Long Term Bisphosphonate Use in Osteoporotic Patients; A Step Forward, Two Steps Back

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Abstract - Purpose. Bisphosphonates are the main class of drugs widely used in prevention and treatment of osteoporosis. Along with the beneficial effects, recent studies point to the harms of long-term treatment with bisphosphonates. **Methods**. The most relevant articles reporting serious adverse effects of bisphosphonates were selected and reviewed with the aim of assessing the risk-benefit of bisphosphonates. We searched PubMed, Web of Science, and Scopus using keywords bisphosphonates, risk of fracture, atrial fibrillation, osteonecrosis jaw, esophageal cancer, and adverse effects with no time limitation. We limited our s research to English articles. **Results.** Our review shows that bisphosphonates reduce vertebral fractures in short term use while in long-term can cause osteonecrosis jaw, esophageal cancer, atrial fibrillation, and increase the risk of atypical fractures and probably adynamic bone disease. There is no consensus on the time limitation of bisphosphonate usage or its long term adverse effects. Thus, more studies on long-term side effects of bisphosphonates are highly recommended. In addition, new approaches for prevention and treatment of osteoporosis seem necessary. **Conclusion.** Prescribers should act cautionary and consider full assessment of risk-benefit and the duration of treatment.

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INTRODUCTION

Osteoporosis is considered as one of the chronic senile diseases with complex complications and comorbidities. One of its major complications is the bone fracture which is associated with high cost and debilitates. Principally its management consists of prevention strategies and pharmacotherapy. Investigation are focused on a better understanding of the pathogenesis of osteoporosis, bone metabolism and the role of inflammation, special cells and inflammatory pathways, oxidative stress as well as the link between chronic senile diseases may help finding a solution [1-9].

In the therapeutic front, treatment modalities of osteoporosis include a wide range of medications with their efficacy and side effects being major concerns. Previously we have reported that various classes of medications for osteoporosis suggest new hopeful therapeutic approaches that are potentially associated with less harm [10]. Treatment of osteoporosis by bisphosphonates reduces the rate of fracture as the primary endpoint and increases bone density and reduces bone metabolism as the

secondary endpoint. Hence, despite the emergence of new treatment approaches, bisphosphonates remain the cornerstone of prevention and treatment in the field albeit the outcomes of recent studies are confusing and disappointing. The efficacy and short-term safety profile of bisphosphonates have been proved in several studies [10,11,12], however, there are concerns about their long-term use. Furthermore bisphosphonates can be released into blood circulation years after discontinuation raising the possibility of long term adverse effects and in this regards, bisphosphonates have a maintenance effect on bone metabolism possibly depending on the dose and duration of treatment [13,14]. We, therefore, aimed at providing the pros and cons of bisphosphonates use and discuss the best approach in the application of bisphosphonates especially their long term use.

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Mechanism of action
Preferentially bisphosphonates are absorbed into the bone tissues and selectively inhibit bone resorption mediated by osteoclasts. Recently it has been suggested that bisphosphonates decrease osteocytes apoptosis [15]. Bisphosphonates decrease bone remodeling which can be measured by bone biomarkers. Initiating bisphosphonates reduces bone resorption biomarkers in the first 3 months and bone formation markers reaches its lowest level in 6 months [15].

Although the most favorable effects of biphosphonates on bone are increased bone mineral density (BMD) and reduced fracture risk which seem to be aquired after long-term use, the results of long-term studies raised major concerns about their efficacy and safety not only on bone but also on the gastrointestinal (GI) and cardiovascular systems. The side effects include osteomalacia, GI disorders, musculoskeletal pain, hypocalcemia and osteonecrosis jaw (ONJ) that are discussed later in details (Figure 1).

Available Bisphosphonates
Structurally bisphosphonates are divided into two groups: early without nitrogen atom including etidronate, clodronate and newer bisphosphonates containing nitrogen atom including alendronate, pamidronate, ibandronate, risedronate and zoledronic acid [15]. Early bisphosphonates have narrow therapeutic window and the difference between their therapeutic and toxic dose is small while the emerging nitrogen-containing bisphosphonates (NCBPs) have extended the therapeutic window. NCBPs are potentially more active on osteoclasts that the former group [15].

