontium Ranelate	SOTI (5 y)	1649	≥50 & menopause ≥5	At least 1 FX (LS ≤ −2 (≤ 0.84 g/cm))	Europe & Australia	New vertebral FX	35
Teriparatide	FPT (21 mos)	1637	42−86 & menopause ≥5	≥2 T or vertebral FX or ≤ 2 T or vertebral FX (LS or hip ≤ −1.0)	North America, Europe, Australia, Argentina, Israel	New vertebral FX	37

BMD = bone mineral density; FN = femoral neck; FX = fracture; LS = lumbar spine; TS = thoracic spine.

one of three groups: placebo, continuous oral ibandronate with a daily dose of 2.5 mg, or intermittent oral ibandronate with 20 mg every other day for 12 doses every 3 months. The diagnosis of fractures was based on morphometric criteria and was further confirmed by qualitative assessment. A new vertebral fracture was diagnosed with a relative height reduction of at least 20% and an absolute decrease of at least 4 mm in any vertebral body height from the baseline radiograph.

SERMs

Raloxifene

Raloxifene hydrochloride, a SERM, is a nonsteroidal benzothiophene that has similar binding ability to ERs as estrogen. Raloxifene is the only SERM currently approved for the prevention and treatment of osteoporosis. The Multiple Outcomes of Raloxifene Evaluation (MORE) study was a multicenter, randomized, blinded, placebo-controlled trial examining the effect of raloxifene on the skeleton [22]. A total of 7705 postmenopausal women were enrolled into this study. Prior to randomization, patients were divided into two study groups, based on any existing vertebral fractures at the time of radiographic screening. Eventually, 2641 women had a low bone mineral density T score and 1 or more moderate or severe vertebral fractures or two or more mild vertebral fractures. The BMD entry criteria depended on the T score of femoral neck or lumbar spine BMD of less than −2.5. Vertebral fractures were evaluated using a semiquantitative scale for each vertebra (T4−L4), with grading scores of 0 to 3 for none to severe fractures. A mild vertebral fracture corresponded to a 20%−25% reduction in height, and a moderate vertebral fracture corresponded to a 25%−40% reduction from expected vertebral height. A new fracture was defined as an incident fracture (grade change of at least one as well as a quantitative definition of a decrease in anterior, mid, or posterior vertebral height of at least 20%, and at least 4 mm), which was absent at baseline.

Within each substudy, women were randomly assigned into treatment groups with either a placebo, or 60 mg or 120 mg of raloxifene. There was a significantly lower incidence of fractures in the women given 120 mg of raloxifene compared with those treated with 60 mg of raloxifene; however, 60 mg per day has been approved as a treatment dose of raloxifene, so we will just focus on the anti-fracture results from this subgroup.

Calcitonin

The Prevent Recurrence of Osteoporotic Fractures (PROOF) study was a randomized, double-blind, placebo-controlled, multicenter trial investigating the effect of nasal spray calcitonin on reducing the risk of recurrent vertebral fractures [44]. A total of 1255 women with osteoporosis who had been postmenopausal for at least 1 year and had one to five prevalent thoracic or lumbar compression fractures were included. The definition of osteoporosis was based on lumbar spine BMD at least two SDs below normal for women aged 30 years. Baseline vertebral fractures were defined as having a ratio of vertebral heights more than three SDs below the

mean population norm for that vertebral level by quantitative morphometry, and a fracture grade 1 or greater using a semiquantitative evaluation. A new vertebral fracture was defined as a decrease of 20% and at least 4 mm in the height of any vertebral body by quantitative morphometry, as well as a change in the fracture grade from 0 to 1 or greater by semiquantitative evaluation.

This study participants were randomly assigned to receive a placebo or salmon calcitonin at a daily dose of 100, 200, or 400 IU. The standardized radiographic evaluation revealed that 334 enrolled patients did not meet the inclusion criteria of one to five vertebral fractures, and one-third of them had no vertebral fractures. This study was not designed to have power to discriminate between doses, and 200 IU per day was approved as the dose for treating osteoporosis. Although there were a relatively small number of patients for an anti-fracture assessment, we will still use the 200 IU/d result as a comparison reference.

Strontium ranelate

The Spinal Osteoporosis Therapeutic Intervention (SOTI) was a 5-year multicenter, placebo-controlled, randomized, double blind trial [45]. The study was designed to evaluate the effect of strontium ranelate on the incidence of new vertebral fractures in 1649 postmenopausal women with osteoporosis who had previously had one or more vertebral fractures. Patients were randomized to receive 2 g of oral strontium ranelate per day or a placebo, and clinical effectiveness was evaluated during a 3-year period. Vertebral radiographs were obtained annually, and measurements of bone mineral density were performed every 6 months.

