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# Idiopathic Osteonecrosis and Atypical Femoral Fracture in Systemic Lupus Erythematosus

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Additional information is available at the end of the chapter

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## Abstract

Osteonecrosis and osteoporosis are frequent adverse effects of glucocorticoid therapy of systemic lupus erythematosus (SLE). Idiopathic osteonecrosis (ION) of the femoral head occurs in 3–40% of patients receiving glucocorticoid, and can also develop in other bones. Higher doses of glucocorticoid and steroid pulse therapy are considered to be risk factors for ION of the femoral head. To analyze these risk factors, it seems important to detect early changes in the femoral head by magnetic resonance imaging and to monitor early clinical events attributable to steroid therapy. Prophylaxis with statins and warfarin remains debatable. The use of glucocorticoid is increase the risk of bone fractures. Bisphosphonate (BP) is used for its prevention and treatment of osteoporosis. Atypical femoral fracture (AFF) has been recently recognized as a complication associated with BP use. AFF is considered to be a form of stress fracture; localized periosteal thickening of the lateral cortex is often present at the fracture site. The thickening has been recently recognized as a complication associated with the use of antiresorptive agents such as BP and denosumab. As long-term BP/glucocorticoid use is a risk factor for beaking in patients with SLE , temporary withdrawal of BP administration should be considered.

**Keywords:** systemic lupus erythematosus, glucocorticoid, osteonecrosis, bisphosphonate, atypical femoral fracture

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## 1. Introduction

Systemic lupus erythematosus (SLE) is a chronic, inflammatory, systemic autoimmune disease of unknown etiology characterized by production of antinuclear autoantibodies. It mainly affects young women and shows a broad spectrum of manifestations such as general fatigue, skin rash, fever, and arthritis and disorders involving the kidney, heart, and central nervous system. These organ involvements occur in patients with severer disease status and indicate

a poor prognosis. Glucocorticoid has been used as a first-line therapy for SLE. Glucocorticoid exerts strong anti-inflammatory effects and is widely used for the treatment of uncontrolled disease activity in patients with SLE, such as central nervous system lupus (CNS), severe lupus nephritis, and other life-threatening conditions [1]. Glucocorticoid therapy is successful in most cases when high doses are employed, and as a result the prognosis of the SLE has improved remarkably. On the other hand, as glucocorticoid has adverse side effects on many organ systems, only the minimum effective dose is used for treatment. For example, skin thinning and purpura are commonly observed, and the risk of both cataracts and glaucoma is increased. Glucocorticoid use is associated with an increased risk of ischemic heart disease and heart failure, and also an increased risk of gastritis, gastric ulcer, and gastrointestinal bleeding. In the musculoskeletal system, osteoporosis is one of the more serious adverse effects of glucocorticoid [2], and osteonecrosis is also a significant problem [3]. Bisphosphonate (BP) is a key drug used for prevention and treatment of osteoporosis. The risk of osteonecrosis caused by glucocorticoid is higher in patients with SLE. Glucocorticoid causes a dose-dependent, mild increase in the fasting glucose level and a greater increase in postprandial hyperglycemia in patients without preexisting diabetes mellitus (DM), whereas it worsens control of the blood glucose level in patients with DM. The adverse effect of glucocorticoid on atherosclerotic vascular disease is thought to be mediated in part by elevated levels of nonfunctional lipoprotein. In patients with SLE, the adverse effects of glucocorticoid on lipid profiles are dose-dependent, occurring only at prednisone doses exceeding 10 mg/day. Systemic glucocorticoid also has many effects on both innate and acquired immunity, resulting in a dose-dependent increase in the risk of infection, especially with common bacterial, viral, and fungal pathogens [4]. Conventional immunosuppressive agents such as mycophenolate mofetil, azathioprine, and cyclophosphamide are also widely used in the management of SLE, and current treatment regimens optimize the use of these agents while minimizing their potential toxicity [5]. Tacrolimus may be particularly useful as adjunctive therapy in patients with persistent proteinuria despite other therapies, and in the management of lupus nephritis in pregnancy. The advent of biological agents has advanced the treatment of SLE, particularly in patients with refractory disease. The CD20 monoclonal antibody rituximab and the anti-BLyS agent belimumab are widely used in clinical practice. The prognosis of SLE has improved markedly, and long-term survival has increased. Prior to 1955, fewer than 50% of patients survived 5 years after diagnosis whereas now, 10-year survival exceeds 90% [6]. Our recent data have also confirmed that the 5-year survival rates of patients diagnosed as having SLE before 1970, between 1970 and 1979, between 1980 and 1989, between 1990 and 1999, and after 2000 were 71.4, 83.1, 94.5, 93.4, and 96.4%, respectively. Previously, the causes of death in patients with SLE were mainly infection and renal disease, but recently atherosclerotic cardiovascular disease emerging in the long term has become a focus of concern. Musculoskeletal conditions that impair the quality of life have also become problematic, including osteonecrosis and atypical femoral fracture (AFF). Here we discuss osteonecrosis and AFF in patients with SLE.

