Features of atypical femoral fractures in a clinical setting

Ph.D. Thesis

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List of publications

1. List of full papers directly related to the subject of the thesis

I. **Dózsai D**, Ecseri T, Csonka I, Gárgyán I, Doró P, Csonka Á. Atypical periprosthetic femoral fracture associated with long-term bisphosphonate therapy: Journal of Orthopaedic Surgery and Research 15: 1 Paper: 414, 7 p. [IF: 2.359, Q2 – 2020]

II. Gárgyán I, **Dózsai D**, Csonka I, Rárosi F, Bodzay T, Csonka Á. Bisphosphonate therapy associated with bilateral atypical femoral fracture and delayed union: Joint Diseases and Related Surgery(Eklem Hastalıkları ve Cerrahisi), 2022:33(1):24-32. [IF: 1.549, Q3 – 2022]

III. **Dózsai D**, Csonka Á, Gárgyán I, Varga E. Atypical periprosthetic femoral fracture [Atípusos periprotetikus femurtörés]: Magyar Traumatológia Ortopédia Kézsebészet Plasztikai Sebészet 63: 1-4 pp. 49-57. ,8 p. (2020) [IF: -, 2020]

IV. Csonka Á, **Dózsai D**, Gárgyán I, Varga E. Atypical femoral fractures association with long-term bisphosphonate therapy [Atípusos femurtörések összefüggése a hosszantartó biszfoszfonát terápiával]: Magyar Traumatológia Ortopédia Kézsebészet Plasztikai Sebészet 64: 1-4 pp. 49-58, 9p (2021) [IF: -, 2021]

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2. Other full paper

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II. Csonka, Á, Ecseri T, **Dózsai D**, Csonka I, Gárgyán I, Varga E. Drainage data analysis of chest-injured patients [Mellkasi sérültek drenázsadatainak vizsgálata] Orvosi Hetilap 160 :5pp.172-178.7p. (2019) [IF: 0.497, Q3 - 2019]

<u>Total cumulative impact factor: **4.902**</u>

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List of abbreviations

AFF: Atypical femoral fracture

AI: Artificial intelligence

AO: Arbeitsgemeinschaft für Osteosynthesefragen - German for "working group for bone fusion issues"

APFF: Atypical periprosthetic femoral fracture

ASBMR: American Society of Bone and Mineral Research

BMI: Body mass index

BP: Bisphosphonate

DM: Diabetes mellitus

GC: Glucocorticoid

ICD: International Classification of Diseases

IM: Intramedullary nailing

LCP: Locking compression plate

PFF: Periprosthetic femoral fracture

PPI: Proton pump inhibitor

RA: Rheumatoid arthritis

Summary

Background and purpose: Atypical femoral fractures are rare stress fractures with still unknown certain causes. In this work, Research 1 aimed to identify the risk factors for developing atypical femoral fractures (AFFs). We also examined the effect of bisphosphonate (BP) therapy on delayed bone union and bilateral fractures. Research 2 sought to prove that AFFs could occur in periprosthetic form, which is officially excluded from the definition of AFFs.

Experimental approaches: In all of our research, we collected data retrospectively from hospital records. In Research 1, a total of 74 AFFs were recorded in two centers. A control fragility fracture group was formed and compared to the AFF group by potential risk factors. Moreover, AFF patients were selected and subdivided according to their BP therapy: Group 1 (no BP administration) and Group 2 (BP administration). Group 2 was further classified into Group 2a (< 5 years of BP) and Group 2b (> 5 years of BP). All the groups were compared by delayed bone union and bilateral fracture occurrence. In Research 2, we reviewed patients with Vancouver type B1 periprosthetic fractures and classified them into two groups, namely atypical and typical PFFs. We noted the proportion of atypical periprosthetic fractures (APFF) among B1 fractures and identified risk factors.

Key results: Among AFFs and APFFs, BP drug administration was the most significant risk factor in the atypical fracture pattern development (AFF: $p<0.001$, APFF: $p=0.03$). The patients on BP showed longer bone union (Group 2 vs. Group 1, $p=0.02$; Group 2b vs. Group 2a, $p=0.09$). Out of all the 19 cases of bilateral fractures, 14 were in Group 2 with BP use ($p=0.11$). Out of the 74 cases, 26 contralateral femoral X-rays were taken on admission (35%) and 24 (92%) showed AFF minor criteria signs. Out of these 24 patients, 10 (42%) developed contralateral AFF. Among the 41 PFFs, five (13%) fractures were classified as atypical PFF based on the radiological characteristics. In the 2nd part of the research, there were no significant differences in other potential risk factors.

Conclusions: The administration of BP was the most significant risk factor in the development of AFF. Longer BP therapy (>5 years) showed longer delayed bone union, although not statistically significant. There was a relatively high risk of developing AFFs and bilateral fractures for patients on BP. There seems to be a correlation between the long-term intake of bisphosphonates and atypical periprosthetic fractures. Atypical femoral fractures can also occur in the periprosthetic form.

1. Introduction

1.1. Case definition and epidemiology of atypical femoral fractures

Atypical femoral fractures (AFFs) have a distinctive radiological characteristic and clinical form compared to more common hip or femoral fractures. In 2010, the definition of AFFs was set by the American Society of Bone and Mineral Research (ASBMR). The criteria were based on early case reports to show specific characteristics of AFFs. In 2014, the AFF criteria were revised with more information on the epidemiology and morphology of the fractures [1]. The most recognizable radiographic characteristic of AFF is the transverse fracture line and the lateral cortex thickening of the femur (beaking), which can be seen in Figure 1. It emphasizes the importance of diagnostic review of radiographic pictures over epidemiological studies (records by hospital codes) of the fractures and summarizes that AFFs are stress fractures. AFFs most commonly occur in the subtrochanteric and shaft regions of the femur. A revised case definition of AFF criteria can be seen in Table 1 [1,2]. The case definition requires at least four out of the five major features [1]. No minor features are required to be present, but they are associated with the fracture morphology.

The proportion of AFFs is very low compared to normal osteoporotic lower extremity fractures, which account for approximately one to two percent of all femoral fractures [3]. The first AFFs were described in 2005, followed with two case series in 2007 and 2008, reporting a correlation with BPs [4–6]. Afterwards, a large number of epidemiological studies have been performed to gain insight into the risk factors of developing AFFs [7,8].

The second ASBMR Task Force report show that AFF incidence is between 50 to 130 cases per 100,000 patients per year [1]. The incidence of AFFs were higher in patients on BPs, and they reported a strong correlation between the duration of drug use and its incidence [1]. However, a recent meta-analysis of 14 papers has also shown that the overall incidence of AFFs ranges from 3.0 to 9.8 per 100,000 persons per year [8].

1.2. Potential risk factors of atypical femoral fractures

The epidemiological evidence for a relationship between BPs and AFFs has become more compelling, and it appears to be more common in patients who have been exposed to it long-term (>5 years) administration of the drug [1,9,10]. BPs inhibit osteoclast resorption of the bone and impair the remodeling of the structure, which makes the bone “stiffer” thus leading to stress fractures [11]. On the other hand, atypical fracture patterns have occurred in patients with no history of BP therapy; however, there may be other potential risk factors in the development of AFFs [12,13]. The pathomechanism of atypical fractures includes every risk factor that impairs bone turnover of previously developed microfractures (with a new bone matrix) by decreasing bone tissue remodeling [14]. On this ground, bone geometry, chronic diseases (e.g., diabetes or hypothyroidism), genetic mutation or genetic alteration that decreases bone remodeling can be a potential risk factor of AFF [15–18].

Table 1 – ASBMR Task Force Revised Case Definition of AFFs

Major criteria	Minor criteria	Exclusion criteria
• transverse or slightly oblique fracture line • complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex • minimal or no trauma • non or minimally comminuted • localized periosteal or endosteal thickening of the lateral cortex at the fracture site	• increase in cortical thickness of the femoral diaphysis • unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh • bilateral incomplete or complete diaphysis fractures • delayed healing	• femoral neck fracture • intertrochanteric fractures with spiral subtrochanteric extension • periprosthetic fractures • pathological fractures related to primary or metastatic bone tumors and miscellaneous bone diseases

1.2.1. Age

The literature reports that patients who develop AFFs are somewhat younger that those who suffer non-AFFs. In a study by Schilcher et al., it has been found that the average age of AFF patients is 77 years compared to the 81 years average age of non-AFF patients [19]. Feldstein et al. have revealed that the average age of AFF patients is 77 years versus 82 years for femoral neck and intertrochanteric fractures [20]. Altogether the current epidemiological studies show that the risk of AFFs increases with age in BP treated patients [21].

1.2.2. Race

A few studies have shown that the risk of AFFs is higher in the Asian population compared to the European one. In a study of 142 AFF cases, 49% of the patients had

Asian descent, while only 10% of the patients were Asians [22,23]. These studies have been conducted in Europe and the United States, and it is unknown whether the same increased risk applies to the Asians living in Asian countries because of the lack of published reports [23]. Several explanations have been proposed, for example, bone geometry variations in different populations explained in Section 1.2.8 of the thesis. Other possible factors such as abnormal lower limb alignments (genu varus – valgus) were found to be associated with AFFs in Asian females [9]. Ethnic related differences in BP drug use and pharmacokinetics, drug adherence, and initiating treatment can all be potential risks, but it remains all speculative at this point [23].

1.2.3. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a risk factor for common osteoporotic fractures as it enhances osteoclast activity favoring the high bone turnover and bone resorption [9]. RA was proposed to be a risk factor in developing AFFs in 2010 [24]. In RA treatment, large doses of glucocorticoids (GC) are used, which can be an explanation of low bone turnover and developing AFFs, but further studies have proved otherwise. In two studies, there are no statistically significant differences in the prevalence of RA in AFF versus non-AFF patients [19,20]. Currently, there is no significant evidence that rheumatoid arthritis is a potential risk factor for developing AFFs.

1.2.4. Diabetes mellitus

Diabetes mellitus (DM - type I and II) is associated with an increased risk of fragility fractures by lowering bone turnover [25]. A recent meta-analysis has shown that low bone turnover appears to be common in DM type I and type II [25]. On this ground, DM can be a potential risk factor of AFF. Giusti et al. have found that in their study patients, the prevalence of DM in AFF cases were 3.6 times higher [24]. Alternatively, Feldstein et al. have reported a lower DM prevalence in AFF patients (15 %) compared to non-AFF patients (33%) [20]. Further evidence that DM does not increase the risk of AFF comes from Schilcher et al., who have described a DM prevalence of four percent in AFF patients compared to non-AFFs (15%) [19]. Overall, studies until this time suggest that DM is not a risk factor for developing AFFs.

1.2.5. Genetic mutations

An association study analysis in 13 patients with AFFs and 268 controls has identified a number of gene variations that may contribute in a polygenic manner to developing susceptibility for AFFs [26]. A recent study has revealed that in three sisters, who were treated with BPs and developed AFFs, an exome sequencing has identified some mutations. The mutations impair enzyme function in three components of the mevalonate pathway (MVD, GGPS1, and CYP1A1), which is targeted by BPs to inhibit bone resorption [27]. This pathway is the target of nitrogen containing BPs and suggesting that these mutations may predispose patient to develop AFFs by amplifying BP action or mimicking it. Further studies are needed to clear the prevalence of these mutations and the connection of developing AFFs.

1.2.6. Glucocorticoid use and proton pump inhibitors

It is well known that glucocorticoid (GC) therapy decreases bone remodeling and making osteoporotic fractures more frequent [28]. Glucocorticoid use and its association with AFF have been shown is several studies [19,29,30], but some have proved otherwise [7,31]. For example, Schilcher et al. have reported that GC use was 31% in AFF cases and 16% in non-AFF control cases [19]. The problem with GC use and its connection to AFF risk lies in the fact that diseases for which GCs are used for longer duration with high doses are also potential risk factors of AFFs (e.g., rheumatoid arthritis) [7]. Also, patients who are on high doses of GC are more likely to be using BPs [32]. Not considering these two factors separately will lead to failure to address this potential confounding. There are not enough data on this matter to disentangle this relationship, and further controlled studies are needed to correctly address this question [7].

Proton pump inhibitor (PPI) usage is slightly higher in patients with AFFs compared to non-AFF controls, but convincing data are still missing. Initial case reports have suggested that there is a risk of PPI administration in several patients, but there is no significant difference [19].

1.2.7. Bisphosphonate therapy

Bisphosphonate (BP) therapy has been used to treat the aging population, who mainly suffer from osteoporosis. About seven to ten percent of the Hungarian population is affected by it [33,34]. It is known that BPs have the ability to increase bone mineral density and decrease the risk of hip and vertebral fractures by as much as 40 to 70 percent [35]. They inhibit resorption of the bone by blocking the action of osteoclasts, so the development of osteoporotic fractures is decreased by minimizing bone loss [36,37]. Microfractures forming in the bone are decreasing indirectly, but the replacement of previously developed microfractures with a new bone matrix is also impaired. This has led to the appearance of atypical femoral fractures (AFF), as a new type of fracture, caused by an artificially developed low bone turnover due to the long-term intake of bisphosphonates [34]. This is why the atypical femoral fracture (AFF) is a stress fracture occurring with low energy or no trauma, and it has a characteristic radiographic appearance (Figure 1) [1].

Figure 1 – (A and B) – Two separate cases of atypical femoral fracture (A - B). The fractures can occur in the subtrochanter (A) and shaft (B) regions of the femur. Lateral cortical thickness can be seen in both X-rays (red arrows)

The use of bisphosphonates has significantly reduced the risk of osteoporotic fractures and hence it has reduced the burden of health care costs [21]. On this ground, despite these concerns, AFFs are extremely rare compared to osteoporotic vertebral and hip fractures [32]. A comparison of the benefits versus risks of BP therapy was recently published [32]. The results show that for short term (three to five years), BP therapy outweighs any AFF risk. For example, if we treat 10,000 osteoporotic females for three years with BPs, around 110 hip fractures would be prevented while causing only 0.08 AFF cases [32].

Despite the overwhelming good results with benefit/risk ratio on BP use, there has been a decline in drug prescriptions in the United States and Europe as well, which is mainly connected to AFF cases and reports [38,39]. Unfortunately, in the public health, there is a misconception and confusion about the interpretation of relative and absolute risk regarding BP therapy in developing AFFs. The ASMBR has issued to address this problem and reinforce the correct use of BPs [1]. Furthermore, the relationship between BP use and AFFs has become more compelling. AFFs are more common in patients who have been exposed to long-term BPs, usually for more than three to five years [1,10].

In a study by Meier et al. [40], it has been found that among 39 AFFs, longer BP exposure (five to nine years) was associated with a greater risk of AFFs than shorter exposure, although the risk was higher even with less than two years of use. Shane et al. have reported that relative risk on AFFs on BP was very high (ranging from 2.1 to 128 case/ 100,000 person-years), and their absolute risk was extremely low, ranging from 3.2 to 50 cases/100,000 person-years [1]. Despite all these, antiosteoporotic medication use remains uncertain and controversial about the relationship between BP therapy duration and the risk of developing AFFs [32].

1.2.8. Generalized cortical thickness and femur bone geometry

Several case reports of AFFs have demonstrated that bone cortices were generally thicker than normally might be expected (Figure 2) [41]. Generalized increase in cortical thickness of the femur is a minor feature in the case definition of AFFs [1]. There is a possible explanation for generally thicker cortices, which can be a risk factor in AFFs. It is reported that long-term BP therapy increases overall bone cortical thickness in some of the patients. This was examined by Chen et al. in a prospective study in which they have assessed the effect of BP use and duration on cortical thickness. They have compared healthy individuals and different BP user groups (short- and long-BP use) by cortical thickness [42]. They have found that there was no significant difference among the groups in cortical thickness by the BP treatment duration. Further data are needed to clarify if there is a correlation between cortical thickness and AFF risk. A few observations on the contribution of mechanical loading and femoral geometry can be found in the literature of AFFs. For example, females who suffer AFFs are generally younger and more active, which can be a higher magnitude loading of the femur. Biomechanical analysis indicates that tensile stresses are the highest at the lateral side of the femur, and also these stresses are dictated by the mechanical axis of the lower limb [43]. On this ground, a femur with greater lateral curvature (bowing) would be predicted to experience greater tensile stresses that a femur of similar size [44]. In the literature, there is a growing number of studies that support that the association of femoral geometry (greater femoral bowing and varus alignment) and AFFs [13,44,45]. Moreover, the measure of mechanical axis of the lower limb – standing femorotibial angle is larger in AFF patients than in typical femoral fractures [13]. Furthermore, it has been reported that patients with AFFs have more varus hip geometry and narrower femoral neck compared to normal femoral fracture cases

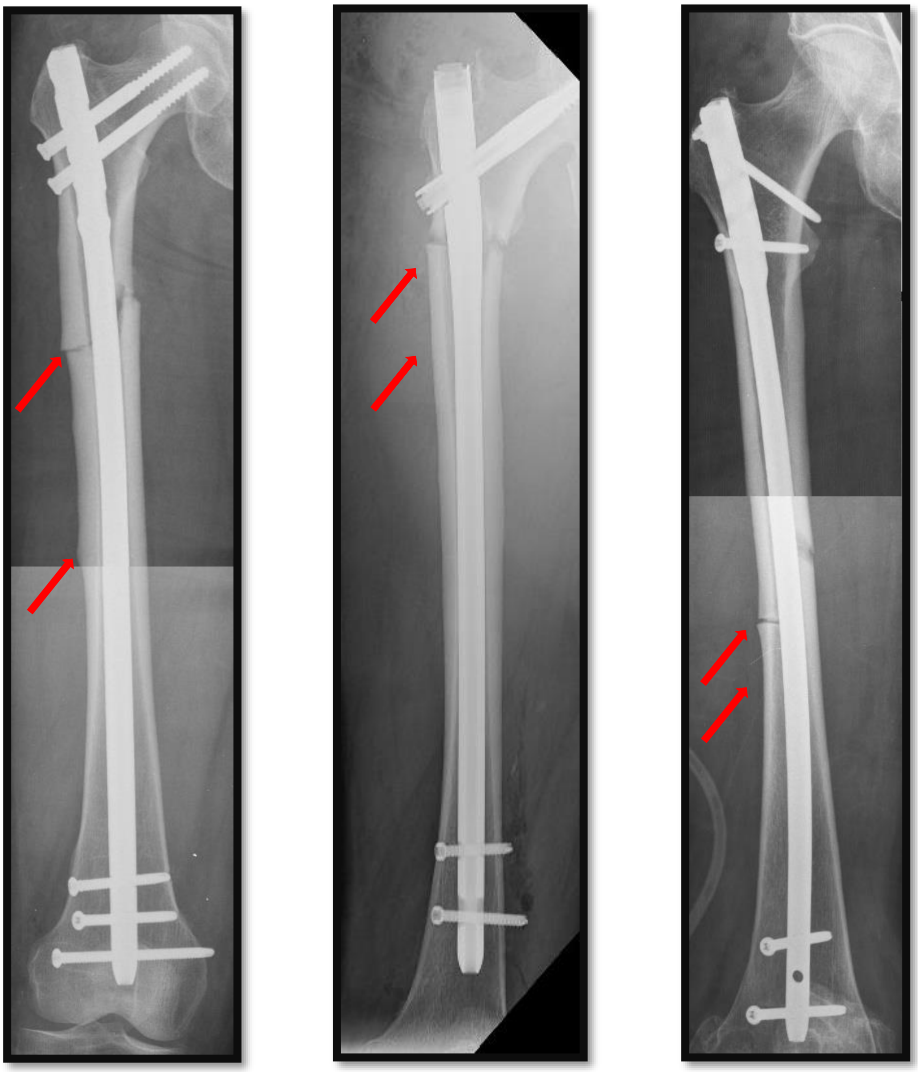

Figure 2 – Postoperative X-rays of three different AFF cases show generalized cortical thickness of the femur (red arrows)

[46,47]. Taken together, these studies suggest that femoral geometry is predicted to increase tensile stress in the lateral cortical aspect of the femur and may contribute to the development of AFFs.

