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Review article

Effects of bisphosphonates on osteoporosis: Focus on zoledronate

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ABSTRACT

Osteoporosis is a bone disease that mainly affects older people and postmenopausal women. Lack of proper treatment for this disease gives rise to many problems in patients and occasionally leads to death. Many drugs have been utilized to treat osteoporosis but the most effective one is the bisphosphonates (BPs) family. This family has several positive effects on bone tissue, including promoting bone healing, enhancing bone mineral density, reducing bone resorption, preventing pathologic fractures, suppressing bone turnover, and modulating bone remodeling. On the other hand, there have also been inconclusive reports that BPs might have a desirable or even adverse impact on osteoporotic patients. Therefore, we set out to examine the positive and negative effects of this family, with a focus on the most potent one that is zoledronate (Zol), in clinical usage. Zoledronate is an amino-BPs and nitrogen-containing drug which is the most powerful BPs on osteoporosis treatment or prevention. Many studies showed its effectiveness in the treatment of osteoporosis and bone healing. As Zol enjoys a considerable potential in treating and preventing osteoporosis, it can be used as one of the effective treatments in this field.

1. Introduction

Osteoporosis is the most usual metabolic bone disorder which is known by skeletal fragility and low bone mass, affecting approximately 200 million people worldwide [1,2]. Over 10 million people suffer from osteoporosis in USA and more people will suffer from it in near future [3]. A significant issue that should be considered following osteoporosis is bone fractures. The medical care has been evaluated to be approximately $17.9 billion for osteoporosis in the USA and £4 billion in UK, annually [4-6]. The morbidity and mortality occur due to fragility fractures in osteoporotic patients and bring about an important socioeconomic and medical burden. Osteoporosis may arise because of the reduction of bone strength, predisposition of failure fixation or nonunion, and decreased suboptimal healing capacity. The administration of some stimulant agents for bone formation to improve the strength of a fixed implant in osteoporotic bone is notable [7–9].

The most targeted population for this disease are postmenopausal women with fracture rates of 91, 54, and 41%, in America, Africa, and Asia, respectively [2,10]. The disease is known as an important reason for morbidity and mortality among men, and its mortality is higher in men than women. Besides, more than 40% of osteoporotic fractures emerge in patients older than 50 worldwide [11]. Almost 30% of the European and American women are affected by osteoporosis and 30% of men and 40% of women will face the osteoporotic fracture for the rest of their life [1,11]. This rate is markedly highest than the other major bone diseases. The quality of life is also affected by chronic pain, disability, and also related osteoporotic symptoms [12]. Bisphosphonates (BPs) are the synthetic analogs of endogenous bone mineralization regulator pyrophosphate and the most common drugs in the treatment of metabolic bone diseases such as bone loss which is induced by glucocorticoids and suppressive hormone therapy [13]. They were widely used in the treatment of osteoporosis in the 1990s and were approved by the US market in 1995 [27]. This family treat osteoporosis though the inhibition of osteoclast-mediated bone resorption to decrease the risk of vertebral fracture so that the bone tissue takes up this family in the resorption active areas [15,16]. One of the most potent drugs in BPs family is zoledronate (Zol) which has been shown to significantly improve the treatment of osteoporotic patients [17]. As such, this article deals with the therapeutic effects of BPs on osteoporosis as a globally challenging concern.

2. Osteoporosis

Osteoporosis disease is known as the decadence of bone tissue, porous bone, and disruption of bone microarchitecture which results in reduced bone strength and increasing fracture risk [15,18]. This is the

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most frequent bone disease in older people and postmenopausal women. It is a silent disease that is characterized by serious secondary health problems and ultimate death [19].

2.1. Definition

Bone mineral density of each patient is narrated based on the differences of the standard deviation and the average of the bone mineral density of an adult reference associated with the healthy and normally spread out [20]. Osteoporosis was defined by WHO as the bone mineral density is greater than 2.5 standard deviations below the mean. More specifically, one standard deviation below the mean points to normal and 1–2.5 standard deviations below it refer to osteoporosis [20]. This classification is not involved in premenopausal women and people younger than 50 years old [21].

