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Atypical subtrochanteric fractures after long-term bisphosphonate therapy

Atypowe złamania podkrętarzowe po długoterminowym leczeniu bisfosfonianami

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Abstract

There have been many reports published in recent years on atypical subtrochanteric fractures after long-term bisphosphonates therapy. In a description of a few series of cases, fractures of typical clinical course and radiological image have been documented. These fractures are estimated as very rare (2.3 per 10,000 patient-years). It is suggested that a subsequent use of steroids or proton pump inhibitors with bisphosphonates may increase the risk of fracture occurrence. **(Pol J Endocrinol 2011; 62 (1): 84–87)**

Key words: *osteoporosis, bisphosphonates, atypical fractures, fatigue fractures*

Streszczenie

W ostatnich latach ukazało się wiele publikacji dotyczących atypowych złamań podkrętarzowych po długotrwałym leczeniu bisfosfonianami. W opisie kilku serii przypadków udokumentowano wystąpienie złamań o typowym przebiegu klinicznym i obrazie radiologicznym. Doniesienia te nie zostały potwierdzone w badaniach epidemiologicznych, które jednak nie mają znamienności statystycznej. Ocenia się, że złamania te są bardzo rzadkie (2,3 na 10 000 lat życia pacjentów). Sugeruje się, że równoczesne stosowanie steroidów lub inhibitorów pompy protonowej z bisfosfonianami może zwiększać ryzyko wystąpienia złamania.
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Słowa kluczowe: *osteoporoza, bisfosfoniany, złamania atypowe, złamania zmęczeniowe*

Introduction

Osteoporosis is a chronic disease requiring long-term treatment. At present, bisphosphonates dominate therapy, with alendronate being the most commonly prescribed medical agent, followed by ibandronate, risedronate and, more rarely, zoledronate. Clinical studies lasting 3–5 years have demonstrated both their safety and high degree of efficacy in preventing osteoporotic fractures (at approximately 50%) [1–3]. The question arises if their use over a much longer period, perhaps 10 years, is also safe.

A recently raised question is the possibility of fatigue subtrochanteric fracture occurrence, the fracture referred to in the literature as 'atypical'. Subtrochanteric fractures (to 5 cm below the smaller trochanter) are the rarest form of the proximal end of the femoral bone. In Poland, they constitute 5.6% of the femoral bone fractures in its proximal end with 50.4% being femoral neck fractures and 44% intertrochanteric fractures [4].

Bone microcracks and fatigue fracture

The therapeutic effect of bisphosphonates in osteoporosis results from their antiresorptive activity. Bisphosphonates reduce the number of newly formed osteoclasts, and decrease their activity while enhancing their apoptosis. In this way, they prevent further bone destruction and, by considerably slowing down its restructuring rate, they induce secondary mineralisation, increasing bone density [1]. Continuous bone remodelling is necessary to maintain its quality in the anti-fracture resistance context. The remodelling process always starts from bone resorption, initiated by the occurrence of microcracks. The resorption stage may proceed to bone formation process. Strong and long-term inhibition of bone resorption disables its remodelling, thus increasing the remineralisation process, which increases bone rigidity and causes an accumulation of microcracks. The accumulation of microcracks leads to microfractures and may bring about a fatigue fracture.

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Such fractures have been seen in subjects with osteoporosis treated with high fluoride doses, which caused excessive bone mineralisation [5]. Fatigue fractures also occur where bone remodelling does not follow excessive mechanical loads being put on the skeleton. These include well-known metatarsal bone fractures in army recruits or subtrochanteric fractures in unadapted runners after long training [6, 7].

Microcracks are rarely described in bone biopsy specimen from patients treated for osteoporosis. This is because, first of all, special staining techniques of bone specimen are necessary to visualise microcracks and such techniques are applied only in exceptional situations. A certain enhancement of microcracks after large doses of bisphosphonates was documented in experimental studies on dogs [8]. Stepan et al. found an increased number of microcracks in women treated with bisphosphonates over a long period as compared to control group [9].

Atypical subtrochanteric fractures: a series of cases

In 2005, one of the first reports was published on fatigue subtrochanteric fractures after long-term therapy with bisphosphonates. Odvina et al. described nine cases of atypical subtrochanteric fractures in female patients treated with bisphosphonates for a period of 1–8 years. Some of those patients had received steroids and oestrogen agents. Delayed fracture healing was noted in four of them [10]. Since then, several dozen reports have been published, describing the characteristic clinical course of the disease and corresponding radiological images.