1.3. Delayed bone union and bilateral fractures in AFFs

Delayed bone union is defined when the fractured bone does not heal completely within six months of the injury. For delayed and non-unions, the most important clinical criteria are the lack of weight bearing, followed by pain at the fracture site and weight bearing status. However, in the literature, there is a lack of a standardized clinical definition of union [10,48,49]. In a study by Tomofumi et al., it is reported that one third of AFF patients developed delayed or non-unions secondary to BP and GC use, despite their correct fracture reduction [50].

In the literature, there are reports on AFFs that presented in bilateral form [51,52]. Probyn et al. have evaluated 124 patients who suffered atypical femoral fractures on BP therapy with 78 cases of bilateral fracture occurrence. It has been concluded that the likelihood to be diagnosed with a contralateral AFF is high within the first year of presentation [53]. Further studies are needed to evaluate risk factors regarding the development of bilateral fractures.

1.4. Atypical periprosthetic femoral fractures

Since the 1960s, hip arthroplasty has been a successful surgical procedure for different problems in orthopedics (e.g., arthritis or femoral neck fractures) and is leading to satisfactory quality of life [54]. Periprosthetic femoral fractures are severe and technically demanding complications and are responsible for one third of revision surgery with a 0.1–2.1% incidence [55]. In case of AFFs, periprosthetic fractures fall in the exclusion criteria based on the case definition of the *American Society of Bone and Mineral Research Task Force Second Report* published in 2014 (see Table 1) [1].

The Vancouver classification of periprosthetic hip fractures are most widely used in the literature [56]. It takes the fracture site, femoral stem status (stable/instable), and the quality of the surrounding femoral bone into account. By this, there are three types of fractures [56]:

- Type A: fracture involves the trochanteric area
    - A(G) – greater trochanter
    - A(L) – lesser trochanter
- Type B: fracture around the stem or just below it
    - B1 – stable stem
    - B2 – stem loose
    - B3 – stem loose and poor bone quality
- Type C: fracture well below the stem

Over the past few years, several case reports have stated that periprosthetic femoral fractures (PFFs) can occur with similar features to those of atypical femoral

Figure 3 – (A) – a 76-year-old female patient with an atypical PFF, who took oral BP for 11-years, (B) – a 79-year-old male patient, who sustained a Vancouver B1 type atypical fracture, and he took oral BP for nine years

fractures (AFFs) arising from the long-term use of bisphosphonates (Figure 3) [57–61].

Atypical periprosthetic femoral fractures (APFFs) are prevalent in the older generation, and as it is common to have joint implants in this population, they are more likely to suffer from osteoporosis and to have other comorbidities (e.g., diabetes, vitamin D deficiency, and the use of the proton pump inhibitor) in their medical record [62]. To the best of our current knowledge, the main principal cause, etiology, diagnostic criteria, and therapeutic recommendations of APFFs still have not been clearly defined [60].

2. Gaps in our current knowledge and the goals of the thesis

As we discussed in detail above, atypical femoral fractures have a wide range of potential risk factors. Until this date, the exact risk factors have not been identified, and further research on this topic is needed. The most cited and researched risk factor is BP use, but the connection between the duration of the drug use and the fracture incidence is still not clear [3,9,34,40,45,63]. In the ageing population with more osteoporotic fractures, BPs are widely prescribed as an anti-osteoporotic drug, thus potentially rising the numbers of AFFs [34]. Also doctors are still unfamiliar with AFFs, cases are often missed, potentially evolving from an early incomplete fracture to a displaced complete fracture with a delay in presentation and diagnosis [64].

In the first part of our research, we gathered data to identify potential risk factors for AFFs. AFFs have been described with longer bone unions and non-unions in several studies [48,65]. On this ground, we tried to find a link between BP use and delayed unions. Also, the incidence of bilateral fractures are described in the literature as a serious complication, but their risk factors are not clearly identified [66]. Our work aimed to identify some of the risk factors and to raise awareness on this complication, which can be a serious burden for the health care systems and the patients.

In 2014, the Second Report of the Task Force of ASBMR clearly defined that periprosthetic fractures fall in the exclusion criteria of the case definition of AFFs. However, some case reports of periprosthetic fractures have emerged in the literature showing the characteristics of an AFF [1,67,68]. In the second part of the research, we aimed to search for APFFs and to prove that this fracture type can also occur in an atypical form. To the best of our knowledge, the main principal cause, etiology, diagnostic criteria, and therapeutic recommendations of APFFs still have not been clearly defined [60].

Moreover, during the review of the Hungarian literature, until this date, there has been no larger study performed on atypical femoral fractures, their risk factors, and complications. This is still a field to be researched in Hungary, and this work aims to fulfill these gaps of our current knowledge of AFFs.

2.1. Specific aims of our research

The following aims and hypotheses were formed to fulfill the aforementioned gaps in our current knowledge.

2.1.1. First part of the research

2.1.2. Aim 1 of the thesis

Aim: To identify the potential risk factors for developing atypical femoral fractures

Hypothesis: The most significant risk factor for developing AFFs is BP therapy, and the long-term (> 5 years) use increases the incidence of fractures.

2.1.3. Aim 2 of the thesis

Aim: To examine the effect of BP therapy on delayed bone union and bilateral fractures

Hypothesis: The long-term (> 5 years) use of BP increases the duration of bone union and bilateral fracture incidence.

2.1.4. Second part of the research

2.1.5. Aim 3 of the thesis

Aim: To analyze the prevalence of atypical periprosthetic fractures falling into the class of Vancouver type B1 fractures and their potential risk factors

Hypothesis: Atypical femoral fractures can occur in the periprosthetic form and display a significant correlation with long-term bisphosphonate use.

3. Materials and methods

3.1. First part of our research – Aims 1 and 2 of the thesis

3.1.1. Study design

In this part of the research, a two-center, retrospective study was conducted at university hospital centers (University of Szeged – Traumatology Department and National Trauma Centre – Budapest) between January 1, 2012 and December 31, 2020. A total number of 4190 patients were enrolled by specific codes of the 10th revised edition of the International Classification of Diseases (ICD-10) coding. We searched for subtrochanteric (S72.20) and diaphyseal femoral fracture (S72.30) patients who were enrolled in this study. After this, we used the 2018 AO/OTA Fracture and Dislocation Classification Compendium for identifying fracture types. In our study, patients were diagnosed with specific subtrochanteric (AO-32A3.a) or diaphyseal (AO-32A3.b) femoral fractures.

Afterwards, three orthopedic surgeons examined X-rays retrospectively and independently, according to the revised AFFs case definition criteria of the American Society for Bone and Mineral Research task group (ASBMR) [1] (Table 1), and established a consensus that there were 74 (1.7%) atypical femoral fractures. At least four out of five major features had to be present for the correct diagnosis. No minor features were required but were mainly associated with the fracture [1].

Inclusion criteria were patients having sustained low-energy trauma.

Exclusion criteria were polytrauma patients, patients younger than 50 years of age, and patients with incomplete medical records.

These 74 patients were reviewed using the inclusion and exclusion criteria, and all were found eligible. A control group of 143 patients were reviewed with the same inclusion and exclusion criteria as mentioned above with a fracture type of AO 32A1.a – subtrochanteric-, 32A3.b – diaphyseal- and some 31A1 – pertrochanteric femoral fractures as fragility fractures.

In the AFF group, the patients were also divided by their BP therapy history into two groups: those without BP therapy (Group 1) and with BP therapy (Group 2). Group 2 was further subdivided according to the length of the BP therapy (Group 2a: < 5 years of BP, Group 2b: > 5 years of BP). The research flow chart is shown in Figure 4.

3.1.2. Methods and assessment of AFF and control patients

Data on potential risk factors were gathered from hospital electronic health records including age, sex, comorbidities, such as hypertension and antihypertensive medication, diabetes, rheumatoid arthritis, osteoporosis, as well as BP and GC therapy history (all listed comorbidities are in potential association with AFFs according to the literature, and in case of thyroid disease, malignancy, neurological disease, hypertension

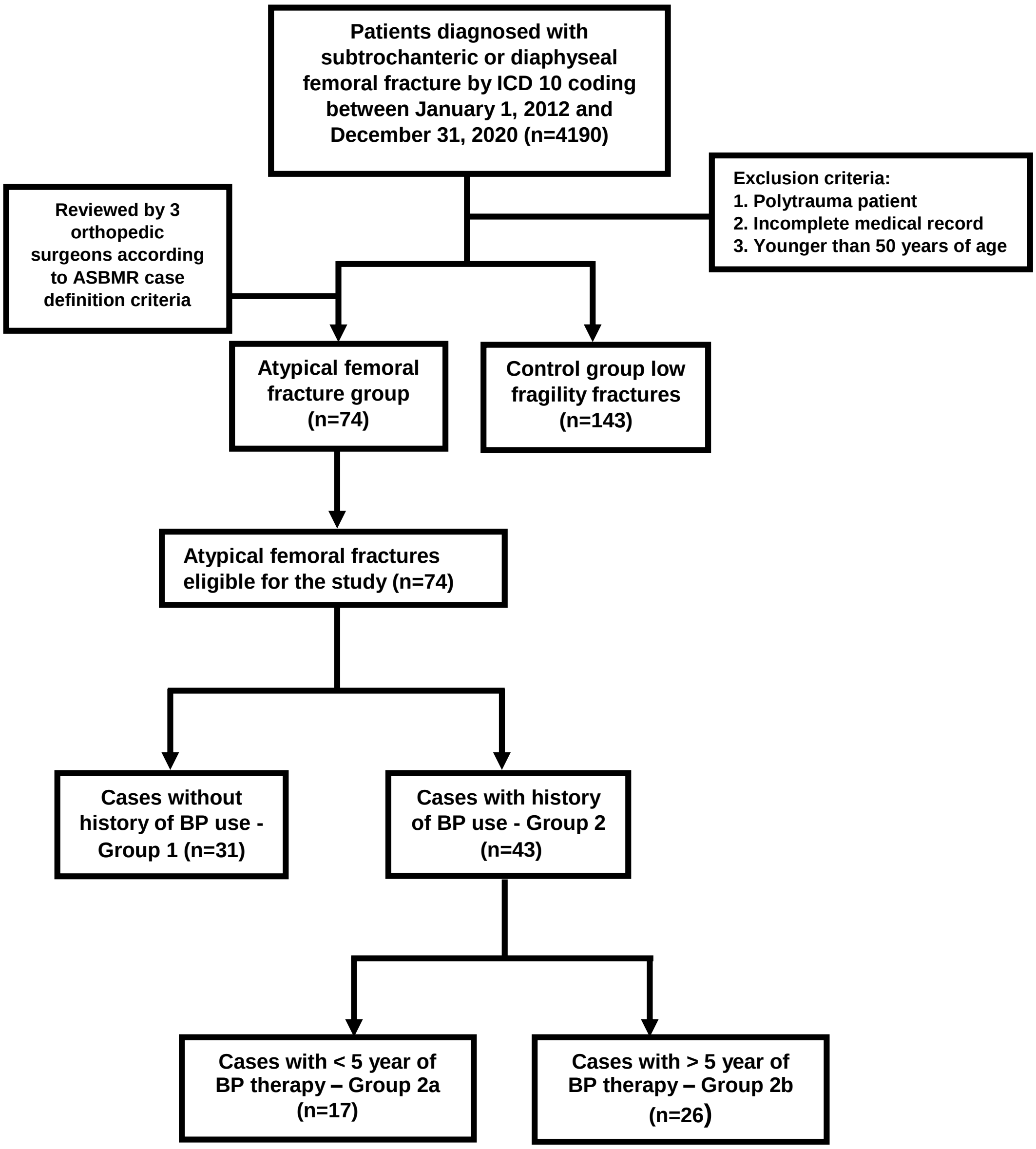

Figure 4 – Research flow chart (first part of the research)

and its medication, there were no studies published for its connection, it was added only for the heterogeneity of data) [7,9,17,51].

Fracture characteristics (delayed bone union cases and durations, contralateral X-ray case numbers, and contralateral signs), surgical fixation methods (intramedullary nail type) and complications (femoral neck fractures, bilateral fractures) were analyzed. Our criteria for bone union were as follows: complete cortical bridging (three out of four) and a fracture line either barely visible or undetectable. We did not calculate any bone union scores. Delayed bone union was noted if it exceeded six months. Follow-up times at weeks 6, 12, 26, and 52 were recorded, and X-rays were retrospectively analyzed for bone union. In this research, all patients, who were operated by cephalomedullary nails with a proximal and middle third fracture location, were encouraged to try and achieve full-weight bearing as soon as possible postoperatively – in line with the AO Surgery Reference guidelines. In cases where delayed union was recognized, more frequent X-rays (every two to three weeks) were performed until bone union was noted. Patients with contralateral minor signs were followed up conservatively. Patients who were on BP therapy and sustained an AFF had their BP therapy discontinued for at least one year.

Groups 1 and 2, and Groups 2a and 2b were compared based on the duration of union, delayed bone union cases, and bilateral fracture occurrence.

3.1.1 Statistical analysis, ethical permission, and conflict of interest

Continuous variables were expressed in mean and standard deviation (SD) or median (min-max), while categorical data were expressed in number and frequency. Means of continuous variables in the formed groups were compared with the Welch's independent samples t-test. The relationship between categorical variables was tested by using chi-square test for independence and Fisher exact test. Further analysis was carried out with multivariate logistic regression model. Thee forward selection model (likelihood ratio) method was used. The possible risk factors were sex, diabetes, rheumatoid arthritis, thyroid disease, malignancy, neurological disease, hypertension, osteoporosis, BP, and corticoid use. Odds ratios (ODs) and 95% confidence intervals (CIs) were calculated. A p-value of $p<0.05$ was considered statistically significant. Statistical analysis was performed by using IBM® SPSS® (26.0 version, Armonk, NY: IBM Corp, U.S.).

In our first part of the study, all the data were collected from medical databases and radiographic viewing programs for analyses. Permission together and process data were obtained prior to the commencement of the study by the regional ethics committees (University of Szeged, Traumatology Department, study number: 22/2019-SZTE, National Trauma Centre – Budapest, study number: B.O.Box: 18/2021). There was no conflict of interest for who participated in this part of the study.

3.2. Second part of our research – Aim 3 of the thesis

3.2.1. Study design

We carried out a retrospective study between January 1, 2011 and December 31, 2018 at the Traumatology Department of University of Szeged. We identified 885 patients by ICD-10 coding with a diaphyseal femoral fracture (S72.30). Afterwards, three orthopedic surgeons retrospectively and independently examined X-rays, and identified 109 patients with hip replacements who had periprosthetic fractures. We used the Vancouver classification of periprosthetic fractures.

Inclusion criteria were patients who were over 50 years and had had a low energy trauma.

Exclusion criteria were patients who were polytraumatized, had incomplete medical records, and sustained a Vancouver type A, B2, B3, or C fracture.

Out of 109 patients, 15 patients who were polytraumatized and 10 patients with incomplete medical records were excluded. After a radiologic review, we excluded patients who had Vancouver type A (n=2), B2 (n=12), B3 (n=4), or C (n=25) fractures.

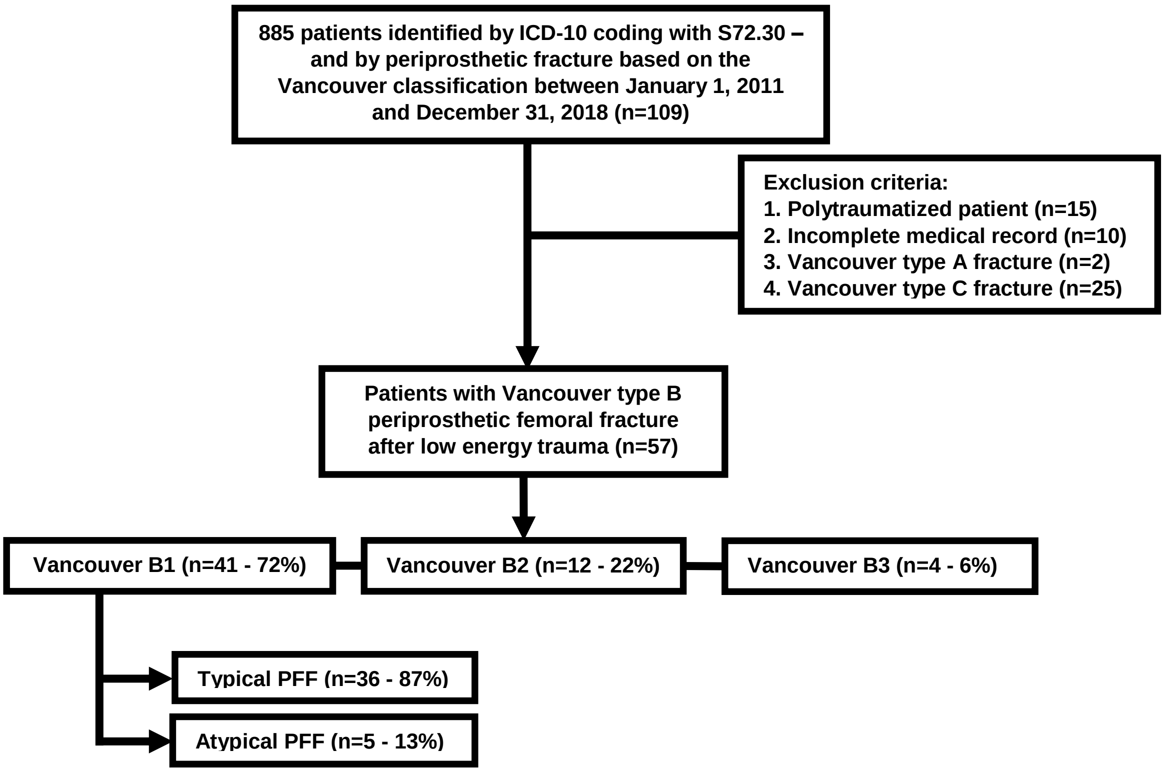

Figure 5 – Research flow chart (second part)

The remaining 41 patients with Vancouver type B1 periprosthetic fractures were subjects of this research (see Figure 5).

3.2.2. Methods and assessment of APFFs

First of all, regarding patient data, we took into account the age, sex, body mass index (BMI), comorbidities (e.g., hypertension, diabetes, rheumatoid arthritis, thyroid disease, neurological disease, malignancy, and osteoporosis) and the use of bisphosphonate and glucocorticoids. We evaluated the position of the femoral stem in the radiograms and the method of fixation (cemented or cementless stem). Then, we determined the interval between PFF and prior hip arthroplasty and the time of bone formation.