2.2. Classification

There are two types of osteoporosis, primary and secondary. The primary osteoporosis is also subdivided into osteoporosis type I and type II. Type I is recognized as postmenopausal osteoporosis due to estrogen deficiency which typically affects trabecular bones. It occurs in women more than men with a proportion of 5.7/4. Senile osteoporosis is the other term for osteoporosis type II and is associated with the loss of bone mass because of aging and involves both trabecular and cortical bones [22]. The secondary osteoporosis happens due to excessive vitamin A in diet, low calcium intake, high salt intake, vitamin D insufficiency, AIDS/HIV, diabetes mellitus, smoking, weight loss, and some other factors pertaining to the lifestyle changes [22,23].

2.3. Inducement

Some lifestyle factors such as low calcium intake, vitamin D insufficiency, genetic factors including cystic fibrosis and porphyria, endocrine disorders like diabetes mellitus, hypogonadal states, for example, hyperprolactinemia and panhypopituitarism, gastrointestinal disorders, rheumatic and autoimmune diseases, hematologic disorders, miscellaneous conditions and diseases like amyloidosis, depression, and emphysema, and medications of heparin and barbiturates are the main risk factors leading to the higher rate of osteoporosis [15]. In fact, osteoporosis was formerly intended as a normal division of aging, but it is recognized as a treatable and preventable disease nowadays, and the fracture risks would be reduced by some interventions such as sufficient combined vitamin D and calcium intake, tobacco restraint, weight-bearing exercises, limited alcohol intake, and anti-resorptive therapy [21,24]. Bone mass loss increase would be inhibited by preventing the addition resorption rate toward the formation rate. Aging and menopause lead to imbalance between the formation and resorption rates and result in increased fracture risk. In addition, by increasing the speed of bone remodeling, the fragility of bone and fracture risk are decreased (Fig. 1) [19].

2.4. Treatment

The postmenopausal osteoporosis is usually treated by hormones such as estrogen, teriparatide, PTH (1,34), and some other therapies like bazedoxifene, tamoxifen, raloxifen, bisphosphonates, strontium ranelate, calcitonin, and denosumab (Fig. 2) [15,19,22,25]. These therapeutic regimens also have some adverse effects on osteoporosis. For example, selective estrogen-receptor modulators hormone therapy

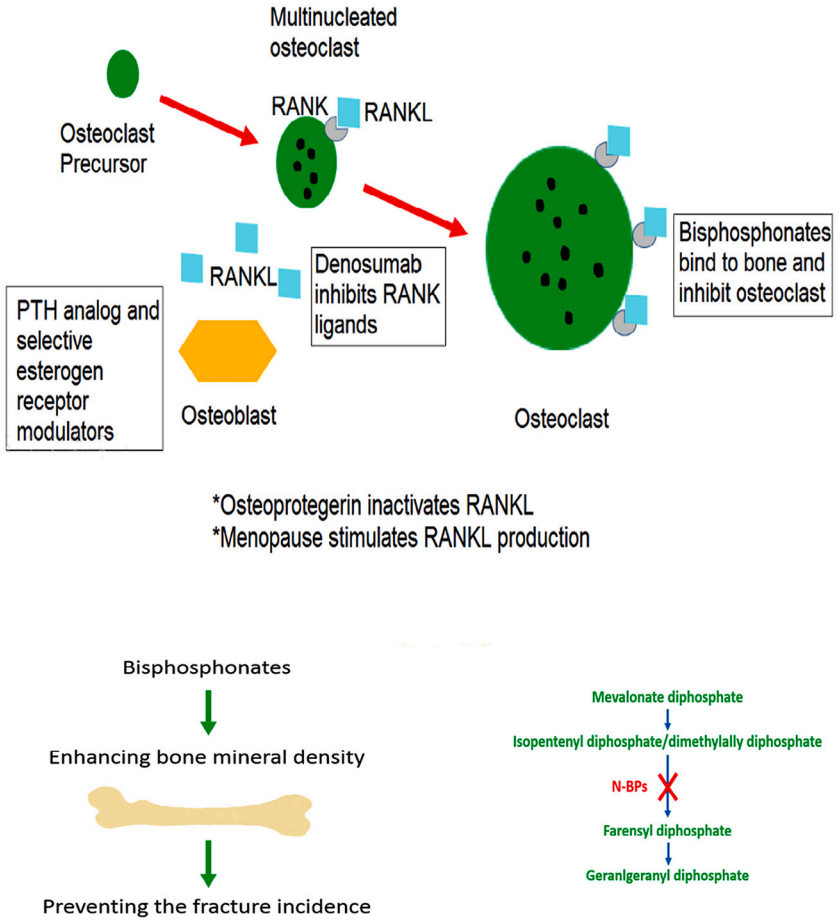

Fig. 1. Some of the effective factors on osteoporosis related to genetics, ages, and nutrition.

