

Features of atypical femoral fractures in a clinical setting

Summary of PhD Thesis

Dávid Dózsai MD

Supervisor:

Ákos Csonka MD, PhD, Habil.

**Department of Traumatology
Albert Szent-Györgyi Medical School
University of Szeged**

**Doctoral School of Interdisciplinary Medicine
University of Szeged**



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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 biszfoszfónát terápiával]: Magyar Traumatológia Ortopédia Kézsebészet Plasztikai Sebészet 64: 1-4 pp. 49-58, 9p (2021) [IF: -, 2021]

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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, 2019]

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Summary

Background and purpose: Atypical femoral fractures are rare stress fractures with still unknown certain causes. In this work, the first part of the research (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. The second part of the research (Research 2) sought to prove that AFFs could occur in a periprosthetic form, which is officially excluded from the definition of AFFs.

Experimental approaches: In Researches 1 and 2, 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 Research 2, 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. Atypical femoral fracture case definition and epidemiology

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. The first AFFs were described in 2005, followed by two case series in 2007 and 2008. In 2014, the AFF criteria were revised with more information on the epidemiology and morphology of the fractures. The most recognizable radiographic characteristic of AFF is the transverse fracture line and the lateral cortex thickening of the femur (beaking). AFFs most commonly occur in the subtrochanteric and shaft regions of the femur. The case definition requires at least four out of the five major features. 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. The second ASBMR Task Force report shows that AFF incidence is between 50 to 130 cases per 100,000 patients per year. 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.

1.2. Overview of the potential risk factors of atypical femoral fractures

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. 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. The following potential risk factors can lead to an atypical femoral fracture:

Age: Patients who develop AFFs are somewhat younger than those who suffer non-AFFs. The risk of AFFs increases with age in BP treated patients.

Race: The risk of AFFs is higher in the Asian population compared to the European one. 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.

Rheumatoid arthritis (RA): In RA treatment, large doses of glucocorticoids (GC) are used, which can be an explanation of low bone turnover and developing AFFs. Currently, there is no significant evidence that rheumatoid arthritis is a potential risk factor for developing AFFs.

Diabetes mellitus: Diabetes mellitus (DM - types I and II) is associated with an increased risk of fragility fractures by lowering bone turnover. Studies until this time suggest that DM is not a risk factor for developing AFFs.

Genetic mutations: Some mutations impair enzyme function in three components of the mevalonate pathway (MVD, GGPS1, and CYP1A1), which is targeted by BPs to inhibit bone resorption. Further studies are needed to clear the prevalence of these mutations and the connection of developing AFFs.

Glucocorticoid use and proton pump inhibitors: Glucocorticoid use and its association with AFF have been shown in several studies, but some have proved otherwise. Patients who are on high doses of GC are more likely to be using BPs. Not considering these two factors separately will lead to the failure to address this potential confounding. There are not enough data available on this matter to disentangle this relationship, and further controlled studies are needed to correctly address this question.

Bisphosphonate therapy: The epidemiological evidence for 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. BPs inhibit osteoclast resorption of the bone and impair the remodeling of the structure, which makes the bone “stiffer” thus leading to stress fractures. Despite the overwhelming good results with benefit/risk ratio on BP use, there has been a decline in the number of drug prescriptions in the United States and Europe as well, which is mainly in connection with AFF cases and reports. Despite all these, antiosteoporotic medication use remains uncertain and controversial about the relationship between BP therapy duration and the risk of developing AFFs.

Generalized cortical thickness and femur bone geometry: The literature reports that there is no significant difference between 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 femur with greater lateral curvature (bowing) would be predicted to experience greater tensile stresses than a femur of similar size. In the literature, there is a growing number of studies that support the association between femoral geometry (greater femoral bowing and varus alignment)

and AFFs. Also, it has been reported that patients with AFFs have more varus hip geometry and narrower femoral neck compared to that of normal femoral fracture cases.

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. In case of AFFs, relatively longer (seven to nine months) bone union is recorded.

Regarding bilateral fractures, the likelihood to be diagnosed with a contralateral AFF is high within the first year of fracture presentation. Moreover, minor signs are present on the contralateral side at the time of the first fracture.

1.4. Atypical periprosthetic femoral fractures

Periprosthetic femoral fractures are severe and technically demanding complications and are responsible for one third of revision surgeries with a 0.1–2.1% incidence. 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. 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. 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.

2. Goals of the thesis

2.1. Gaps in our current knowledge

Until this date, the exact risk factors of AFFs 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. In the ageing population with more osteoporotic fractures, BPs are widely prescribed as an anti-osteoporotic drug, thus potentially rising the number of AFFs. 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.

2.2. Main focuses of the research

In Research 1, we gathered data to identify potential risk factors for AFFs. AFFs have been described with longer bone unions and non-unions. On this ground, we tried to find a link between BP use and delayed unions. Also, the incidence of bilateral fractures is described as a serious complication, but their risk factors are not clearly identified. In Research 2, 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 have not been clearly defined yet.

2.2.1. Specific aims of present work

2.2.2. Research 1 – Aims 1 and 2 of the thesis

The main aims were to identify the potential risk factors for developing atypical femoral fractures, and also to examine the effect of BP therapy on delayed bone union and bilateral fractures.

The research questions were the following:

- Is BP therapy the most significant risk factor for developing AFFs?
- How does long-term BP (> 5 years) therapy influence the incidence of atypical fractures?
- Does the long-term (> 5 years) use of BPs increases the duration of bone union and bilateral fracture incidence?

