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Surgical and Pharmacological Management of Periprosthetic Atypical Femoral Fractures: A Narrative Literature Review

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Abstract

Introduction: An increasing number of patients is annually undergoing total hip arthroplasty (THA), and a significant proportion of these patients are elderly and consequently at a higher risk of complications because of age, osteoporosis, and medical comorbidities. Periprosthetic femoral fractures (PFFs) are one of the worst complications of THA associated with high rates of unfavorable prognosis. Besides, in the last decade, a new independent disease entity called "atypical femoral fracture" (AFF) has been identified and defined by the American Society for Bone and Mineral Research (ASBMR) task force. Some PFFs present clinical history and radiographic aspect consistent with an AFF, meeting the ASBMR criteria for the diagnosis of AFF except that PFFs by themselves are an exclusion criterion for AFF. However, there is an increasing number of published studies suggesting that periprosthetic atypical femoral fractures (PAFFs) exist and should not be excluded by definition. **Significance:** Nowadays, although there is an increasing interest in PAFFs, there are still very few studies published on the topic and a lack of consensus regarding their treatment. This narrative literature review aims to introduce this new emerging topic to a wider readership describing the characteristics of PAFFs and the state-of-the-art in their management. **Conclusions:** Many authors agree that PAFFs should be considered as a subgroup of PFFs that have atypical characteristics; they also show a significant correlation with prolonged bisphosphonate use. A correct diagnosis is paramount for proper treatment of the disease that requires both surgical and medical actions to be taken.

Keywords

PAFF, Teriparatide, AFF, insufficiency fracture, incomplete fracture

Introduction

In the last decade, a new independent disease entity called "atypical femoral fracture" (AFF) has been identified. AFFs are burdened by a high rate of complications such as delayed union, nonunion, and implant failure,[1-6] thus since their first description in 2005,[7] a considerable effort has been made to define epidemiology, pathogenesis, and correct management of this new nosological entity.[3,8] In 2010, the American Society for Bone and Mineral Research (ASBMR) defined specific diagnostic criteria for

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the correct identification of AFF,[9] and updated them in 2014 revising several features to be more specific for qualities that distinguish these fractures from "typical" low-trauma fragility fractures (Table 1).[3] To satisfy the definition of AFF, the fracture must be located along the femoral shaft, in the region just distal to the lesser trochanter down to the supracondylar flare. In addition, at least 4 of 5 major features must be present, while none of the minor features is mandatory but have sometimes been associated with AFFs. The diagnosis specifically excludes fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathological fractures associated with primary or metastatic bone tumors and miscellaneous bone disease (such as Paget's disease, fibrous dysplasia), and periprosthetic femoral fractures (PFFs). Major features include association with no or minimal trauma, origin of the fracture line at the lateral cortex with substantially transverse orientation which may become oblique as it progresses medially across the shaft, lack of comminution or minimally comminuted fracture, localized periosteal or endosteal thickening of the lateral cortex at fracture site that may appear as cortical "beaking" or "flaring" adjacent to a transverse fracture line.[10,11] Complete fractures extend through both cortices and may be associated with a medial spike, while incomplete fractures involve only the lateral cortex.[3] Minor features include generalized increase in cortical thickness of the femoral diaphysis, presence of unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh,[12,13] bilateral incomplete or complete fractures of the femoral shaft, and delayed fracture healing. Finally, the features associating AFFs with comorbidities and medication exposure, including bisphosphonates (BPs) and glucocorticoids (GCs), were removed because it was considered more appropriate for further studies to seek these association, rather than including them in the case definition.[3]

However, AFFs appear to be linked to a long-term use of BPs,[3,14,15] since these drugs can create a brittle hypermineralized bone that can suffer from low-impact stress.[16] BPs have been known to have favorable effects on the skeletal system such as a decreasing risk of fragility fracture. They act by promoting osteoclast apoptosis with the result of a reduction of bone resorption and turnover, and an increase in the overall bone mineral density and strength. A prolonged BPs use has been related to the suppression of bone turnover with an increment in micro-impairment, a reduction in bone healing capacity and an overall worse bone quality.[16] Probably, the long-term inhibition of bone turnover results in a frozen bone unable to repair the microcracks that may arise in the

Table 1. ASBMR Task Force criteria to define an AFF.