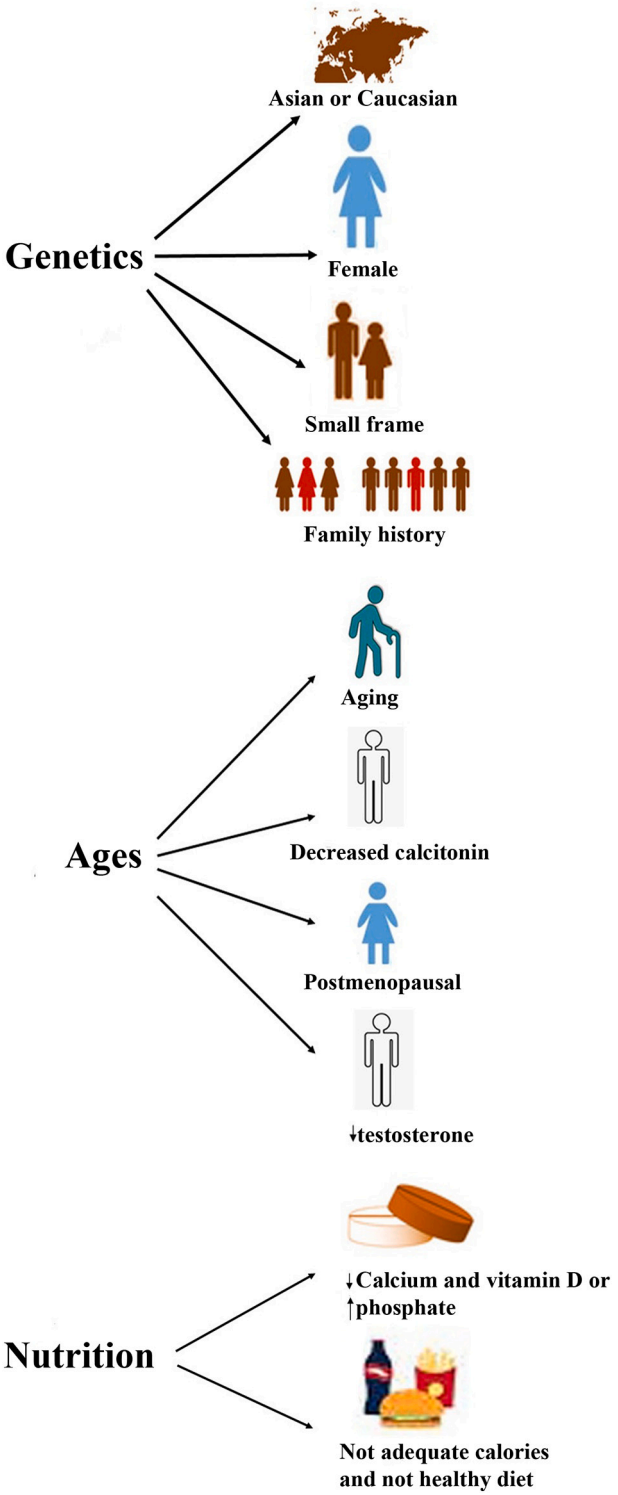

Fig. 2. This profile shows the effects of denosumb, hormone therapy, and bisphosphonates on bone cells.

causes urogenital and vasomotor symptoms, pulmonary embolism, deep vein thrombosis, and cardiovascular insufficiencies [21,26–28]. Nausea, reactions in the injected area, leg cramps, and dizziness emerge following PTH administration [21,28]. Calcitonin creates epistaxis and rhinitis and denosumab brings about dermatitis, peripheral edema, hypocalcemia, nasopharyngitis, hypercholesterolemia, rash, pain in the back and limb sites, arthralgia, and also gastrointestinal tract symptoms like vomiting, diarrhea, and nausea [21,29,30]. It should be highlighted that all osteoporotic therapeutic strategies reduce both vertebral and nonvertebral fracture rates in the high risk cases [15].