In 2008, Kwek et al. [11], having analysed all the admissions of patients with low-energy fractures over a period of two years, identified 17 cases of subtrochanteric fractures. All the patients had been receiving bisphosphonates for 4.4 years on average (range 2–8 years). None of the patients had received any additional bone metabolism-affecting agent. In most patients, subtrochanteric fractures were preceded by pain, lasting from one week to two years. Thickened cortical bone layer dominated in radiological images, followed by transverse fracture. In three patients, a new fracture occurred on the other side a few months after the first fracture (Figures 1–3) [11].

In 2009, Lenart et al. [12] compared low-energy subtrochanteric fractures to femoral neck and intertrochanteric fractures among patients admitted over a period of seven years. This included 41 subtrochanteric fractures and 82 femoral neck and intertrochanteric fractures. Out of 15 patients with subtrochanteric fractures, ten had been receiving bisphosphonates for 7.3 years on average. In radiological images, thickened cortical bone layer was observed, with its internal prominence. Performed studies have demonstrated significantly longer duration of bisphosphonate therapy in subjects with atypical fractures vs. those with intertrochanteric or femoral neck fractures [12].

Atypical subtrochanteric fractures: epidemiological data

Atypical subtrochanteric fractures constitute 5–10% of fractures of the proximal femoral bone [4, 13, 14]. The described series of atypical fracture cases do not find support in epidemiological data, mainly due to the rarity of subtrochanteric fractures in all circumstances.

In 2010, Black et al. [15] evaluated proximal femoral bone fractures in large clinical studies: the FIT study of alendronate, the FLEX study, where theFIT study was extended by a further 10 years, and the HORIZON study on zoledronate. All the proximal femoral bone fractures were analysed and the material comprised 14,195 women of post-menopausal age, in whom only 284 fractures of the proximal femoral bone were found.

Just 12 subtrochanteric fractures were identified in ten patients. Unfortunately, the authors had only one radiogram to view (sic!) and possible examples of atypical fractures were described only on the basis of radiological reports. The risk of subtrochanteric fracture was estimated at the incidence level of 2.3 per 10,000,000 patient-years. In particular studies with placebo, the relative risk of its occurrence vs. the control group was: 1.03 for alendronate (FIT 95% CI, 0.06–16.46), 1.5 for zoledronate (HORIZON-PFT 95% CI, 0.25–9.00), and 1.33 for prolonged alendronate (FLEX 95% CI, 0.12 to 14.67). The results did not have statistical significance. The large dispersion of results was the consequence of a small number of cases. It should be stated, however, that no subtrochanteric fractures were found in the FLEX study after the ten-year administration of alendronate [15].

We would like to draw attention to the fact that fractures can be influenced by additional factors, such as the use of steroids [16, 17] and proton pump inhibitors [18,19].

Summary

It appears from the available reports that fatigue fractures may occur in bisphosphonate-treated patients, and such fractures are also seen in cases unrelated to osteoporosis therapy. In the series of described cases of atypical subtrochanteric fractures, their characteristic radiological picture was presented, which was identical in the reports of several different authors. Epidemiological data does not unequivocally confirm the increased risk of the occurrence of these fractures in the course of bisphosphonate use, but neither does it ex-

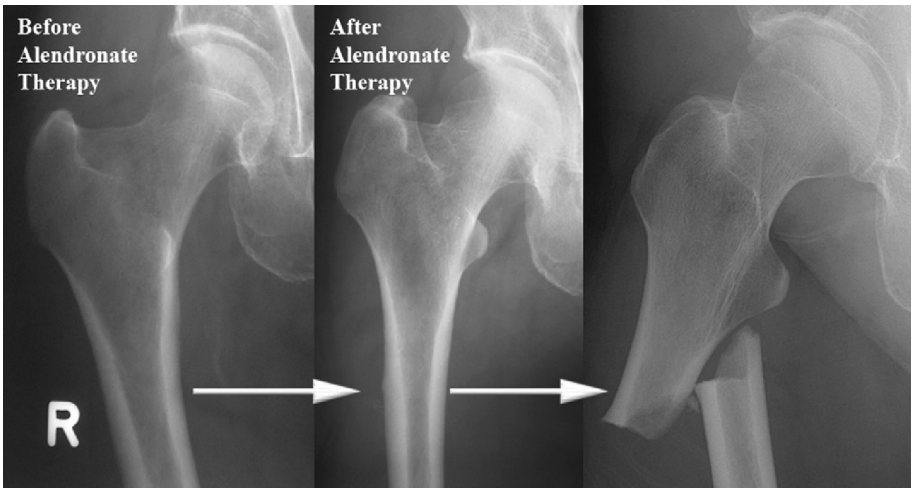

Figure 1. *Radiogram of a female patient shows the characteristic picture of atypical subtrochanteric fracture. Cortical thickening with medial spike and transverse, short, oblique fracture [11], by courtesy of Prof. Ernest Kwek*