The other trial was the Treatment of Peripheral Osteoporosis Study (TPOS), which was undertaken to assess the effect of strontium ranelate on non-vertebral and vertebral fractures in postmenopausal women with osteoporosis in a 5-year, double-blind, placebo-controlled trial [46]. A total of 5,091 postmenopausal women with osteoporosis were randomized to receive either strontium ranelate at 2 g/day or a placebo for 5 years.

Teriparatide

The Fracture Prevention Trial (FPT) was a multicenter, randomized, placebo-controlled trial testing the effect of teriparatide treatment on postmenopausal women with prior vertebral fractures [47]. All participants underwent radiography of the thoracic and lumbar spine at baseline, to grade vertebrae as normal, mildly, moderately, or severely deformed based on a decrease in vertebral height of approximately 20%–25%, 26%–40%, or more than 40%, respectively. Only those women with at least one moderate fracture or two mild fractures were eligible for enrollment. The mean BMD of the spine was 2.6 SDs below the mean value of normal young white women. A new fracture was reported when a normal vertebra became deformed, but not with a worsening of preexisting deformities.

A total of 1637 women were randomly assigned into three arms: placebo, or teriparatide at a dose of 20 μg/day or 40 μg/day. Since 20 μg is used as the treatment dose for osteoporosis, this review will focus on the effect of the 20 μg daily dose.

Effects on bone markers and bone tissue

Most available therapies, including bisphosphonates, raloxifene, and calcitonin, decrease the rate of bone turnover by suppressing the level of bone resorption markers coupled with a subsequent reduction of bone formation activity. Data from the SOTI trial indicated strontium ranelate had an uncoupling effect on the bone remodeling process, with decreased bone resorption markers, but a slight increase in bone formation markers compared with placebo therapy [48]. There was no available information in terms of changes in bone turnover markers from the FPT trial.

The effects on bone remodeling or the mechanisms of action can be also obtained from bone histomorphometric parameters of bone turnover, although the study design or a small sample size probably limits the application of this kind of survey. Histologic and histomorphometric analyses of baseline and post-treatment biopsy samples in the VERT-NA, as well as an extension study with an additional 2-year treatment of risedronate, showed a reduction of bone turnover without any evidence of pathologic findings [44,48].

Through data on comparative changes in bone biopsy or biochemical markers of bone turnover, some head-to-head studies have provided us a more precise idea about the mechanism of action in the bone tissue. In the comparative study of teriparatide and alendronate, not surprisingly, bone formation indices of histomorphometry were significantly greater in the teriparatide group than in the alendronate group [49]. A study comparing the effects of teriparatide and strontium ranelate on bone biopsies and biochemical markers of bone turnover confirmed that the bone-forming activity (anabolic effect) of teriparatide was superior to that of strontium ranelate treatment [50]. However, a small, but significant reduction of bone formation marker procollagen type I N-propeptide (PINP) was found with strontium ranelate treatment.

Summary of effects on bone markers and bone tissue

Bisphosphonates, raloxifene, and calcitonin have a direct inhibitory effect on osteoclastic bone resorption, although coupled subsequently with a suppression of osteoblastic bone formation. The function of strontium ranelate on stimulating bone formation is equivocal due to the lack of robust evidence. Based on the change in biochemical bone formation markers as well as the proof of bone biopsy, it is reassuring that teriparatide is an effective bone-formation agent. Table 2 [14,30,33–35] is a summary of the bone turnover marker changes with the anti-osteoporotic therapies used in the prospective clinical trials.

Effects on BMD

All the antiresorptive agents were of the same treatment duration. The percentage of BMD changes in the PROOF trial

Table 2
Summary of bone turnover markers change of antiosteoporotic therapies from prospective clinical trials.

Agent	Study population	Bone turnover markers	% change of bone turnover markers at study endpoint	*p* value	Reference
Bisphosphonate					
Alendronate		NA	NA		
Risedronate	32% of the total study population	Serum BSAP	−33% at Y 3 (−7%placebo)	NA	30
		Deoxypyridinoline/creatinine	−26% at Y 3 (−1%placebo)	NA	
Ibandronate		CTX/creatinine	−65.3% at Y 3 (continuous 2.5 mg/d) from baseline −52.7% at Y 3 (intermittent 20 mg)	<0.0001	33
		NTX/creatinine	−68.3% at Y 3 (continuous 2.5 mg/d) −59.2% at Y 3 (intermittent 20 mg)	<0.0001	
		Serum osteocalcin	−35.8% at Y 3 (continuous 2.5 mg/d) −40.9% at Y 3 (intermittent 20 mg)	<0.0001	
Raloxifene		Serum osteocalcin	−17.7% at Mo 36 (tx−26.3, placebo−8.6%)	<0.001	14
		Urinary CTX	−25.9% at Mo 36 (tx−34.0, placebo−8.1)	<0.001	
Calcitonin		Serum CTX	−12% (vs placebo)	0.01	34
		Serum BSAP	Decreased but NA	<0.05	
		Serum osteocalcin	Decreased but NA	NS	
Strontium Ranelate	20% of the total study population	Serum CTX	−12.2% at Mo 3 (vs placebo)	<0.001	35
		Serum BSAP	+8.1 at Mo 3	<0.001	
Teriparatide		NA	NA		