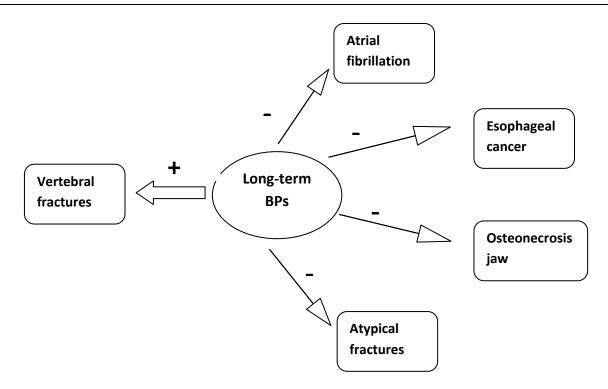**METHODS**

Evidence Acquisition
The most relevant articles reporting the serious adverse effects of bisphosphonates were selected and reviewed for the risk-benefit assessment of bisphosphonates. We searched PubMed, Web of Science, and Scopus using keywords bisphosphonates, risk of fracture, atrial fibrillation, osteonecrosis jaw, esophageal cancer, and adverse effects with no time limitation. We limited our results to articles published in English.

Some key studies on the effects of bisphosphonates are presented in Table 1.

Table 1. Summary data of long-term studies conducted on bisphosphonates

Study	Subjects	Duration	Design	Conclusion
Pols et al. (53)	1908 PMOW	1 yr	Randomized double-blind	Alendronate →↑BMD*, ↓NVF*
Bone et al. (85)	247 W	10 yrs	Randomized double-blind	BPs discontinuation after 10 yrs→↓BMD, but does not mean loss of benefit
Mellström et al. (84)	164	7 yrs	Randomized double-blind	Risedronate →↑BMD*, ↓bone turnover*, no indication of loss of anti-fracture efficacy
Odvina et al. (61)	9 P	2 yrs	Case report	ALN→delayed fracture healing, severe suppression of bone metabolism
Felsenberg et al. (83)	1964 PMOW	3 yrs	Retrospective analysis of BONE study	Ibandronate → ↓VF*
Black et al. (86)	1099 PMW	10 yrs	Randomized double-blind	BPs discontinuation after 5 yrs→↓BMD*, ↑BBMs*, ↑VF
Goh et al. (63)	13	Long-term	Retrospective	ALN →Prolonged suppression of bone remodeling & new form of femur fracture
Stepan et al. (79)	66 PMOW	Long-term	Retrospective	The association of lower femoral neck BMD & increased age with microdamage accumulation in ALN users

