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Nonsurgical Treatment Strategies after Osteoporotic Hip Fractures

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Osteoporosis is a metabolic disease that is increasing in prevalence as people live longer. Because the orthopedic surgeon is frequently the first and often the only physician to manage patients with osteoporotic hip fractures, every effort should be made to prevent future fractures. A multidisciplinary approach is essential in treatment of osteoporotic fractures. Basic treatment includes calcium and vitamin D supplementation, fall prevention, hip protection, and balance and exercise programs. Currently available pharmacologic agents are divided into antiresorptive and anabolic groups. Antiresorptive agents such as bisphosphonates limit bone resorption through inhibition of osteoclastic activity. Anabolic agents such as parathyroid hormone promote bone formation.

Key Words: Osteoporosis, Medication, Hip fractures

INTRODUCTION

Orthopedic surgeons, unlike medial doctors, manage osteoporosis and osteoporotic spine, distal radius or hip fractures. Osteoporotic hip fracture commonly occurs in geriatric patients and has a high perpetual re-fracture rate despite various interventions. Since elderly people are primarily affected, early mortality rate is high due to development of bed sore or pneumonia following the fracture. Hence, osteoporotic hip fracture and osteoporosis should be treated simultaneously with early rigid fixation for immediate mobilization. Treatment methods for osteoporosis are exercise, dietary supplementation and calcium and vitamin D supplementation along with pharmacologic treatment. Pharmacologic intervention is rendered by anti-resorptive agents, bone forming agents or a combination of both. Anti-resorptive agents include bisphosphonate, selective estrogen receptor modulator (SERM) and estrogen. Bone forming agents are parathyroid hormone (PTH) and bone growth hormone. Strontium is the bone forming and anti-resorptive agent. Clinical outcome for new drugs are being reported, which include third generation SERMs Such as bazedoxifence and human monoclonal antibody to receptor activator of nuclear factor kappa-B ligand (RANKL) such as denosumab. This paper aims to address anti-osteoporotic agent that an orthopedic surgeon must know.

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MAIN SUBJECTS

1. Calcium and Vitamin D

Vitamin D is essential for normal bone growth and maintenance of healthy bone. Appropriate calcium and vitamin D intake is crucial to prevent and treat osteoporosis. Calcium supplementation for treatment of osteoporosis aims to improve bone mineral density (BMD) and prevent vertebral or nonvertebral fractures[1,2]. Recent studies reported an increased risk of cardiovascular complication with calcium supplementation to make this treatment and its dosage controversial[3-5]. Nevertheless, a large number of studies have suggested that the prolonged use of calcium does not affect the rate of heart diseases[6,7]. Further studies are necessary, yet appropriate calcium intake should be taken into consideration.

The 2010 Canadian guidelines recommend daily intake of 1,200 mg calcium for women older than 50 years of age[8]. According to the Korea National Health and Nutrition Examination Survey, the amount of calcium intake is 65.4% of the recommended dose with more than 50% of respondents receiving less than the daily recommended level in all age groups. These findings indicate the need for calcium supplementation. The two main forms of calcium in supplements are calcium carbonate and calcium citrate, with latter being more commonly used.

Vitamin D is involved in controlling the serum calcium level by facilitating absorption of calcium in the intestine and reabsorption of calcium in the kidney. Vitamin D reduces the risk of geriatric falls by improving the neuromuscular function and preventing muscular atrophy. Vitamin D deficiency is defined as a serum 25 (OH) D level below 30 ng/mL. Sun exposure is the most important source of vitamin D. Egg and salmon are good dietary sources for vitamin D. Lack of vitamin D is commonly compensated by food supplements. The US National Osteoporosis Foundation recommends a daily intake of 800-1,000 IU vitamin D for adults over the age of 50 years. No side effect is seen with supplemental daily vitamin D intakes over 10,000 IU. Single injection of high-dose vitamin D (150,000 IU) is recently introduced. Additional studies are warranted to verify the effect and safety of vitamin D supplementation. Dosage of vitamin D supplementation needs to be increased in elderly people or individuals with limited sun exposure[9].