BSAP = bone-specific alkaline phosphatase; CTX = C-telopeptide of the α-chain of type I collagen; NA = not applicable; NTX = N-telopeptide of the α-chain of type I collagen.

was not shown in the report. In addition, it should be noted that the value of reference for BMD change was the placebo instead of the baseline in the BONE and MORE trials [22,42].

In summary, all of the anti-osteoporotic agents had significant efficacy in increasing lumbar spine BMD. The bisphosphonates had a similar effect on changes in BMD, ranging from 5.9% for risedronate to 6.5% for ibandronate 2.5 mg/day [24,38,42]. Among all the anti-resorptive agents, strontium ranelate had the most apparent impact on BMD, not only at the lumbar spine but also at the femoral neck and hip bone [44,45]. However, the striking increment of BMD was probably associated with the high atomic mass of strontium, while strontium atoms replaced calcium atoms in the bone hydroxyapatite crystals. Compared with other antiosteoporosis agents, teriparatide, with bone-formation preference, achieved a remarkable elevation in BMD within a relatively short treatment period [36,41]. Table 3 [14,16,29,30,33–35,37,42] summarizes the clinical efficacy of the anti-osteoporotic

Table 3
Summary of BMD percentage changes of antiosteoporotic therapies from prospective clinical trials.

Agent	BMD measurement	BMD at baseline (T-score)	Percentage change in BMD from baseline to endpoint									Reference
			Lumbar spine	Femoral neck	Trochanter	Intertrochanter	Total hip	Distal radius	Shaft of radius	Proximal forearm	Total-body (Hologic)	
Bisphosphonate												
Alendronate	3 y		6.2***	4.1***	6.1***		4.7***			1.6***	1.8***	29
Risedronate	3 y (VERT-NA)		5.4*†	1.6*†	3.3*†				0.2			30
	3 y (VERT-MN)	−2.8	5.9***†	3.1***†	6.4***†				2.1***†			16
	5 y (VERT-MN)		9.3*	2.2*	5.7*							42
Ibandronate	3 y	−2.8	6.5****[a]	2.8****[a]	5.5****[a]		3.4****[a]					33
			5.7****[b]	2.4****[b]	5.2****[b]		2.9****[b]					
Raloxifene	3 y		2.6***	2.1***								14
Calcitonin	5 y		1.2**	NS	NS							34
Strontium Ranelate	3 y		12.7***†	7.2***†			8.6***†					35
Teriparatide	21 mo	−2.6	9.7***†	2.8***†	3.5***†	2.6***†	2.6***†	−0.1	−2.1		0.6 (Hologic)/3.1 (Lunar)***†	37

BMD = bone mineral density.
***$p < 0.001$ versus placebo.
*$^{\dagger}p < 0.05$ versus baseline and placebo.
*$p < 0.05$ versus baseline.
***$^{\dagger}p < 0.001$ versus baseline.
****$p < 0.0001$ versus baseline.
**$p < 0.01$ versus placebo.
[a] Continuous ibandronate 2.5 mg/day; [b] Intermittent ibandronate 20 mg every other day with 12 doses every 3 months.

therapies in relation to BMD, as reported in the large prospective clinical trials.

Effects on fracture risks

Since the objective of osteoporosis treatment in all studies was to prevent fractures, the methods of assessing vertebral fractures, involving both semiquantitative and morphometric evaluations, were similar in these trials (Table 4 [14,16,29,30,33–35,37,42]).

Bisphosphonates

Alendronate

From the analysis of the vertebral fracture arm of the FIT, the primary endpoint of one or more new radiographic vertebral fractures was 47% lower in women given alendronate than in the placebo group [38]. Compared with the placebo arm, significantly fewer women in the alendronate group had clinical vertebral fractures. In terms of non-vertebral fractures, there was no significant difference between patients receiving alendronate and patients in the placebo arm.

Risedronate

The VERT-NA study found the cumulative incidence of new vertebral fractures during a 3-year risedronate treatment regimen was lower by 49%, and there was a 33% reduction in nonvertebral fractures compared with the placebo [24]. The VERT-MN study report shows that the reduction of fracture risk was observed in the first year to be 61%. Comparing with the control arm, the vertebral and non-vertebral fracture risk in the risedronate 5 mg group was reduced by 49% and 33%, respectively. An extension study of the VERT-MN trial, with only one-third of the women randomized in the original study, demonstrated a continuing effect on the reduction of new vertebral fractures (59% reduction in risk; $P = 0.01$) [51]. A pooled summary of these two randomized studies indicated a risk reduction of new vertebral fractures by 62% and of multiple new vertebral fractures by 90% after treatment with risedronate 5 mg/day for 1 year versus the control [52].