Table 1, Continued…

Study	Subjects	Duration	Design	Conclusions
McCloskey et al. (43)	5579 PMW	3 yrs	Randomized double-blind	Clodronate→↓clinical fracture* except for hip fracture
Chapurlat et al. (80)	50 PMOW	3yrs	Cross-sectional	Low microcrack in iliac bone; No association between microcrack frequency and duration of BP therapy,
Kwek et al. (64)	17 P	4.8 yrs	Retrospective	ALN→insufficiency stress fracture
Visekruna et al. (67)	3 P	Long-term	Case report	ALN combined with anti-remodeling therapy→atypical skeletal fragility because of SSBT*
Lenart et al . (66)	15 PMOW	5.4 yrs	Retrospective	ALN→atypical low-energy fractures
Neviaser et al. (65)	70 OP	2.5-7 yrs	Retrospective	ALN→low energy fractures of femoral shaft
Lee (69)	1 P	8 yrs	Case report	ALN for 8 yrs→ atypical FF
Abrahamsen et al. (59)	27505 P	Not specified	Cohort & cross sectional	No relationship between BPs and increased FR; Similar ratio of fracture in alendronate and control groups, ALN→↑FR
Ing-Lorenzini et al. (72)	8 P	Long term	Case report	Possible negative interaction between BPs, PPIs & corticosteroids→↑FR
Lenart et al. (75)	41 PMOW(R)	Long-term	Retrospective case-control study	The association of higher FR with long term BP
Capeci et al. (73)	7 PMOW(R)	8.6 yrs	Retrospective	Considering discontinuation of ALN therapy after presenting fracture
Black et al. (60)	14195 W	Not specified	Analyzed the results of FIT, FLEX, HORIZON, & PFT	No significant increase in FR is associated with BP use
Schwartz et al. (87)	1099 PMW	10 yrs	Post hoc analysis on FLEX study data	ALN→↓NVF in women without prevalent VF, but not in women with T Score > -2
Occhicone et al. (120)	101 PMOW	Not specified	Prospective	The incidence of new SF was the same in treated and not treated patients
Odvina et al (74)	13 OP	3-11 yrs	Retrospective	Long term BP→↑risk of atypical bone fracture
Isaacs et al. (76)	100 P(R)	Not specified	Retrospective case-control study	Long term BP→↑risk of insufficiency fractures
Girgis et al. (77)	152 P(FR)	Long-term	Retrospective	Association between atypical femur fracture and BPs
Venkatanarasimha et al. (68)	3 P	> 3 yrs	Case review	ALN→atypical low-energy fractures
Park-Wyllie et al. (71)	10439 OW	7 yrs	Cohort	Treatment with BPs≥ 5yrs→↑ risk of atypical fractures (the absolute risk is low); ↓ risk of typical fractures
Harrington et al (56)	1172 PMOW	3 yrs	Randomized double-blind	Significant reduction of the incidence of NVF as early as 6 months by risedronate
Hwang et al. (121)	323 OW	3 yrs	Pos hoc analysis of HORIZON	ZA →↓VF*, ↑BMD*
Iba et al. (112)	13 OP	42 months	Retrospective	Treatment did not cause atypical fracture
Kim et al. (70)	1200 PMW	3 yrs	Retrospective	Prevalent VF is a strong risk factor for new VF independent of BMD.
Vestergaard et al. (95)	414245 P	10 yrs	Cohort	BPs→↑risk of typical and atypical fractures, but the role of confounding should be considered

PMOW= postmenopausal osteoporotic women; PMW= postmenopausal women; OP= osteoporotic patients; OW= osteoporotic women; W= women; P= patients; (R)= presented with fracture; BMD= bone mineral density, NVF= non-vertebral fracture; VF- vertebral fracture; FF= femoral fracture; FR= fracture risk; SF- subtrochanteric fracture; SSBT= severely suppressed bone turnover; BBMs= bone biomarkers; BPs= bisphosphonates; ALN= alendronate; ZA= zoledronic acid; PPIs= proton pump inhibitors.

Figure 1. The overall health effects of bisphosphonates - BPs= bisphosphonates

Reported Side effect

Upper GI

One of the most common side effects of this class of drugs is GI disorders including dyspepsia, abdominal pain, nausea, and gastritis. Based on the case reports from United States, Europe and Japan, the U.S. Food and Drug Administration (FDA) in 2009 warned the public of the association of esophageal cancer with oral bisphosphonates [16]. The warning was based on 23 esophaseal cancer cases associated with alendronate usage for median time of 2.1 year [15].

The association of esophageal cancer with risedronate, ibandronate and etidronate were also reported in Europe and Japan after median time of 1.3 years of usage [15]. The relationship between esophageal cancer and oral bisphosphonates can be explained by the esophagitis – esophageal inflammation caused by bisphosphonates – followed by squamous cell carcinoma and adenocarcinoma of the esophagus. Solomon et al. could not confirm this association in a U.S. Medicare health plan database [17], and Abrahamsen et al. even reported a reduced risk of esophageal cancer by oral bisphosphonates

compared with control group for a mean of 2.8 years [18].