## 2. Incidence, etiology, and pathogenesis

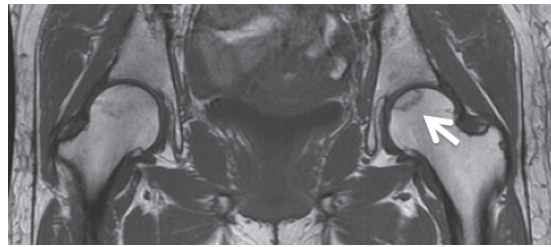
Idiopathic osteonecrosis (ION) of the femoral head occurs frequently (3–40%) in patients receiving glucocorticoid for underlying conditions such as nephrotic syndrome and renal

transplantation [7–10]. It is also known to occur as one of the serious complications of glucocorticoid treatment of SLE. Among several factors *related to* ION, glucocorticoid therapy is considered to be one of *essential* importance [3]. There have been *a lot of* reports of ION onset in SLE patients to date, but the *exact* incidence of ION in this group is unknown. The etiology or pathogenesis of this disorder has not been fully clarified, and no prophylaxis has been established to date. The risk of ION in SLE patients is considered to be due to both the SLE itself and the concomitant use of glucocorticoid because, in occasional cases, ION has been noted in the absence of glucocorticoid therapy [3]. In addition, the risk of developing ION has been linked to numerous factors such as glucocorticoid use, alcohol consumption, cigarette smoking, and several rheumatic diseases including SLE. Although the pathogenesis remains unclear, involvement of lipid metabolism abnormality [11], hypercoagulability [12], oxidative stress [13], and vascular endothelial dysfunction [14] has been suggested from basic and clinical research. Several studies investigating the association of ION with steroid treatment have yielded conflicting results with regard to the cumulative dosage, maximum dose, route of administration, and duration of treatment. Glucocorticoid dose and duration seem to be important factors related to ION, but there is considerable controversy about this issue [3, 15–20]. ION may develop in patients who have received high-dose, short-term, or long-term steroid. However, in the early phase, the relationship between steroid and ION has yet been not fully investigated. In our present study, the patients were treated with steroid for the first time, and our observation period was short. Additionally, the initial dose of prednisolone (PSL) for treatment of SLE has sometimes been determined according to the patient's weight or body surface area (BSA) [21]. Therefore, we investigated the relationship of body mass index (BMI) [22] and BSA with the initial dose of PSL. We found that the initial dose of PSL, steroid pulse therapy, BMI, and BSA were not correlated with asymptomatic ION, similar to the results obtained by Sekiya et al. [23]. Also, we failed to identify any relationship between BMI, BSA, the initial dose of PSL per unit BW, the initial dose of PSL relative to BMI, or the initial dose of PSL relative to BSA. None of the factors evaluated were associated with asymptomatic ION. Recent meta-analysis data have shown that the likelihood of ION developing in patients receiving glucocorticoid at more than 20 mg/day is significantly higher than in patients receiving less than 20 mg/day. In the early phase, corticosteroid at over 20 mg/day may trigger ION. In addition, it has been revealed that increasing the steroid dose at the time of SLE recurrence is a risk factor for development of new ION [24].