2. Bisphosphonates

Bisphosphonates lower the bone turnover rate by slowing down osteoclastic activity, inducing apoptosis in osteoclasts, decreasing the level of interleukin-6 (IL-6 stimulates osteoclastic activity) and promoting the production of factors that inhibit osteoclast formation. Nitrogen-containing bisphosphonates are clinically used to inhibit bone resorption activity, which is regulated by their affinity for bone minerals and ability to bind and inhibit the enzyme farnesyl pyrophosphate synthase in osteoclasts.

Etidronate (Dinol®) is the first clinically used bisphosphonate and clodronate is another first-generation bisphosphonate. Second generation bisphosphonates include alendronate (Fosamax®) and pamidronate (Panorin®). Third generation bisphosphonates are risedronate (Actonel®), ibandronate (Bonviva®) and zoledronate (Aclasta®). In recent years, combined bisphosphonates and vitamin D are introduced, which include Risenex plus®, Maxmarvil®, Fosamax-plus D® and Bonviva plus® (Table 1). Most bisphosphonates have well-documented evidence of vertebral and nonvertebral fracture prevention. US Food and Drug Administration (FDA) approved bisphosphonates that include alendronate, risedronate, ibandronate and zolendronate significantly increase the BMD[10,11]. The effect of ibandronate on prevention of hip fracture is not

Table 1. Generations of Bisphosphonate

Generations	Example	Brand name	Antiresorptive potency	Route	Dosing regimen
First	Etidronate	Dinol	1	Oral	Daily
	Clodronate		10		
Second	Pamidronate	Panorin	100	Oral or IV	Daily
	Alendronate	Fosamax	100-1,000	Oral	Daily or weekly
Third	Risedronate	Actonel	1,000-10,000	Oral	Daily or weekly
	Ibandronate	Bonviva	1,000-10,000	Oral or IV	Monthly
	Zoledronate	Aclasta	10,000	IV	Yearly

IV: intravenous.

yet been fully investigated. Zoledronate is found to reduce the incidence of hip, vertebral and non-vertebral fractures. Thanks to their effect on preventing the fractures, bisphosphonates are the first-line drugs in the management of osteoporotic fractures. To improve the patient compliance and adherence to bisphosphonate treatment, intake interval may be prolonged or the drug may be administered as intravenous injection instead of the oral route. They are administered at different frequencies such as daily, weekly and monthly (Table 2).

Erosive gastritis, gastrointestinal irritation and increased risk of electrolyte imbalance are the side effects of bisphosphonates due to irritation of the epithelium of the gastrointestinal tract. Common side effects of zoledronate are flu-like symptoms and atrial fibrillation[12].

Bisphosphonate-related osteonecrosis of the jaw (BRONJ)[13,14] and atypical fracture of the femur are reported to be associated with bisphosphonates. There is no evidence of bisphosphonate interference with fracture healing, so early administration for maintain bone densitometry is recommended[15-17].

1) Bisphosphonate-related osteonecrosis of the jaw (BRONJ)

BRONJ is defined as the presence of exposed necrotic bone that does not resolve within 8 weeks in a patient with no history of radiation therapy to the facial bone (Fig. 1). Although dental exanimation is unnecessary in all patients taking bisphosphonates, patients should be informed about the risk factors and symptoms of BRONJ. Bisphosphonates are withheld from patients with BRONJ. These patients should be treated by experienced dentists. Surgical removal can be performed as the border between the necrotic and healthy bone is well demarcated. This is performed after 6-12 months from drug withholding. Other drugs can be considered to treat the osteoporotic fracture if the patient's condition allows[14].