Rycina 1. *Radiogram chorej dokumentuje charakterystyczny obraz atypowego złamania podkrętarzowego. Pogrubienie warstwy korowej z uwypukleniem wewnętrznym oraz poprzeczne, skośne złamanie [11], dzięki uprzejmości Prof. Ernesta Kweka*

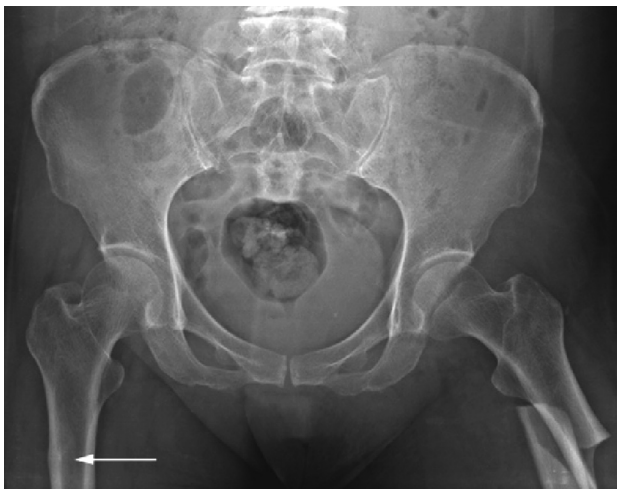

Figure 2. *A female patient, 55 years old, treated with alendronate for 5 years. On the right side, typical, short oblique fracture, and on the left side, cortical thickening are visible. [11], by courtesy of Prof. Ernest Kwek*

Rycina 2. *Chora 55 lat, leczona 5 lat alendronianem. Po prawej typowe złamanie krótkie skośne a po lewej pogrubienie warstwy korowej [11], dzięki uprzejmości Prof. Ernesta Kweka*

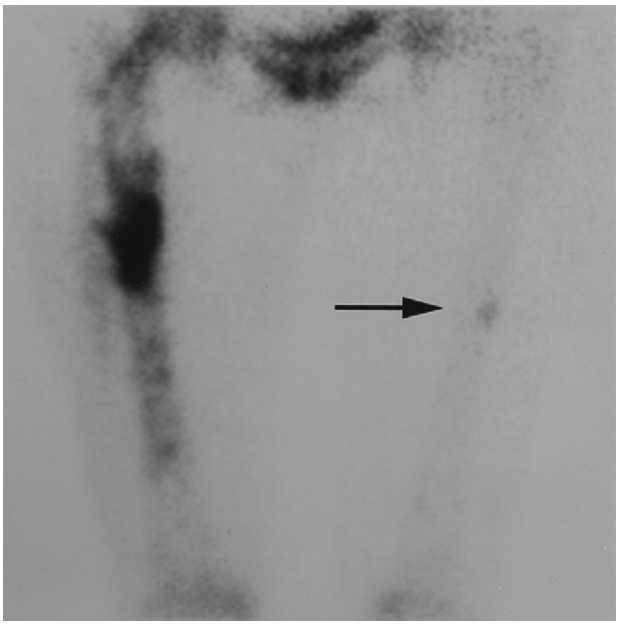

Figure 3. *Bone scintigraphy of a patient presented on Figure 2. Status after subtrochanteric fracture fixation on the left, and increased uptake of marker on the right side*

Rycina 3. *Scyntygrafia chorej z ryciny 2. Stan po zespoleniu złamania podkrętarzowego po stronie lewej. Widoczne zwiększenie wychwytu znacznika po stronie prawej [11], dzięki uprzejmości Prof. Ernesta Kweka*

clude such a possibility. It is known, however, that these fractures are extremely rare (2.3 per 10,000,000 patient-years). Most probably, the risk for their occurrence may result from the concomitant use of steroids or proton pump inhibitors. All agree that this problem requires further study.

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