# Long-term Bisphosphonates for Osteoporosis: A Factor Effecting Fracture Pattern?

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**ABSTRACT** **Background:** The incidence of fragility hip fractures, intracapsular and extracapsular, has been increasing worldwide. Fracture stability is important for treatment decision-making and is related to the expected rate of complications. It is unclear whether metabolic therapy explains the increased incidence of unstable fractures.

**Objectives:** To investigate the possible association between treatment with bisphosphonates and the various patterns encountered with intertrochanteric hip fractures.

**Methods:** Patients with fragility hip fractures who were treated in our department between 2013 and 2014 were included in this study. They were classified into three groups: group 1 had a stable extracapsular fracture, group 2 had an unstable extracapsular fracture, and group 3 had an intracapsular fracture. Collated data included: osteoporosis preventive therapy and duration, fracture-type, history of previous fractures, and vitamin D levels.

**Results:** Of 370 patients, 87 were previously treated with bisphosphonates (18.3% prior to fracture in group 1, 38.3% in group 2, and 13.8% in group 3). Of those treated with bisphosphonates, 56.3% had an unstable fracture, 21.8% had a stable fracture, and the rest an intracapsular fracture. In contrast, only 27.9% of patients who were not treated with bisphosphonates had an unstable fracture and 30.0% had stable fractures.

**Conclusions:** Our findings show a higher proportion of complex and unstable fractures among patients with fragility hip-fractures who were treated with bisphosphonates than among those who did not receive this treatment. The risk for complex and unstable fracture may affect the preferred surgical treatment, its complexity, length of surgery, and rehabilitation.

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**KEY WORDS:** bisphosphonates, fragility fracture, hip fracture, hip surgery, osteoporosis

The incidence of osteoporotic hip fractures is increasing worldwide [1]. Commonly known as fragility fractures, these fractures usually result from a low energy fall from a standing position. Hip fragility fractures are commonly classified as intracapsular or extracapsular. Several classification systems are used to further describe these fractures, including the degree of displacement, stability, and the number of fragments [2-5]. Stratifying extracapsular fractures as stable or unstable may contribute to surgical decision making and help predict complication rates [6,7].

A significant change in fracture pattern was shown during the first decade of the millennium, from stable to unstable fractures [8], although an explanation is elusive.

A national survey of bisphosphonate administration in the United Kingdom conducted between 2000 and 2010 showed an increase in bisphosphonate usage following hip fracture, from 7% to 46% [9]. However, only 9.7% of patients were actively treated prior to fracture diagnosis. An increasing awareness of fragility fractures among community physicians has prompted an increase in the proportion of individuals with osteoporosis who are treated with bisphosphonates for osteoporosis [10,11]. The U.S. National Osteoporosis Foundation (NOF) recommends bisphosphonate use as the first choice for osteoporosis [12]. Bisphosphonate treatment is thought to reduce bone resorption and to reinforce bone structure [13]. Treatment with bisphosphonates has also demonstrated effectiveness in reducing the risk of vertebral and hip fragility fractures in approximately half of individuals with a *t*-score lower than -2.5 [13]. NOF also recommends vitamin D and calcium supplementation for all postmenopausal women. However, despite their clear importance to bone metabolism, supplementation with calcium and vitamin D has not demonstrated effectiveness in preventing fragility fractures [14,15].

There is no consensus regarding an association between fracture stability and the type of treatment. Specifically, it is not known whether a given metabolic therapy contributes to the risk of development of unstable fractures. Thus, the aim of this study was to investigate an association of bisphosphonate use with intertrochanteric hip fractures.

## PATIENTS AND METHODS

In this descriptive case controlled and retrospective study, we retrieved data from patients who were treated for fragility fractures during a random 1-year period. Inclusion criteria were operation at our institution during the research year with full clinical and radiographic data that we could retrieve.

**Table 1.** Bisphosphonate treatment before fractures, according to the classification of the fracture

| Group | AO classification | Bisphosphonate treatment before fracture | | Total |
|---|---|---|---|---|
| | | no | yes | |
| 1 | A1.1–A2.1 | 85 (30.0%) | 19 (21.8%) | 104 (28.1%) |
| 2 | A2.2–A3.2 | 79 (27.9%) | 49 (56.3%) | 128 (34.6%) |
| 3 | B | 119 (42.0%) | 19 (21.8%) | 138 (37.3%) |
| Total | | 283 (100.0%) | 87 (100.0%) | 370 (100.0%) |

Study participants completed questionnaires during their follow-up clinic visit. The information accessed from the electronic medical records included demographics, co-morbidities, history and type of preventive therapy for osteoporosis, and duration of treatment. For patients who discontinued bisphosphonate therapy prior to the fracture, we examined the time elapsed from cessation and whether the treatment was modified. In addition, we recorded other fractures experienced by the study group. Since we routinely test vitamin D levels in all our patients with fragility hip fractures, we classified these levels according to three categories: deficient (< 50 nmol/L), insufficient (50–75 nmol/L), and adequate (> 75 nmol/L). Patient radiographs were evaluated by two senior orthopedic surgeons who classified each fracture according to the Muller AO classification. Patients were classified into three groups according to fracture stability: group 1 included all stable extracapsular fractures (AO A1.1–A2.1), group 2 included unstable extracapsular fractures (AO A2.2–A3.2), and group 3 included intracapsular fractures (AO B, subcapital fractures).