Table 2. FDA Approved Medications in the Treatment and Prevention of Osteoporosis

Agents	Route	Spine Fx	Hip Fx	Side effect	Comment
Calcium/vitamin D	Oral	+	++	Minor GI trouble	Basic treatment
Alendronate	Oral	++	++	GI trouble Irritation/Osteonecrosis	First line drug
Risedronate	Oral	++	++	Osteonecrosis	First line drug
Ibandronate	IV/Oral	+	?	Osteonecrosis	Monthly
Zoledronic acid	IV	++	++	Osteonecrosis	Yearly
Raloxifene	Oral	+	?	Thromboembolism	Treatment for breast cancer
Bazedoxifene	Oral	+	?	Thromboembolism	Treatment for breast cancer
Parathyroid hormone	Subcutaneus	++	?	Slight nausea	Not available data

FDA: US Food and Drug Administration, IV: intravenous, GI: gastrointestinal

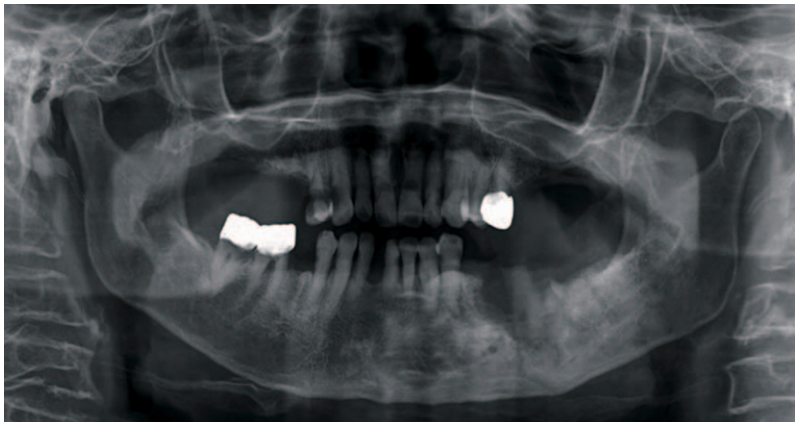

Fig. 1. A 77-year-old wonam who underwent teeth extraction followed-by osteonecrosis of mandible.

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2) Atypical fracture of the femur

Atypical fracture of the femur is occurring increasingly in patients receiving long-term bisphosphonate treatment. Bisphosphonates are effective in preventing fractures by promptly increasing the BMD of a severely suppressed bone turnover. However, increase in BMD has long-term limitation as excessive suppression of bone formation and accumulation of microfractures may lead to bone problems[18,19]. Bone formation and resorption should be balanced, but excessive inhibition of bone resorption may result in the inhibition of bone turnover, leading to the so-called "frozen bone"[20]. Atypical fracture in the elderly is associated with prolonged bisphosphonate use. It is defined as a simple transverse fracture with a unicortical beak along the fracture line (Fig. 2). After the recent description of atypical fracture, comminution is included to categorize the atypical fractures[21,22]. Although atypical fractures are relatively well treated with intramedullary nailing, delayed union may occur. The American Society for Bone and Mineral Research (ASBMR) defined provisional cases of atypical femoral fractures to provide clinical guidelines. ASBMR definitions of atypical femoral fractures are (1) anywhere distal to the lesser trochanter down to the supracondylar; (2) no trauma or minor trauma; (3) transverse or short oblique fracture; (4) noncomminuted or minimally comminuted; and (5) localized periosteal thickening of the lateral cortex[23].

PTH, a stimulator of bone formation, is thought to be effective in atypical femoral fractures after bisphosphonate use[23]. No large-scale clinical trial has been conducted yet. Carvalho et al.[13] achieved bone union in three patients with atypical fracture in 2011 using strontium ranelate in two and PTH in one. This study showed that these agents can be used for patients with atypical fracture, yet it is not clear if the patients had actually atypical fractures. Well-designed large-scale clinical trials are warranted to verify the effect of bone forming agents on atypical femoral fractures. Although some studies have reported non-problematic healing of atypical fractures, a large number of authors have suggested that delayed healing or nonunion may occur more frequently in bisphosphonate-associated atypical fractures[24,20]. This is because bisphosphonates inhibit bone resorption of osteoclasts and prohibit bone remodeling, which leads to damaged mechanical strength and limits bone repair capacity. These should be considered in determining the surgical treatment. Therefore, intramedullary nailing is more favorable compared to plate fixation that is associated with a higher failure rate due to delaying the endochondral repair of atypical fractures[24]. However, plate fixation can be used when intramedullary nailing is not feasible in narrow medullary canals. Since refracture