In order to establish the diagnosis of atypical femoral fractures, we used the revised criteria of the American Bone and Mineral Research Taskforce (see Table 1) [1]. A diagnosis of atypical femoral fractures was made when at least four out of five major criteria were met.

Three orthopedic surgeons retrospectively and independently examined X-rays and came to the same consensus that there were five (13%) atypical femoral fractures.

We applied locking compression plates (LCP) in each case to fixate the atypical periprosthetic fracture, completing it with cerclage, cable and attachment, where necessary (Figure 6).

3.2.3. Statistical analysis, ethical permission, and conflict of interest

Continuous variables were expressed in mean and standard deviation (SD) or median (min-max), while categorical data were expressed in number and frequency. Univariate statistical comparisons were performed using the Mann-Whitney U test for continuous variables, and Fisher exact test for categorized data. The confidence interval (CI) level was set at 95%. Then, a multivariable regression analysis was performed for seven risk factors that displayed the most significant value based on the univariate comparison. For statistical analysis, the statistical computer software IBM® SPSS® (26.0 version, Armonk, NY: IBM Corp, U.S.) was used.

In this part of the study, all the data were collected from medical databases and radiographic analyses. Permission to gather and process data was obtained prior to the commencement of the study, by the Regional Ethics Committee of Clinical Research Coordination Centre in Szeged (Study number 22/2019-SZTE). There was no conflict of interest for those who participated in this second part of the study.

Figure 6 – Postoperative X-rays of two (different patients) atypical periprosthetic fractures (18 hole locking compression plate and two pieces of attachment)

4. Results

4.1. First part of our research – Aims 1 and 2 of the thesis

4.1.1. Patient characteristics and risk factors – Aim 1 of the thesis

The mean age of patients in the AFF group was 75.4 ± 7.2 (8 males, 66 females, range: 51 to 94) years versus the control group 74.3 ± 11.8 (35 males, 108 females, range: 51 to 95) years (p = 0.4). A total of 74 patients (19 bilateral, altogether 93 AFFs) were diagnosed with AFF, which was 1.7% of all femoral fractures (Figure 1). Demographic data, records of chronic diseases, and medications of patients are shown in Table 2. Different types of statistical methods were performed on risk factors of AFFs. The most significant risk factors were BP use together with osteoporosis and hypertension.

Multivariate analysis revealed (forward likelihood ratio model) that the most important risk factors for development of AFFs were hypertension (p=0.019, OR=0.387, 95% CI: 0.175–0.858), osteoporosis (p=0.008, OR=3.258, 95% CI: 1.367–7.767), and BP use (p<0.001, OR=10.749, 95% CI: 3.886–29.733).

Table 2 – Demographic and chronic disease data of AFF group and control group patients

Demographic data of patients	AFF group (n=74)	Control group (n=143)	p-value (statistical method)
Age (years mean ± SD)	75.4 ± 7.2	74.3 ± 11.8	0.403 (Welch two sample t-test)
Sex (male/female)	8/66	35/108	0.017 (Chi-squared test)
Diabetes	9 (12%)	33 (23%)	0.054 (Chi-squared test)
Rheumatoid arthritis	4 (5%)	2 (1%)	0.184 (Fisher exact test)
Thyroid disease	11 (15%)	10 (7%)	0.063 (Chi-squared test)
Malignancy	5 (6%)	5 (3%)	0.315 (Fisher exact test)
Neurologic disease	7 (9%)	9 (6%)	0.398 (Chi-squared test)
Hypertension	49 (66%)	115 (80%)	0.021 (Chi-squared test)
Osteoporosis	50 (67%)	25 (17%)	<0.0001 (Chi-squared test)
Bisphosphonate use	43 (58%)	8 (6%)	<0.0001 (Chi-squared test)
Corticosteroid use	5 (6%)	4 (3%)	0.279 (Fisher exact test)

4.1.2. Bisphosphonate therapy

In the AFF group, 43 patients received BP therapy compared to only eight patients in the control group (p<0.001). The mean duration of drug use was 7 ± 3.5 years in the AFF group versus 2.9 ± 0.8 years in the control group (p<0.001) (Table 3). In the AFF group, 26 patients received BP for longer than 5 years. In the Group 2a, the mean time of the BP therapy was 4.2 ± 0.8 (range 3–5), and in Group 2b, it was 8.7 ± 3.6 (range, 6–20) years. In the control group, there was no BP use longer than four years. In the AFF group, the most commonly used BPs were alendronic and ibandronic acids. In the control group, six patients were on alendronic and two patients on ibandronic acids. Discontinuing BP therapy for at least one year was the postoperative osteoporosis medical treatment protocol which we followed.

Table 3 – Data on anti-osteoporotic drug therapy

	AFF group (n=74)	**Control group (n=143)**	**p-value**
Patients on BP therapy	43	8	p<0.0001
Medication duration (years mean ± SD)	7 ± 3.5	2.9 ± 0.8	p<0.001
Medication duration > 5 years	26 (53%)	0	p<0.0001
Anti-osteoporotic drug types			
Alendronic acid	22 (48%)	6 (75%)	-
Denosumab	1 (2%)	0	-
Ibandronic acid	14 (33%)	2 (25%)	-
Sodium clodronate	1 (2%)	0	-
Risendronic acid	2 (5%)	0	-
Zolendronic acid	4 (10%)	0	-

4.1.3. Fracture characteristics and fixation types

Among 93 AFFs, there were delayed bone unions in 65 fractures (70%). The mean duration of union in the AFF group (7.5 ± 3.5 months) was significantly higher compared to the control group (4.5 ± 2.2 months, p<0.001). Also, delayed union time was significantly higher in BP users in the AFF group (Group 2 – 8.3 ± 3.5 months, p=0.003) (Table 4). The most common AFF fracture location was the shaft region (Table 4). Data regarding contralateral X-rays and signs are shown in Table 4. Contralateral radiograms were not applied in all AFF patients due to the fracture itself being rare; and on primary admission, not being recognized in 65% of the cases. Patients who were on BP therapy and had suffered an AFF had a contralateral femoral X ray, and along with noticing minor signs, their BP therapy was discontinued for at least a one-year period, with a conservative follow-up. The application of a prophylactic surgical treatment was done only once, due to the patient suffering severe pain on the contralateral femur, with an impending fracture later located.

Table 4 – Fracture types and characteristics with surgical fixations

		AFF group (n=74)	Control group (n=143)	p-value (statistical method)
Fracture type and characteristics	Total number of femoral fractures	93	143	-
	Femoral shaft	71	34	-
	Subtrochanter	22	85	-
	Pertrochanter	-	24	-
	Delayed union	65	26	-
	Duration of union all patients (mean months ± SD)	7.5 ± 3.5	4.5 ± 2.2	p<0.001 (Welch two sample t-test)
	Duration of union on BP (mean months ± SD)	8.3 ± 3.5	4.4 ± 2.9	p=0.003 (independent sample t-test)
	Duration of union on steroid (mean months ± SD)	7.3 ± 3.6	4.1 ± 1.9	p=0.005 (independent sample t-test)
	Bilateral fracture	19	-	-
	Interval between primary and contralateral fracture occurrence in bilateral form (mean months ± SD)	27.7 ± 7.3	-	-
	Contralateral X-ray	26	-	-
	Contralateral signs (minor criteria)	24 (92.3%)	-	-
	Contralateral signs and bilateral fracture incidence	10 (41.6%)	-	-
Surgical fixation type	Stryker® – Gamma 3 System	28 (30%)	4 (4.1%)	-
	Sanatmetal® – Fi-nail	40 (43.1%)	119 (83%)	-
	Synthes® – Lateral Femoral Nail	4 (4.3%)	1 (0.7%)	-
	Küntscher nail	17 (18.3%)	13 (9.1%)	-

Surgical fixation methods can be seen in Table 4. We used both intramedullary and cephalomedullary nails. The most common AFF fixation was Sanatmetal® Fi-nail (43%). Traditional Küntscher intramedullary nailing was carried out in 17 cases (18%) in the AFF group, and in 13 cases (9.1%) in the control group. As a late complication, in the AFF group, three femoral neck fracture were reported, and two cases were found in the control group. There were eight reoperations due to five femoral neck fractures (see Figure 7), one hypertrophic non-union in the AFF group (see Figure 8) and one plate breakage occurred. Septic complication occurred in one case.

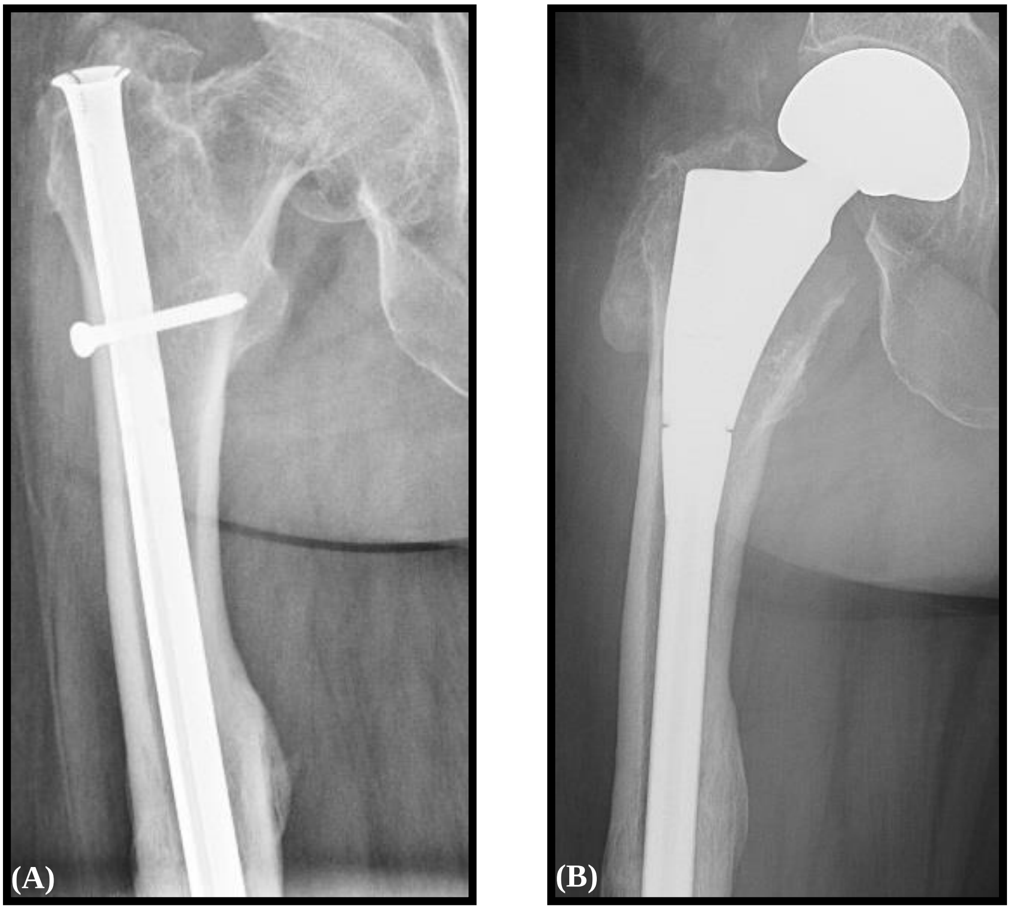

Figure 7 – (A) a case of a femoral neck fracture as a late complication of gold-standard IM nailing in femoral shaft fracture, (B) hemiarthroplasty was done with a long femoral stem

Figure 8 – (A) A 68-year-old patient with an atypical femoral fracture after a low energy fall (B) postoperative X-ray – cephalomedullary fixation (C) Follow-up after 8 months showed delayed union, nail dynamization was done previously (D) Follow-up after 15 months postoperatively showed no sign of complete bone healing, LCP (lateral compression plate) was put at the fracture site (E) 20 months after the injury, bone completely healed

4.1.4. Characteristics in different groups by duration of union, delayed union and bilateral cases – Aim 2 of the thesis

Patients in Group 2 (on BP therapy) showed a significantly longer bone union (8.3 ± 3.5 months) compared to Group 1 (without BP) (6.4 ± 3.1 months, p=0.02) (see Table 5). The number of cases with delayed bone union was also significantly higher in Group 2 (n=34) versus Group 1 (n=16) (p=0.01) (see Table 5).

Group 2b showed a longer union time (9 ± 3.8 months) compared to Group 2a (7.3 ± 2.9 months, p=0.1). Group 2b compared to Group 1, had a strong, statistically significant difference by union time (p=0.001).

Fourteen of the total 19 bilateral fractures were in Group 2 with a history of BP use (p=0.11). There was no significant difference between Groups 2a and 2b regarding the bilateral occurrence (p=0.307) (see Table 5.). The highest number of bilateral cases were in Group 2b (n=10, p=0.307).

Table 5 – Characteristics in the different groups by duration of union, delayed union, and bilateral fracture cases

	Group 1 (without BP therapy, n=31)	Group 2 (with BP therapy, n=43)	p-value
Duration of union (months ± SD)	6.4 ± 3.1	8.3 ± 3.5	0.02 (Welch two sample t-test)
Delayed union	16	34	0.01 (Chi-squared test)
Bilateral fracture	5	14	0.11 (Chi-squared test)
	Group 2a (< 5 years of BP , n=17)	**Group 2b (> 5 years of BP, n=26)**	**p-value**
Duration of union (months ± SD)	7.3 ± 2.9	9 ± 3.8	0.099 (Welch two sample t-test)
Delayed union	12	22	0.445 (Fisher exact test)
Bilateral fracture	4	10	0.307 (Chi-squared test)

4.2. Second part of our research – Aim 3 of the thesis

After the selection of the patients (see Figure 5), our aim was to analyze the prevalence of atypical periprosthetic fractures falling into the class of Vancouver type B1 fractures and their potential risk factors in their development.

Among 41 Vancouver type B1 PFFs, five (13%) were classified as atypical PFF. The mean age of patients with typical PFFs was 79.5 ± 1.6 [min – max: 54-94] years, compared to 80 ± 3.3 [min–max: 76–85] years for patients with atypical PFFs. As regards sex, there were 27 men and 14 women; however, atypical fractures occurred only in women (n=5). There were no significant differences in age, sex, BMI, comorbidities, the proportion of osteoporosis (T score <-2.5), positioning of the femoral stem, and the method of fixation between the typical PFF and atypical PFF groups. Hypertension, neurological diseases (e.g., stroke, dementia, or Parkinson’s disease), and malignancies were added because of the heterogeneity of data; nonetheless, there is no publication in correlation between these diseases and AFF occurrence. In terms of sex, atypical fractures occurred only in women, which presumably did not play any significant role in the development of this fracture type (p=0.26) (see Table 6). There was no significant difference between the two groups regarding the length of time of bone development, but the upper leg bone took longer to heal in the atypical group (APFF group – 9.2 ± 4.7 months vs. TPFF group – 5.7 ± 1.4 months, p=0.27). In every case, the bisphosphonate therapy applied was alendronate. In the APFF group, four out of five patients used BP, and we observed a significant correlation between the history of bisphosphonate use (p=0.01) and the duration of bisphosphonate therapy (APFF group - 8.2 ± 5.5 months vs. TPFF group - 4 ± 0.7, p=0.01) in the development of AFF in our univariate analysis (see Table 6)

Table 6 – Demographics of typical PFF group and atypical PFF-group

Vancouver type B1 fracture distribution	**Typical PFF (n=36, 87%)**	**%**	**Atypical PFF (n=5, 13%)**	**%**	**p-value**
Age (mean ± SD (min-max) years)	79.5 ± 1.6 (54–94)		80 ± 3.3 (67–85)		0.24
Sex (male/female)	9/27		0/5		0.26
BMI – body mass index	24.9 ± 3.3		23.2 ± 1.8		0.53
Chronic diseases					
Diabetes	7	19.5%	0	0%	0.37
Rheumatoid arthritis	1	2.8%	1	20%	0.21
Hypertension	35	97.2%	5	100%	0.87
Thyroid disease	5	13.9%	2	40%	0.66
Malignancy	3	8.3%	0	0%	0.62
Neurological disease	9	25%	2	40%	0.29
Osteoporosis	16	44.4%	4	80%	0.20
History of bisphosphonate use	5	13.9%	4	80%	0.01
Duration of bisphosphonate use (mean ± SD years)	4 ± 0.7		8.2 ± 5.5		0.01
Corticosteroid use	1	2.78%	0	0 %	0.87
Stem position					
Central	32	88.9%	4	80%	0.39
Varus	2	2.8%	1	20%	0.29
Valgus	2	2.8%	0	0%	0.76
Cemented stem	31	86.1%	5	100%	0.50
Cementless stem	5	13.9%	0	0%	0.50
Duration of bone union (mean ± SD months)	5.7 ± 1.4		9.2 ± 4.7		0.27
Interval between prior arthroplasty and PFF (mean ± SD years)	10 ± 8		6 ± 3.5		0.26

After all this, we performed a multivariate logistic regression model in APFF group in terms of age, sex, history of rheumatoid arthritis and osteoporosis, the duration and history of bisphosphonate use and the time lapse from before the primary prosthesis implantation to the PFF, and the only independent significant risk factor was the duration of bisphosphonate use ($p=0.03$, 0.08 (CI 0.008–0.16). In our regression model, we got an R squared value of 0.43.

5. Discussion

In this work, our first part of the research aimed to identify the risk factors for developing atypical femoral fractures (Aim 1 of the thesis). We also examined the effect of bisphosphonate therapy on delayed bone union and bilateral fractures (Aim 2 of the thesis). Our second part of the research (Aim 3 of the thesis) sought to prove that AFFs can occur in periprosthetic form, which is officially excluded from the definition of AFFs.

5.1. New findings according to our hypothesis

- It was found that bisphosphonate therapy is the most significant risk factor for developing AFFs, usually in patients using it longer than five years.
- Long-term bisphosphonate therapy (> 5 years) causes longer delayed bone union and non-union.
- The incidence of bilateral fractures on bisphosphonate therapy is high, especially in long-term drug use.
- Other risk factors besides bisphosphonate use should be considered in case of atypical fractures.
- Contralateral femoral X-rays performed on primary admission can show an impending fracture.
- Atypical femoral fractures can occur in the periprosthetic form regardless of the case definition of AFFs.
- The long-term use of bisphosphonate is an associated risk factor with atypical periprosthetic femoral fractures.

5.2. Reflection on potential risk factors in the research

Our first part of the research (Aim 1 of the thesis) aimed to identify any potential risk factors in developing AFFs. Regarding patient characteristics, the incidence of AFFs was 1.7% of all femur fractures, which is consistent with reported AFF percentage in the literature (around one to two percent) [3].

In the AFF group, 89% of the patients were female (vs. the control group - 75%), which was significant $p=0.01$. Also, all five APFF patients were female ($p = 0.26$). These results can be explained by the fact females are more exposed to postmenopausal osteoporosis, thus potentially taking more BP medication in their lifetime.

5.2.1. Age

In the literature, we can read that patients who develop AFFs are somewhat younger than those who suffer non-AFFs [19]. In our study, the average age was almost the same in both patient groups (AFF vs. Control group – Table 2 and TPFF vs. APFF group – Table 6) with a little deviation. Although with the ageing of the population, the burden of fragility fractures is supposed to increase in the future.