Ibandronate

With regard to the effect on new vertebral fracture reduction, the BONE study observed a significant reduction in the relative risk of new or worsening vertebral fractures after a 2-year treatment with ibandronate [42]. At the end of the study, the relative risk reductions compared with the placebo were 62% and 50% for the daily and intermittent groups, respectively. An effect of ibandronate on the risk of a new clinical vertebral fracture was also found. Nevertheless, a significant relative risk reduction of clinical non-vertebral fractures was found only in those patients with a baseline femoral neck BMD T-score less than −3.0 and who were treated with oral daily ibandronate [53].

Raloxifene

In the MORE study, the reduction in the relative risk of one or more new vertebral fractures for the subset of women with prevalent vertebral fractures and daily treatment with 60 mg of raloxifene was 30% [22]. In addition, women receiving raloxifene had a risk reduction in non-vertebral fractures, although the results were from an analysis of pooled raloxifene groups.

Strontium ranelate

For strontium ranelate, the effect on fracture reduction was apparent from the end of the first year of treatment. Over the entire 3-year study period, patients in the strontium ranelate group had a 41% lower risk of a new vertebral fracture than those in the placebo group [44]. A new fracture diagnosed by quantitative assessment was confirmed by semi-quantitative evaluation, as well.

Calcitonin

Compared with the placebo, there was a 33% reduction in the relative risk of developing a new vertebral fracture in patients treated with calcitonin 200 IU, and the number of multiple new vertebral fractures was reduced by 35% [43]. Compared with the placebo, there was a nonsignificant reduction in the risk of non-vertebral fractures and hip fractures in the calcitonin 200-IU group.

Table 4
Summary of antifracture efficacy of antiosteoporotic therapies from prospective clinical trials.

Agent	Trial	Fracture End Point (duration)	Fracture with Treatment n/N (%)	Fracture with Placebo n/N (%)	Absolute risk reduction	RR of Fracture (95% CI)	*p* value	Reference
Bisphosphonate								
Alendronate	FIT-1	Vertebral (3 Y)	78/1022 (8.0)	145/1005 (15.0)	7.0	0.53 (0.41–0.68)	<0.001	29
Risedronate	VERT-NA	Vertebral (3 Y)	61/540 (11.3)	93/571 (16.3)	5.0	0.59 (0.43–0.82)	0.003	30
	VERT-MN	Vertebral (3 Y)	53/293 (18.1)	89/307 (29.0)	10.9	0.51 (0.36–0.73)	<0.001	16
		Vertebral (5 Y)	15/109 (13.8)	29/103 (28.2)	11.8	0.41 (0.21–0.81)	0.01	42
Ibandronate 2.5 mg	BONE	Vertebral (3 Y)	NA (4.68)	NA (9.56)	4.88	0.38 (0.25–0.59)	0.0001	33
Ibandronate 20 mg	BONE	Vertebral (3 Y)	NA (4.90)	NA (9.56)	4.66	0.50 (0.34–0.74)	0.0006	33
Raloxifene	MORE	Vertebral (3 Y)	113/769 (14.7)	163/770 (21.2)	6.5	0.7 (0.6–0.9)		14
Calcitonin	PROOF	Vertebral (5 Y)	51/287 (18)	70/270 (26)	8	0.67 (0.47– 0.97)	0.03	34
Strontium Ranelate	SOTI	Vertebral (3 Y)	150/719 (20.9)	237/723 (32.8)	11.9	0.59 (0.48–0.73)	<0.001	35
Teriparatide	FPT	Vertebral (21 M)	22/444 (5.0)	64/448 (14.3)	9.3	0.35 (0.22–0.55)	<0.001	37

Antivertebral fractures efficacy from of antiosteoporotic prospective clinical trials [3–35,37,42] CI = confidence interval, M = months, N = patient number in treatment group, n = patient number of incident fractures, RR = relative risk.

Teriparatide

For recurrent vertebral fractures, the teriparatide 20 μg daily dose reduced the risk of one or more fractures and two or more fractures by 65% and 77%, respectively [46]. Furthermore, women treated with the 20-μg dose of teriparatide were 35% and 53% less likely to have 1 or more new non-vertebral fractures and fragility fractures, respectively. Based on the information of cumulative incidence, the protective effects of parathyroid hormone treatment became evident after 9−12 months. The incidence of new hip fractures was not significantly different between the treatment group and the placebo group; however, this finding was probably related to the small numbers when performing analysis by the site of fracture.