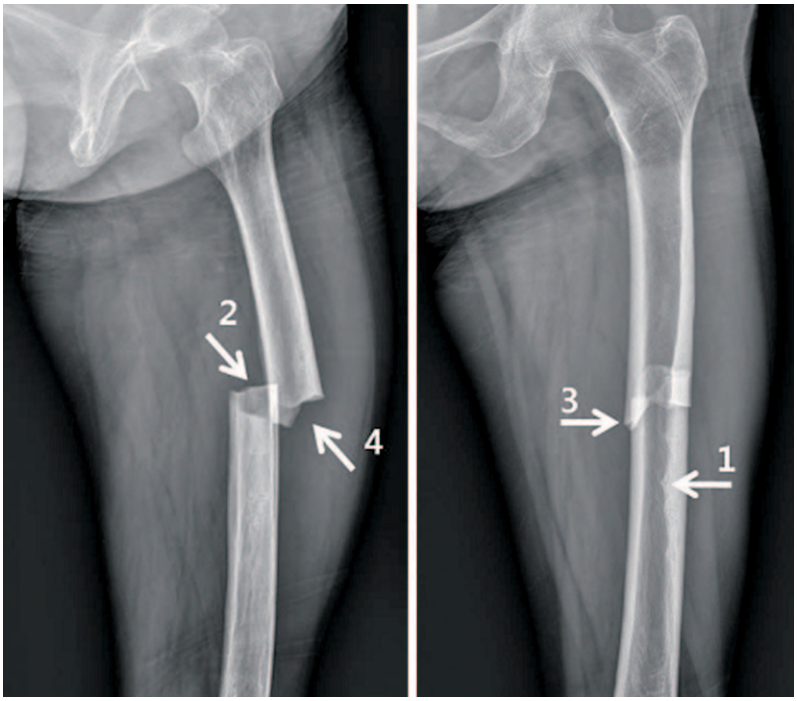

Fig. 2. Radiological characteristics of atypical femoral fractures. 1: localized endosteal thickening, 2: transverse fracture pattern, 3: medial spike, 4: localized periosteal thickening at fracture site.

can occur in overstressed areas due to insufficient instrument length, fixation should be performed over the whole femoral length. The medullary canal should be over-reamed at least 2.5 mm larger than the intramedullary nail diameter to remove the sclerotic dead bone and facilitate bone healing through bone induction and conduction. It will also compensate for the narrow intramedullary diameter, allow easy intramedullary nail insertion and lower iatrogenic fracture rates in the operating room.

The contralateral femur needs to be carefully monitored as atypical fractures often occur bilaterally (Fig. 3). Since incomplete fracture of the contralateral femur may progress to complete fracture in some patients, preventive internal fixation is being proposed[25]. Das et al.[24] have recommended preventive nailing in patients complaining from hip or thigh pain while taking prolonged bisphosphonate for osteoporosis. They have also recommended this strategy in those with elliptical lateral cortical buckling in the area of pain (Fig. 4) and those with findings of stress fracture on magnetic resonance imaging or bone scan. These authors have also recommended that patients need to be monitored and managed proactively when classical radiographic findings of atypical fracture are detected before the debut of pain.

3. Hormone Replacement Therapy (HRT)

A combination therapy with estrogen and medroxyprogesteron is effective in relieving postmenopausal vasomotor symptoms and preventing osteoporosis. However, it is rarely used for therapeutic purposes in osteoporosis due to the risks of breast cancer, endometritis, cardiovascular side effects and thromboembolism[26]. Starting HRT within 5 years of menopause is effective in reducing the incidence of vertebral and nonvertebral fractures, but it is not effective after five years from menopause as all skeletal benefits are likely to be lost with discontinuation of HRT. HRT should be continued indefinitely after menopause, therefore it is reserved for women with severe postmenauposal symptoms.