Among the agents that augment bone mass, only stronsium ranelate and BPs including residronate, zoledronate (Zol) and alendronate decreased hip and vertebral fractures and have also been effective in healing vertebral fracture. Furthermore, the increase in mortality, cost of health care and morbidity in the hip fractures are comparable to the vertebral fractures. In fact, based upon the positive effects of treatment regimens in osteoporotic patients, the BPs are more widely used in the treatment of osteoporosis [31].

3. Bisphosphonates

Bisphosphonates prevent pathologic fractures, promote bone healing accompanied by minimum bone resorption, suppress bone turnover, enhance bone remodeling, and significantly promote bone mineral density in the osteoporotic patients [13,32-36]. Therefore, many skeletal diseases including Paget's disease, osteogenesis imperfecta, fibrous dysplasia, malignant hypercalcemia, and metastatic cancers, in addition to the osteoporosis could be treated by this drug family [13].

3.1. Molecular structure and mode of action

The P-C-P substitutes the P-O-P in the BPs' structure; this results to withstand from the enzymatic and chemical hydrolysis [38,39]. The P-C-P chain permits variation in the family which lead to preventing the osteoclastic bone resorption due to the change in the two lateral chains of carbon atom or the esterifying phosphate group. Attachment to the bone mineral is increased when the R^1 side is the hydroxyl and the R^2 counterpart is BPs [38]. There are two groups of bisphosphonates including nitrogen-containing BPs and non-nitrogen containing ones. The difference between these two groups lies in their adherence of the central carbon to the R^1 or R^2 side [38,40].

The nitrogen-containing BPs include some drugs such as alendronate, zolendronate, pamidronate, and risedronate. The single nitrogen atom at the aliphatic side chain exists in the alendronate and pamidronate and the ring structure with a second nitrogen is observed in the zoledronate which is an imidazole derivative. To affect the osteoclasts activity, the nitrogen-containing BPs intervene with protein prenylation, mevalonate biosynthetic, and farnesyl pyrophosphonate (FPP) synthase pathways [35,36,38,41]. The nitrogen-containing BPs are effective in some functions of osteoclasts such as cytoskeletal arrangement, apoptosis, vesicle trafficking, and cell morphology [36,41,42]. They also stimulate osteoblast activity, control osteoblastic differentiation and proliferation, regulate the secretion of many types of growth factors and cytokines, promote maturation and proliferation of bone marrow stromal cells to the osteoblastic lineage, inhibit osteocytes and osteoblasts apoptosis following glucocorticoid administration, and modulate the production of extracellular matrix proteins by osteoblasts [43,44]. On the other hand, Cl or CH_3 are at the R^2 counterpart (nitrogen-free ring) structure in the non-nitrogen containing BPs, including clodronate, etidronate, and tiludronate [38,40]. The phosphate chain from the adenosine triphosphates is involved in this group, and induces apoptosis in the osteoclasts by combining with the cellular ATP. Finally, bone resorption decreases due to the reduction of active osteoclasts [36,45]. This process takes place through the intracellular metabolites which inactive the analogs of ATP via the mitochondrial ADP/ATP translocase prohibition [38].

3.2. Current application in clinical practice

Bisphosphonates have been used both as tablets and infusion in the treatment of osteoporosis. Alendronate and residronate are also utilized as tablets in curing and preventing postmenopausal osteoporosis along with treating the osteoporotic women and men who take glucocorticoids [22]. Tablets and intravenous injections of ibandronate have also been

used for osteoporotic postmenopausal women [33]. Zoledronate has been utilized via infusion to prevent and cure postmenopausal osteoporosis cases. It has also been used for men and women who were treated with glucocorticoids [46]. Oral intake of this family is complicated and due to their poor adherence to the mucous membrane of the gastro-intestinal cavity, they might cause compromised effects and increase medical care costs [16]. Bisphosphonates have been used orally to treat osteoporosis that brought about atypical fractures in the femur and also in reducing the risk of fracture in postmenopausal osteoporotic patients; however, this might be because of variable absorption, poor compliance, complex dosing instruction, and GI intolerance requiring repeated prescription [7,47]. Although, intravenous administration creates mild to moderate symptoms of post-infusion after first administration which resolves over 3 days, it overcomes all these problems and results in decreased fracture and high efficacy [47]. Local delivery of BPs in the osteoporotic animal models improved the osseointegration of the implants and supported the bony integration [48].