5.2.2. Rheumatoid arthritis

In our research, among 74 AFF patients, only four were diagnosed with RA, and compared to the control group, there was no correlation (p=0.184). Also, in the APFF group, only one patient had RA (p=0.21). In our study, we came to the same consensus as the current literature, which is that there is no evidence in correlation of rheumatoid arthritis and AFF occurrence, but further controlled research is needed [20].

5.2.3. Diabetes mellitus

Studies have shown that patients diagnosed with diabetes mellitus have a suppressed bone turnover [17]. Further evidence that DM does not increase the risk of AFF comes from Schilcher et al., who reported a DM prevalence of 4% in AFF patients compared to non-AFFs (15%) [19]. Overall, studies until this time suggest that DM is not a risk factor for developing AFFs.

In our study, DM did not seem to play a significant role in developing AFFs (p=0.054, see Table 2), and in the APFF group, no cases of DM (p=0.37, see Table 6) were identified.

5.2.4. Further risk factors

No sufficient data were collected in our research on the patients regarding race, genetic mutations, proton pump inhibitor use, and femur geometry adaptations in relation as risk factors of AFFs.

5.3. First part of our research (Aims 1 and 2 of the thesis)

5.3.1. Bisphosphonate therapy and AFF

The published ASBMR report states that BP therapy is a relative (but not an absolute) risk factor for the occurrence of AFFs [1]. The absolute risk factor of AFFs by BP use is considered low, only because there are 3.2 to 50 cases /100,000 patients/year [40]. It is known in the literature that there is a correlation between BP use and AFFs

[1,29,40,59], and in this study, the same results were found, that is, BP therapy was the most significant risk factor in the development of AFF ($p<0.001$, OR=10.749, 95% CI: 3.886–29.733). In the AFF group, 58% patients were on BP, and among them 26 (53%) received therapy for longer than five years ($p<0.0001$), whereas in the control group, the longest received therapy was four years. Therefore, we concluded that the incidence of AFFs is higher in long-term BP drug (> 5 years) use.

5.3.2. AFF cases with no predisposing risk factors

In our study, out of 74 AFF cases, there were seven patients who had no chronic disease, drug use or any known predisposing risk factor. In this group, the mean time of fracture healing was 4.9 ± 2.3 months. This finding may be due to some missed or unknown genetic mutation, individual predisposition, bone metabolic errors, or bone geometric changes, which are reported in the literature [13,15,69–71].

In our study, for the heterogeneity of the data, hypertension was added to the search of potential risk factors for AFFs. Interestingly, according to our patient data, the risk of AFF development reduced with the presence of hypertension and the use of antihypertensive medication. After searching the literature for an explanation, to this date, no publication or cause has been found to explain this mechanism. Therefore, the correlation between hypertension and AFF incidence requires further investigation.

5.3.3. AFFs with delayed bone union and bilateral occurrence

Several studies have reported that in atypical fractures, delayed bone union and bilateral fractures can occur during BP therapy [50,51,65,72]. In the present study, we also examined the effect of BP therapy on the duration of bone union and the incidence of bilateral fractures.

Both mechanical and histological factors are known to possibly have an effect on the pathophysiology of delayed unions [72–74]. In a study of 109 atypical fractures, one of the associated risk factors has been long-term BP use in delayed unions [72]. Prasarn *et al.* report that long-term BP therapy is associated with longer bone union (6.5 vs. 4.8 months) compared with non-BP users [75]. In a recent meta-analysis, the mean time of union in patients on BP has been about 8.5 months, and a third of all BP-related fractures has resulted in delayed or non-union [70].

In our study, we found that in 74 patients (93 fractures), the mean time of union was 7.5 ± 3.5 months, and delayed bone union was recorded in a total of 65 fractures (70%). Among them, BP use was noted in 43 individuals (58%), indicating the suppression of bone remodeling that caused delayed bone union. Patients in Group 2 (on BP therapy) showed a significantly longer bone union compared to Group 1 (without BP) ($p=0.02$) (Table 4).

Delayed bone union case numbers were also significantly higher in Group 2 than in Group 1. Group 2b showed longer union time compared to Group 2a, but it was not statistically significant. Group 2b compared to Group 1 had a strong, statistically significant difference in union time ($p = 0.001$).

The postoperative treatment protocol undertaken was a discontinuation of bisphosphonate therapy for at least one year (a so-called drug holiday), which is recommended by the literature after an AFF [21]. A comparison of different groups based on the duration of drug holidays and the continuation of drug use later was not performed.

Probyn *et al.* have evaluated 124 patients who suffered from AFFs on BP therapy and compared them with 78 cases of bilateral fracture occurrence [53]. They have concluded that the likelihood to be diagnosed with a contralateral AFF was high within the first year of presentation. In our study, in 19 cases of bilateral fractures, the contralateral fracture occurred over a one-year period (Table 4), and bilateral fractures occurred mostly in BP users (Group 2), although there were no statistically significant differences. Longer BP therapy (> 5 years) also showed no statistically significant difference in the occurrence of bilateral fractures. In all 26 cases, where contralateral X-rays were taken on primary admission, signs of localized periosteal or endosteal thickening were found in 24 (92.3%) cases. Of these 24 cases, 10 cases were confirmed to be a bilateral fracture afterwards (Table 4).

Clinical studies have reported that prophylactic intramedullary (IM) nailing can be beneficial for patients who have a risk of secondary stress fracture displacement. The indications for surgery are prodromal pain on the contralateral side and prevention of secondary stress fracture displacement [76–78]. In this study, due to its retrospective nature, there were insufficient data on prodromal pain. The cases in which impending fractures (minor signs) were recognized were followed closely conservatively. The literature reports a high rate of secondary displacement of non-operated cases [76,78]. Ha et al. have reported that 5 out of 14 cases had secondary displacement. Unfortunately, in this study, out of 24 recognized cases, 10 developed a contralateral complete fracture and needed fixation surgically.

5.4. Second part of our research (Aim 3 of the thesis)

In our second part of the research (Aim 3 of the thesis) sought to prove that AFFs can occur in periprosthetic form, which is officially excluded from the definition of AFFs. In the literature, studies on atypical periprosthetic fractures are mainly case reports [60,68,79].

In our study, among the 41 PPFs, five fractures were classified as atypical PFF based on the radiological characteristics and were associated with long-term bisphosphonate use ($p=0.03$, 0.08 (CI 0.008–0.16)). By case definition according to the second, revised recommendation of the American Society of Bone and Mineral Research, no strong association was found between atypical fractures and other comorbidities or the use of drugs such as bisphosphonates. Case studies report a significant association between AFFs and BP use; even though the strength of the association and size of the effect vary, just the relative risk of patients with AFFs taking BPs is high [1,2]. However, long-term use may be associated with AFFs [1]. Although the use of bisphosphonate was excluded in the case definitions of AFF, their long-term use is still considered as one of the most important pathophysiological mechanisms of AFF. As reported in the literature, there is a strong association between atypical femoral fracture and bisphosphonate use, especially in the case of long-term treatment (>5 years) [79,80].

A strong correlation has been found between those taking bisphosphonates and atypical fractures including periprosthetic types according to a multicenter study that processed 10 years of follow-up studies of the National Trauma Registries in Canada and the United States of America [60]. Level I evidence might be needed to demonstrate that bisphosphonates play a leading role in the development of atypical fractures.

It is known that the frequency of late periprosthetic fracture is the highest in the case of fixation of the cemented stem. However, periprosthetic fracture usually occurs within six months in cementless hip arthroplasty, but it is not correlated with the atypical fracture type [81]. In our work, atypical fractures occurred in cemented hip arthroplasty, but they did not play any significant role in the development of an atypical fracture type ($p=0.50$). In terms of positioning of the stem, it is known that varus positioning increases the stress, and fractures are more likely to occur at the tip of the femoral stem [18].

In our study, none of the positions (central, varus, or valgus) played a significant role in the development of atypical fractures related to the location of the prosthetic stem. The surgical treatment of the periprosthetic Vancouver type B1 fractures is based on the

LCP systems, and they can be combined with cerclage, cable, or plate attachment; moreover, the allograft can be implanted in order to stabilize the fixation of the fracture in the case of bone loss [82,83].

In case of APFFs, radiological characteristics are usually bilateral, including microfractures and the lateral cortex thickening [1]. Radiography should include bilateral views of the full length of both femurs in the case of atypical femoral fractures arising from lateral cortex thickening and microfractures, which might suggest an impending fracture.

In our study, no significant difference was found between the atypical periprosthetic B1 fractures and the typical periprosthetic fractures in terms of fixation, but it is should be recalled that a delayed healing process, higher mortality rate, and more complications can occur after osteosynthesis [1,79].

5.5. Limitations of our study

- In the first part of our study, we had some limitations: the retrospective nature, relatively small sample size, and a low number of BP users in the control group. The latter demonstrates that some of the statistics are not statistically significant. There were some overlaps between BP use and chronic diseases, which both can cause AFFs. These cases cannot be divided due to the small case numbers and the complicated study design.
- Additionally, the lack of coherence of standardized weight bearing scores in the patient groups led us to insufficient information regarding the patients achieving full-weight bearing.
- Information on prodromal pain was also deficient. Pain on palpation at the site of the injury is currently widely used among physicians to judge union; however, it is a highly subjective outcome, given individual and cultural differences in perception and tolerance level of pain among the population [84].
- The second part of the study (APFFs) had some limitations, such as the small patient number (due to extremely rare fracture occurrence), incomplete patient history (no knowledge of prodromal pain in the thigh), and the lack of radiographs of the contralateral femur.

5.6. Future potential research areas

- There is widespread concern among patients and physicians that BPs could cause more fractures than they can prevent. This is a clear misinterpretation of epidemiological data and its risk ratio [34]. It is important to develop public health efforts to educate patients and physicians (mainly family doctors) on the correct BP use and to dissolve their concerns towards it.

- We do not have complete evidence about risk factors for AFFs among those starting and discontinuing BPs. More controlled cohort studies are needed to help clinicians individualize treatment durations and the type of medications given [7].

- Further studies are needed in the development strategies to evaluate patients on long-term BP therapy for AFF risk, including standardized monitoring of groin pain and imaging of focal thickening in the lateral cortex [7].

- In the past few years, new research has emerged on the use of teriparatide medication in case of osteoporotic fractures and its potential use in case of AFFs [7].

- More studies are needed on the potential interventions for incomplete AFFs, such as prophylactic intramedullary nailing benefits vs. conservatively treated patients with decreased physical activity.

- The currently accepted 2014 AFF case definition by the ASBMR, especially on periprosthetic fractures, should be revised.

- In the 21st century, computer programs use artificial intelligence (AI) in almost every field of science. Atypical fractures occur in repetitive fracture patterns according to the definition of AFFs; therefore, in the future, AI can be used by computer programs for the detection of these rare fracture patterns in digitalized X-rays.

6. Conclusions

Atypical femoral fractures occur with minimal or no trauma in the subtrochanteric or femoral shaft region of the femoral bone. The causes are associated with BPs and other anti-osteoporotic medication, but they can occur without them as well.

In our first part of the study, in conclusion, it was found that BP use is the most significant risk factor for developing AFF; moreover, no correlation with other potential risk factors, such as age, sex, rheumatoid arthritis, diabetes mellitus, or malignancy was revealed. Our evidence is not complete, more cohort studies are needed to help with treatment durations and type of medications, and cessation of drug administration.

We found that longer BP therapy (> 5 years) causes longer delayed bone union or non-union, which might be a burden for the patients' wellbeing and the health care financial system as well. We recommend in line with the literature that BP therapy should be suspended in case of an impending fracture or AFF occurrence. It is known that AFF treatment can be challenging, but even in the most unfavorable of scenarios, the risk/benefit ratio is highly positive for BP use, particularly during a 3–5-year use [85].

Our study showed that the risk of developing an atypical fracture and the incidence of bilateral fractures on BP is high. Other risk factors, besides BP use (e.g., femur geometry, race, glucocorticoid use, or genetic predisposition), should also be considered in case of atypical fractures.

We proved that in case of an AFF, the occurrence of an impending fracture (minor signs) on the contralateral X-ray is high. In line with this, a contralateral femoral X-ray should always be performed for signs of an impending fracture or complete fracture. Prophylactic IM nailing can be beneficial for patients who have a risk of secondary stress fracture displacement. Cephalomedullary nailing should be applied in all cases of AFF to prevent late femoral neck fractures.

We recommend a postoperative treatment protocol, which is a discontinuation of bisphosphonate therapy for at least a one-year period, and it is also recommended to take temporary drug holidays after three to five years of BP therapy depending of the drug type in low-fracture risk patients [21]. In the past few years, new research has emerged on the use of teriparatide medication in case of osteoporotic fractures, which gives more potential research areas in this matter.

Periprosthetic fractures represent a big challenge for orthopedic surgeons because the observed frequency of these fractures, due to the rising number of patients with prosthetics, is increasing [82]. The American Society of Bone and Mineral Research excluded periprosthetic fractures in the case of atypical fracture, but they were mainly published as case studies in the literature [57–59,86].

In our second part of the study, we came to the result that the long-term use of bisphosphonate is the only independent risk factor associated with atypical periprosthetic femoral fractures; moreover, previous related publications have arrived at a similar conclusion [58–60,62].

On the basis of our results and the literature, it appears that atypical femoral fractures can occur in the periprosthetic form and display a significant correlation with bisphosphonate use [59,79].

The medical management of atypical fractures is a big challenge, and the outcome is much poorer than that of the typical fractures because of the delayed healing process, poor bone consolidation, difficulty of fracture fixation, and high mortality rate [87–89]. Nevertheless, our results indicate that clinicians should consider the possibility of atypical fracture, when periprosthetic Vancouver type B1 fracture occurred if long-term bisphosphonate therapy is mentioned in the patient history. In these cases, bisphosphonate therapy should be applied carefully as well, always bearing in mind the risk–benefit ratio. Keeping up to date with the latest antiresorptive medications and follow-up care of the patients is crucial for correct patient treatment.

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RESEARCH ARTICLE Open Access

Atypical periprosthetic femoral fracture associated with long-term bisphosphonate therapy

Check for updates

Dávid Dózsai[1], Tamás Ecseri[1], István Csonka[1], István Gárgyán[1], Péter Doró[2] and Ákos Csonka[1*]

Abstract

Background: Atypical femoral fracture is one of the many complications after the long-term use of bisphosphonates. The American Society for Bone and Mineral Research has officially excluded periprosthetic femoral fractures (PFFs) from the definition of atypical femoral fractures (AFFs). Several case reports found that PFFs can occur with characteristics similar to those of AFFs. The purpose of our study was to evaluate the proportion of atypical fractures among Vancouver type B1 fractures, and to determine the association between the long-term use of bisphosphonates and the occurrence of atypical periprosthetic femoral fractures (APFFs).

Methods: In this retrospective study, we reviewed 41 patients with Vancouver type B1 periprosthetic fractures between January 1, 2011 and December 31, 2018. We classified them into two groups, namely atypical and typical PFFs, based on the fracture morphology. We noted the proportion of atypical periprosthetic fractures among B1 fractures and identified risk factors.

Results: Among the 41 PFFs, 5 (13%) fractures were classified as atypical PFF based on the radiological characteristics. The longer duration of bisphosphonate use was probably the only independent risk factor that significantly increases the occurrence of APFF ($p = 0.03$, 0.08 (CI 0.008 – 0.16)). There were no significant differences in age, gender, body mass index, comorbidities, corticosteroid use, positioning of the femoral stem, the method of fixation (cemented or cementless) and time lapse from before the primary prosthesis implantation to the PFF in the development of atypical fracture type.

Conclusions: There seems to be a correlation between the long-term intake of bisphosphonates and the atypical periprosthetic fracture. Atypical femoral fracture can also occur in the periprosthetic form.

(Continued on next page)

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(Continued from previous page)
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Keywords: Periprosthetic fracture, Atypical femoral fracture, Bisphosphonate, Atypical periprosthetic femoral fracture

Introduction

Today, osteoporosis is a disease that affects many millions of people worldwide. About 7-10% of the Hungarian population suffer from it [1]. The use of bisphosphonates has significantly reduced the risk of osteoporotic fractures and hence it has reduced the burden of health care costs [2].

Bisphosphonates have been known to have beneficial effects on the skeletal system such as the reduced risk of fracture. They inhibit resorption of the bone by blocking the action of osteoclasts, so the development of fractures is decreased by minimizing bone loss [3, 4]. Microfractures, forming in the bone, are decreasing indirectly; but the replacement of previously developed microfractures with a new bone matrix is also impaired. This has led to the appearance of atypical femoral fractures (AFF), as a new type of fracture, caused by an artificially developed low bone turnover due to the long-term intake of bisphosphonates [5]. Atypical femoral fracture (AFF) is a stress fracture occurring with low energy or no trauma and it has a characteristic radiographic appearance (Fig. 1) [6]. With atypical subtrochanteric and middle third femoral fractures, periprosthetic fractures should be treated as exclusion criteria based on the recommendation of the American Society for Bone and Mineral Research, published in 2014 [6]. Over the past few years, several case reports have stated that periprosthetic femoral fractures (PFFs) can occur with similar features to those of atypical femoral fractures (AFFs) arising from the long-term use of bisphosphonates (Fig. 2) [7–11]. Atypical periprosthetic femoral fractures (APFFs) are prevalent in the older generation because it is common to have joint implants in this population, they more likely to suffer from osteoporosis, and to have other comorbidities (e.g., diabetes, vitamin D deficiency and the use of the proton pump inhibitor) in their medical record [12]. To the best of our knowledge, the main principal cause, etiology, diagnostic criteria and therapeutic recommendations of APFFs still have not been clearly defined [10].

In our study, we examined one of the possible side-effects of the long-term intake of bisphosphonates on the skeletal system and the incidence of atypical periprosthetic femoral fractures. We analyzed the prevalence of atypical periprosthetic fractures falling into the class of Vancouver type B1 fractures, and we looked for a correlation between the long-term use of bisphosphonate and APFF.