ASBMR Task Force Criteria to Define an AFF
Mandatory criterion
— Fracture must be located along the femoral diaphysis between the lesser trochanter and the supracondylar flare
Major criteria (4 out of 5 must be present)
— The fracture is associated with no or minimal trauma
The fracture line originates at the lateral cortex and it is substantially transverse or short oblique
An incomplete fracture involves only the lateral cortex, while complete fracture extends through both cortices and may be associated with a medial spike
The fracture is noncomminuted or minimally comminuted
Presence of localized periosteal or endosteal thickening ("beaking" or "flaring") of the lateral cortex at fracture site
Minor criteria (not necessary, sometimes associated with AFFs)
— Generalized increase in cortical thickness of the femoral diaphysis
Unilateral or bilateral prodromal symptoms (dull or aching pain in the groin or thigh)
Bilateral incomplete or complete femoral diaphyseal fractures
Delayed healing of the fracture
Exclusion criteria
— Fracture of the femoral head and neck
Intertrochanteric fracture with spiral subtrochanteric extension
Periprosthetic femoral fractures[a]
Pathological fractures associated with primary or metastatic bone tumors and with miscellaneous bone diseases (Paget's disease, fibrous dysplasia)
Removed minor criteria with 2014 revision
— Some diseases: hypovitaminosis D, autoimmune diseases (such as RA), endocrinologic diseases (such as hypoparathyroidism)[a]
Assumption of some drugs (BPs, GCs, proton-pump inhibitors)[b]

[a]evidence now exists that PAFFs can occur.
[b]some evidence exists that they are at least a risk factor for AFFs.

femoral shaft and could evolve in both incomplete and complete AFF.[3,8,13,17] And, in fact, AFFs are often the result of low-energy trauma but they have also been reported as spontaneous fractures.

Definition

An increasing number of patients are annually undergoing total hip arthroplasty (THA), and a significant proportion of these patients are elderly and consequently at a higher risk of complications because of age, osteoporosis, and comorbidities. PFFs are one of the worst complications of THA associated with high rates of unfavorable prognosis. Some PFFs present clinical history and radiographic aspect consistent with an AFF, entirely meeting the criteria for AFF except that PFFs by themselves are excluded from the diagnosis of AFF. However, there are a number of published studies suggesting that periprosthetic atypical femoral fractures (PAFFs) can occur and should not be excluded by definition.[18-42] Subsequently, PAFFs could be considered as a subset of PFFs that present AFFs' features.[21,36] Unfortunately, the lack of data available on this topic does not allow the development of precise diagnostic criteria to identify PAFFs in order to avoid misdiagnosis.

Epidemiology

The prevalence of PAFFs in patients with hip and knee arthroplasties is currently poorly understood compared to that of typical osteoporotic hip fractures, mainly because diagnostic coding cannot distinguish between typical and atypical patterns and radiographs are required to identify features of atypia.

Fractures of the femoral shaft occur in a small fraction of osteoporotic patients and even a smaller fraction is atypical. Fractures of the femoral neck and the intertrochanteric region, of the subtrochanteric and diaphyseal regions account for 91, 3, and 3% of all femoral fragility fractures, respectively.[43] The association between AFFs and long-term use of BPs is complex and slightly controversial since a greater risk is associated with longer duration of treatment and a declining risk after cessation of treatment. However, AFFs have also been observed in patients who were never exposed to antiresorptive agents.[43] When it comes to PAFFs, the topic is even more complex. Other than case reports[18,20,22,25-31,37,38,44] and case series,[19,23,32,41] there are only 6 studies present in literature looking for PAFFs to date,[21,24,36,39,40,45,46] with a reported prevalence between 5.1%[40] and 13%.[24] Our group recently confirmed the existence of PAFFs and found a prevalence of 5.3% for Vancouver type B1 and C PFFs and 3.5% for all surgically treated PFFs.[46]

Classification

The Vancouver classification[47,48] represents the current standard for assessing and reporting PFFs, and therefore can be applied to PAFFs. It considers the location of the fracture, the stability of the implant and eventually associated bone loss. However, it is necessary to make some adjustments to the classification to allow its use even for PAFFs as well.