3.3. Advantages of BPs administration

Increase in the average wall thickness and bone mineral density, reduction in fracture risk, health care cost, and morbidity besides a significant increase in survival are some positive effects of BPs family in the treatment of osteoporosis [13,49]. In addition, it has been reported that three months oral treatment with this family resulted in a reduction of bone resorption and the biochemical bone markers were properly expressed and remained nearly constant by the continuation of BPs therapy [50]. The BPs with amino group have a potential in reducing bone resorption as they inhibit the osteoclast function in addition to their anti-fracture ability in osteoporotic patients [26,51].

The incidence of hip and spine fractures showed almost 50% reductions over 3 years, by alendronate treatment in the cases who had a former vertebral fracture or osteoporosis at the hip region [52]. Besides, alendronate decreased the vertebral fracture incidence to 48% in the cases without an old vertebral fracture, over three years [22]. The incidence of morphometric vertebral fractures showed a reduction in men, over two years, by the administration of alendronate [53,54]. Administration of ibandronate resulted in 50% reduction in the incidence of vertebral fractures over three years but there was no evidence indicating a decrease in the non-vertebral fracture risk [33].

Risedronate administration resulted in 41–49% diminish in the incidence of vertebral fractures and 36% nonvertebral fractures, over three years. A significant risk reduction was also observed in the cases with old vertebral fractures, after one year post-treatment [55]. Administration of risedronate in the ovariectomized induced osteopenic rats resulted in increased bone mass in the tibial bone and suppressed bone turnover and resorption to prevent further bone loss [38]. Risedronate and alendronate reduced both hip and nonvertebral fractures in the osteoporotic women [16]. The US National Osteoporosis Foundation stated that 5 mg/day alendronate for five years and then five years drug-free holiday was beneficial for bone tissue and did not increase fracture risk [14]. Alendronate, ibandronate, zolendronate, and risedronate prevent and cure some cases such as postmenopausal osteoporotic women and glucocorticoid-induced osteoporotic men [37,38,56,57].

3.4. Side effects of BPs administration

Difficult oral treatment, medication cost, side effects, lack of motivation, strict dosing commitment, and the inability of patients to understand the improvement of symptom are the main issues that limit the utilization of BPs [58]. Atypical femoral fracture, impaired fracture healing, flu-like symptoms, hypocalcemia, GI intolerance, and impairment of renal function are the main BPs' side effects [49]. The adverse effects of BPs can be divided into short-term and long-term effects. The short-term effects involve severe musculoskeletal pain, adverse effect on upper GI, acute phase reaction, hypocalcemia, ocular inflammation, and esophageal cancer in the case of oral administration. The long-term defects include jaw osteonecrosis, subtrochanteric femoral fractures, atrial fibrillation, and suppression of bone turnover [56].

One of the adverse effects of BPs is related to the upper GI, which is more commonly reported for those patients who could not tolerate the oral BPs. These cases could not maintain at the upright posture after oral administration for 30–60 min due to the establishment of erosive esophagitis [59]. It seems there is no clear relation between atrial fibrillation and using the drugs of this family. Further, the patients who use BPs are old and may represent the fibrillation independent of utilizing this family. The metabolic bone diseases such as subtrochanteric femoral fracture and suppression of bone turnover should be considered in regard to the side effects of BPs therapy [56].

Those cases who receive BPs by IV route are characterized by arthralgias, myalgias, fever and severe joint, musculoskeletal, and bone pain, for 24–72 h due to the acute phase reaction [16,19]. Uveitis, episcleritis, scleritis, and conjunctivitis accompanied by photophobia and ocular pain are also observed following IV and oral therapy of this family [60]. The jaw osteonecrosis is the most reported side effect of the long-term therapy of BPs administration. It is particularly the case in those with cancer for whom high doses of IV therapy of BPs has been prescribed that is more damaging than other conditions. In addition, some conditions like invasive dental procedure, poor oral hygiene, and high IV doses of BPs accompanied by prolonged exposure enhance the risk of jaw osteonecrosis [60]. It was also shown that the incidence of jaw osteonecrosis in cases with multiple myeloma cured by high IV doses of BPs family was reduced by antibiotic prophylaxis before the invasive dental procedures [61].