Accordingly another case report mentioned no association between oral bisphosphonates and esophageal adenocarcinoma in Barretts esophagus [19]. In contrast Green et al. [20] observed a significant increase in risk of esophageal cancer by oral bisphosphonates in a large case-control study within a UK cohort. They reported more significant risk from 1/1000 to 2/1000 in 60-79 year old range with 10 or more bisphosphonate prescriptions / patient in over 3 years as compared with one to nine prescriptions. This was for all type of bisphosphonates and for all ages regardless of the BMI, sex, smoking or alcohol use. In contrast, they find no change in the risk of cancer of stomach and colorectum by oral bisphosphonates [20]. Interestingly, when Cardwell et al. analyzed the information extracted from the Green et al study in nearly twice as long as Green et al period of time, they could not confirm a significant association between risk of esophageal or gastric cancer and oral bisphosphonates [21]. According to the new announcement of FDA, there have been conflicting findings in this issue and FDA is still reviewing data [22].

Osteonecrosis jaw

Osteonecrosis of the jaw (ONJ) which was firstly reported in 2003 is one of the side effects of NCBPs with an incidence of approximately 1/10000 to 1/100000 patient treatment years [23,24].

Firstly, the problem is presented as a non-healing extraction socket or exposed jawbone associated with swelling and purulent discharge refractory to antibiotic treatment [25]. According to the American Society for Bone and Mineral Research, ONJ is described as an area of a non-healing exposed bone in the maxillofacial region in a patient who is/was exposed to a bisphosphonate and did not undergo radiation to the craniofacial region [23].

The pathogenesis behind this side effect is proposed as suppression of bone turnover and vascular insufficiency caused by bisphosphonates [26]. Its incidence is correlated with cumulative dose and length of usage, potency of the bisphosphonate, route of administration, oral hygiene as well as the age and race of the patient, cancer diagnosis and underlying diseases [25,27]. In 2003 Bamias et al assessed 252 patients who received bisphosphonates for 6 years prospectively. They confirmed the association of bisphosphonate usage and ONJ and considered duration of exposure as an important risk factor for ONJ. They reported a higher cumulative hazard with zoledronic acid compared with pamidronate alone or pamidronate and zoledronic acid sequentially [28]. The risk of ONJ by oral bisphosphonates seems to be lower than IV route of administration [29]. Formerly cancer was considered as a risk factor for ONJ but a prospective phase III trial in women with stage II/III breast cancer ruled out the role of cancer as a risk factor for ONJ [30]. However, cancer patients with bone metastasis using intravenous NCBPs are at the highest risk of developing ONJ [31]. King et al reviewed 44 case reports and determined more frequent ONJ in intravenous bisphosphonate users (453 patients [94.2%] out of 481) than in patients receiving oral bisphosphonates (28 patients [5.8%]) [32]. Some investigators suggest the development of necrosis even after bisphosphonate cessation [33]. The result of a case review study revealed the higher risk of ONJ to be within 2 years of bisphosphonate use which increased fourfold after 2 years [34].

Risk of fracture

Vertebral fractures are the most reliable indicators of reduced bone density, hence, a reduction of fracture risk is often the first endpoint in osteoporosis studies. The FDA has approved all bisphosphonates as efficient drugs in reducing rates of vertebral fractures but there is no consistency on reducing hip fractures. However, investigations on the effect of bisphosphonates on non-vertebral fractures have also been carried out.

There are several potential trials reporting reduction in new vertebral, non vertebral, hip and wrist fractures, by alendronate, risedronate, ibandronate, clodronate and zoledronic acid [35-51]. Meta-analyses on alendronate have shown 0significant efficacy in reducing vertebral, non vertebral, hip and wrist fractures as secondary prevention with no significant results for primary prevention except for vertebral fractures [52, 53]. However, studies on etidronate and residronate demonstrated their effectiveness only in secondary prevention of vertebral fractures with no significant effect on primary prevention and non vertebral fractures [54-56].