Summary of effects on antifracture risks

All of these antiosteoporotic fracture studies provided strong evidence to support an absolute reduction in the occurrence of any new vertebral fracture in the previously fractured studied population compared with the placebo population, ranging from one-third to more than three-fourths (Fig. 2). However, the effects on the reduction of non-vertebral fractures are not so significant. The main reason is that they are rare events; in the majority of anti-fracture site-specific analyses, the small number of hip fractures usually precluded a meaningful statistical analysis.

Effects on back pain

Chronic back pain associated with or without vertebral fracture is a great challenge to health care professionals and profoundly affect the quality of life to the patients. Emerging evidence suggests that, in addition to reducing the incidence of vertebral fractures, calcitonin, intravenous bisphosphonates, strontium ranelate, and teriparatide may also have a direct effect on bone pain [54].

Strontium ranelate

Over the 3-year treatment period, back pain was reported by 17.7% of the women in the strontium ranelate group and by 21.3% in the placebo group ($P = 0.07$) [44]. The number of patients without back pain was significantly increased by 30% ($P = 0.005$) [55]. More patients were without back pain ($P = 0.005$) with strontium ranelate than with the placebo over a 4-year period [56].

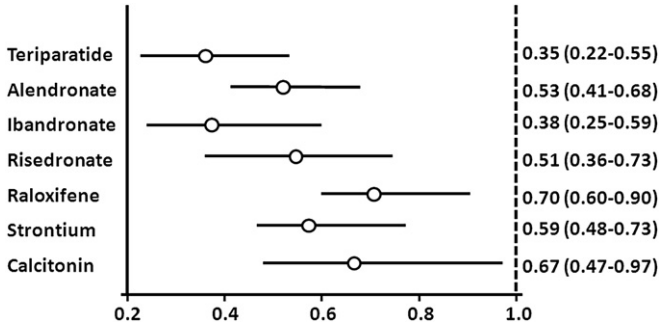

Fig. 2. All of these anti-osteoporotic fracture studies provided strong evidence to support an absolute reduction in the occurrence of any new vertebral fracture in the previously fractured studied population compared with the placebo population, ranging from one-third to more than three-fourths.

Teriparatide

Patients in the pooled teriparatide group had reduced risk for any back pain [relative risk, 0.73 [95% confidence interval (CI) = 0.61-0.87], moderate or severe back pain [0.72 (CI = 0.58-0.89)], and severe back pain [0.39 (CI = 0.25-0.61)] compared with pooled controls, from initiation of the study to the end of follow-up [57].

The European Forsteo Observational Study (EFOS) was a prospective observational study to observe the effects of teriparatide in 1648 postmenopausal women with osteoporosis treated for up to 18 months in European countries [58]. In this study, more than 90% of enrolled patients had a previous fracture, so they were as high risk a population as the patients in the FPT. The study found that mean back pain 100 mm Visual Analogue Scale (VAS) was reduced by 25.8 mm at the endpoint ($P < 0.001$), and mean change from baseline in VAS was 13 mm by 18 months.

In addition, teriparatide treatment was shown to be associated with significant reductions in back pain, regardless of the presence of recent vertebral fracture. Five hundred three patients who received teriparatide for up to 2 years showed that those with a recent vertebral fracture had a greater decrease in back pain than those without ($P < 0.05$) and those with and without mild back pain ($\geq$30 mm); those with and without severe back pain ($\geq$60 mm) at baseline all had a statistically significant reduction in back pain after 24 months ($P < 0.05$) [59].

Effects on quality of life

Health-related quality of life (HRQoL) is a multidimensional health concept that mainly represents subjective symptoms that may influence the sense of well-being and day-to-day function. Physical capacity is one of the essential factors for maintaining well-being. An undiagnosed or untreated vertebral fracture may lead to chronic pain, bone deformity, or a compromise of daily performance and activity, and potentially a progression of disability in maintaining personal or social roles [60]. Vertebral fractures have been proven to be associated with a deterioration of quality of life among post-menopausal women with osteoporosis [61].

There have been numerous instruments for investigating HRQoL. Because of the heterogeneity of the evaluation instruments, it is difficult to make a direct comparison among the antiosteoporotic trials.

The inconsistent results from the two questionnaires were explained to be associated with the differences between the generic and disease-specific instruments.