Among the small number of studies looking for PAFFs, any Author decided to include (or exclude) a certain type of PFFs. Apophyseal (Vancouver Type A) PFFs are excluded "by definition" from being PAFFs, not being at the required level. Vancouver type B1 PFFs are fractures around a stable stem or just below it and were consensually looked for atypical pattern by all Authors. Vancouver type B2 PFFs present a loose stem and there is no consensus among the Authors on their inclusion in the studies. Mondanelli et al.[46] asserted that either the stem is already loose before the fracture or if it loosens with the fracture, the pattern would be such as not to be considered atypical. On the other hand, Leclerc et al.,[21] Schaeffer et al.,[22] and Moya-Angeler et al.[30] considered some B2 cases as PAFFs when meeting the inclusion criteria for AFFs. Vancouver B3 PFFs present a deficient bone stock and eventually a loose stem; type B3 PAFFs are not reported in literature. Fractures clear of the implant (Vancouver type C PFFs) can have radiological characteristic of AFFs and they were consensually examined by all Authors.

Clinical Presentation and Diagnosis

Adequate collection of anamnestic data and physical examination is crucial to diagnose an AFFs, as well as PAFFs, especially in cases of incomplete fractures. It is imperative to investigate the patients' history with special attention to prior and current medications, mechanism of injury and possible occurrence of prodromal symptoms. Most patients received long-term BPs therapy, typically for more than 3 years.[3] PAFFs usually occur spontaneously or result from a low-energy trauma, defined as a fall from a standing height or less,[3,12] and could be anticipated by prodromal symptoms such as mild thigh pain or groin pain, discomfort on weight bearing or related to daily activities and relief with rest.[21,36] Moreover, it is advisable to exclude infection as a possible cause of thigh pain through blood tests including white cell count and inflammatory markers (C-reactive protein and erythrocyte sedimentation rate).[36,48,49]

Various imaging modalities are available to diagnose AFFs as well as PAFFs. The natural history of AFFs suggests that they evolve over time. Plain radiographs of the entire femur in anteroposterior and lateral views are usually able to detect the fracture and show radiological signs compatible with an impending or a stress fracture, such as a transverse radiolucent line on a hypertrophic lateral cortex with endosteal or periosteal reaction ("beaking"),[50] or with a transverse fracture which appears as cortical lucency.[3] Nevertheless, especially incomplete fractures need to be investigated using second-line modalities such as computed tomography (CT) scan, magnetic resonance imaging (MRI) and bone scintigraphy (BS).[19] MRI is highly sensitive in assessing areas of cortical thickening and eventually reveals bone edema around the fracture. A CT scan may demonstrate cortical fracture or lucency and bone formation. BS has high sensitivity but low specificity and can identify incomplete and radiographically occult AFFs.[30]

Complete and incomplete AFFs affect the contralateral femur in 28% of cases.[3] Thus, if a PAFFs is observed, an adequate radiographical study of the entire contralateral femur is advisable even if prodromal pain is absent to guarantee early detection and treatment of an eventual fracture.[3,8]

Pathogenesis

The exact pathogenesis of these "atypical" fractures (AFFs and PAFFs) remains unclear, although several mechanism have been proposed.[3,51,52] Some authors proposed that AFFs represent a form of osteoporotic fracture,[53,54] but there are several radiological and clinical features that greatly differ between these 2 entities and suggest a distinct pathogenesis. The distinctive features include a slow progression during a variable period of time, detected both radiographically (localized cortical proliferation that may evolve into a frank fracture and bilateral onset) and clinically (occurrence of worsening prodromal pain). These pathognomonic manifestations, along with delayed fracture healing, resemble stress fractures and support the hypothesis of an intrinsic bone deficiency over local stresses.[3,8] Fractures with similar features to AFFs have been described in patients with other bone disease including osteopetrosis,[55-58] pycnodysostosis and hypophosphatasia, indeed.[57,58]

On this basis, research has been focused on 4 categories of investigation:

(1) similarities between lower limb stress fractures and AFFs;
(2) the effect of bone remodeling suppression on bone's material properties;
(3) the effect of remodeling suppression on healing of stress fractures;
(4) the relationship between hip and lower limb geometry and AFFs.