Despite the overwhelming data to support the effectiveness of bisphosphonates in reducing risk of fracture, there are some case reports suggestive of increased risk of atypical femoral fracture associated with long term use of these drugs [57,58]. This notion, however, is not generally agreed upon [59,60]. Part of the problem is that the optimal duration of bisphosphonate therapy to achieve beneficial effects, hence, the duration of monitoring the side effects are still undecided. Some have reported a loss of efficacy after 2 years [61] while some others did not notice antifracture activity following 10 years of bisphosphonate treatment [62]. Recent evidences are indicating suppression of the bone turnover and increased risk of bone fragility after long term bisphosphonate therapy [57]. The delayed recovery from fracture and evidences of severe suppression of bone metabolism were, first, observed by Odvina [61]. Between 2006 and 2007 the first case report indicating atypical insufficiency fractures after long term exposure to bisphosphonates was published [63]. The other case reports, indicated subtrochantric, atypical proximal femoral, and femoral fractures with or without clinical and radiographic features by insisting on the long-term exposure to bisphosphonates [64-67]. In a brief

case report, femoral fractures after long-term bisphosphonate administration in patients with inflammatory diseases such as rheumatoid arthritis, Crohn's disease, have appeared [68]. In addition, Venkatanarasimha et al provided evidence of a link between bisphosphonate usage and subtrochanteric fractures in a review article[69]. Lee et al reported atypical femoral fractures in a patient after 8 years of bisphosphonate therapy with their X-ray showing typical horizontal fracture line in both femurs. The histopathology examination showed lack of osteoblasts and osteoclasts in the tissue extracted from fracture ends and osteopenia over the femoral neck confirmed by bone densitometry [70].

Kim et al conducted a propensity score matched cohort study to measure incidence rate and risk of subtrochanteric or diaphyseal femur fractures in bisphosphonate users in comparison to raloxifene or calcitonin users. Their results showed that the incidence rate of subtrochanteric or diaphyseal femur fractures is rare and no evidence of the increased incidence with bisphosphonates was found while they did not deny the possible impact of long-term bisphosphonates [71].

A population-based study confirmed the association between increased risk of subtrochanteric or femoral shaft fractures and more than 5 years bisphosphonate usage, however they reported the risk as low [72]. Other case reports stated the possible association between long-term bisphosphonate therapy and other drug classes affecting bone metabolism that may yield increased risk [73]. However, similar fractures were seen after long-term use of bisphosphonate without other medications affecting bone metabolism [74].

Noteworthy is the observation of new fractures after both the long-term bisphosphonate (mostly alendronate) alone and also in combination with other medications with the potential to affect bone metabolism.[75,76]. The results of a retrospective case-control study performed by Lenart et al showed significant unique X-ray pattern after bisphosphonate use [76] which is in agreement with the findings of the study of Isaacs et al [77]. The opposing reports that argue against the increased risk include an analysis of a cross-sectional study on Danish patients showed similar ratio of fractures between alendronate-treated patients and untreated controls and the investigators observed that increased use of alendronate in patients with high risk of fracture, augments the risk of fractures in alendronate users [59]. Girgis et al supported the

association between atypical fracture and bisphosphonates by reviewing 152 femoral fractures in women [78]. In a retrospective analysis, Schilcher et al reported smaller risk of fractures due to bisphosphonate usage in comparison with osteoporosis alone [79]. Stepan et al found microcracks in bone biopsy after long-term alendronate therapy [80], however after about 6.5 years of alendronate administration, Chapurlat et al could not find those remarks [81]. Black et al analyzed the results of three bisphosphonate trials, the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON), Pivotal Fracture Trial (PFT), the Fracture Intervention Trial (FIT) and the FIT Long-Term Extension (FLEX) trial. They analyzed the records of more than 14000 patients for approximately 10 years. They indicated that the correlation between risk of atypical femoral fractures and bisphosphonate therapy is extremely low [60]. Rizzoli et al thoroughly reviewed the subject and concluded that more than a 5 year treatment doubles the risk of subtrochantric femoral fractures, however, they suggested the risk-benefit ratio to be favorable [82]. In a recent survey, Colón-Emeric et al determined the impact of zoledronic acid on the modification of risk of fracture after low-trauma hip fracture in a post-hoc analysis. They randomized 2127 patients and followed them for 90 days after hip surgery to receive zoledronic acid or placebo. They concluded that zoledronic acid could not lessen the influence of risk factors including age, sex, BMI and fall on the subsequent fractures [83].