A Prospective Observational Scientific Study Investigating Bone Loss Experience (POSSIBLE US), enrolling 5015

participants for up to 3 years, evaluated women who were new to and stable on osteoporosis therapies at study entry and in the following year [62,63]. The data examined included patient reports of gastrointestinal adverse events overall and by drug class (bisphosphonates, such as alendronate, risedronate, ibandronate vs. non-bisphosphonates, such as oral or transdermal postmenopausal estrogen, raloxifene, calcitonin, teriparatide, or calcium and/or vitamin D only), and the association between gastrointestinal adverse events and medication discontinuation, HRQoL, and treatment satisfaction [63]. Women new to osteoporosis therapy with gastrointestinal adverse events at month 6 had lower mean HRQoL (OPAQ-SV Emotional Status: 72.3 vs. 78.2, $P = 0.005$) and treatment satisfaction scores (adverse events: 71.4 vs. 82.9; efficacy: 58.6 vs. 65.6; global: 55.0 vs. 64.4; all $P \leq 0.02$) than those without gastrointestinal adverse events. Women reporting any gastrointestinal adverse event had a higher therapy discontinuation rate than those without gastrointestinal adverse events (6-month OR = 1.39, 95% CI: 1.05-1.84; 12-month OR = 1.30, 95% CI: 1.03-1.63; both $P \leq 0.03$), which suggested that gastrointestinal adverse events were more common in bisphosphonate than nonbisphosphonate users, and were associated with increased therapy discontinuation [63].

Strontium ranelate

In the SOTI study, the SF-36 questionnaire and osteoporosis-specific QUALIOST (The QUAlity of Life questionnaire In OSTeoporosis) were used to evaluate the impact of strontium ranelate versus placebo on HRQoL [55]. The score changes in the SF-36 from baseline to endpoint showed deteriorations in HRQoL in both the strontium ranelate and placebo groups. There were also no significant between-group differences in any of the individual scores, in either the mental or physical component. The QUALIOST scores in patients treated with strontium ranelate versus the placebo group showed a significantly negative change (total score, emotional dimension, physical dimension; $P = 0.028$, $P = 0.024$, $P = 0.046$, respectively) demonstrating that an improvement in HRQoL was observed in the treated group.

Teriparatide

In the EFOS, HRQoL was measured by using the European Quality of Life Questionnaire (EQ-5D) [58]. After 18 months, fewer patients reported the need to assist themselves with their arms when standing up from a chair (54.6%), compared with baseline (62.9%) ($P < 0.001$).

Safety and adherence

Most of the apparent adverse effects related to anti-osteoporotic medication are associated with their administration pathway. However, some might be related to the drugs or medication themselves.

Bisphosphonates

Gastrointestinal adverse events have been shown to affect the tolerability and compliance of alendronate [64,65]. However, the frequency of upper gastrointestinal adverse events was reported to be comparable in the placebo and treatment arms in the FIT-VFA, VERT, and BONE trials [24,38,39,42]. The report on adverse events from the FIT-VFA study showed that there were no significant differences in adverse events between the alendronate group and the placebo group, including upper gastrointestinal problems [38]. It is noteworthy that the proportion of upper gastrointestinal problems in both the placebo arm and the alendronate arm was more than 40%. In the VERT-NA and VERT-MN studies, there was a similar incidence of adverse events in the risedronate and placebo groups, but the percentage of upper gastrointestinal tract events in both groups was around 30% [24,39]. In the VERT-NA study, the proportion of subjects that withdrew was as high as 40%, and digestive complaints were the commonest reason for study discontinuance, accounting for 36% in the risedronate group [39]. In addition, oral bisphosphonates are known to cause serious esophagitis in some users [66]. It has been long considered that there is a close correlation between esophagitis and esophageal cancer, especially in those in which esophagitis related to reflux is an "established risk factor" for esophageal cancer through the Barrett pathway. Therefore, it is rationale to suppose the possibility of an increased risk of esophageal cancer in oral bisphosphonate users. In fact, Wysowski [67] published the first-ever report on cases of esophageal cancer in users of oral bisphosphonates in 2009. However, a recent large cohort study from the United Kingdom showed that oral bisphosphonates are not significantly associated with esophageal or gastric cancer (the adjusted hazard ratios for the risk of esophageal and gastric cancer combined and for the risk of esophageal cancer alone were 1.19 (95% CI, 0.69−2.05) and 1.23 (95% CI, 0.66−2.30), respectively, for any bisphosphonate use) [64].

Since 2002, osteonecrosis of the jaw (ONJ) has been linked to the use of bisphosphonates [25]. The definition of bisphosphonate-associated ONJ is the presence of necrotic bony tissue in the jaw or face for at least 8 weeks in a patient who has been treated with a bisphosphonate, but has not been exposed to radiation therapy. The mechanism of bisphosphonate-related ONJ is not completely understood. Two new studies [68,69] found no increase in jaw surgery for inflammatory conditions—a proxy for ONJ—with oral bisphosphonates, but the risk of jaw necrosis was increased almost eight times in those receiving intravenous bisphosphonates.