Fig. 1 A 68-year-old patient with an atypical femoral fracture after a low energy fall

Methods

We carried out a retrospective study between 1st January, 2011 and 31st December, 2018 at the Traumatology Department of University of Szeged. We reviewed the medical records and radiographs of 109 patients with hip replacements who had periprosthetic fractures

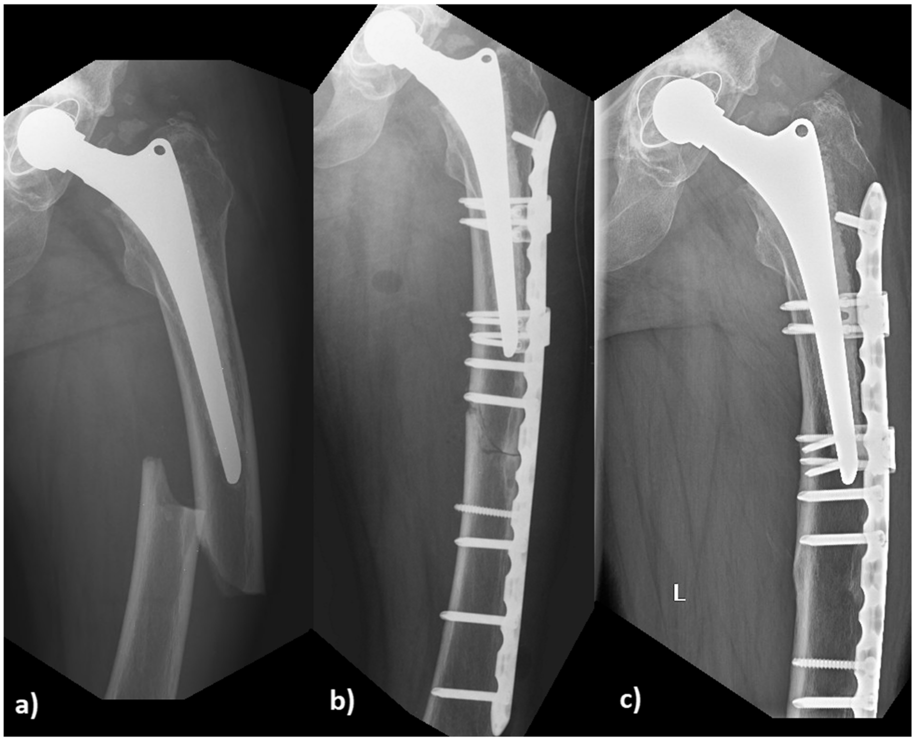

Fig. 2 a 76-year-old female patient with an atypical periprosthetic femoral fracture, who took bisphofonates for 11 years. **b** Postoperative x-ray of the atypical fracture (operative fixation method with an 18 hole locking compression plate and 2 pieces of attachment). **c** X-ray of a healed atypical fracture after 1 year

Table 1 Flow diagram of the retrospective study

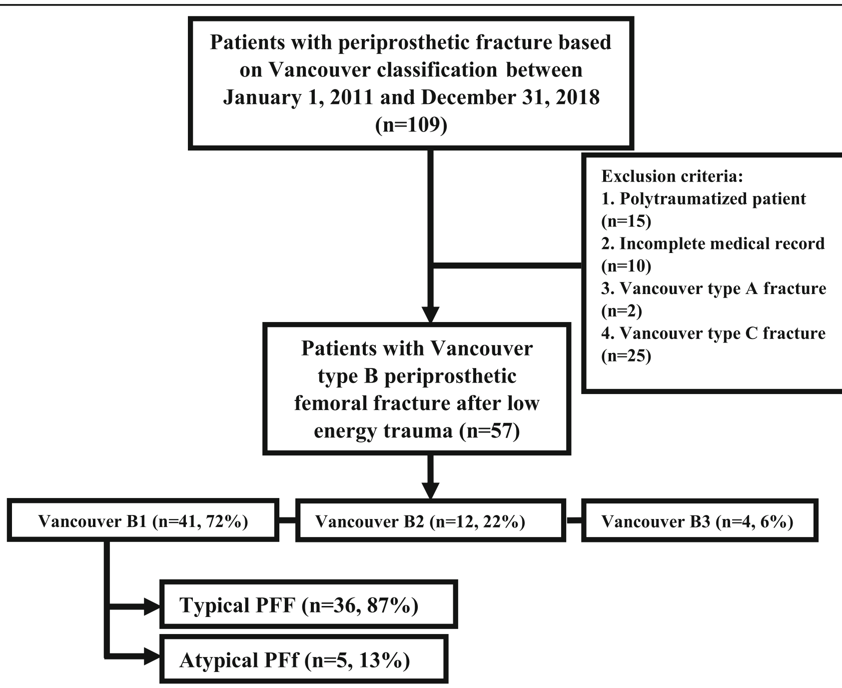

Table 2 ASBMR Task Force 2013 Revised Case Definition of AFFs [6]

Major criteria	Minor criteria	Exclusion criteria
• minimal or no trauma • Transverse or slightly oblique fracture line • Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex • non or minimally comminuted fracture • Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site	• increase in cortical thickness of the femoral diaphyses • Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh • Bilateral incomplete or complete diaphysis fractures • Delayed healing	• femoral neck fracture • intertrochanteric fractures with spiral subtrochanteric extension • periprosthetic fractures • pathological fractures related to primary or metastatic bone tumors and miscellaneous bone diseases

afterwards. Inclusion criteria were patients who were over 50 years and had had a low energy trauma.

Out of 109 patients, 15 patients who were polytraumatized and 10 patients with incomplete medical records were excluded. After a radiologic review, we excluded patients who had Vancouver type A ($n = 2$), B2 ($n = 12$), B3 ($n = 4$) or C ($n = 25$) fractures. The remaining 41 patients (Vancouver type B1 periprosthetic fracture) were subjects of our study (see Table 1).

First of all, we took into account the age, gender, body mass index (BMI), comorbodities (e.g., hypertension, diabetes, rheumatoid arthritis, thyroid disease, neurologic disease, malignancy, osteoporosis) and the use of bisphosphonate and glucocorticoid. We evaluated the position of the femoral stem on the radiographs and the method of fixation (cemented or cementless stem). Then we determined the interval between PFF and prior hip arthroplasty and the time of bone formation. In every case the bisphosphonate therapy applied was alendronate.

In order to establish the diagnosis of atypical femoral fractures, we used the revised criteria of the American Bone and Mineral Research Taskforce (see Table 2) [6]. A diagnosis of atypical femoral fractures was made when four or more of the major criteria were met.

Table 3 Demographics of typical PFF group and atypical PFF group

Vancouver type B1 fracture distribution	Typical PFF (n = 36, 87%)	%	Atypical PFF (n = 5, 13%)	%	p-value
Mean age	79.5 (54-94)		80 (67-85)		0.24
Gender (male/female)	9/27		0/5		0.26
BMI – body mass index	24.9 ± 3.3		23.2 ± 1.8		0.53
Chronic diseases					
Diabetes	7	19.44%	0	0%	0.37
Rheumatoid arthritis	1	2.78%	1	20%	0.21
Hypertension	35	97.22%	5	100.0%	0.87
Thyroid disease	5	13.89%	2	40%	0.66
Malignancy	3	8.33%	0	0%	0.62
Neurologic disease	9	25.00%	2	40%	0.29
Osteoporosis	16	44.44%	4	80%	0.20
History of bisphosphonate use	5	13.88%	4	80%	0.01
Duration of bisphosphonate use (years average)	4 ± 0.7		8.2 ± 5.5		0.01
Corticosteroid use	1	2.78%	0	0%	0.87
Stem position					
Central	32	88.89%	4	80%	0.39
Varus	2	2.78%	1	20%	0.29
Valgus	2	2.78%	0	0%	0.76
Cemented stem	31	86.11%	5	100%	0.50
Cementless stem	5	13.89%	0	0%	0.50
Duration of healing process (months average)	5.7 ± 1.4		9.2 ± 4.7		0.27
Interval between prior arthroplasty and PFF (years average)	10 ± 8		6 ± 3.5		0.26

We applied locking compression plates (LCP) in each case to fixate the atypical periprosthetic fractures, completing it with cerclage, cable and attachment, where necessary (Fig. 2.).

Statistics

Univariate statistical comparisons were performed using the Mann-Whitney U test for continuous variables, and Fisher ´ s Exact test for categorized data. The confidence level was set at 95%. Then, a multivariable regression analysis was performed for 7 risk factors that displayed the most significant value based on a univariate comparison. Also the chosen risk factors for the multivariable regression analysis were the most common in the literature as main risk factors of AFF (eg. RA, BP use, gender (female), diabetes). All the analyses were conducted using Windows Microsoft Excel (2016 version).

Results

Among 41 Vancouver type B1 PFFs, 5 (13%) were classified as atypical PFF. The mean age of patients with typical PFFs was 79.5 (54-94) years, compared to 80 (76-85) years for patients with atypical PFFs. As regards gender, there were 27 men and 14 women. Atypical fractures occurred only in women ($n = 5$). There were no significant differences in age, gender, BMI, comorbodities, the proportion of osteoporosis (T score < – 2.5), positioning of the femoral stem and the method of fixation between the typical PFF and atypical PFF group. In terms of gender, atypical fractures occurred only in women, which presumably did not play any significant role in the development of this fracture type ($p = 0.26$). There was no significant difference between the two groups ($p = 0.27$) regarding the length of time of bone development, but the upper leg bone took longer to heal in the atypical group. We observed a significant correlation between the history of bisphosphonate use ($p = 0.01$) and the duration of bisphosphonate therapy (p = 0.01) in the development of AFF in our univariate analysis.

The only independent significant risk factor was probably the duration of bisphosphonate use ($p = 0.03$, 0.08 (CI 0.008 – 0.16)) in APFF in terms of age, gender, history of rheumatoid arthritis and osteoporosis, the duration and history of bisphosphonate use and the time lapse from before the primary prosthesis implantation to the PFF in the multivariate regression analysis. In our regression model we got an R squared value of 0.43 (see Table 3).

Discussion

Atypical femoral fractures typically occur as stress fractures. Prodomal pain in the thigh preceding the fracture was described previously in the literature. Radiological characteristics are usually bilateral, including microfracture and the lateral cortex thickening [6]. Radiography should include bilateral views of the full length of each femur in the case of atypical femoral fractures arising from lateral cortex thickening and microfracture, which might suggest impending fractures. It is known that the frequency of late periprosthetic fracture is the highest in the case of fixation of the cemented stem. However, periprosthetic fracture usually occurs within six months in cementless hip arthroplasty, but it is not correlated with the atypical fracture type [13]. Atypical fractures occurred in cemented hip arthroplasty, but they did not play any significant role in the development of an atypical fracture type ($p = 0.50$). In terms of positioning of the stem, it is known that varus positioning increases the stress and fractures are more likely to occur at the tip of the femoral stem [14].

None of the positions (central, varus, valgus) played a significant role in the development of atypical fractures related to the location of the prosthetic stem. The surgical treatment of the periprosthetic Vancouver type B1 fractures is based on the LCP systems, and these can be combined with cerclage, cable or plate attachment, and moreover, allograft can be implanted in order to stabilize the fixation of the fracture in the case of bone loss [15, 16].

In our study no significant difference was found between the atypical periprosthetic B1 fractures and the typical periprosthetic fractures in terms of fixation, but it is should be recalled that a delayed healing process, higher mortality rate and more complications can occur after osteosynthesis [6, 17].

PFFs represent a big challenge for orthopedic surgeons because the observed frequency of these fractures due to the rising number of patients with prosthetics is increasing [15]. The American Society for Bone and Mineral Research excluded periprosthetic fractures in the case of atypical fracture, but they were mainly published as case studies in the literature [7–9, 18].

In this study among the 41 PPFs, 5 fractures were classified as atypical PFF based on the radiological characteristics and among these, 4 were associated with longterm bisphosphonate use. This retrospective study has some limitations, such as the small patient number, incomplete patient history (no knowledge of prodromal pain in the thigh) and the lack of radiographs of the contralateral femur. By case definition according to the second, revised recommendation of the American Society for Bone and Mineral Research no association was found between atypical fractures and other comorbodities or the use of drugs such as bisphosphonates. Case studies report a significant association between AFFs and bisphosphonate use; even though the strength of the association and size of the effect vary, just the relative risk of patients with AFFs taking BPs is high [6, 19]. However, long-term use may be associated with AFFs [6]. Although the use of bisphosphonate was excluded in the case definitions of AFF, their long-term use is still considered as one of the most important pathophysiologic mechanisms of AFF. As reported in the literature, there is a strong association between atypical femoral fracture and bisphosphonate use especially in the case of long-term treatment (> 5 years) [17, 20].

A strong correlation was found between those taking bisphosphonates and atypical fractures including periprosthetic types according to a multicentric study that processed 10 years of follow-up studies of the National Trauma Registries in Canada and the USA [10]. Level I evidence might be needed to demonstrate that bisphosphonates play a leading role in the development of atypical fractures. In the literature, studies on atypical periprosthetic fractures are mainly case reports [10, 17, 21].

In our study, the long-term use of bisphosphonate seemed to be the only independent risk factor associated with atypical periprosthetic femoral fractures. Previous related publications arrived at a similar conclusion [8–10, 12].

Conclusions

On the basis of our results and the literature it appears that atypical femoral fractures can occur in the periprosthetic form and display a significant correlation with bisphosphonate use [9, 17].

The medical management of atypical fractures is a big challenge and the outcome is much poorer than that of the typical fractures because of the delayed healing process, poor bone consolidation, difficulty of fracture fixation and high mortality rate [22–24]. Nevertheless, our results indicate that clinicians should consider the possibility of atypical fracture, when periprosthetic Vancouver type B1 fracture occurred if long-term bisphosphonate therapy is mentioned in the patient history. Bisphosphonate therapy should be applied carefully, always bearing in mind the risk-benefit ratio. Keeping up to date with the latest antiresorptive medications and follow up-care of patients is crucial for correct patient treatment.

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Authors' contributions
DD: Wrote the criteria (exclusion, inclusion), collected and analyzed the data, performed the intra- and inter-reader analysis, and wrote the paper. TE: collected and analyzed the data, supervised the data collection and analysis. ICS: supervised the data collection and analysis, revised the paper. IG: Organized the study, revised the protocol, performed the intra- and inter-reader analysis. PD: Revised the paper. ACS: Planned the study, wrote the study protocol, wrote and revised the paper. All authors read and approved the final manuscript.

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Availability of data and materials
Raw data were generated at the university hospital. Derived data supporting the findings of this study are available from the corresponding author on request.

Ethics approval and consent to participate
This is a retrospective study, all the data having been collected from medical databases and radiographic analyses. Permission to gather and process data was obtained prior to the commencement of the study, by the university ethical committee (Study number 22/2019-SZTE).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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ORIGINAL ARTICLE

Bisphosphonate therapy associated with bilateral atypical femoral fracture and delayed union

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ABSTRACT

Objectives: The aim of this study was to identify the risk factors for developing atypical femoral fractures (AFF) and to examine the effect of bisphosphonate (BP) therapy on delayed bone union and bilateral fractures.

Patients and methods: Between January 1st, 2012 and December 31st, 2020, a total of 74 AFF patients (8 males, 66 females; mean age: 75.4±7.2 years; range, 51 to 94 years) were recorded in two centers and retrospectively analyzed. A control fragility fracture group (n=143) was compared to the AFF group according to fracture characteristics, surgical fixation methods, comorbidities, and medications. The AFF patients were selected and subdivided according to their BP therapy: Group 1 (without BP) and Group 2 (with BP). Group 2 was further classified into Group 2a (<5 years of BP) and Group 2b (>5 years of BP).

Results: The multivariate logistic regression model showed that, BP drug use was the most significant risk factor in development of AFF (p<0.001, odds ratio= 10.749, 95% confidence interval: 3.886-29.733). The patients on BP showed longer bone union (Group 2 - 8.3±3.5 *vs*. Group 1 - 6.4±3.1 months, p=0.02; Group 2b - 9±3.8 *vs*. Group 2a - 7.3 ±3.9 months, p=0.09). Of all 19 cases of bilateral fractures, 14 were in Group 2 with BP use (p=0.11). Of 74 cases, 26 (35%) contralateral femoral X-rays were taken on admission and 24 (92%) showed AFF minor criteria signs. Of these 24 patients, 10 (42%) developed contralateral AFF.

Conclusion: The most significant risk factor in development of AFF was BP drug use. Longer BP therapy (>5 years) showed longer delayed bone union, which was not significant. There was a relatively high risk of developing AFFs and bilateral fractures on BP therapy. In case of an AFF, a contralateral femoral X-ray must be always performed for signs of an impending fracture.

Keywords: Atypical femoral fractures, bilateral fracture, bisphosphonate therapy, delayed bone union, stress fracture.

The proportion of atypical femoral fractures (AFFs) is very low compared to normal osteoporotic lower extremity fractures, accounting for approximately 1 to 2% of all femoral fractures in the aging population, who mainly suffer from osteoporosis.[1,2] In the literature, bisphosphonates (BPs) have the ability to increase bone mineral density and decrease the risk of hip and vertebral fractures by as much as 40 to 70%.[3] Furthermore, the relationship between BP use and AFFs has become more compelling. Such fractures are more common in patients who have been exposed to long-term BPs, usually for more than three to five years.[4,5] In a study by Meier et al.,[6] they found that among 39 AFFs, longer BP exposure (5 to 9 years) was associated with a greater risk of AFFs than shorter exposure, although the risk was higher even with less than two years of use. Shane et al.[4] reported that relative risk on AFFs on BP was very high ranging from 2.1 to 128, and their absolute risk was extremely low ranging from 3.2 to 50 cases/100,000 person-years.

Delayed bone union is defined as a fractured bone that did not heal completely within six months of

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injury. For delayed and non-unions, the most important clinical criterion was the lack of weight bearing, followed by pain at the fracture site and weight bearing status; however, in the literature, there is a lack of a standardized clinical definition of union.[7] In case of AFFs, relatively longer (7 to 9 months) bone unions were recorded in several studies.[5,8] The AFFs are associated with a high prevalence rate of prodromal pain and contralateral impending fracture which needs a close follow-up and probable surgical fixation.[5]

Atypical fracture patterns have occurred in patients with no history of BP therapy; however, there may be other potential risk factors in bone turnover.[9,10] The pathomechanism of atypical fracture includes every risk factor that impairs bone turnover of previously developed microfractures (with a new bone matrix) by decreasing bone tissue remodeling.[11] Bone geometry, chronic disease (e.g., diabetes, hypothyroidism), genetic mutation or genetic alteration that decreases bone remodeling can be a potential risk factor of AFFs.[12-15]

In the present study, we hypothesized that the long-term (>5 years) use of BP increased the incidence of AFFs, duration of bone union, and the bilateral fracture occurrence. We, therefore, aimed to identify the risk factors for developing AFFs and to examine the effect of BP therapy on delayed bone union and bilateral fractures.

PATIENTS AND METHODS

This two-center, retrospective study was conducted at National Institute of Traumatogy, Budapest and Universtity Hospital Szeged, Department of Traumatology between January 1st, 2012 and December 31st, 2020. A total of 4,190 patients by the International Classification of Diseases-10 (ICD-10) coding who were diagnosed with subtrochanteric (AO-32A3.a) or diaphyseal (AO-32A3.b) femoral fracture were reviewed. Three orthopedic surgeons retrospectively and independently examined X-rays, according to the revised AFFs case definition criteria of the American Society for Bone and Mineral Research task group (ASBMR) (Table I)[4] and established a consensus that there were 74 (1.7%) AFFs. At least four out of five major features had to be present to confirm the diagnosis. No minor features are required, but are mainly associated with the fracture.[4]

Inclusion criteria were patients having sustained low-energy trauma. Exclusion criteria were polytrauma patients, patients younger than 50 years of age, and patients with incomplete medical records. These 74 patients (8 males, 66 females; mean age: 75.4±7.2 years; range, 51 to 94 years) were reviewed using the inclusion and exclusion criteria and all were found to be eligible. A control group of 143 patients were reviewed with the same inclusion and exclusion criteria mentioned above with a fracture type of AO 32A1.a - subtrochanteric-, 32A3.b - diaphyseal- and some 31A1 - pertrochanteric femoral fractures as fragility fractures. In the AFF group, the patients were also divided by their BP therapy history into two groups: those without BP therapy (Group 1) and with BP therapy (Group 2). Group 2 was further subdivided by the length of the BP therapy (Group 2a: <5 years of BP, Group 2b: >5 years of BP). The study flow chart is shown in Figure 1.