4. Effects of zoledronate on osteoporosis

Zoledronate is not metabolized in the body and is finally excreted intact in the urine, so the cytochrome P450 enzyme system has minor or no interaction with Zol metabolism. The binding potential of this drug to the plasma proteins is approximately 22% and after infusion, its concentration reduces in the plasma because bone tissue captures it. Besides, during bone turnover, Zol is released from bone and is detected in plasma after some days post-injection. This drug is excreted via kidneys and after up to 28 days of injection, it is detected in urine [62]. Sclerostin was released from the osteoclast precursors which were accumulated after BPs administration. The Zol therapy caused an increase in the serum sclerostin level which has a role in coupling bone resorption and this led in formation of bone tissue [63]. Zoledronate inhibited new clinical fractures in both sexes with low-trauma hip fractures and led to a reduction of 70% in the incidence of vertebral fracture, 25% in non-vertebral fracture, and 41% hip fracture, over three years, in the osteoporotic cases [16,46].

4.1. Zoledronate in comparison with other BPs

Alendronate is an effective medication in cases that have old vertebral fractures, but IV administration of 5 mg Zol once a year is effective in the treatment of high fracture risk osteoporosis [64]. The spinal fracture risk of postmenopausal osteoporotic women was also decreased by ibandronate therapy; however, there was no evidence to show the decrease of hip or non-vertebral fractures after the treatment by this drug [33]. In the light of the finding that the utilization of glucocorticoid drugs increases fractures risk and bone loss, the Reid and colleagues' investigation was conducted to prevent and treat the glucocorticoid-induced osteoporosis, using IV administration of 5 mg Zol once or oral treatment by 5 mg risedronate, daily. They showed that Zol therapy was superior to risedronate treatment in increasing the bone mineral density in the lumbar spine. Their findings also suggested that a single Zol infusion was more acceptable and effective than oral risedronate therapy [34]. The annual prescription of Zol makes up for the shortcoming of

oral BPs [65]. The bone mineral density was enhanced and preserved after one-year of treatment with Zol to a larger extent than everyday risedronate therapy in men who received glucocorticoid treatment [66].

4.2. Administration

Yearly administration of Zol had a suitable effect on the treatment of postmenopausal osteoporotic women and decreased the risk of bone fracture [67]. The patients who discontinued Zol therapy after six years demonstrated a non-significant, small increase in bone turnover markers in comparison to the patients who continued using this drug for nine years. Black et al. suggested that those patients who were treated by six years of Zol administration, once a year, did not need to continue their medication for up to three years [68]. In addition, two annual infusions of this drug over two years showed 67% reduction in fracture risk between osteoporotic men and 71% among osteoporotic postmenopausal women [16]. Huang and colleagues also demonstrated that IV administration of 5 mg Zol, annually, was an effective and safe therapy for patients of both sexes who had osteoporosis and osteopenia related to HIV [69]. Another investigation on premenopausal cases showed that annual Zol infusion reduced the bone turnover markers and was accompanied by a significant response after the 3rd injection [70]. One dose IV administration (5 mg Zol) enhanced bone mineral density in the frail elderly osteoporotic women who also received vitamin D and calcium daily over 2 years [71]. Using both local and systemic (SC) doses of 0.1 mg/kg Zol showed better results than just a single dose of this drug for osteoporosis treatment in rabbits [72].

4.3. Advantages

Zoledronate had a positive effect on bone density and significantly suppressed bone turnover on the transplant-related bone injury [73]. This drug also resulted in a significant reduction in vertebral fracture risk between the osteoporotic men [17]. Forty-one percent decrease in hip fracture risk was observed after Zol therapy, once-yearly over 3 years, in the osteoporotic postmenopausal women [28]. The morphometric vertebral fracture risk, clinical fracture, nonvertebral fracture, and clinical vertebral fracture decreased by treatment with Zol so that a significant promotion in bone metabolism markers and bone mineral density were observed in response to this therapeutic strategy [17]. Zoledronate therapy is a safe treatment strategy that is not sex-dependent and provides a significant antiresorptive effect on osteoporotic cases [28]. Similar to other BPs, Zol promoted the density of the bone mineral and decreased bone turnover markers in the osteoporotic men and women [16,53,55,74–76]. Black and colleagues showed that there was no need to continue Zol therapy after three years and the expression of bone markers and bone density in the patients who continued the treatment for six years had a small difference with the cases who stopped the treatment after three years. Besides, it is worth noting that continuation of treatment resulted in a reduction of vertebral fracture in the patients with a high risk of fracture [77].