Stress and Insufficiency Fractures

Firstly, a definition of stress and insufficiency fracture is required. The term "stress fracture" implies excessive load on a healthy bone, whereas "insufficiency fracture" indicates normal load on a deficient bone. In both cases, bones subjected to repetitive loading that overcomes the body's healing power are at risk for developing a fracture. Since routinely subjected to higher loading than other skeletal sites, lower extremities are the most common site to develop stress or insufficiency fractures. Over time, fatigue damage develops within the bone cortex and accumulates in the form of microcracks which will further coalesce and may eventually grow to a critical-sized defect that provokes a frank fracture.[59] As it happens with stress or insufficiency fractures, AFFs' development during time has been demonstrated to be characterized by an initial presence of periosteal callus and the eventual appearance of a transverse cortical fracture leading up to overt fracture.[60,61] Therefore, AFFs can be considered as a stress or insufficiency fracture that evolve over time. Nevertheless, AFFs differ in some respects from exercise-induced femoral stress fractures. The latter usually starts on the medial cortex of the femur, tends to localize in the proximal one-third of the femoral diaphysis and results in a more oblique fracture surface than AFFs do.[62-64] On the contrary, AFFs initiate on the lateral cortex, can be found in the femoral shaft between the trochanteric region up to the supracondylar flare, and result in a transverse surface like a brittle material. This distinguishing location in the lateral cortex can be explained by the fact that the lateral cortex sustains higher levels of tensile stress due to bending which may precipitate the damage in this location especially in those patients with lower limb geometry that could trigger that effect (for example, a bowed femur).

Remodeling Suppression on Bone Material Properties

Recent studies[65,66] have investigated differences in bone tissue properties in subjects with femoral fractures of all types comparing subjects taking BPs and those who are BPs-naïve. Anyway, no study leads to conclusive evidence that the mechanical and physical properties of bone are negatively affected by long-term therapy with BPs.

Effects of Remodeling Suppression on Healing of Stress Fractures

An evolving stress fracture is initially stabilized by endosteal and periosteal bridging callus of the crack, followed by normal coupled bone remodeling processes. This allows intracortical remodeling to repair the crack before a full fracture occurs. BPs treatment seems not to diminish the development of both periosteal and endosteal surface callus in AFFs,[61,67,68] but as BPs suppress bone remodeling they could act by facilitating the accumulation and propagation of microcracks that may grow to a critical size and progress to a full fracture. This is possible because bone metabolism is "frozen" by the drug.[8] Moreover, since BPs localize at site of high bone turnover including fracture formation locations (which require repair, also) they may be the accelerating event that allows the damage to progress to a full fracture. Clinical data support this mechanism. It has been observed that the risk of AFF decline by 70% in the following year if BP treatment is removed.[43]

Lower Limb Geometry

The geometry of the entire lower limb could be considered as a risk factor that potentially contributes to altered stress on the lateral cortex of the femoral shaft that may predispose to development of an AFF, in combination with other damaging changes in the bone itself. In fact, the stresses that are experienced on the lateral aspect of the femoral cortex are partially determined by the geometry of the hip and proximal femur.[69] In addition, the bilateral incidence of AFFs and the similar fracture location[70] on the contralateral femur highlight the relationship between the axis of the lower limb and risk for AFF.

Treatment

A proper and early diagnosis of a PAFF could improve its outcome ensuring the earliness of an appropriate treatment. Their outcome is worse, and their management is more challenging than typical PFFs since it is burdened with higher rate of delayed healing, nonunion, and fixation