The increased risk of fracture secondary to the use of bisphosphonates has not been noticed by Felsenberg et al, who retrospectively analyzed the results of Ibandronate Osteoporosis Vertebral Fracture (BONE) trial noticed a dominant effect for ibandronate on reducing the risk of new vertebral fractures in the more severe forms of vertebral fractures at years 1, 2 and 3 [84]. Mellstrom et al who evaluated the effects of 7 years risedronate therapy observed maintenance of increase in BMD, decrease in bone biomarkers and no indication of loss of anti-fracture efficacy [85]. The results were confirmed by others following 10 years of alendronate therapy [62]. Black et al showed that discontinuation of alendronate after 5 years does not significantly increase fracture risk and further, continuing alendronate treatment beyond 5 years may benefit women at higher risk of vertebral fractures [86]. Schwartz et al differentiated women

with femoral T score of -2.5 or less after 5 years alendronate therapy and those with higher T scores and resulted that extending therapy for 10 years reduces non-vertebral fractures in the first group (T score ≤ -2.5) [87].

Other than duration of treatment the effect of the size of bisphosphonates dose has recently attracted attention. Makras et al studied the effect of different doses of intravenous pamidronate on the incidence of fracture in 92 postmenopausal osteoporotic women. They observed that every prevalent vertebral fracture increases the risk of a new vertebral fracture by 32% in comparison with 25% for patients with non-vertebral fractures who received lower dose of pamidronate. The patients who followed intravenous pamidronate by oral pamidronate had higher incidence of nonvertebral fractures [88].

Atrial fibrillation

Thus far, a few trials have raised awareness toward association of serious cardiac arrhythmias especially atrial fibrillation (AF) after bisphosphonate therapy [89,90]. Therefore the US FDA is reviewing this potential cardiac adverse effects of bisphosphonates [91].

Black et al [38] studied annual zoledronic acid injection in postmenopausal osteoporotic women and demonstrated significant risk of serious AF in the treatment group versus placebo but they could not find difference in the rate of stroke between two groups. However, a subsequent post-hoc analysis of the data using a randomized clinical fashion on alendronate in 6459 postmenopausal women for 4 years showed no difference in total AF events between treatment and placebo groups. Nevertheless, 47 cases of serious AF were reported in the treatment group [89]. The re-analysis of data from 3 clinical trials on bisphosphonates could not confirm the association between bisphosphonates usage and risk of AF [90].

An observational study of Heckbert et al [92] indicated a strong association between sustained AF rather than transient AF and alendronate which was supported by analysis of the National Prescription Database from 1995 to 2005 [93]. In contrast no correlation between bisphosphonates and risk of AF was demonstrated in six observational studies [94-98].

Loke et al and Kim et al in two meta-analysis indicated that heterogeneity of the existing evidences and paucity of some information limit our understanding of the association between serious AF and bisphosphonates [99,100]. Further meta-analysis by Mak et al could not show higher risk of AF with bisphosphonates while they suggested clinicians to consider the probability [101]. In contrast Bhuriya et al included 26126 postmenopausal women in their meta-analysis and indicated a significant increase in risk of serious AF after bisphosphonate use [102].

Contrary to the above mentioned studies frequent zoledronic acid doses in oncology patients did not increase risk of AF [103,104]. Lyles et al evaluated the risk of AF in 1065 patients receiving zoledronic acid in HORIZON Recurrent Fracture trial and could not find significant difference between those patients with patients receiving placebo [105].

DISCUSSION

With regards to the therapeutic outcome of bisphosphonate therapy, there seems to be a significant difference between short and long term regimens. The function of these drugs appears to be biphasic. There exists an overwhelming body of literature supporting the short term beneficial effects of bisphosphonates. However, the efficacy and safety of these drugs during the second phase, i.e., long term effect, is uncertain.