### 3. Timing of osteonecrosis-related ischemia in patients with SLE

Radiographically, at the earliest stage of ION, plain radiographs show normal features, whereas axial and coronal T1- and T2-weighted MR images show low-density signals in the femoral head (**Figure 1**).

From this viewpoint, osteonecrosis associated with renal transplantation can provide important information. The band patterns on MRI correspond to repair tissue located between necrotic and intact areas [25, 26]. Thus, there is a time lag between the occurrence of ischemia and the appearance of the band pattern. It has been reported that 1 month after internal fixation of a femoral neck fracture, MRI can reveal band patterns in the femoral head away



**Figure 1.** A T1-weighted image demonstrates a ring-like subchondral area of osteonecrosis (white arrow) present in the femoral head.

from the fracture line [27]. In patients who develop ION after renal transplantation, it is presumed that intraosseous ischemia occurs earlier than 6–12 weeks postoperatively [28, 29] when band patterns are observed on T1-weighted MRI. In experimental animal models of osteonecrosis, it has been shown that intraosseous ischemia occurs quite soon after administration of large doses of steroid, that is, on the fifth and third day, respectively. The total dose of steroid administered in the first 2 weeks after renal transplantation is related to ION development [30]. This suggests the occurrence of an event in the bone that may lead to the development of ION at a very early stage after steroid administration. The widespread use of MRI now makes it possible to detect osteonecrotic change in SLE patients soon after administration of glucocorticoid, thus facilitating early diagnosis. Nagasawa et al. reported that 33% of patients developed ION within 3 months after the start of glucocorticoid treatment and that symptomatic ION became apparent at 2 years and beyond [31]. Radiographically, a subchondral radiolucency known as the crescent sign appeared at a late stage in ION, indicating subchondral fracture. However, that study was a multicenter one, and several strategies were selected for treatment of SLE according to the clinical conditions of the patients, resulting in slight differences among the participating hospitals. Several strategies have been selected for treatment of SLE *in conformity with* the clinical conditions of the affected patients, and there are *many* differences among hospitals, such as the indications for immunosuppressants. However, for any study performed at a single institution, the *strategy of treatment*, the steroid *selection*, the initial dose of steroid, and concomitant drugs would be more uniform. In addition, the speed of steroid tapering would also be quite uniform. This would allow better clarification of the background factors associated with ION. On the basis of this concept, we investigated the early development of ION in a cohort of strictly selected SLE patients using MRI and the early changes in laboratory parameters associated with steroid therapy [32].

#### 4. Classification of osteonecrosis

Diagnosis of ION of the femoral head relies on the combination of clinical symptoms and radiographs and/or magnetic resonance imaging (MRI) *changes*. To evaluate the evolution of ION of the femoral head, the Ficat (**Table 1**) [33] and the Association Research Circulation Osseous (ARCO) classification (**Table 2**) [34] are *generally* used to *evaluate* both imaging modalities. For comparative purposes, these classifications need to be reliable and *uniform definition* to provide sufficient therapy options for the patient.

Stage	Radiographic signs	Clinical features
0	Inconspicuous/normal findings	0 ("silent hip")
I	Inconspicuous findings or minor changes (slight patchy osteoporosis, blurring of trabecular pattern, subtle loss of clarity)	+
II A	Diffuse/focal radiological changes (osteoporosis, sclerosis, cysts)	+
II B	Subchondral fracture ("crescent sign") segmental flattening of femoral head ("out-of-round appearance")	+
III	Broken contour of femoral head, bone sequestrum, joint space normal	++
IV	Flattened contour of femoral head, decreased joint space collapse of femoral head, acetabular osteoarthritic changes	+++

**Table 1.** Scheme of Ficat classification (1985).

Stage	Radiological findings	Subclassification
0	Positive: histology negative/normal: radiograph/CT/MRI/scintigraphy	–
I	Positive: MRI and/or bone scintigraphy negative/normal: radiograph/CT	+ (a)
II	Radiograph: sclerotic, cystic or osteoporotic changes of femoral head	+ (a)
III	Radiograph: subchondral fracture ("crescent sign")	+ (a)
IV	Radiograph: flattening of femoral head	++ (b)
V	Radiograph: flattening of femoral head and osteoarthritic changes: decreased joint space and acetabular changes	+++ (b)
VI	Complete joint destruction	–

Note: (a) Location of femoral head necrosis: (1) medial third, (2) median third, and (3) lateral third. Size of femoral head necrosis: (A) <15%, (B) 15–30%, (C) >30%.

