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ATYPICAL FEMORAL FRACTURES DUE TO THE USE OF BISPHOSPHONATES: EPIDEMIOLOGIC STUDY IN A TERTIARY HOSPITAL

FRATURAS ATÍPICAS DE FÊMUR POR USO DE BIFOSFONATOS: ESTUDO EPIDEMIOLÓGICO EM UM HOSPITAL TERCIÁRIO

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ABSTRACT

Objective: Show the relationship between atypical femoral fractures and prolonged use of bisphosphonates and analyze the limit of its beneficial use. Methods: Retrospective cohort study (level of evidence 2B). From Atypical fracture cases, patients who used bisphosphonates were selected and the time period of their use was analyzed. Additionally, the variables sex, age, and the side most affected were studied. Results: Nine atypical femur fractures were found, all associated with the use of bisphosphonates. The average period of use of this medication was nine years (minimum of three years; maximum of 14 years). The patients' mean age was of 78 years (69-88 years) and all were women, with the right member being the most affected. Conclusion: The use of bisphosphonates to prevent osteoporotic fractures has been increasingly frequent and, when used for a prolonged period, it has been related to atypical fractures. Further scientific studies on doses, maximum periods of treatment, and risk-benefit in the indication of these medications are needed to assist in therapeutic management for each case. ***Level of Evidence II, Retrospective Study.***

Keywords: Bisphosphonates. Adverse Effects. Insufficiency Fractures. Subtrochanteric Fractures. Femoral Fractures. Osteoporosis.

RESUMO

Objetivo: Demonstrar relação entre as fraturas atípicas de fêmur e o uso prolongado de bifosfonatos, descrever sua incidência e analisar até qual momento o seu uso é benéfico. Métodos: Estudo de coorte retrospectivo (nível de evidência 2B). Análise de 151 prontuários de pacientes com diagnóstico de fratura de fêmur em um hospital terciário, no período de janeiro de 2013 a dezembro de 2018. Foram selecionados os casos de fraturas atípicas e, dentre esses, os que faziam uso de bifosfonatos e o tempo de utilização. Ademais, foram estudadas as variáveis sexo, idade e lado mais acometido. Resultados: Constatadas 9 fraturas atípicas de fêmur, todas associadas ao uso de bifosfonatos. O período médio de uso dessa medicação foi de 9 anos (mínimo – 3 anos; máximo – 14 anos). A idade média dos pacientes foi de 78 anos (69-88 anos) e ocorrência unicamente em mulheres, tendo como membro mais acometido o direito. Conclusão: O uso dos bifosfonatos na prevenção de fraturas osteoporóticas tem sido cada vez mais frequente e relacionado às fraturas atípicas, quando empregado por tempo prolongado. A coleta de mais informações científicas que estudem doses, períodos máximos de tratamento e risco-benefício na indicação dessas medicações é essencial para auxiliar no manejo terapêutico apropriado para cada caso. ***Nível de Evidência II, Estudo Retrospectivo.***

Descritores: *Bifosfonatos. Efeitos Adversos. Fraturas por Insuficiência. Fraturas Subtrocantericas. Fraturas do Fêmur. Osteoporose.*

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INTRODUCTION

Bisphosphonates are a class of drugs prescribed mainly for the treatment of senile and postmenopausal osteoporosis since they reduce the incidence of vertebral and non-vertebral fractures.[1,2] Its mechanism is based on antiresorptive activity in bone, reducing the number of osteoclasts, as well as decreasing its function and increasing apoptosis, preventing bone destruction. The strong and continuous inhibition of resorption unbalances the normal bone remodeling, necessary to maintain bone quality, leading to exaggerated mineralization and increased bone density. This process increases bone stiffness, resulting in the accumulation of microcracks, followed by increased microfractures and possibly

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leading to the appearance of fractures, especially when associated with extrinsic factors, such as the action of asymmetric mechanical burden in the femur. Other medications may also be related to the suppression of bone remodeling, such as estrogens, glucocorticoids and/or proton-pump inhibitors.[3-5]

Multiple reports within the literature indicate a probable relationship between the use of bisphosphonates and the increase of non-osteoporotic femur fractures with atypical patterns in patients medicated for six years or more with this class of drug. The first case of this association was reported in 2005.[6] Other similar cases of fractures appeared in the sequence, which had in common, in addition to the use of bisphosphonates, small or no trauma involved and pain in the thigh/groin of the affected leg in approximately 70% of patients.[7,8]