The risk of atrial fibrillation with alendronate may be increased in the first weeks of treatment [70,71], but no excess risk was seen in long-term users based on the General Practice Research Database (GPRD; a self-controlled case-series analysis of 40,253 women who were prescribed bisphosphonates), since the incidence rate ratio was 1.07 (95% CI 0.94−1.21) for development of atrial fibrillation (2195 patients who developed atrial fibrillation within the predefined study

window) in the exposed time periods, compared with the unexposed periods [72].

There is a concern about renal adverse events in patients with osteoporosis treatment. Although bisphosphonates have not been associated with renal adverse events in patients with a clearance of creatinine (CCr) above 30−35 ml/minute, FDA product labeling states that it is not recommended to use these medications in patients with a lower CCr due to the lack of experience with such patients [70]. A retrospective analysis of the FIT data revealed no difference in the incidence of adverse events in the treatment groups regardless of renal function, and therapy was as effective in terms of preservation of BMD and reduction of fractures [73]; however, the data regarding the use of bisphosphonates in patients with more severe chronic kidney disease and in end-stage renal failure (CCr $<$ 15 ml/minute) are not available.

Three recent publications focusing on the adverse events with long-term use of bisphosphonates might help the audience become familiar with these types of anti-osteoporotic medication [71,74,75].

Raloxifene

The most common adverse effects of raloxifene treatment, compared with the placebo, were hot flashes and leg cramps [28]. The elevated risk of venous thromboembolic events or endometrial cancer with tamoxifen treatment [76] was not found in the STAR study. In addition, the occurrence of breast cancer was less frequent in the women receiving raloxifene in the MORE study (RR, 0.38; 95% CI, 0.24−0.58 for pooled dose vs. placebo) [77]. An extension study of the MORE study—the Continuing Outcomes Relevant to Evista (CORE)—confirmed a significant reduction in the incidence of invasive breast cancer and ER-positive invasive breast cancer during 8 years of raloxifene treatment, with no safety concerns [78,79].

Calcitonin

The only significantly increased adverse effect reported in the PROOF trial of calcitonin nasal spray was rhinitis; however, 97% of nasal events in the calcitonin-treated groups were of mild or moderate severity [43].

Teriparatide

The compliance issue with teriparatide is related to its administration by subcutaneous injection. The average rate of compliance ranged from 79%−83% at each follow-up visit, and the rates did not significantly differ between the treatment group and the placebo group [46].

Cost-effectiveness of osteoporosis treatment

Osteoporotic fragility fractures constitute a significant public health concern. Since the lifetime risk of any osteoporotic fracture is very high (40%−50% in women and 13%−22% in men), fractures are associated with significant mortality and morbidity and represent a substantial economic burden to society [80]. However, direct comparisons of the cost-effectiveness of different kinds of antiosteoporotic drugs or among different populations or countries are not available; therefore, the following data presentations should be used with caution.

Bisphosphonates

A recent publication discussed the cost-effectiveness of the use of bisphosphonates in the treatment or prevention of osteoporosis [80], suggesting the cost-effectiveness might vary in different populations and different countries. For example, among women with low BMD and previous fractures, bisphosphonate therapy was most cost-effective in those populations aged $\geq$70 years, and unlikely to be cost-effective in populations aged $\leq$50 years; there was uncertainty concerning the cost-effectiveness in populations aged 60−69 years. Furthermore, in women with low BMD without previous fractures, treatment with alendronate or risedronate appeared to be cost-effective across countries (like the United Kingdom, the United States, and Denmark), but there was some uncertainty about the cost-effectiveness of etidronate in patients in the highest age groups. In women with osteopenia, alendronate therapy may be cost-effective in women with a T-score of −2.4 in the United States. Screening for low BMD and treatment with alendronate or etidronate appear to be cost-effective in postmenopausal women in general and in women with rheumatoid arthritis initiating corticosteroid therapy. Alendronate therapy without screening was also shown to be potentially cost-effective in certain at-risk male populations, as well as in women initiating corticosteroid therapy after the age of 40 years.

Strontium ranelate

Based on six studies [81], strontium ranelate is a cost-saving drug for women with osteoporosis aged over 80 years, and is a cost-effective treatment compared with no treatment for osteoporotic women aged over 70 years and for younger women with clinical risk factors for fragility fracture. Strontium ranelate was also cost-effective compared with branded risedronate in osteoporotic women aged over 75 years [82].