4. Selective Estrogen Receptor Modulator (SERM)

SERMs act as antagonists in the breast and endometrium by binding to the estrogen receptors. They inhibit production of cytokines that are associated with bone resorption through their antagonist activity in the bone and cardiovascular system. Important SERMs are bazedoxifene (Viviant®), raloxifen (Evista®) and

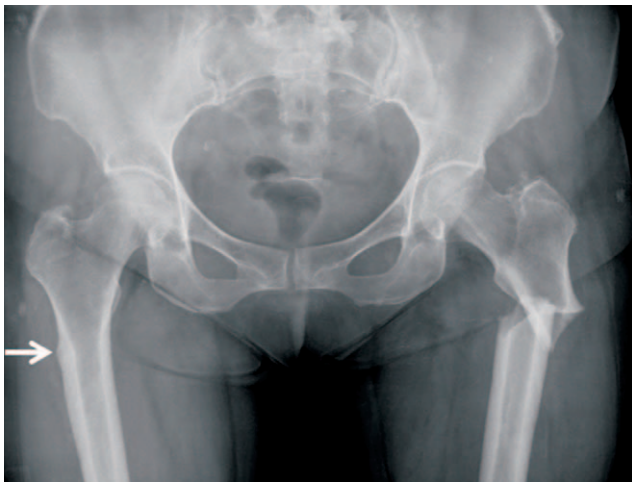

Fig. 3. Contralateral incomplete atypical subtrochanteric fracture. Arrow: localized periosteal thickening (beaking or flaring).

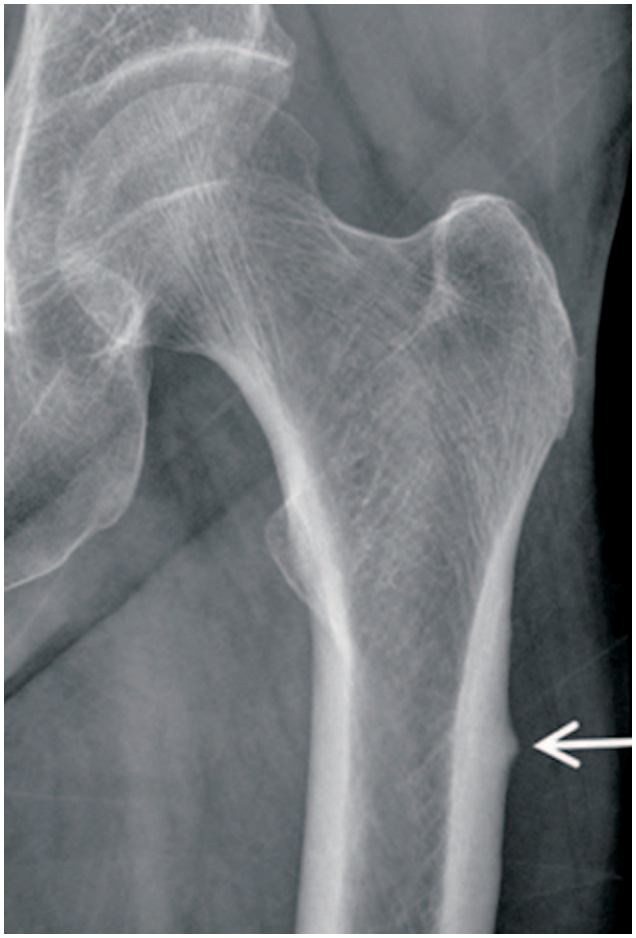

Fig. 4. Elliptical lateral cortical buckling. Arrow: localized periosteal thickening (beaking or flaring).