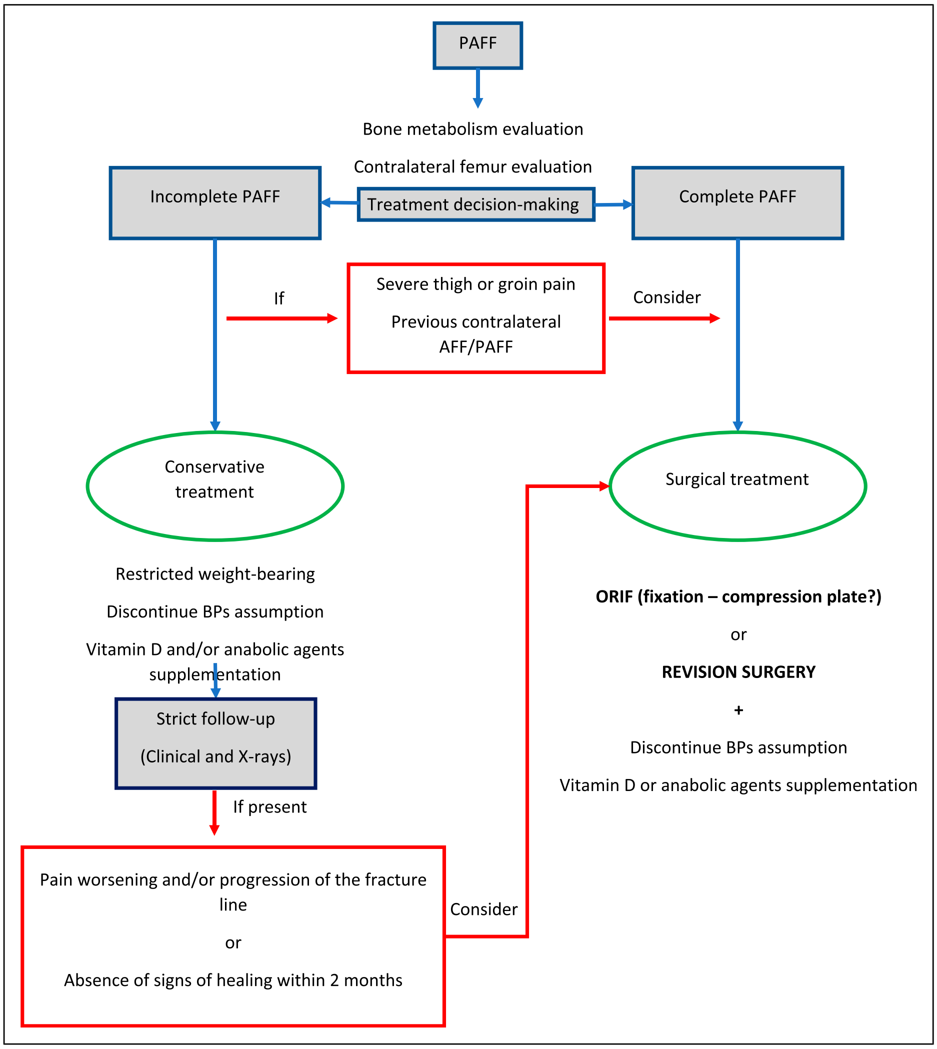

Figure 1. Algorithm of treatment for PAFFs.

Table 2. Suggested "short" panel for studying phosphocalcic metabolism. ALP: alkaline phosphatase, Ca: calcium, P: phosphorus, PTH: Parathyroid hormone, CTX: C-telopeptide of type I collagen, P1NP: aminoterminal pro-peptide of type I procollagen, 25 (OH)D: cholecalciferol (vitamin D3).

Suggested "Short" Panel for Phosphocalcic metabolism
ALP, U/L (range 55–142)
Ca, mg/dL (range 8.9–10.1)
P, mg/dL (range 2.5–4.5)
PTH, pg/mL (range 15–65)
CTX, ng/L (range 100–700, over 50 years)
P1NP, µg/L (range 15–75, over 50 years)
25(OH)D, ng/mL (range 30–100)
Creatinine, mg/dL (range .6–1.1)

Figure 2. A transverse radiolucency line is visible on the lateral cortex. This is an incomplete PAFF, that may eventually progress to complete.

failure.[36,71] However, there is lack of clear recommendation for the management of PAFFs.

Whenever identified, a PAFF should be approached in a multidisciplinary way: together with surgery, medical treatment is advisable. In addition, it is recommended to evaluate the contralateral femur which could frequently present early changes of impending fracture or an AFF and could be amenable to prophylactic surgery.[8]

Regardless of the radiographical pattern (complete or incomplete PAFF), medical management should be implemented. BPs should be discontinued,[72] and an alternative antiosteoporotic medical therapy should be considered.[73,74] Appropriate laboratory workup including calcium, 25-OH vitamin D, bone alkaline phosphatase and parathyroid hormone (PTH) levels should be obtained (Table 2). After surgery, treatment with calcium and vitamin D supplies and/or bone anabolic drugs such as Teriparatide should be initiated. It is thought that administration of Teriparatide is associated with an increase in osteoblast number and activity, which results in an increased bone remodeling rate and trabecular thickness and connectivity.[34,75,76] Vitamin D levels should be maintained above 30 ng/mL,[77] or whatever level is necessary to assure a normal PTH level as chronically elevated PTH will deplete bone stores.