Grbic and colleagues depicted that delayed healing occurred in the osteoporotic postmenopausal patients regardless of whether they utilized BPs or not; however, the incidence of jaw osteonecrosis was rare. Low occurrence of jaw osteonecrosis was estimated as the beneficial effect of Zol therapy on subtraction of vertebral, non-vertebral, and hip fractures in the osteoporotic postmenopausal cases. The cases who had osteoporosis without fractures no other therapeutic regimen in addition to the routine dental care was needed in the cases that received BPs therapy [78]. The other positive effects of this drug concerned the enhancement of spinal fusion rate, improvement of clinical outcomes, prevention of subsequent adjacent vertebral compression fractures, inhibition of the immobilization-induced bone loss, and shortening of the fusion time [79]. Tu et al. showed that infusion of the lumbar interbody of osteoporotic patients was enhanced after Zol therapy in clinical and radiographic observations [80]. Qi and colleagues stated that local or systemic utilization of Zol with autologous iliac bone grafting following ovariohysterectomy in rabbits reversed the negative effects of osteoporosis, enhanced bone mineralization, improved fixation of dental implants, and osseointegration under osteoporosis condition [72]. Using a biodegradable magnesium-based implant loaded with Zol resulted in increased callus size, enhanced mechanical strength, improved structural quality, and augmented bone regeneration of the newly formed bone [81].

In fact, the therapeutic effect of Zol on osteoporosis was maintained for a year [65]. Zoledronate is also effective in the thalassemia-induced osteoporosis by representing a significant increase in bone mineral density and osteoprotegerin and also a decrease in osteocalcin, type I collagen (N-terminal cross-linking telopeptide), and insulin-like growth factor-1 [82]. A significant increase in bone mineral density in the lumbar spine was observed after once-yearly Zol IV therapy after three years in addition to the significant increase of the trabecular bone score after two years [83]. Gamsjaeger and colleagues reported that Zol administration enhanced mineral crystallites and bone matrix formation with a suitable anti-resorptive effect and antifracture efficacy [84]. It has also been observed that the new morphometric vertebral fracture risk decreased after two years of Zol therapy and all evidences, in general, showed that this treatment strategy was safe [85]. Significant increases in the bone mineral density were found in the femoral neck (4.3%), trochanter (7.0%), and total hip (4.9%) after Zol administration. Besides, the effects of bone protection were seen based on increasing the bone mineral density and reducing the vertebral fracture risk with once-yearly Zol treatment in the osteoporotic postmenopausal Chinese women [86].

Sixty postmenopausal osteoporotic middle-aged women were intravenously treated with 5 mg Zol annually or 3 mg ibandronate every three months and the expression level of type I collagen, β-carboxy telopeptide (βCTX), high-density lipoprotein cholesterol (HDL-C), bone alkaline phosphatase (B-ALP), low-density lipoprotein cholesterol (LDL-C), 25-hydroxyvitamin D (25OHD), carotid artery intima-media thickness (CA-IMT), osteocalcin (OC), fibroblast growth factor 23 (FGF-23), total cholesterol (TC), and sclerostin were measured after 12 months. It was found that all these factors, except CA-IMT and sclerostin, were comparable in both groups. In the Zol-treated group, on the one hand CA-IMT decreased, and on the other, the sclerostin serum levels increased in comparison with the ibandronate group [87]. Overall, the BPs with IV administration like Zol are generally safe but the incidence of unstable influenza-like symptoms frequently occurs in this therapeutic regimen. In addition, abnormalities such as jaw osteonecrosis, delayed fracture healing, and arrhythmia were not observed after Zol therapy in the Sieber and colleagues study [88].

4.4. Limitation

There is some limitation in using Zol such as hypocalcemia which is mostly observed in cases with impaired renal function, hypoparathyroidism, limited calcium intake, some diseases of bone with a high velocity of osteoclast-mediated resorption like large skeletal tumor, Paget disease, and hypovitaminosis D [89]. Additionally, this drug causes jaw osteonecrosis especially after high doses [61]. This drug induced avascular necrosis of the jaw in addition to likely risk of jaw osteonecrosis in the patients with multiple myeloma [90,91].

5. Discussion

The outcome of osteoporosis include loss of 10–15 cm of height because of spine compression and fractures due to the reduced movement and fall along with vertebrae collapsing accompanied by stooped posture. Besides, upper back curvature, kyphosis, and neck or back pains, due to pinching of the nerves by collapsed vertebrae, are among other consequences of this disease [92].