Raloxifene

To identify cost-effective scenarios of raloxifene treatment compared with no treatment in younger postmenopausal women at increased risk of invasive breast cancer and with a fracture risk below 20%, a microsimulation model populated with data specific to American Caucasian women was used to quantify the costs and benefits of 5-year raloxifene treatment. The population evaluated was selected based on 10-year major fracture probability as estimated with the FRAX(R) being below 20% and a 5-year invasive breast cancer risk as estimated with the Gail risk model ranging from 1%−5%. The conclusions revealed that raloxifene is potentially cost-effective in cohorts of young postmenopausal women who

do not meet the suggested National Osteoporosis Foundation 10-year fracture risk threshold, and that this cost-effectiveness is contingent on the 5-year invasive breast cancer risk of these women [83]. In addition, a systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis, based on 90 randomized controlled trials, showed that only raloxifene appeared to reduce the risk of vertebral fracture in postmenopausal women unselected for low BMD [84], suggesting a rationale for the use of raloxifene in the prevention of both osteoporosis and breast cancer [28].

In summary, all interventions, including alendronate, etidronate, risedronate, raloxifene, strontium ranelate, and teriparatide provided gains in quality-adjusted life-years compared with no treatment in women with sufficient calcium and vitamin D intakes. The size of the quality-adjusted life-years gain for each intervention was strongly related to the age of the patients, because the estimated costs varied widely for the interventions and these net costs were markedly different by age, with some interventions becoming cost-saving at higher age ranges in patients with a prior fracture [84].

Discussion

Osteoporotic fracture, a debilitating condition with significant morbidity and mortality, has important implications for public health. Given the lack of head-to-head comparison trials, indirect comparison of various anti-osteoporosis treatments may be an alternative way to develop a preliminary idea. Although all the antiresorptive agents were of the same treatment duration, direct comparisons cannot be made, there are several limitations to be taken into account, such as differences in study design may have contributed to the heterogeneity of the results. Discrepancies in patient populations or baseline disease severity including fracture risk limit comparisons. The interpretation of study results is also complicated by the pooling of dosage groups, the changing of dosage during the study, or a post-hoc analysis of subpopulations [24,52]. Of note, some biologic outcomes were disclosed using a per-protocol analysis instead of an intent-to-treat population, so a parallel should be drawn with caution [42]. Furthermore, although randomized controlled trials are considered as the gold standard for investigating drug efficacy, their design limits a reflection of the results to the real world.

The definition of osteoporosis continues to evolve as we gain a better understanding of the underlying changes in bone and the mechanisms for those alterations. Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength, and bone strength reflects the integration of bone density and bone quality [85]. Currently, the mainstream method for diagnosis of osteoporosis is the measurement of BMD using dual-energy X-ray absorptiometry (DXA). BMD is indeed a good predictor of bone strength. However, bone strength is not only determined by BMD values, but also various parameters such as bone geometry and bone morphology [86]. Although the majority of antiosteoporosis studies used BMD as the primary endpoint and regarded BMD as an indicator of treatment response, BMD may not be the most appropriate measure to evaluate the response to therapy. For example, in the histomorphometric trial investigating the effect of teriparatide on bone remodeling, the discordance existed between the alteration of bone formation indices and the magnitude of BMD change [49]. Furthermore, the effect of fracture reduction is not clearly related to an increase in BMD. For example, fluoride induced a remarkable increase in BMD but did not reduce the incidence of BMD [87–90]. In this review, the much greater reduction in the vertebral fracture risk than the increase in lumbar spine BMD also echoed such a discrepancy.

Still, the patients in the majority of antiosteoporosis trials were predominantly Caucasians. However, there is some evidence showing an ethnic difference in the incidence of postmenopausal complaints, such as Asian women experiencing fewer vasomotor symptoms [91,92]. Whether any ethnic difference exists in the antiosteoporosis treatments is still unknown and should be answered only by a placebo-controlled trial conducted in an Asian population.

Many research institutes and industries have continued their efforts in exploring novel antiosteoporosis agents. Non-pharmacologic adjustments include optimizing calcium intake from dietary sources, engaging in adequate weight-bearing physical activities, acquiring a proper amount of sun exposure, improving lighting in a gloomy room, keeping the floor clear of obstructions, and enhancing the public awareness of osteoporosis. In addition, adequate supplementation of calcium and vitamin D is essential for individuals with osteoporosis. Supplementation of vitamin D and calcium has been proven to be an effective modality to reduce the risk of hip fractures modestly [93]. An adequate daily intake of calcium is 1000 mg for adults up to the age of 50, and 1200 mg for adults older than 50 years of age [94]. The National Osteoporosis Foundation recommends a calcium intake of at least 1200 mg and a vitamin D intake of 800–1000 IU per day for postmenopausal women [95]. The combination of pharmacologic and non-pharmacologic approaches should provide the most beneficial effects in the prevention of fractures in patients with osteoporosis.

Conclusions

Since osteoporosis may be considered as a part of the aging process globally, treatment of patients with pre-existing fracture should have the priority in utilization of medical resources. Direct comparison between different strategies and a consideration for different populations and countries might provide a more concise and reasonable direction in the management of the women with pre-existing osteoporotic fracture.

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