From a surgical point of view, most PAFFs are amenable to fixation rather than to revision whilst remaining technically challenging. Long intramedullary nailing, which is the first-line surgical treatment for AFFs,[8] is not always possible due to the presence of the prosthetic stem. Their transverse or short oblique pattern (by definition) demands a construct that must be resistant to axial and rotational forces. A long-locked plate with or without cerclages and structural graft results to be the method of choice. The addition of a structural graft may provide both a mechanical and biological advantage, by granting the required construct stiffness and osteoconductive support for bone healing.[36,40]

Opting for surgical management of a PAFF depends on the radiographical pattern of the fracture, complete or incomplete (Figure 1). Potentially, incomplete PAFFs could be treated both conservatively and surgically. Conservative treatment consists in avoiding weight bearing, in addition to medical management. When conservative treatment is performed, the patient must be strictly monitored both clinically and radiographically: if signs of fracture progression, pain worsening or nonunion occur, prophylactic surgery should be performed. Surgery should even be considered if the patient shows one of the following characteristics: contralateral previous fracture, presence of an uncemented stem and severe symptoms.[33,36] Complete PAFFs should be treated surgically, paying attention to the high rotational instability of the fracture. In this case, the addition of a medial strut graft may enhance fixation stability and outcomes.[36]

In the clinical practice, different scenarios may occur:

Patient with Only Minimal Pain and Incidental Radiological Features. A discussion with the patient about the risk of impending fracture and eventually prophylactic plating must take place. Alternatively, the patient must be closely

Figure 3. A complete PAFF clear of the stem (Vancouver type C).

monitored. In both cases, BPs must be discontinued, and eventually anabolic therapy with Teriparatide must be started.[46,78,79]

Patient with Pain on Weight Bearing, but Normal Radiographs. Second-line radiological modality (MRI or BS) is needed to detect an early stress fracture. Protect weight bearing should be considered if pain is present. When a developing fracture is diagnosed, BPs should be discontinued, and alternative medical therapy should be administered. The risk of fracture shall be described to the patient and serious consideration should be given about a prophylactic fixation. If the patient decides upon nonoperative treatment, a strict radiograph and clinical monitoring is fundamental.[72,80]

Presence of an Incomplete Fracture. A transverse radiolucency line is visible on the lateral cortex (Figure 2). The patient should be counseled about the risk of fracture, and surgical prophylactic fixation should be examined. Question arises between the need for a bridging plate that can share tensile forces of the lateral cortex or if there is the need for transforming tensile forces into compressive ones with a compression plate. Both fixation methods can be obtained through a MIPO approach, with a reduce risk of infection with respect to an open approach. Another question is if there is the need to add some mechanical and biological support with a structural graft or not, in which case on open approach is required and more biological support can be indicated.[81] Anyway, such an aggressive approach is reserved, in our practice, to fractured PAFFs. BPs must be stopped and treatment with Teriparatide could be initiated. According to literature data, healing should be expected within 8 months when surgical and medical management are correctly performed.[36,82,83]

Complete PAFF. Surgery is obviously indicated (Figure 3). Immediate BPs should be suspended and Teriparatide started in the post-operative period, if there is no contraindication.[1,76,81,84] In our experience,[46] as a matter of fact, PAFFs occur around a stable stem. Surgical treatment can be MIPO, retrograde nailing a more aggressive surgical fixation or revision to a long stem, depending on different factors, and surgeon's preference.[81]

Conclusions

Orthopedic surgeons must consider PAFFs as a separate pathological entity, resembling AFFs more than PFFs. These fractures represent a rare event, whose real incidence has not yet been defined, and they show a significant correlation with prolonged BPs use. PAFFs can be burdened with high rate of complications such as fixation failure and nonunion. A correct and early diagnosis is mandatory for treatment implementation and to obtain better clinical outcomes. PAFFs are often misdiagnosed and the knowledge they exist will lead to their diagnosis. Moreover, it is plausible that with the increase in annually performed THAs and the expanding indication for BPs use, the number of PFFs and subsequently PAFFs would raise. There are still very few studies published on the topic, therefore, new scientific research is needed to deepen the topic.

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