The issue becomes even more complicated when one realizes that there is no conventional agreement on the definition of the short and long term bisphosphonate regimens. The plausible mechanism for long-term effects of bisphosphonates on the bone appears to stem from their penetration into the bone tissue and their subsequent influence in affecting microdamage repair mechanisms with increases in bone fragility as the outcome. This may also cause degenerative bone disease [106,107]. It is important to emphasize that reported human bone biopsies taken 6 months to 10 years after drug administration do not support the idea of suppression of bone remodeling [108,109]. Animal data on this subject has been controversial [110,111].

Other than the long term effects of bisphosphonates on bone, their adverse effects on the gastrointestinal tract and the cardiovascular system must be considered. Similarly, although controversial, consideration must be given to the risk of esophageal cancer caused by bisphosphonate

particularly in patients in premalignant conditions. Another points the begs attention is the musculoskeletal pain in some patients under bisphosphonate therapy that may involve bone, joint, or musculoskeletal tissue at any time after starting drug therapy that may not stop for some time after discontinuation of the drug [15].

Overall, the side effects appear to be influenced by factors such as the type of the drug, duration and route of administration, old age, fracture prevalence and combined drug therapy. An additional factor to consider is the dosing frequency and the size of the dose. Shiraki *et al* who evaluated the possible association between the metabolic effects of bisphosphonates and fractures, identified old age, higher number of prevalent fractures, higher osteocalcin levels, and lower lumbar BMD as risk factors for incident fractures despite of bisphosphonate use [112]. For bisphosphonates, the side effects ascribed to daily doses, the long-term treatment nature of the therapy and the prolong after-dose effect, has prompted the sponsors to develop and market once weekly, once monthly and once yearly drug regimens. Whether, these treatment regimens will yield differences in the long term safety and efficacy of the class of the drugs has remained unknown.

It is worthy to note that most studies reporting long-term exposure to bisphosphonates have focused on alendronate with only a few case reports on ibandronate, risedronate and zoledronic acid [65,68,75,113]. This is expected since the latter was the first to be marketed.

In the recent decades promising advancements have been made in identifying bone biomarkers as surrogates of bone metabolism. Iba *et al* have shown that the N-telopeptide of type I collagen levels returns to normal in 13 osteoporotic patients who were under therapy with bisphosphonates who had reduced level of the biomarker [114]. In another recent study, the investigators demonstrated that age, prevalent fractures, pentosidine and homocysteine are independent predictors of incident vertebral fractures under bisphosphonate usage [115]. Therefore, it has been suggested that more investigations into annual changes of bone biomarkers in osteoporotic patients after bisphosphonate treatment may provide clues as to the therapy outcome.

The difference in the baseline fracture risk may also provide a clue in the safety outcome. This has been suggested by Abelson *et al* who compared the fracture risk in three cohorts of women (>200,000) treated by either alendronate, ibandronate and risedronate [116]. Kim *et al* have confirmed that prevalent vertebral fractures are strong risk factors for new vertebral fractures among bisphosphonate users [117].

It has been suggested that vitamin D deficiency negatively influence the outcomes of bisphosphonates therapy [118]. However, this finding did not rule out the adverse effects of long-term bisphosphonate therapy in patients with adequate vitamin D levels.

Another issue which should be considered is the individual differences in response to bisphosphonates. Sebba *et al* reviewed clinical trials and found that BMD does not increase in all patients on bisphosphonate therapy and the rate of 2-year non-responders differs between bisphosphonates [119].

Taken together, the need for more carefully designed investigations in the area of long-term bisphosphonate therapy is obvious. In the future studies, consideration should be given to the baseline BMD, prevalent fractures and risk of fractures in osteoporotic patients, monitoring of bone biomarkers. Furthermore, attention should be paid to the size of the dose and the dosing interval.

In conclusion, until the concerns raised in this review are addressed, prescribers should exercise extra caution in assessing the already known risk factors and consider the risk:benefit ratio of long-term bisphosphonate therapy based on the individual patient's characteristics.

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