A written informed consent was obtained from each patient. The study protocol was approved by the Regional Institutional Ethics Committee, Budapest (date/no: 2021.10.01,18/2021). The study was conducted in accordance with the principles of the Declaration of Helsinki.

TABLE I
ASBMR Task Force Revised Case Definition of AFFs

Major criteria	Minor criteria	Exclusion criteria
• Transverse or slightly oblique fracture line • Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex • Minimal or no trauma • Non or minimally comminuted • Localized periosteal or endosteal thickening of the lateral cortex at the fracture site	• Increase in cortical thickness of the femoral diaphyses • Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh • Bilateral incomplete or complete diaphysis fractures • Delayed healing	• Femoral neck fracture • Intertrochanteric fractures with spiral subtrochanteric extension • Periprosthetic fractures • Pathological fractures related to primary or metastatic bone tumors and miscellaneous bone diseases

ASBMR: American Society for Bone and Mineral Research task group; AFFs: Atypical femoral fractures.

Assessment

Data on potential risk factors were gathered from hospital electronic health records including age, sex, comorbidities such as hypertension and antihypertensive medication, diabetes, rheumatoid arthritis, thyroid disease, malignancy, neurological disease, as well as BP and glucocorticoid therapy history (all listed comorbidities are in association with AFFs according to the literature - and in the case of hypertension and its medication, there is no such study available - it was added only for the heterogeneity of data).[14,16-18] Fracture characteristics (delayed bone union cases and duration, contralateral X-ray case number, contralateral signs), surgical fixation methods and complications (bilateral fractures) were analyzed. Our criteria for bone union were as follows: complete cortical bridging (3 out of 4), and a fracture line either barely visible or undetectable. We did not calculate any bone union scores. Delayed bone union was noted, if it exceeded six months. Follow-up at Weeks 6, 12, 26, and 52 were recorded, and X-rays were retrospectively analyzed for bone union. In this study, all patients who were operated by cephalomedullary nails with a proximal- and middle- third fracture location were encouraged to attempt and achieve full-weight bearing as soon as possible postoperatively, according to the AO Surgery Reference guidelines. In cases where delayed union was recognized, more frequent X-rays (every two or

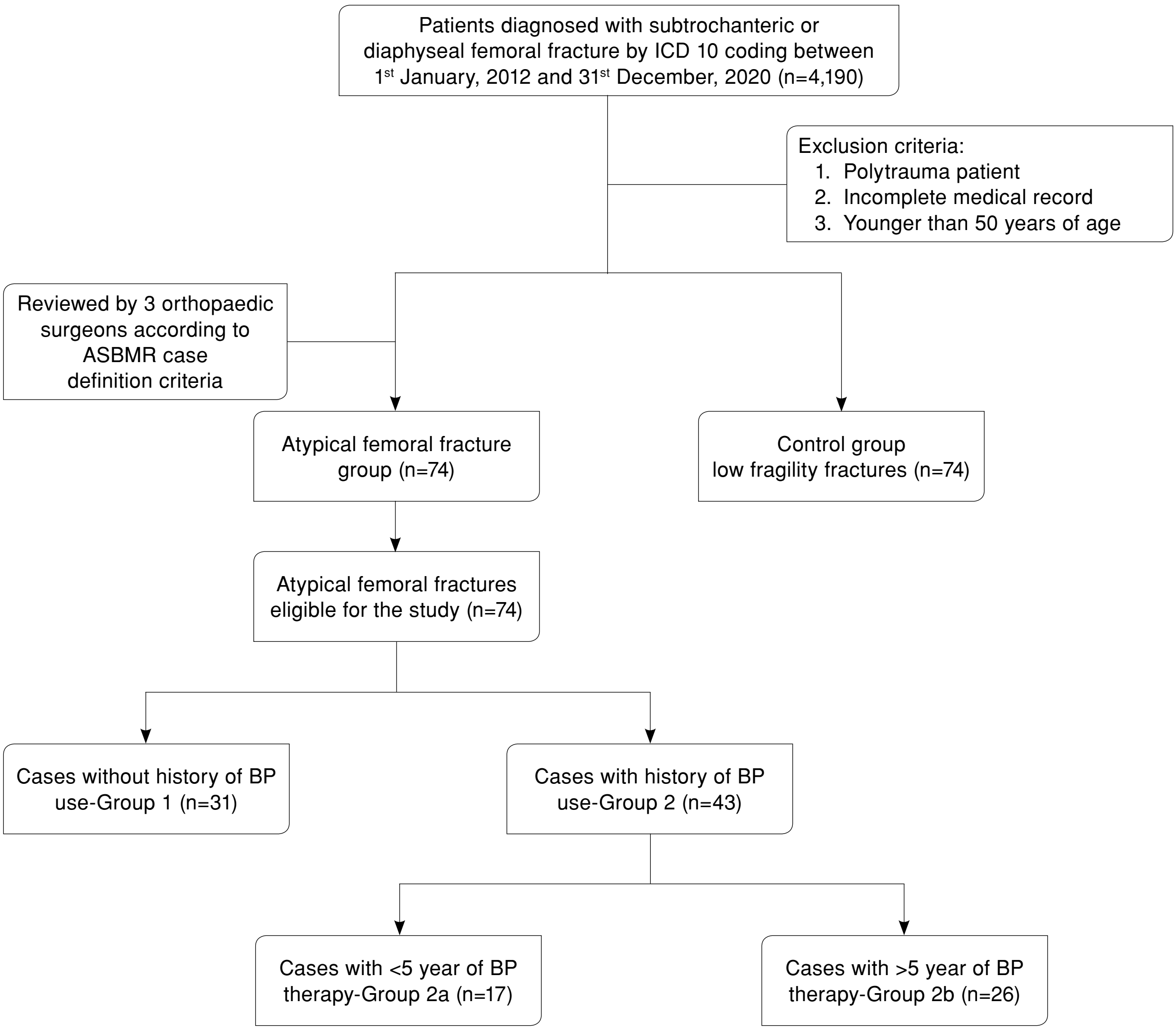

FIGURE 1. Study flow chart.
ICD: International Classification of Diseases; ASBMR: American Society for Bone and Mineral Research; BP: Bisphosphonate.

FIGURE 2. A case of a 79-year-old man who suffered from an atypical femoral fracture and received oral bisphosphonate therapy for eight years.

three weeks) were performed, until bone union was noted. The patients with contralateral minor signs were followed conservatively. Those who were on BP therapy and sustained an AFF had their BP therapy discontinued for at least one year.

Group 1 and 2, and Group 2a and 2b were compared by the duration of union, delayed bone union cases, and bilateral fracture occurrence.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed in mean ± standard deviation (SD) or median (min-max), while categorical data were expressed in number and frequency. Means of continuous variables in the formed groups were compared with the Welch's independent samples t-test. The relationship between categorical variables was tested using the chi-square test for independence and Fisher exact test. Further analysis was carried out with multivariate logistic regression model. Forward likelihood ratio model selection method was used. Possible risk factors were sex, diabetes, rheumatoid arthritis, thyroid disease, malignancy, neurological disease, hypertension, osteoporosis, and BP and corticoid use. Odds ratios (ORs) and 95% confidence intervals (Cis) were calculated. A *p* value of <0.05 was considered statistically significant.

RESULTS

A total of 74 patients (19 bilateral, all together 93 AFFs), were diagnosed as with AFF, which was 1.7% of all femoral fractures (Figure 2). Demographic data, records of chronic diseases, and medications of patients are shown in Table II. Different types of statistical methods were performed on risk factors of AFFs (Table II).

In the AFF group, 43 patients received BP therapy, compared to only eight patients in the control group ($p<0.001$). The mean duration of drug use in the AFF group -7±3.5 years *vs.* the control group -2.9±0.8 years ($p<0.001$). In the AFF group, 26 patients received BP for longer than five years. In Group 2a, the mean time of the BP therapy was 4.3±0.9 (range, 3 to 5) years and, in Group 2b, it was 8.7±3.6 (range, 6 to 20) years. In the control group, there was no BP use longer than four years. In the study group, the most commonly used BPs were alendronic and ibandronic acids. In the control group, six patients were on alendronic and two patients on ibandronic acids. Discontinuing BP therapy for at least one year was the postoperative osteoporosis medical treatment protocol followed.

Among 93 AFFs, there were delayed bone unions in 65 fractures (70%). The mean duration of union in all AFF cases (7.5±3.5 months) was significantly higher compared to the control group (4.5±2.2 months, $p<0.001$). Also, delayed union time was significantly higher in BP user patients in the AFF group (Group 2, -8.3±3.5 months, $p=0.003$). The most common AFF fracture location was the shaft region (Table III). Data regarding contralateral X-rays and signs are shown in Table III. Contralateral radiographs were not applied in all AFF patients due to the fracture itself being rare; and, on primary admission, not being recognized in 65% of the cases by surgeons. The patients who were on BP therapy and had suffered from an AFF had a contralateral femoral X-ray, and along with noticing minor signs, their BP therapy was discontinued for at least one year, with a conservative follow-up. The application of a prophylactic surgical treatment was done only once, due to the patient suffering from severe pain on the contralateral femur, with an impending fracture later located.

Surgical fixation methods can be seen in Table III. The most common AFF fixation was Sanatmetal® Fi-nail (43%).

TABLE II
Demographic and chronic diseases data on AFF and control group patients

	AFF group (n=74)			Control group (n=143)			
Demographic data of patients	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			75.4±7.2			74.3±11.8	0.403*
Sex							0.017†
Male	8			35			
Female	66			108			
Diabetes	9	12		33	23		0.054†
Rheumatoid arthritis	4	5		2	1		0.184‡
Thyroid disease	11	15		10	7		0.063†
Malignancy	5	6		5	3		0.315‡
Neurologic disease	7	9		9	6		0.398†
Hypertension	49	66		115	80		0.021†
Osteoporosis	50	67		25	17		<0.0001†
Bisphosphonate use	43	58		8	6		<0.0001†
Corticosteroid use	5	6		4	3		0.279‡

AFF: Atypical femoral fractures; SD: Standard deviation; * Welch two sample t-test; † Chi-squared test; ‡ Fisher exact test.

TABLE III
Fracture type and characteristics with surgical fixations

	AFF group (n=74)			Control group (n=143)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Fracture type and characteristics							
Total number of femoral fractures	93			143			-
Femoral shaft	71			34			-
Subtrochanter	22			85			-
Pertrochanter	-			24			-
Delayed union	65			26			-
Duration of union all patients			7.5±3.5			4.5±2.2	<0.001*
Duration of union on BP			8.3±3.5			4.4±2.9	=0.003†
Duration of union on steroid			7.3±3.6			4.1±1.9	-
Bilateral fracture	19			-			-
Interval between primary and contralateral fracture occurrence in bilateral form			27.7±7.3	-			-
Contralateral X-ray	26			-			-
Contralateral signs (minor criteria)	24	92.3		-			-
Contralateral signs and bilateral fracture incidence	10	41.6		-			-
Surgical fixation type							
Stryker®-gamma 3 system	28	30		4	4.1		-
Sanatmetal®-fi-nail	40	43.1		119	83		-
Synthes®-lateral femoral nail	4	4.3		1	0.7		-
Küntscher nail	17	18.3		13	9.1		-

SD: Standard deviation; BP: Bisphosphonate; * Welch two sample t-test; † Independent sample t-test.

TABLE IV
Characteristics in different groups by duration of union, delayed union and bilateral fracture cases

	Group 1 (without BP therapy, n=31)		Group 2 (with BP therapy, n=43)		
	n	Mean±SD	n	Mean±SD	*p*
Duration of union		6.4±3.1		8.3±3.5	0.02*
Delayed union	16		34		0.01†
Bilateral fracture	5		14		0.11†
	Group 2a (<5 years of BP, n=17)		Group 2b (>5 years of BP, n=26)		
	n	Mean±SD	n	Mean±SD	*p*
Duration of union		7.3±2.9		9±3.8	0.099*
Delayed union	12		22		0.445‡
Bilateral fracture	4		10		0.307†

BP: Bisphosphonate; SD: Standard deviation; * Welch two sample t-test; † Chi-squared test; ‡ Fisher exact test.

Patients in Group 2 (on BP therapy) showed a significantly longer bone union (8.3±3.5 months) compared to Group 1 (without BP) (6.4±3.1 months, p=0.02) (Table IV) The number of cases with delayed bone union was also significantly higher in Group 2 (n=34) *vs.* Group 1 (n=16) (p=0.01) (Table IV).

Group 2b showed a longer union time (9±3.8 months) compared to Group 2a (7.3±2.9 months, p=0.1). Group 2b, compared to Group 1, had a strong, statistically significant difference by union time (p=0.001).

Fourteen of the total 19 bilateral fractures were in Group 2, with a history of BP use (p=0.11). There was no significant difference between Group 2a and 2b regarding the bilateral occurrence (p=0.307) (Table IV).

Multivariate analysis revealed that the most important risk factors for development of AFFs were hypertension (p=0.019, OR=0.387, 95% CI: 0.175-0.858), osteoporosis (p=0.008, OR=3.258, 95% CI: 1.367-7.767), and BP use (p<0.001, OR= 10.749, 95% CI: 3.886-29.733).

DISCUSSION

Regarding patient characteristics, the incidence of AFFs was 1.7% of all femoral fractures, which is consistent with reported AFF percentage in the literature.[1]

The published ASBMR report states that BP therapy is a relative (but not an absolute) risk factor to the occurrence of AFFs.[4] The absolute risk factor of AFFs by BP use is considered low, only as there are 3.2 to 50 cases/100,000 patients/year.[6] It is known in the literature that there is a strong correlation between BP use and AFFs.[4,6,19,20] In this study, similar results were shown, in that BP therapy was the most significant risk factor for the development of AFF compared to the control group (p<0.001, OR=10.749, 95% CI: 3.886-29.733). More interestingly, according to the patient data, in patients with hypertension and using hypertension medication, the risk of AFF development reduced. After searching the literature for an explanation, no publication or cause was found for this mechanism. Therefore, the correlation between hypertension and AFF incidence requires further investigation.

In our study, among 74 AFF cases, there were seven patients in whom there was no chronic disease, drug use or predisposing risk factor. In this group, the mean time of fracture healing was 4.9±2.3 months. This may be due to genetic mutation, individual predisposition, bone metabolic errors or bone geometric changes, which is reported in the literature.[10,12,21,22] Studies have shown that patients diagnosed with diabetes mellitus have a suppressed bone turnover, which is thought to be caused by osteocyte dysfunction and higher level of sclerostin, that forms microfractures in the bone.[14] Atypical fractures are associated with many medical conditions such as osteopetrosis, hypophosphatasia, vitamin D deficiency, pycnodysostosis, rheumatoid arthritis, and certain types of non-Hodgkin lymphomas, as these diseases inhibit bone metabolism as a mechanism of action.[23-25]

Several studies have reported that, in atypical fractures, delayed bone union and bilateral fractures can occur during BP therapy.[17,26-28] In the present study, we also examined in what proportion BP therapy increased duration of bone union and the incidence of bilateral fractures.

Both mechanical and histological factors are known to possibly have an effect on the pathophysiology of delayed unions.[28-30] In a study of 109 atypical fractures, one of the associated risk factors was long-term BP use in delayed unions.[28] Prasarn et al.[31] reported that long-term BP therapy was associated with longer bone union (6.5 *vs.* 4.8 months), compared to non-BP users. In a recent meta-analysis, the mean time of union in patients on BP was about 8.5 months, and a third of all BP-related fractures resulted in delayed or non-union.[32] In this study, of 74 patients (93 fractures), the mean time of union was 7.5±3.5 months and delayed bone union was recorded in a total of 65 fractures (70%). Among them, BP use was noted in 43 individuals (58%), indicating the suppression of bone remodeling that caused delayed bone union. Patients in Group 2 (on BP therapy) showed a significantly longer bone union, compared to Group 1 (without BP) ($p=0.02$). Delayed bone union case numbers were also significantly higher in Group 2 than Group 1. Group 2b showed longer union time compared to Group 2a, but was not statistically significant. Group 2b, compared to Group 1, had a strong, statistically significant difference by union time ($p=0.001$). As a result, longer BP therapy (>5 years) causes longer delayed bone union, although not statistically significant. It is known that AFF treatment can be challenging, but even in the most unfavorable of scenarios, the risk/benefit ratio is highly positive for BP use, particularly during three to five years of use.[33] The postoperative treatment protocol undertaken was a discontinuation of BP therapy for at least one year (a so-called drug holiday), which is recommended by the literature after an AFF.[34] A comparison of different groups based on the duration of drug holidays and the continuation of drug use later was not performed.

Probyn et al.[35] evaluated 124 patients who suffered from AFFs on BP therapy with 78 cases of bilateral fracture occurrence. They concluded that the likelihood to be diagnosed with a contralateral AFF was high within the first year of presentation. In this study, in 19 cases of bilateral fractures, the contralateral fracture occurred for one year period. In this study, bilateral fractures occurred mostly in BP users (Group 2), although there were no statistically significant differences. Longer BP therapy also showed no statistically significant difference in the occurrence of bilateral fracture. In all 26 cases where contralateral X rays were taken on primary admission, signs of localized periosteal or endosteal thickening were found in 92.3% of the cases. Of 24 cases, 10 cases confirmed a bilateral fracture afterwards.

Clinical studies have reported that prophylactic intramedullary (IM) nailing can be beneficial for patients who have a risk of secondary stress fracture displacement. The indications for surgery are prodromal pain on the contralateral side, and prevention of secondary stress fracture displacement.[36-38] In this study, due to its retrospective nature, there were insufficient data on prodromal pain. The cases in which impending fractures (minor signs) were recognized were followed closely conservatively. The literature reports a high rate of secondary displacement of non-operated cases.[36,38] Ha et al.[37] reported that five of 14 cases had secondary displacement. Unfortunately, in this study, out of 24 recognized cases, 10 developed a contralateral complete fracture and needed fixation surgically.

In this retrospective study, the lack of coherence of standardized weight bearing scores in the patient groups led to insufficient information regarding patients achieving full-weight bearing. Information on prodromal pain was also missing. Pain on palpation at the site of injury is currently widely used among physicians to judge union; however, it is a highly subjective outcome, given individual and cultural differences in perception and tolerance level of pain among the population.[39]

Furthermore, this study reports no femoral neck fracture complications. Femoral neck fractures may occur, when gold-standard IM nails have been used and it is recommended to use cephalomedullary nails in AFFs.[18,28,30]

The retrospective nature, a relatively small sample size, and a low number of BP users in the control group are the other limitations of this study. The latter demonstrates that some of the statistics are not statistically significant. They are, however, supported by the literature. There were some overlaps between BP use and chronic diseases which both can cause AFFs. These cases cannot be divided due to small case numbers and complicated study design.