Our hypotheses were that:

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

2.2.3. Research 2 – Aim 3 of the thesis

In this part of our work, the goal was to analyze the prevalence of atypical periprosthetic fractures falling into the class of Vancouver type B1 fractures and their potential risk factors.

Our hypothesis was that:

- 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. Research 1

3.1.1. *Study design, methods, and assessment of patients – Aims 1 and 2 of the thesis*

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 01, 2012 and December 31, 2020. A total number of 4190 patients were enrolled by specific (ICD-10) coding. We searched for subtrochanteric (S72.20) and diaphyseal femoral fractures (S72.30), and these patients were enrolled in the study. After this, 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) and established a consensus that there were 74 (1.7%) atypical femoral fractures. The inclusion criterion was that patients having sustained low-energy trauma, and the exclusion criteria were having a polytrauma, being younger than 50 years of age, and having incomplete medical records. A control group of 143 patients were reviewed with the same inclusion and exclusion criteria as mentioned above with a fracture type of subtrochanteric, diaphyseal, and pertrochanteric femoral fractures labeled as “fragility” fractures.

In the AFF group, the patients were also divided by their BP therapy history into two groups: 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 and Group 2b: > 5 years of BP).

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. 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 or bilateral fractures) were analyzed.

Delayed bone union was noted if the union exceeded six months. Our criteria for bone union were as follows: complete cortical bridging (three out of four) and a fracture line either barely visible or undetectable. No bone union scores were calculated. 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 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 by the duration of union, delayed bone union cases, and bilateral fracture occurrence.

3.2. Research 2

3.2.1. Study design, methods and assessment of patients – Aim 3 of the thesis

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. The inclusion criteria were to be over 50 years and have had a low energy trauma.

Patients were excluded if they were polytraumatized, had incomplete medical records, and sustained a Vancouver type A, B2, B3, or C fracture. Out of 109 patients, 41 patients had Vancouver type B1 periprosthetic fracture.

In order to establish the diagnosis of atypical femoral fractures, we used the revised criteria of the American Bone and Mineral Research Taskforce. Three orthopedic surgeons retrospectively and independently examined X-rays and came to the same consensus that there were five (13%) atypical femoral fractures.

First of all, regarding patient data, 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 were taken into account. 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.

3.3. Statistical analysis

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 the multivariate logistic regression model. 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.).

4. Results

4.1. Research 1

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 years (8 males and 66 females, age range: 51 to 94 years) versus the control group 74.3 ± 11.8 years (35 males and 108 females, age 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 the femoral fractures. Various types of statistical methods were performed to assess the risk factors of AFFs, which showed that the most significant risk factor was BP use together with osteoporosis and hypertension. Multivariate analysis revealed (forward likelihood ratio model) that the most important risk factors for the 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).

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 ($p < 0.001$). In the AFF group, 26 patients received BP for longer than 5 years. In 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. The

postoperative osteoporosis medical treatment protocol which we followed was to discontinue BP therapy for at least one year.

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, $p = 0.003$). The most common AFF fracture location was the shaft region. No contralateral radiograms were 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 located later. 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 in the AFF group, and in 13 cases in the control group. Among them, as a late complication, femoral neck fractures occurred in 5 cases.

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, $p = 0.02$). The number of cases with delayed bone union was also significantly higher in Group 2 ($n = 34$) versus Group 1 ($n = 16$) ($p = 0.01$). 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 ($p = 0.307$). The highest number of bilateral cases was in Group 2b ($n = 10$, $p = 0.307$). In our study, in 19 cases of bilateral fractures, the contralateral fracture occurred over a one-year period, and bilateral fractures occurred mostly in BP users (Group 2), although there were no statistically significant differences. 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.

4.2. Research 2 – Aim 3 of the thesis

The mean age of patients with typical PFFs was 79.5 ± 1.6 years (range: 54–94 years), compared to 80 ± 3.3 years (range: 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 ($p=0.26$). 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. TPF 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. TPF group – 4 ± 0.7 , $p=0.01$) in the development of AFF in our univariate analysis. After this, we performed a multivariate logistic regression model in the 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, the R squared value was 0.43.

5. Discussion and conclusions

In this work, Research 1 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). Research 2 (Aim 3 of the thesis) sought to prove that AFFs can occur in periprosthetic form, which is officially excluded from the definition of AFFs. 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 the administration of BPs and other anti-osteoporotic medications, but they can occur independently as well.

In our studies, 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 data are not statistically significant. There were some overlaps between BP use and chronic diseases, which both can cause AFFs. These cases cannot be distinguished due to the small case numbers and the complicated study design.

In conclusion, in Research 1, BP use was found to be 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 to 5-year use.

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 on the drug type in low-fracture

risk patients. In the past few years, new research has emerged on the use of teriparatide medication in case of osteoporotic fractures, which provides 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. 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.

In Research 2, 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. 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.

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 case of bone loss.

The medical management of atypical fractures poses a big challenge to surgeons, 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. Nevertheless, our results indicate that clinicians should consider the possibility of an 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 patient are crucial for the correct patient treatment.

5.1. New findings according to our hypotheses

- 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 also 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. 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. It is important to develop public health efforts to educate patients and physicians (mainly family physicians) on the correct BP use and to dissolve their concerns towards it.
- We do not have complete evidence about the risk factors of 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.
- 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.
- 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.
- 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.

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