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tamoxifene. SERMs increase BMD less than estrogen. Although they lower vertebral fracture rates by 30-50%, their effect on nonvertebral fractures has not yet been verified[27]. Despite a decrease in breast cancer by 70%[28] and cardiac event, the rate of thromboembolic phenomena is like HRT[29]. Hence, SERMs are recommended in patients with heart diseases or in the setting of osteoporotic spine fracture in patients that have a high risk for breast cancer.

5. Parathyroid Hormone (PTH)

PTH is approved by the FDA in 2002 for the treatment of osteoporosis. PTH increases the number and activity of osteoblasts, decreases osteocyte apoptosis and promotes bone formation as an anabolic agent. Teriparatide (Forsteo) is the most common form of PTH. This drug is shown to increase BMD, reduce the risk of fracture and prevent vertebral fractures, but its effect on nonvertebral fracture is not yet established. PTH is also given to male osteoporotic patients with a single administration being more effective than concurrent therapy with alendronate[30]. This drug is given subcutaneously. However, it requires daily injection and is expensive. Recently, once-weekly subcutaneous injection preparation of PTH is developed and is under clinical trial[31,32].

6. Strontium Ranelate

The mechanisms of action of strontium ranelate remain unclear. Nevertheless, this drug appears to dissociate bone resorption by either direct blocking the osteoclastic activity or inhibition of osteoclastic differentiation[33]. According to a recent study on 1,649 postmenopausal women, a 3-year administration of 2 mg oral strontium increased vertebral and nonvertebral BMD and reduced the risk of vertebral fracture by 41-49% and the risk of hip fracture[34]. The incidence rate of heart diseases following prolonged administration of strontium ranelate is 4 in 1,000 patients. Thus, it is less likely to be recommended for the treatment of osteoporosis due to severe adverse effects[35].

7. Denosumab

RANKL is a member of the tumor necrosis factor (TNF) super-family and a protein expressed by osteoblasts. RANKL binds to receptor activator of nuclear factor kappa-B ligand (RANKL)-expressed on both osteoclast precursor cells and osteoclasts- to promote osteoclast differentiation and activation. Denosumab is a monoclonal antibody against RANKL and blocks RANKL binding to RANK. Denosumab given subcutaneously twice yearly for 36 months was associated with a reduction in risk of vertebral, nonvertebral and hip fracture in women with osteoporosis[36]. It is more effective than bisphosphonates in increasing BMD, but is associated with serious side effects. Although the therapeutic effects of denosumab disappear with discontinuation of treatment, the outcome of resumed therapy is not affected by previous denosumab administration[37].

8. Cathepsin-K Inhibitors

Cathepsin-K inhibitors have been developed for treatment of osteoporosis by reducing the bone resorption. They are known to block the activity of cathepsin (a potent protease for osteoclasts) and their effects resemble those of bisphosphonates. Since cathepsin-K inhibitors have less gastrointestional side effects, they are recommended as alternatives for bisphosphonates. Clinical trials are currently in progress[38].

9. Verification of Medicinal Efficacy

BMD and biochemical markers can be used to monitor the therapy yet their clinical values are still unclear. Bone turnover markers have been extensively used to monitor the efficacy of new drugs. Bone specific alkaline phosphatase and osteocalcin are mainly used as bone formation markers. NTX (urine N-telopeptide of collagen cross links) and CTX (serum C-telopeptide of collagen cross links) are primarily used as bone resorption markers. Compliance to therapy is the most important parameter affecting the effectiveness of osteoporosis treatment. The medication administration interval needs to be adjusted at convenience of patients. Although an optimum duration of therapy has not been established, a minimum of 3-5 years of treatment is recommended if there are no other complications.

CONCLUSION

We have used exercise, dietary supplementation, calcium and vitamin supplementation to prevent the secondary fracture and treat osteoporosis in patients with osteoporotic fractures. At least bisphosphonate was

used in the treatment of osteoporosis. Although there is no report that SERMs reduce the risk of hip fracture, they can be used in postmenopausal women who are at high risk of breast cancer. Further investingation on PTH is required theoretically meaningful.

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