In conclusion, BP use is the most significant risk factor for developing AFF. Longer BP therapy

(>5 years) causes longer delayed bone union. The BP therapy must be suspended in case of impending fracture or AFF occurrence. The risk of developing atypical fracture and the incidence of bilateral fractures on BP is high. Other risk factors, besides BP use, should be also considered in case of atypical fractures. In case of an AFF, a contralateral femoral X-ray must be always performed for signs of an impending fracture. Prophylactic IM nailing can be beneficial for patients who have a risk of secondary stress fracture displacement.

Declaration of conflicting interests

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III. published paper

A Szegedi Tudományegyetem Általános Orvostudományi Kar Traumatológiai Klinika közleménye

Atípusos periprotetikus femurtörés

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ÖSSZEFOGLALÁS

Az atípusos femurtörések kialakulását elsősorban a hosszú távú biszfoszfonát kezeléssel hozzák összefüggésbe. Az American Society for Bone and Mineral Research (ASBMR) által 2014-ben közzétett ajánlás egyértelműen meghatározza az atípusos törés definícióját és ebben a periprotetikus törés, mint kizáró tényező szerepel. Ennek ellenére egyre több közlemény számol be arról, hogy egyes periprotetikus femurtörések az atípusos törések karakterisztikájával jelennek meg. Tanulmányunkban egy periprotetikus törést elszenvedett beteg esetén keresztül mutatjuk be, hogy a hosszú távú biszfoszfonát terápia és az atípusos törésforma között korreláció lehet, illetve az atípusos femurtörés periprotetikus formában is jelentkezhet.

Kulcsszavak: ***Biszfoszfonát kezelés; Femurtörés; Gyógyszer mellékhatás; Osteoporosis; Periprotetikus törés;***

D. Dózsai, Á. Csonka, I. Gárgyán, E. Varga: Atypical periprosthetic femoral fracture

The development of the atypical femoral fracture is mainly associated with the long-term use of bisphosphonates. In 2014 a report was published by The American Society for Bone and Mineral Research (ASBMR) which has clearly identified the case definition of the atypical fractures and excluded periprosthetic femoral fractures from it. Even so, several case reports found that periprosthetic femoral fractures can occur with similar characteristics to those of definition of the atypical fractures. The purpose of our study was to feature a case report of an atypical periprosthetic femoral fracture, and its possible correlation between the long-term use of bisphosphonate and atypical fracture form. Thus, atypical femoral fracture can occur in periprosthetic form as well.

Keywords:
Diphosphonates – Adverse effects;
Bone density conservation agents – Adverse effects;
Femoral fractures – Chemically induced/Pathology;
Osteoporosis – Complications/Drug therapy;
Periprosthetic fractures – Epidemiology/Etiology;

BEVEZETÉS

Az osteoporosis világszerte több százmillió embert súlyt, Magyarországon a lakosság körülbelül 10%-át (23). A biszfoszfonát tartalmú készítmények használata jelentősen csökkentette az osteoporosis alapú törések rizikóját, és az egészségügyi rendszerre nehezedő terhet (14).

A csontrendszerre kifejtett előnyös hatásuk a törési kockázat csökkentésében nyilvánul meg. Az osteoclastok működését gátolva csökkentik a csont reszorpciót, így a csontszerkezet további leépülését megakadályozva csökken a törések kialakulásának esélye (9, 20). Indirekt módon csökkennek a csontban létrejövő mikrofraktúrák, azonban a már korábban keletkezett mikrofraktúrák új csontmátrix-szal történő helyettesítése is zavart szenved. Ez az alapja annak, hogy az atípusos femurtörés (AFT) a biszfoszfonátok több éven át tartó használata mellett új töréstípusként jelent meg (18, 20), amelyet egy mesterségesen létrehozott alacsony csontátépülés okoz. Az atípusos femurtörés alacsony energiájú vagy esetenként trauma nélkül létrejövő stressztörés, amelyre sajátos megjelenésű röntgenkép jellemző (22). A 2014-ben megjelent American Society for Bone and Mineral Research ajánlás alapján az atípusos subtrochanterikus és középső harmadi femurtörések esetében a periprotetikus törés, mint kizáró kritérium szerepel (22). Az elmúlt években azonban jelentős számú esettanulmány jelent meg arról, hogy a hosszú távú biszfoszfonát kezelés melletti periprotetikus femurtörések (PFT) atípusos femurtörésekre jellemző morfológiával is előfordulhatnak (3, 5, 10, 15, 16, 19). Ezeket nevezzük atípusos periprotetikus femurtörésnek (APFT). Az APFT-k az idősebb generációt érintik, hiszen ezen populációban a biszfoszfonát kezelés mellett gyakori az ízületi implantátum megléte, és egyéb társbetegségek (diabétesz, D–vitamin hiány, proton pumpa inhibitor használat) is szerepelhetnek az anamnézisükben (1, 6). Mindezek ismerete mellett az APFT-ek kiváltó oka, etiológiája, diagnosztikus kritériumai és terápiás javaslatai továbbra sem egyértelműen meghatározottak (19).

Tanulmányunkban egy esettanulmányon keresztül mutatjuk be, hogy az atípusos femurtörések ritkán, periprotetikus formában is megjelenhetnek.

ANYAG ÉS MÓDSZER

A Szegedi Tudományegyetem Traumatológiai Klinikáján prospektív vizsgálat folyik az atípusos femurtörések felismerése, gyógyszeres és műtéti kezelése tekintetében. A vizsgálatok során észleltük, hogy egyes periprotetikus Vancouver B1 töréseknél atípusos törésmintázat figyelhető meg.

2015-ben öt beteget kezeltünk periprotetikus Vancouver B1 törés miatt. Közülük két esetben figyelhettünk meg atípusos törésmintázatot. Anamnézisükben 5 évnél hosszabb ideig tartó biszfoszfonát terápia szerepelt. Az atípusos femurtörések diagnózisának felállításához az American Society for Bone and Mineral Research munkacsoport ajánlásait alkalmaztuk, amely alapján 5 kritériumból legalább 4-nek kell teljesülni (*I. táblázat*) (22).

A diagnózis felállításához nélkülözhetetlenek az anamnesztikus adatok (időszakos combfájdalom, gyógyszerszedés, társbetegségek), illetve a röntgenfelvételeken az *I. táblázat*ban felsorolt eltérések.

I. táblázat Az American Society for Bone and Mineral Research kritériumai

Major kritérium	Minor kritérium	Kizáró kritérium
• *Minimális vagy trauma nélküli sérülés által létrejött törés* • *Haránt vagy rövid ferde törés* • *Komplett törés mindkét cortexen keresztül halad, és medialis csipkeképződés látható, az inkomplett törés csak a lateralis cortexet érinti* • *Nem vagy minimálisan darabos törés* • *Lokális periostealis vagy endostealis reakció látható a lateralis cortexnél a törési zónában*	• *A combcsont diaphysisnél a corticalis rész megvastagodott* • *Unilateralis vagy bilateralis prodromalis tünetek, mint tompa vagy égető fájdalom a glutealis vagy comb régiójában* • *Bilateralis inkomplett vagy komplett diaphysis törés* • *Elhúzódó törésgyógyulás*	• *Combnyaktörés* • *Intertrochanterikus törés, amely a subtrochanter régióba terjed* • *Periprotetikus törés* • *Patológiás törés, amelyet primer vagy metasztatikus csonttumor okoz vagy egyéb csontbetegségek*

MEGFIGYELÉSEK

2015-ben két betegnél találtunk APFT-re jellemző törésmintázatot. A betegek minor trauma hatására szenvedték el a töréseket.

Klinikánkon a periprotetikus törések rögzítésére leggyakrabban szögstabil lemez rendszereket alkalmaztunk. A lemezeket szükség szerint kiegészítettük cerclage, kábel vagy attachment alkalmazásával. A műtétek után posztoperatív röntgenfelvételek készültek az operált oldalról és az ellenoldalról egyaránt. A műtéteket követő 6., 12., és 52. héten kontroll röntgenfelvételek készültek. Szeptikus szövődményünk nem volt.

ESETISMERTETÉS

80 éves nőbeteg minor traumára szenvedte el jobb oldali periprotetikus Vancouver B1 típusú törését. A készült röntgenfelvételen atípusos törésmintázat látható: haránttörés, medialis csipkeképződés, minimálisan darabos törés és a lateralis femurcortex megvastagodása (*1. ábra*). Az anamnézisében hypertonia és postmenopauzális osteoporosis szerepelt, amely miatt 12 évig biszfoszfonátot (alendronsav) kapott. 2010-ben bal oldali középső harmadi femurtörés miatt velőűrszegezés történt (*2. ábra*). Akkor a radiológiailag és klinikailag is egyértelmű atípusos törés nem került felismerésre, ezért a gyógyszeres terápiában sem történt változtatás. A törés szövődmény nélkül tökéletesen átépült (*3. ábra*).

2014-ben az implantátumot eltávolítottuk, hogy megelőzzük a fokozott stressz miatti későbbi combnyaktörést. 2015-ben szenvedte el minor traumára jobb oldali atípusos periprotetikus femurtörését. Az atípusos töréseket esetenként előrejelző prodromális combfájdalomról nem rendelkezünk információval. A jobb oldali periprotetikus törés ellátása egy 18 lyukas J&J DePuy Synthes® LISS DF implantációval történt, két attachment-tel kiegészítve (*4. ábra*). A posztoperatív időszakban mindkét femurról röntgenfelvételek készültek, amelyeken az ellenoldali femur lateralis cortexén mikrofractura nem igazolódott, csak a korábbi törésből adódó callus. Az ASBMR ajánlás alapján a gyógyszeres kezelést módosítottuk. A korábban alkalmazott alendronate terápiát azonnal felfüggesztettük. Kalcium és D-vitamin kiegészítés mellett teriparatid kezelést indítottunk. A műtét után a beteg panaszmentes volt, operált végtagját tehermentesítve, segédeszközzel közlekedett, valamint aktív és passzív gyógytornát végzett. A 12. héten készült röntgenfelvételen a törés jó ütemű átépülését láttuk, a beteg panaszmentesen, továbbra is segédeszköz segítségével közlekedett. Az egy éves kontrollvizsgálaton a törés teljesen átépült (*5. ábra*).

1. ábra
Jobb oldali atípusos periprotetikus törés. Medialis csipkeképződés és lateralis cortex megvastagodás

2. ábra
Bal oldali atípusos femur törés

3. ábra
Bal oldali átépült atípusos femur törés

4. ábra
Posztoperatív felvétel a jobb oldali atípusos periprotetikus törés ellátást követően

5. ábra
Egyéves kontrollfelvétel a jobb oldali periprotetikus törés átépülése teljes

MEGBESZÉLÉS

Az atípusos femurtörések stressz törésként jelennek meg. Hónapokkal a törés bekövetkezte előtt időszakos combfájdalom jelentkezhet. A radiológiai elváltozások legtöbbször kétoldali megjelenésűek, a lateralis femurcortex megvastagodik, mikrofraktura látható (2, 4). Az atípusos femurtörés bekövetkezte esetén ajánlott az ellenoldali femurról is röntgenfelvételt készíteni, mert előfordulhat megvastagodott cortex és mikrofractura, amely előrevetítheti egy jövőbeni törés bekövetkeztét. Bizonytalan esetekben CT vagy MRI vizsgálat is megfontolandó (19).

A periprotetikus Vancouver B1 típusú törések műtéti ellátása az LCP rendszerek alkalmazásán alapul, amely cerclage-zsal, kábellel, illetve a lemezhez rögzített attachment-tel kombinálható. Csonthiány esetén auto- vagy allograft is beültethető a törésgyógyulás elősegítésére, indukálására és stabilabb rögzítés elérésére (11). Az atípusos periprotetikus B1 típusú törések rögzítése nem különbözik a típusos periprotetikus törések rögzítésénél alkalmazott módszerektől, de szem előtt kell tartanunk, hogy az osteosynthesist követően gyakran elhúzódó törésgyógyulás, magasabb mortalitás és több szövődmény fordulhat elő (13, 22).

A periprotetikus femurtörések ellátása komoly kihívás elé állítja a baleseti sebészeket, egyre több esettel kell számolni, hiszen egyre több a protetizált beteg (11). Az American Society for Bone and Mineral Research ajánlása alapján a periprotetikus törés, mint kizáró tényező szerepel az atípusos femurtörés esetén. Ennek ellenére a szakirodalomban, főleg mint esettanulmányok, egyre gyakrabban kerülnek bemutatásra az ilyen típusú törésformák (7, 10, 15, 16, 25). Az ASBMR módosított ajánlása alapján az atípusos törések nem hozhatók szoros összefüggésbe más betegségekkel vagy gyógyszerrel, így a biszfoszfonát tartalmú készítményekkel sem. Az ajánlásban azonban az is megfogalmazódik, hogy a hosszú távú BF alkalmazás és az AFT-ek között összefüggés lehet (22). Egyre több tanulmány igazolja az atípusos femurtörés és a biszfoszfonát használat közötti lineáris összefüggést, főként hosszú távú kezelés esetén (>5 év) (8, 13, 24).

Az általunk bemutatott eset is rávilágít az atípusos periprotetikus femurtörések és a hosszú távú biszfoszfonát terápia kapcsolatára.

Az atípusos törések komplex kezelése nehéz feladat, és az eredmények sokkal szerényebbek, mint a típusos törések esetén. Ennek oka az elhúzódó törésgyógyulás, a rossz csontkonszolidáció, a törésrögzítés nehézsége, a magas mortalitás és a gyógyszeres kezelés szövődményei (12, 17, 21). A törés megfelelő mechanikai rögzítése mellett rendkívül fontos a törésgyógyulás biológiai elősegítése, a korszerű teriparatid alkalmazása. Periprotetikus Vancouver B1 típusú femurtörés esetén, amenynyiben hosszú távú biszfoszonfát kezelés szerepel az anamnézisben, mindig gondoljunk az atípusos törés lehetőségére. A biszfoszfonátok alkalmazása nagy körültekintést igényel, mindig szem előtt tartva a kezelés előnyeit és hátrányait. Elengedhetetlen a folyamatosan megjelenő új típusú osteoporosis elleni készítmények ismerete és a betegek folyamatos és szoros utánkövetése.

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IV. published paper

A Szegedi Tudományegyetem Általános Orvostudományi Kar Traumatológiai Klinika közleménye

Atípusos femurtörések összefüggése a hosszantartó biszfoszfonát terápiával

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ÖSSZEFOGLALÁS

Az atípusos femurtörés kialakulását elsősorban a hosszantartó biszfoszfonát (BP) kezeléssel hozzák összefüggésbe, de létrejöttében egyéb tényezők is szerepet játszhatnak. Retrospektív tanulmányunkban, 2013. január 1. és 2019. december 31. közötti időszakot feldolgozva, 30 esetben észleltünk atípusos femurtörést. Az eseteket a BP alkalmazása alapján két csoportra osztottuk: I. BP-t nem használók és II. BP-t használók. A II. csoportot további két alcsoportra osztottuk a terápia időtartamának megfelelően, IIa (< 5év BP) és IIb (> 5 év BP). A II. csoportnál a törésgyógyulási idő hosszabbnak bizonyult (7 ± 4.9 hónap) az I. csoporthoz (5.8 ± 4.6 hónap, p = 0.24) képest. 17 esetben (57%) észleltünk elhúzódó törésgyógyulást (> 6 hónap), amelyek közül 11 esetben igazolódott BP használat (64%). A IIb csoportnál (9.1±5.1 hónap) a törésgyógyulás időtartama szignifikánsan meghaladta a IIa csoportét (5.6±3.4 hónap, p = 0.03). Elhúzódó törésgyógyulás a IIb csoportban 6 esetnél, a IIa csoportban 3 esetnél jelentkezett (p = 0.19). Bilateralis törés 6 betegnél jött létre, amelyek közül 5 alkalmazott BP-t és tartozott a II. csoporthoz (p= 0.26). A bilateralis törésmegjelenés szempontjából szignifikáns különbséget a IIa és IIb csoport között nem észleltünk (p = 0.38). Öt atípusos femurtörött beteg esetén nem találtunk olyan rizikófaktort, amely összefüggésbe hozható a törés kialakulásával. Eredményeink alapján megállapíthatjuk, hogy a hosszú távú BP terápia (>5 év) elhúzódó törésgyógyulást okozhat, megnövelheti a bilateralis törések létrejöttét és az atípusos törés incidenciáját.

Kulcsszavak: ***Biszfoszfonát; Csontátépülés; Femurtörés; Osteoporosis; Stressztörés;***

Á. Csonka, D. Dózsai, I. Gárgyán, E. Varga: Atypical femoral fractures association with long-term bisphosphonate therapy

Atypical femoral fractures (AFF) have been mainly associated with long-term (> 5 year) bisphosphonate (BP) therapy; however, there may be other factors that also play a role in its development. In our retrospective study, 30 cases with AFFs between January 1 2013 and December 31, 2019 were selected and subdivided according to their BP therapy: Group I (without BP) and Group II (with BP). Group II was classified into Group IIa (< 5 year of BP) and Group IIb (> 5 year of BP). Group II showed longer bone union (7.0 ± 4.9 months) than Group I (5.8 ± 4.6 months, p = 0.24). Delayed bone union was noted in 17 cases (57%) and amongst these, 11 were exposed to BP intake (64%). Group IIb (9.1±5.1 months) had longer union time than Group IIa (5.6±3.4 months) (p = 0.03). There was twice the number of delayed bone union in Group IIb (6 cases) compared to Group IIa (3 cases, p = 0.19). Out of all 6 cases of bilateral fractures, 5 were in Group II with BP use (p = 0.26). There was no significant difference between Group IIa and IIb regarding the bilateral occurrence (p = 0.38). No risk factor was found for 5 patients diagnosed of having atypical femoral fracture. This study shows that long-term use of BP therapy (> 5 years) causes delayed bone union and that there is a high risk of developing atypical fracture and the incidence of bilateral fractures on BP.

Keywords: ***Diphosphonates – Adverse effects; Bone remodeling – Drug effects;***
Femoral fractures – Chemically induced/Pathology;
Fractures, Stress – Chemically induced/Pathology;
Osteoporosis, postmenopausal – Drug therapy;

BEVEZETÉS

Az atípusos femurtörések (AFT) gyakorisága az elmúlt években jelentősen megnőtt, de ennek ellenére előfordulásuk alapvetően ritka, a combcsont-törések körülbelül 1–2%-át teszik ki (10). A világ idősödő lakosságát érintő osteoporosis miatt egyre nagyobb arányban alkalmaznak biszfoszfonát (BP) tartalmú készítményeket (16, 24). A biszfoszfonát terápia magas relatív rizikót képez az atípusos femurtörések létrejöttében (21). Az AFT összefüggését a hosszú távú BP terápiával (>5 év) egyre több tanulmány igazolja (20, 25). Az atípusos törésmintázat azonban olyan esetekben is leírásra került, ahol BP kezelést nem alkalmaztak, így más kockázati tényezőket is figyelembe kell venni, amelyek befolyásolhatják a csontátépülést (4, 11, 23). Az atípusos törés pathomechanizmusában minden olyan tényező szerepet játszik, amely a csontszövet remodellációját csökkentve, a keletkező microfrakturák új csontmátrix-szal történő helyettesítésében zavart okoz (18). Alapvetően bármilyen gyógyszeres terápia, krónikus betegség, illetve génmutáció, genetikai eltérés, amely csökkenti a csont remodellációt, rizikótényezőként szerepel az AFT kialakulásában. Az American Society for Bone and Mineral Research (ASBMR) meghatározta az atípusos törések definícióját (*I. táblázat*). Az öt fő kritériumból legalább négynek teljesülnie kell a diagnózis kimondásához. A minor tényezők megléte nem feltétel a diagnózishoz, de sok esetben megfigyelhetőek (21).