Data were analyzed using chi-square for nominal variables and a *t*-test or the Mann-Whitney test for continuous variables. *P* value < 0.05 was considered significant.

Multivariate logistic regression models were performed to control for potential confounders and to determine independent predictors of intertrochanteric hip fractures among patients treated with bisphosphonates. Significant variables in the univariate analysis were included in the models.

The study was approved by the local institutional review board according to the International Conference on Harmonization Good Clinical Practice standards.

## RESULTS

During the one-year study period, 887 patients were treated for fragility fractures at our institution. However, due to limitations in electronic medical record data collection, only 370 were included in this study.

The mean age of the patients was 80.7 ± 10.4 years, 71.3% were women. Ninety-four patients (25.2%) included in the study group had a previous osteoporotic fracture. Classifying patients according to fracture stability revealed the following distribution: 104 (28.1%) in group 1 (stable fracture), 128 (34.6%) in group 2 (unstable fracture), and 138 (37.3%) in group 3 (intracapsular fracture). Only 87 patients (23.5%) had been treated with bisphosphonates prior to the fracture. In total, 145 patients (39.3%) reported taking vitamin D and calcium. Seven patients (1.9%) received subcutaneous Teriparatide (Forteo®) injections as therapy for osteoporosis.

Only 18.3% of the patients in group 1 (stable fractures) were treated with bisphosphonates prior to the fracture compared to 38.3% of the patients in group 2. This difference was significant ($P < 0.001$). In group 3, 13.8% of patients had been treated with bisphosphonates. Of the 87 patients who were treated with bisphosphonates, 49 (56.3%) had an unstable fracture, 19 (21.8%) had a stable fracture, and 19 (21.8%) had an intracapsular fracture. In contrast, among the 283 patients who were not treated with bisphosphonates prior to the fracture, 79 (27.9%) had an unstable fracture, 85 (30%) had a stable fracture, and 119 (42%) were diagnosed with an intracapsular fracture. The difference between groups 1 and 2 in the proportion treated with bisphosphonates was statistically significant ($P < 0.001$) [Table 1]. Logistic regression analysis showed a significant risk of unstable fractures in patients treated with bisphosphonates, from 2.1 years of treatment [Table 2].

Plasma vitamin D level was deficient in all the patients, despite treatment with vitamin D and calcium prior to the fracture, by 39.3% of the study group. Vitamin D level was not associated with the type of fracture.

## DISCUSSION

The main finding of this study was an association of long-term treatment with bisphosphonates and fracture type. At the writing of this article, to the best of our knowledge, the effect of long-term bisphosphonates usage was only known in relation to atyp-

**Table 2.** Results of a logistic regression analysis of factors associated with unstable fractures

| Type of fracture | Age, years | Vitamin D serum level | Duration of treatment, years |
|---|---|---|---|
| Unstable extracapsular fractures, mean ± SD (group 2) | 82.3 ± 9.1 | 46.2 ± 32.4 | 2.1 ± 3.6 |
| Other fractures, mean ± SD (groups 1+3) | 79.8 ± 11.0 | 41.7 ± 22.4 | 0.7 ± 2.3 |
| Total, mean ± SD | 80.7 ± 10.4 | 43.3 ± 26.5 | 1.2 ± 2.9 |
| *P* in *t* test | 0.029 | 0.179 | 0.000 |

According to logistic regression analysis showing the years of treatment as risk factor for unstable fracture
SD = standard deviation

ical fractures. We were able to show an association of long-term treatment with fracture type. This finding suggests that bisphosphonates may affect bone elasticity and physical properties, thus leading to more complex and unstable fracture patterns, which were not commonly seen a few decades ago [16,17]. Bone mineral density (BMD) was not considered in the multi variant analysis but it is logical to consider that patients who were treated with bisphosphonates had higher BMD. Unfortunately, this conclusion remains a bias in this study and could have been proven if BMD was available. Bisphosphonates have demonstrated effectiveness in preventing fractures, specifically for vertebral and hip fractures [14,15]. Long-term treatment with bisphosphonates is now recognized to pose an increased risk of atypical fractures [18]. More than one-third of our patients with unstable hip fracture were treated with bisphosphonates. The risk of unstable fractures in these patients was significant from 2.1 years of treatment.