Clinically, atypical fractures of the femur are difficult to be identified due to nonspecific symptoms, such as persistent pain in the thigh, with worsening when supporting the foot on the ground, vague discomfort and/or subjective fatigue. However, in the presence of these symptoms along with the use of bisphosphonates, it is recommended to investigate fractures through pelvis and thigh radiographs in two planes and both limbs to rule out differential diagnoses.[3,5,9]

In 2013, the Brazilian Health Regulatory Agency (Anvisa) issued a report to physicians on the prolonged use of bisphosphonates and its safety, recommending the interruption of treatment after three years to analyze each patient individually to determine the necessity of its use for a longer period.[10]

Based on the aforementioned concepts, it becomes relevant to alert all physicians about the adverse effect of this drug class. This study aimed to show the relationship between atypical fractures of the femur and the prolonged use of bisphosphonates, describe its incidence and analyze to what extent the use of this medication is beneficial.

MATERIALS AND METHODS

From January 2013 to December 2018, 151 cases of femoral fractures from a tertiary hospital in the city of Cascavel, in the state of Parana, were reviewed; those with atypical fractures related to prolonged use of bisphosphonates were selected and analyzed.

To classify the fractures, the criteria established by the American Society for Bone and Mineral Research (ASBMR) were used, considering as atypical fractures those with all major criteria, accompanied or not by any of the minor criteria. Some of the major criteria are: absence of a marked history of local trauma or low-energy trauma; fracture located in any region distal to the lesser trochanter and proximal to the supracondylar area; transverse or short oblique configuration; simple, non-fragmented/comminuted fracture; medial spur in complete fractures and involvement of only lateral cortical in incomplete ones. The minor criteria are: thickening of the periosteum next to the lateral cortical; generalized thickening of femoral corticals; prodromal symptoms; association with symptoms or bilateral fracture; evidence of de-consolidation; presence of comorbidities (rheumatoid arthritis, rickets, osteomalacia, and renal osteoarthritis) or use of some medication (bisphosphonates, glycochoticoids and proton-pump inhibitors). Furthermore, fractures of the femoral neck, intertrochanteric region with extension to the subtrochanteric region, pathological fractures associated with neoplastic lesions, and periprosthetic fractures should be excluded.[5,8]

RESULTS

The epidemiological study included patients aged 50 years or older, with a shaft, subtrochanteric or diaphyseal femoral fracture, hospitalized between January 2013 and December 2018. Patients with changes in bone integrity, high-energy trauma fractures, proven pathological fractures, and periprosthetic fractures were excluded. Radiographs were properly studied and classified, according to ASBMR criteria, into atypical or typical femoral fractures; medical records were analyzed and patients or family members were contacted via telephone was made when necessary to gather further information on the occurrence of the fracture and the duration of the use of bisphosphonates (Figures 1, 2, 3, and 4).

Figure1. Female patient, 73 years old, three years of bisphosphonate use. Radiography of femur evidencing atypical fracture of the right femur, simple traits, medial spur, and cortical thickening.

Figure 2. Female patient, 86 years old, three years of bisphosphonate use. Radiography of femur with evidence of atypical fracture on the right femur, simple trait medial spur.