With due attention to find an effective agent to treat osteoporosis

which is a worldwide concern, the effects of BPs was taken into account. Many positive effects of this family on osteoporosis, metabolic bone disease, and several fracture endpoint trials have been recognized in this article, the most significant of which, is their antiresorptive impact in decreasing the vertebral, nonvertebral, and hip fracture risks in the osteoporotic postmenopausal women [16]. To be noted is the reminder that most of drugs have side effects and BPs is no exception. Most studies pointed the anti-resorptive potential of BPs albeit their controversially effective impact on bone remodeling. BPs enhance bone mineral density and reduce the risk of bone fracture [93]. The relevant literature, in general, suggest that BPs except ibandronate decrease the risk of vertebral fracture in osteoporotic patients and the risk of the hip fracture in non-vertebral fractures [94].

Long-term therapy of the amino-BPs in the osteoporotic patients protects them from the moderate to high risk fractures and the atypical subtrochanteric femoral fractures. The jaw osteonecrosis risk due to this therapy is deemed to be negligibly small compared with the anti-fracture effect of these drugs on the moderate to high-risk fractures [49]. BPs are exclusively excreted through the urinary system and Boonen and colleagues found that though transient changes may occur in the renal function according to the annual infusion of this drug, the function of kidneys and other organs of the urinary tract did not change after long-term BPs administration [47]. The incidence of some symptoms such as dyspepsia, gastritis, nausea, and abdominal pain was seen in cases that used ibandronate [33], alendronate, risedronate [95], and also placebo [59].

The most powerful drug of this family is Zol on which the vastest clinical investigations in regard to osteoporosis have been undertaken. The most important characteristic of Zol is the prevention of further loss of bone tissue in postmenopausal women [96]. The occurrence of clinical vertebral and non-vertebral fractures were found to significantly reduce in the postmenopausal women who used Zol after three years, though, the reduction was not significant for the hip fracture incidence [97]. Some adverse effects like change in renal function and atrial fibrillation have also been attributed to Zol treatment. Black and colleagues stated that the level of bone remodeling was not different after first, second, and third infusion of Zol but the incidence of jaw osteonecrosis in a large number of osteoporotic women was negligible [16]. Intravenous administration of BPs suppresses bone resorption more quickly and the suppression duration is in agreement with the potency of BPs in osteoclast inhibition. For example, IV administration of 5 mg Zol suppresses the biochemical markers of bone resorption for two years after beginning the therapy in the postmenopausal cases [98]. Promotion of bone turnover and bone density showed a reduction by IV administration of Zol for one year after prescription [99]. But, given the insignificant side effects of this family, it has been admitted that their positive effects on osteoporosis treatment are more remarkable than their negative effects.

In this study, we comparatively reviewed the drugs in BPs family looking into their therapeutic potential on osteoporosis and Zol depicted the best results on this disease despite the fact of its limitation. This is a comprehensive study with due to the attention to the superiority of Zol over other drugs of this family on osteoporotic bone. Based upon the studies on the effectiveness of Zol in preventing the reduction of mechanical strength and recovering the long bone and vertebrate structure in the ovariectomized rats, more complementary investigations on the effects of this drug in curing and preventing osteoporosis are needed [65,96]. Furthermore, as Zol delays bone remodeling and decreases the number of osteoclasts [100], it may not be appropriate to prescribe it for the osteoporotic patients with pathological fractures. Overall, although several studies depicted the beneficial effects of the drugs of the BPs family on osteoporotic cases, it is recommended that more experiments be conducted on the BPs, in general, and on Zol, in particular, in view of various aspects of osteoporotic patients.

6. Conclusion

Bisphosphonates are a drug family that prevent and cure osteoporosis and decrease the risk of bone fracture. Zoledronate is viewed the most powerful drug in this family which has been heeded most in respective empirical studies. Zoledronate inhibits bone resorption which, in turn, leads to reduction of bone mass loss. Zoledronate also, not exceptionally, has some side effects on the body, which cannot outweigh the positive effects accrued in the literature on osteoporotic patients. Thus, in view of the inconclusive findings, we tend to call for more comprehensive, detailed, focus and reliable experiments to be conducted.

Declaration of competing interest

The authors declare no potential conflicts of interest.

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