Hipotézisünk alapján a hosszú távú biszfoszfonát kezelés növelheti az atípusos törések előfordulását, elhúzódó törésgyógyuláshoz, illetve bilateralis törés kialakulásához vezethet.

I. táblázat
Az American Society for Bone and Mineral Research kritériumai

Fő kritériumok	Minor kritériumok	Kizáró kritériumok
• *Minimális vagy trauma nélküli sérülés által létrejött törés* • *Haránt vagy rövid ferdetörés* • *Komplett törés, amely medialis csipkeképződéssel járhat* • *Inkomplett törés csak a lateralis cortexet érinti* • *Egyszerű, vagy minimálisan darabos törés* • *Lokális periostealis vagy endostealis reakció a lateralis cortexen a törési zónában*	• *Combcsont diaphysisnél a corticális rész megvastagodott* • *Unilateralis vagy bilateralis prodromalis tünetek, mint tompa vagy égető fájdalom a glutealis vagy comb elülső régiójában* • *Bilateralis inkomplett vagy komplett diaphysis törés* • *Elhúzódó törésgyógyulás*	• *Combnyaktörés* • *Intertrochanterikus törés, amely a subtrochanter régióba terjed* • *Periprotetikus törés* • *Patológiás törés, amit primer vagy metasztatikus csont tumor okoz, vagy egyéb csont betegségek*

ANYAG ÉS MÓDSZER

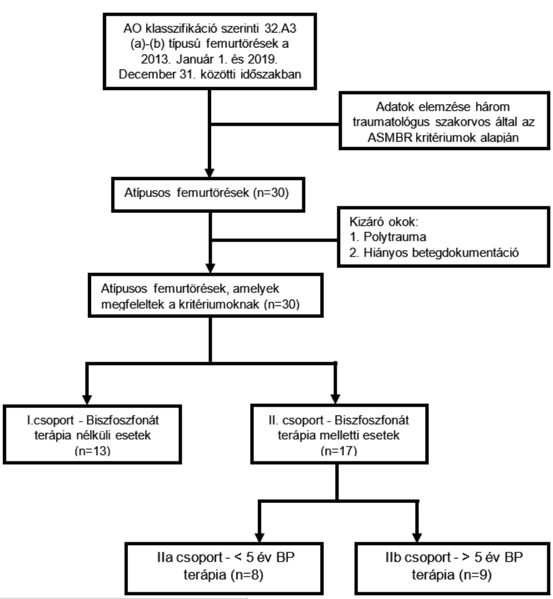
Retrospektív tanulmányunkban, a 2013. január 1. és 2019. december 31. közötti időszakban, a Szegedi Tudományegyetem Traumatológiai Klinika beteganyagát feldolgozva, 1667 beteget kezeltünk AO törés klasszifikáció szerinti 32.A3(a) és 32.A3(b) típusú femurtörés miatt.

Az ellátott betegek röntgenképeit az ASBMR kritériumai alapján három traumatológus szakorvos egymástól függetlenül elemezte (I. táblázat). Atípusos törésmintázat 30 esetben (1.8%) igazolódott. A biszfoszfonát terápia alapján két csoportba osztottuk betegeinket: BP terápia nélküli (I. csoport) és BP terápiában részesülők (II. csoport). A II. csoportot további két alcsoportra osztottuk a BP terápia hossza alapján (IIa csoport: < 5év, IIb csoport: > 5 év BP) (*1. ábra*).

A tanulmányba beválasztás feltétele az 50 évnél idősebb életkor és az alacsony energiájú sérülés volt. A polytraumatizált betegeket és a hiányos dokumentációval rendelkezőket kizártuk. Az atípusos femurtörések diagnózisának felállításához az ASBMR definíciója alapján a periprotetikus törés kizáró tényezőként szerepel, de a szakirodalomban egyre több publikáció jelenik meg azzal kapcsolatban, hogy a periprotetikus törés nem kizáró ok a létrejöttében (9, 17).

Mindezek mellett figyelembe vettük a betegek életkorát, nemek szerinti megoszlását, társbetegségeket (magas vérnyomás, diabétesz, rheumatoid arthritisz, pajzsmirigy-, daganatos betegség), biszfoszfonát, illetve szteroid alkalmazását. Vizsgáltuk a törések karakterisztikáját és lokalizációját, hogy azok a subtrochanter régióban vagy a diaphysis középső részén jöttek létre. Feljegyeztük az osteosynthesis módját és a szövődményeket. Amennyiben a csontgyógyulás hat hónapon belül nem következett be, azt elhúzódó törésgyógyulásnak véleményeztük. Az I. és II., valamint a IIa és IIb csoportok a törésgyógyulás hossza és bilateralis megjelenés alapján kerültek összehasonlításra.

Az adatok statisztikai szempontjából a folyamatos változók esetén az átlagok és azok szórásai kerültek meghatározásra. A kategorizált adatok esetén a számuk és ezek százalékai kerültek kiszámításra. Az I. és II., valamint a IIa és IIb csoportoknál a kategorizált adatok esetén Fisher Exact tesztet, míg a folyamatos változók esetében a Mann-Whitney U tesztet alkalmaztuk. A konfidencia intervallumot 95%-nak adtuk meg. Az elemzéseket a Windows Microsoft Excel (2016) programban végeztük el.



1. ábra
Folyamatábra a betegkiválasztásról

EREDMÉNYEK

Tanulmányunkban 30 esetben fordult elő atípusos femurtörés, ami 1.8% az összes femurtöréshez viszonyítva. A nemek szerinti eloszlás tekintetében 24 nő és 6 férfi volt. Az átlagéletkor 77±7.5 év, férfiak esetében 71±2 év, míg nők esetében 78±2.5 év. Hét esetben gyógyszeresen kezelt hypothyreosis, 3 esetben hosszantartó szteroid terápia (>5év), 2 esetben II. típusú diabétesz, 1 esetben daganatos megbetegedés és 3 esetben rheumatoid arthritis szerepelt az anamnézisben (*II. táblázat*).

A II. csoportnál hosszabb törésgyógyulási időt (7 ± 4.9 hónap) észleltünk az I. csoporttal (5.8 ± 4.6 hónap, p = 0.24) szemben. Elhúzódó törésgyógyulást (> 6 hónap) 17 esetben észleltünk (57%), amelyek közül 11 esetben igazolódott BP használat (64%) (*III–IV. táblázatok*).

A IIb csoportnál a törésgyógyulás hossza (9.1±5.1 hónap) szignifikánsan meghaladta a IIa csoportét (5.6±3.4 hónap, p = 0.03). Elhúzódó törésgyógyulás a IIb csoportban 6 esetben, míg a IIa csoportban 3 esetben fordult elő (p = 0.19).

A 6 esetben létrejött bilateralis törés esetén 5 beteg alkalmazott BP-t és tartozott a II. csoporthoz (p = 0.26). A kétoldali törésmegjelenés szempontjából szignifikáns különbséget a IIa és IIb csoport között nem észleltünk (p = 0.38) (*IV. táblázat*).

Biszfoszfonát alkalmazását 17 betegnél regisztráltunk (57%), és 9 esetben (52%) ez 5 évnél hosszabb ideig tartott. Az átlagos biszfoszfonát használat 4.8±5.7 év volt. A biszfoszfonáton kívül gyógyszeresen kezelt pajzsmirigy betegség (n=7), II. típusú cukorbetegség (n=2), daganatos elváltozás (n=1), rheumatoid artritisz (n=3) és hosszú távú szteroid kezelést (n=3) regisztráltunk, amelyekkel az atípusos törések kapcsolatba hozhatóak (*II. táblázat*).

Jobb oldali femurtörés 18, bal oldali 12 esetben fordult elő. Az ellenoldali femurról 13 esetben (43%) készült röntgenfelvétel, amelyek közül 11 esetben igazolódott a minor kritériumoknak megfelelő elváltozás (*III. táblázat*). A törés elhelyezkedése alapján 22 esetben (73%) a diaphysis középső területe és 8 esetben (27%) a subtrochanter régió volt érintett (*2. ábra*). Az ellenoldali törés létrejötte és a primer törés között átlagosan 22.3±8.1 hónap telt el. Hat esetben atípusos periprotetikus (Vancouver B1 típusú) törés következett be, a csípőprotézis szára alatt. Minden betegnél legalább 4 major kritérium teljesült az atípusos törés definíciójának megfelelően.

Implantátum választás szempontjából 16 esetben (53%) Stryker® Gamma3 velőűrszegezés (*3. ábra*), 4 esetben (13%) Synthes® LFN (2 esetben recon csavarral), 4 esetben (13%) hagyományos Küntscher velőűrszegezés történt, ebből 3 esetben későbbi szövődményként combnyaktörés jött létre. Lemezes osteosynthesis (LCP) 6 esetben, a periprotetikus törések ellátása során történt. Négy alkalommal a protézis szár mellé kiegészítő rögzítésként 2 attachment került felhelyezésre. Öt esetben történt reoperáció (3 stress shielding miatti combnyaktörés, egy velőűrszeg mellett létrejött hypertrophiás álízület miatt, amely során a femur lateralis felszínére addicionális LCP felhelyezés történt (*4–6. ábrák*), illetve egy esetben csavarlazulás és lemez kiszakadás miatt). Egy esetben szeptikus szövődmény alakult ki. Egy betegnél pedig megelőző velőűrszegezést végeztünk a fenyegető törésveszély miatt, ahol a primer törés során készült ellenoldali röntgenfelvételen felismert jelentős perioszteális megvastagodás és „kacsacsőr” jelenség volt észlelhető. Ennél a betegnél a röntgenképeken kívül pár hónapja megjelenő combfájdalom is jelen volt az anamnézisben.

2. ábra
76 éves nőbeteg atípusos törése, 10 éven át alkalmazott BP-t

3. ábra
Posztoperatív röntgenfelvétel – Stryker ® – Gamma 3 System

4. ábra
Nyolc hónappal a műtétet követően, elhúzódó törésgyógyulás. Dinamizálás megtörtént

5. ábra
15 hónapos kontroll. A dinamizáció nem hozta meg a várt eredményt. A csont lateralis felszínére LCP felhelyezése történt a stabilitás fokozása céljából.

6. ábra
20 hónappal a sérülést követően teljes a csontátépülés

II. táblázat
A betegek demográfiai és krónikus betegségeinek adatai az atípusos femurtörések esetében

Betegek demográfiai adatai	Betegszám (N=30)
Átlagéletkor	77±7.5 év
Nem (férfi/nő)	6/24
Krónikus betegségek	
Diabétesz	2 (7 %)
Rheumatoid arthritis	3 (10 %)
Pajzsmirigy betegség	7 (23 %)
Daganatos betegség	1 (3 %)
Biszfoszfonát használat	17 (57 %)
Szteroid használat	3 (10%)

III. táblázat
A törések elhelyezkedése és karakterisztikája, valamint a választott rögzítések módja

Töréstípus és karakterisztika	Femur diaphysis	22 (73%)
	Subtrochanter	8 (27%)
	Ellenoldali röntgenfelvételek száma	13 (43%)
	Ellenoldali röntgenfelvételen észlelhető indirekt jelek esetszámai	11 (85%)
	Törésgyógyulási idő rizikófaktorok megléte esetén	7.1 ± 4.8 hó.
	Törésgyógyulási idő rizikófaktorok megléte nélkül	4.4 ± 2.3 hó.
	Elhúzódó törésgyógyulás esetszámai	17 (57%)
	Kétoldali törésmegjelenés	6 (20%)
	Időintervallum a primer és az ellenoldali törés létrejötte között bilaterális esetekben	22.3 ± 8.1 hó.
	Periprotetikus törések	6 (20%)
Operatív töréskezelés eszközei	Stryker® Gamma 3 system	16 (53%)
	Syntes® Lateral Femoral Nail	4 (13%)
	Küntscher szeg	4 (13%)
	Locking Compression Plate	6 (20%)

IV. táblázat
Elhúzódó törésgyógyulások és bilateralis törések előfordulása

	I. csoport (BP terápia nélkül) n=13	II. csoport (BP terápia mellett) n=17	P-érték
Törésgyógyulás (hónapok)	5.8 ± 4.6	7.0 ± 4.9	0.24
Elhúzódó törésgyógyulás (n=17)	8	9	0.13
Kétoldali törésmegjelenés (n=6)	1	5	0.26
	IIa csoport (<5 év BP) n=8	IIb csoport (<5 év BP) n=9	P-érték
Törésgyógyulás (hónapok)	5.6 ± 3.4	9.1 ± 5.1	0.03
Elhúzódó törésgyógyulás (n=9)	3	6	0.19
Kétoldali törésmegjelenés (n=5)	2	3	0.38

MEGBESZÉLÉS

Az elmúlt évtizedben megjelent tanulmányok alapján elmondható, hogy az atípusos törések esetén elhúzódó törésgyógyulás és bilaterális előfordulás jöhet létre (6, 7).

Tanulmányunkban megfigyelhető, hogy nők esetén gyakoribb az atípusos törés (12). Ennek oka, hogy gyakrabban részesülnek posztmenopauzális osteoporosis miatt biszfoszfonát kezelésben vagy egyéb okból szteroid terápiában, így esetükben többszörösen érvényesül a csontremodelláció gátlás (16).

Egy nemrégiben megjelent metaanalízis szerint az átlagos törésgyógyulás ideje BP-ot szedő betegek esetében 8.5 hónap volt és a törések egyharmada esetében fordult elő elhúzódó törésgyógyulás vagy álízület képződés (26).

Eredményeink alapján elmondható, hogy a BP kezelésben részesült betegeknél a csontremodelláció szenvedett zavart, ami elhúzódó törésgyógyulást okozott.

Egy tanulmányban, ahol a bilateralis atípusos töréseket vizsgálták, a primer atípusos femurtörés kialakulása után egy éven belül következett be az ellenoldali törés (15). Tanulmányunkban a bilateralis törések túlnyomóan a II. csoportnál jelentkeztek és az ellenoldali törés létrejötte, valamint a primer törés között átlagosan 22.3±8.1 hónap telt el. Statisztikailag szignifikáns eltérések azonban a csoportok között ezen szempont alapján nem voltak (IV. táblázat). A radiológiai elváltozások legtöbbször kétoldali megjelenésűek, a lateralis femurcortex megvastagszik, mikrofrakturák láthatók (1). Azoknál a betegeknél, akik esetében ellenoldali femurfelvétel is készült, lokális periostealis és endostealis megvastagodást észleltünk az esetek 85 %-ban (III. táblázat). Az atípusos femurtörések esetén ezért javasolt az ellenoldali femurról is röntgenfelvételt készíteni, mert előfordulhat cortex megvastagodás és mikrofractura, amely utalhat egy lehetséges jövőbeni törés bekövetkeztére (3, 19). Ismert, hogy hónapokkal az atípusos törés bekövetkezte előtt időszakos combfájdalom jelentkezhet, így a fizikális vizsgálat és a részletes anamnézis felvétel nélkülözhetetlen része a diagnózis felállításának (17).

Természetesen voltak átfedések a BP használat és a krónikus betegségek megléte között, amelyeket nem részleteztünk a kis esetszám miatt. A 30 beteg közül 5 esetben nem igazolódott olyan krónikus betegség, gyógyszerhasználat, vagy egyéb hajlamosító tényező, amely szerepet játszhatott volna az atípusos törésmintázat kialakulásában. Ennél a csoportnál az átlagos törésgyógyulás időtartama 4.4±2.3 hónap, amely az átlag törésgyógyulási időhöz képest jóval kevesebb (7.1±4.8). Az 5 beteg közül egy esetben fordult elő elhúzódó törésgyógyulás (> 6 hónap). Ezen 5 beteg esetében létrejött AFT hátterében genetikai eltérés vagy egyéni hajlam, csontanyagcsere zavar, esetleg femur geometriai eltérés játszhatott szerepet, amely a szakirodalom által is leírt (2, 5, 22).

Az atípusos törések definíciója alapján a periprotetikus törés kizáró tényező, amelynek oka az ASBMR által kiadott 2014-es második jelentésében sincs egyértelműen megfogalmazva (21). Tanulmányunkban 6 esetben észleltünk periprotetikus törést atípusos radiológiai mintázattal. Az utóbbi időben egyre több tanulmány jelent meg, amelyekben a periprotetikus törések atípusos formája került közlésre (8, 9, 13). Az atípusos periprotetikus törések rizikótényezői hasonlóak az egyszerű atípusos törések rizikóival (pl. hosszútávú BP és szteoridterápia, stb.), hiszen ugyanaz a mechanizmus okozza a csontanyagcserezavart és hajlamosít a törés kialakulására.

Tanulmányunk hátránya a retrospektív jelleg és a relatív alacsony esetszám, így bizonyos statisztikai következtetések, még ha logikusak is és a szakirodalom is alátámasztja, mégsem szignifikánsak.

Az elhúzódó törésgyógyulás és az álízület létrejötte jelentősen befolyásolja a beteg funkcionális rehabilitációját. Elhúzódó törésgyógyulás esetén támogatni kell a csontgyógyulást, így gyógyszeres és biológiai augmentációra is szükség van. A legjobb biológiai augmentációt a csont graft beültetés jelenti, ami viszont újabb műtétet jelent a beteg számára. A gyógyszeres terápia a parathyroid hormon (PTH) alkalmazását jelenti, valamint a biszfoszfonát szedésének azonnali felfüggesztését, illetve Ca- és D-vitamin szupplementációt (17).

A hagyományos Küntscher velőűrszegezés (n=4) során tanulmányunkban 3 esetben késői szövődményként combnyaktörés jött létre. Ez igazolja, hogy a patológiás femurtörések esetében (úgy, mint az atípusos femurtörés is) a teljes szegmentum cephalomedullaris szeggel való rögzítése ajánlott (21).

Ellenoldali femuron látható radiológiai jelek felismerése (perioszteális megvastagodás, kacsacsőr jelenség, stb.) és időszakos combfájdalom esetén a szakirodalom javasolja a profilaktikus velőűrszegezést (14). Véleményünk szerint is ajánlatos a radiológiai jelek és a figyelmeztető anamnézis esetében elvégezni a profilaktikus velőűrszegezést. Amennyiben nem látható röntgenfelvételen eltérés, CT felvétel elvégzése javasolt, illetve a beteg szoros utánkövetése.

Következtetésként elmondható, hogy a hosszú távú BP terápia (>5 év) fokozott rizikót jelent az atípusos törés kialakulásában, elhúzódó törésgyógyulást okoz, illetve jelentősen megnöveli a bilaterális törések előfordulását. A hosszú távú BP terápiában részesülő atípusos törésen átesett betegek esetében az antiresorptív terápiát fel kell függeszteni, és a törésgyógyulást gyógyszeresen szükséges támogatni, megfelelő kalcium és D vitamin szupplementációval. A prodromális, alarmírozó combfájdalomra, valamint a bilateralis törés megjelenésére fokozott figyelmet kell fordítani a betegek szoros utánkövetésével.

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