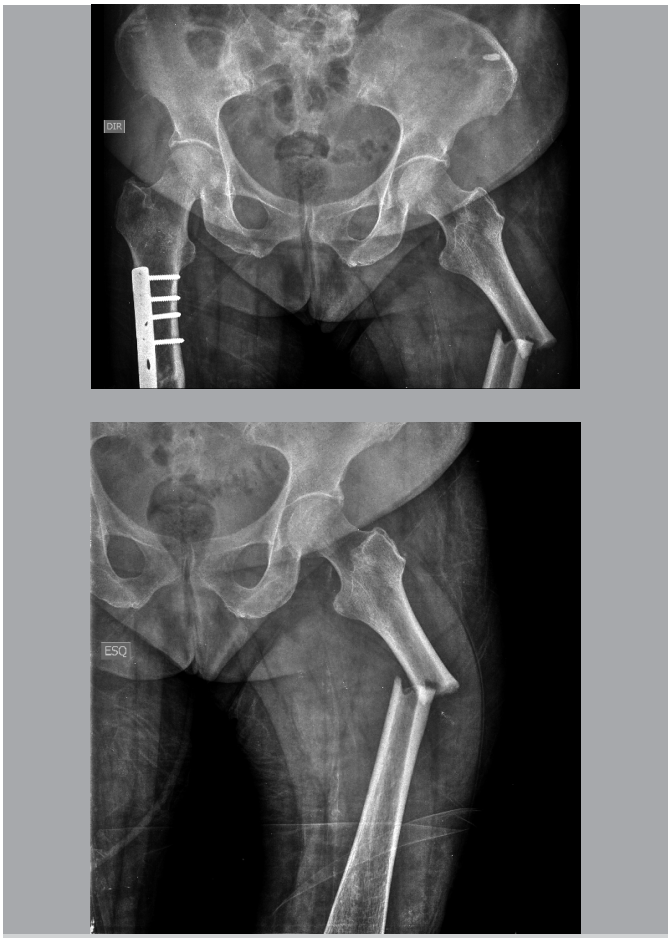

Figure 3. Female patient, 78 years old, atypical fracture of four years on the right, 10 years of bisphosphonate use. Radiography of the hip and femur evidencing synthesis material on the right and new atypical fracture on the left femur; there is an increase in cortical thickness and density.

Figure 4. Female patient, 74 years old, three years of bisphosphonate use. Atypical fracture on the right femur; there is an increase in the cortical thickness and density.

In total, 151 medical records were identified with femoral fractures diagnosis; nine patients presented atypical fractures, of which all made use of bisphosphonates. Thus, the incidence of atypical fractures was approximately of 6% (Figure 5).

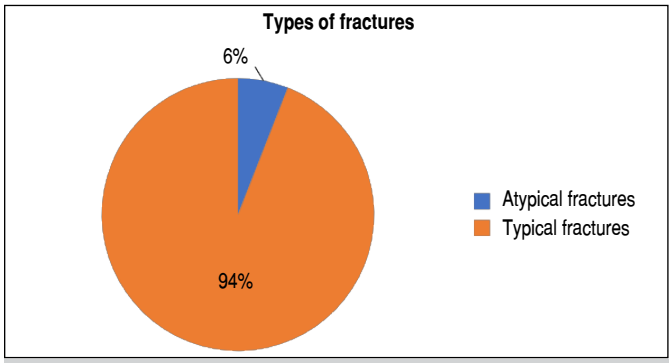

Figure 5. Typical fractures × Atypical fractures.

The approximate mean age of patients with atypical fracture was 78 years (minimum of 69 years of age; maximum of 88 years of age), with an incidence of 45% of people aged 80 years or over, 44% of patients aged 70 to 79 years, and 11% of patients under 70 years of age (Figure 6).

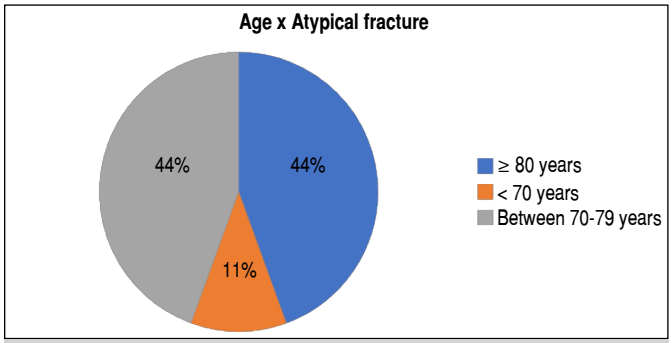

Figure 6. Age × Atypical fracture

The mean period of bisphosphonates use was of nine years (minimum of three years; maximum of 14 years); In view of the analysis of the data and consensus of treatment for osteoporosis, 89% of the patients who had atypical fracture used their medication for more than five years, while 11% used them for less than five years (Figure 7).

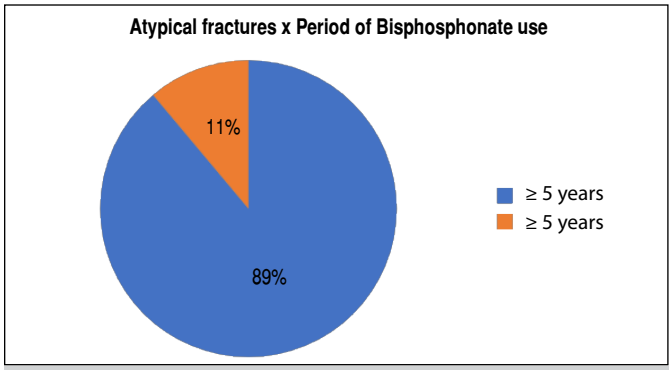

Figure 7. Atypical fractures × period Bisphosphonate of use.