Awareness among orthopedic surgeons for medical prevention remains low. Previous studies [19,20] have investigated the approach of orthopedic and family physicians toward treatment of osteoporosis, especially following mild osteoporotic fractures including wrist and vertebral compression fractures. They reported that most orthopedists do not recommend treatment for osteoporosis, despite warning signs that were clinically obvious. Moreover, various studies reported that some family physicians do not refer patients for diagnostic studies or initiate preventive treatment when should [20-22].

Despite the extensive reports in the literature and debate on treatment for osteoporosis, only 25.4% of patients in our cohort were treated before the fracture. Almost all those treated received bisphosphonates. Although 39.3% of the patients reported taking supplemental vitamin D and calcium prior to the fracture, no association was found between vitamin D plasma levels and the type of fracture. Klop and colleagues [9] found that only 9% of patients hospitalized with fragility fractures had been treated for osteoporosis before hospitalization. This proportion is extremely low as 100% of the patients in that study were diagnosed with osteoporosis; 24.9% of them had a previous osteoporotic fracture. Undoubtedly, more should have been done to prevent fractures.

According to the American Society for Bone and Mineral Research, the risk of atypical hip fractures is negligible compared to the risk of vertebral fracture in patients who discontinue osteoporosis treatment after 5 years. The task force recommends cessation of therapy for 2 to 3 years after 5 years of treatment with bisphosphonates, for patients with low risk of fracture; however, replacement therapy is not mentioned [24].

## LIMITATIONS

Due to lack of data, the analysis included only 42% of the patients with hip fractures treated at our institute during the study period. BMD was not obtained or available and was not considered as a possible predisposing factor affecting fracture morphology. It is possible that patients with more severe osteoporosis (by BMD, or by prevalence of prior fractures) were allocated to receive bisphosphonate treatment and thus the severity of the underlying condition and not the treatment itself predisposed to fracture instability.

This study is a small observational study; therefore, our conclusion regarding the effectiveness of bisphosphonates versus the fear of its possible harm should be further investigated in larger cohorts.

## CONCLUSIONS

While bisphosphonate treatment has demonstrated effectiveness in decreasing the incidence of fragility fractures, the findings of this study show an association of this therapy with increased risk of unstable fractures (i.e., complex hip fractures). This information may have consequences on the type of treatment, the complexity and timing of surgery, and the rehabilitation process.

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**Capsule**

## Metabolic control of TFH cells and humoral immunity by phosphatidylethanolamine

T follicular helper (TFH) cells are crucial for B cell-mediated humoral immunity. Although transcription factors such as BCL6 drive the differentiation of TFH cells, it is unclear whether and how post-transcriptional and metabolic programs enforce TFH cell programming. **Fu** et al. showed that the cytidine diphosphate (CDP)–ethanolamine pathway co-ordinates the expression and localization of CXCR5 with the responses of TFH cells and humoral immunity. Using in vivo CRISPR-Cas9 screening and functional validation in mice, they identify ETNK1, PCYT2, and SELENOI–enzymes in the CDP-ethanolamine pathway for de novo synthesis of phosphatidylethanolamine (PE)–as selective post-transcriptional regulators of TFH cell differentiation that act by promoting the surface expression and functional effects of CXCR5. TFH cells exhibit unique lipid metabolic programs and PE is distributed to the outer layer of the plasma membrane, where it colocalizes with CXCR5. De novo synthesis of PE through the CDP–ethanolamine pathway co-ordinates these events to prevent the internalization and degradation of CXCR5. Genetic deletion of *Pcyt2*, but not of *Pcyt1a*, which mediates the CDP–choline pathway), inactivated T cells impairs the differentiation of TFH cells, and this finding is associated with reduced humoral immune responses. Surface levels of PE and CXCR5 expression on B cells also depend on *Pcyt2*. These results reveal that phospholipid metabolism orchestrates post-transcriptional mechanisms for TFH cell differentiation and humoral immunity, highlighting the metabolic control of context-dependent immune signaling and effector programs.

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**Capsule**

## Intratumoral follicular regulatory T cells curtail anti-PD-1 treatment efficacy

Immune-checkpoint blockade (ICB) has shown remarkable clinical success in boosting antitumor immunity. However, the breadth of its cellular targets and specific mode of action remain elusive. **Eschweiler** and colleagues found that tumor-infiltrating follicular regulatory T (TFR) cells are prevalent in tumor tissues of several cancer types. They are primarily located within tertiary lymphoid structures and exhibit superior suppressive capacity and in vivo persistence as compared with regulatory T cells, with which they share a clonal and developmental relationship. In syngeneic tumor models, anti-PD-1 treatment increases the number of tumor-infiltrating TFR cells. Both TFR cell deficiency and the depletion of TFR cells with anti-CTLA-4 before anti-PD-1 treatment improve tumor control in mice. Notably, in a cohort of 271 patients with melanoma, treatment with anti-CTLA-4 followed by anti-PD-1 at progression was associated with better a survival outcome than monotherapy with anti-PD-1 or anti-CTLA-4, anti-PD-1 followed by anti-CTLA-4 at progression or concomitant combination therapy.

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