The right limb was the most affected, totaling six exclusive fractures, including 45% diaphyseal and 22% subtrochanteric. The left limb presented only one isolated fracture, located in the diaphysis, representing 11%. In total, two patients had bilateral fractures in the region of the diaphysis, a total of 22% (Figure 8).
In our study, atypical fractures due to the use of the drug occurred only in women.

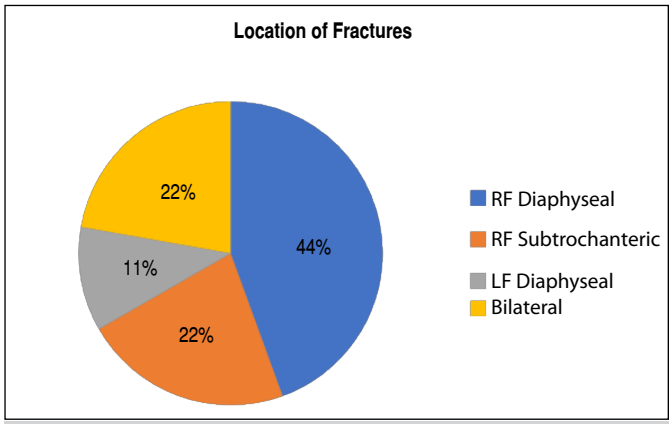

Figure 8. Location of atypical fractures.

DISCUSSION

Regarding the occurrence of atypical fractures among the cases selected in our study, this lesion was still rare (9%), an incidence already manifested within the literature.[8,11] However, our study showed the relationship with the prolonged use of bisphosphonates, reinforcing the association established in the study by Odvina et al. in 2005.[6] On the other hand, in comparison to this and other studies, a lower percentage of atypical fractures in our study (22%) was found in the subtrochanteric region, most of them (78%) in the diaphyseal region.[6,12] There is no definitive relationship between atypical fractures and greater involvement of the right lower limb (RLL), despite the large difference compared to the left lower limb involvement (LLL) in this study (67% RLL; 11% LLL). Bilateral involvement is frequently mentioned, since it may be present in 28 to 44.2% of patients, and it may lead to the consideration of a contralateral prophylactic fixation.[8,13,14] Several authors have reported an increase in atypical femoral fractures in patients older than 65 years and with five or more years of bisphosphonate use. In 2009, Capeci and Tejwani presented seven patients with bilateral atypical subtrochanteric fracture with an average of 8.6 years of use of this medication, a value similar to that found among the studied patients (nine years).[15]

The increased life expectancy of the population and its proven preventative actions will increase the indication of bisphosphonates and, eventually, the period of its use. This shows the importance of establishing an appropriate relationship between the duration of treatment and the risk of fracture. Unfortunately, the best period of use is not yet defined, but it is known that the use of these drugs for up to five years is effective in reducing osteoporotic fractures. From this period on, one should evaluate the need for medication continuity by analyzing bone densitometry (Femoral T-score <= −2.5 – treatment should be continued for up to six to 10 years), concomitant diseases, polypharmacy, and the risk of fall of the patient (frail older adult).[10] Prolonged time os use and predilection for females have often been reported by other authors.[16] The predominance of low-energy subtrochanteric and diaphyseal fractures in females and mean age > 65 years, with all exclusion criteria contained in our study, were also highlighted by Neviaser et al. in a retrospective analysis with 70 patients published in 2008 in New York City, with an average age of 67 years and 84% of occurrence in women.[17]

CONCLUSION

The low incidence of atypical fractures makes the screening to evaluate bone abnormalities in patients using bisphosphonates impossible. However, the prevalence of this type of injury in patients older than 65 years and femoral fractures subsequent to low-energy trauma scans in females show the importance of discriminating the methods of prevention of osteoporotic fractures in these cases, since a prolonged use of bisphosphonates is progressively associated with this complication. Obtaining and disseminating more scientific information is exceptionally relevant to establish doses, maximum treatment periods, and the risk-benefit of the indication of these medications.

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