(b) Intrusion degree of femoral head contour: (A) <2 mm, (B) 2–4 mm, and (C) >4 mm.

**Table 2.** Scheme of ARCO classification system (1992).

## 5. Early changes in MRI features and laboratory parameters of SLE patients

In previous multicenter studies, several strategies were selected for treatment of SLE according to the clinical conditions of the patients, resulting in slight differences among the participating hospitals. This allowed us to investigate the very early development of ION at 3 months after

the start of steroid therapy using MRI imaging to clarify the background factors associated with ION. We found that the prevalence of asymptomatic ION among our patients was 26.9%, similar to that described previously [23]. We found no differences in the clinical characteristics of the patients, such as sex, age, height, and body weight and clinical features. The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) *is shown to be a valid and reliable measure of disease activity of SLE patients* [35]. The SLEDAI score *is assessed using a combination of clinical history, physical examination, organ-specific function test and serological test*. Almost all of our patients showed high or very high disease activity at the time of steroid initiation. However, the SLEDAI score was not correlated with asymptomatic ION [32]. In SLE, as is the case for antiphospholipid syndrome (APS), about 30–40% of patients have detectable antiphospholipid antibodies [36] and a positive lupus anticoagulant test and anticardiolipin antibody are detected in approximately 10–30% and 20–40% of patients, respectively. The prevalence of a so-called clinically significant anticardiolipin profile is considered to be about 30–40% [37]. APS antibodies as a prothrombotic factor might predispose to ION by causing microvascular thrombosis. However, the link between APS antibodies and ION is controversial [38–41]. In our study, there was no significant association between APS antibody and ION [32]. A Japanese nationwide study revealed that cigarette smoking was an independent risk factor for ION [42]. However, in our present study, cigarette smoking was not correlated with ION in SLE patients [32].

## 6. Serological parameters and ION

Serological activity of SLE was determined on the basis of decreased CH50 and increased anti-DNA antibodies. We also investigated serological parameters such as C3, C4, CH50, and anti-ds DNA antibody, as well as renal function parameters such as the serum creatinine level, estimated glomerular filtration rate, and *proteinuria*. However, these factors were *not* correlated with ION. Thus, both *initial* serological *disease* activity and *initial* renal function, as the most common forms of organ involvement, did not appear to be correlated with ION [32]. Similar results were obtained in a previous single-center study [23].

## 7. Lipid levels, statins, and ION

Several studies of ION have indicated the association of lipid. Nagasawa et al. [31] investigated the rate of increase in serum total cholesterol (TC) levels 1 month after glucocorticoid administration in patients with new-onset SLE, and found that they were significantly high in the ION group. It was also found that lipid levels, and the rates of increase in almost all the TC and triglyceride (TG) parameters, were higher in the group that developed ION. TC levels tended to be higher than that in the non-ION group, and the maximum levels and *increasing rates* were significantly higher, suggesting that a rapid rise in serum lipids soon after an increase in glucocorticoid dose might affect the onset of ION [23]. Our data *suggested* that the level of TG both before and after the *initiation* of steroid *therapy* was higher in patients with ION [32]. *The TG level before PSL therapy was associated future risk of asymptomatic ION*. As the association between TG before PSL therapy and the initial dose of PSL was not significant, the effect of TG before PSL

therapy on asymptomatic ION would not have been modified by the initial dose of subsequent PSL. Several studies have *shown* that a high TG level is a strong risk factor for *stroke and ischemic heart disease* [43–45]. ION is caused by partial or total *interruption* of blood flow to the femoral head, and SLE patients *thought to* develop asymptomatic ION through a similar mechanism. *Additionally*, it is well known that steroid *therapy* induces iatrogenic metabolic syndrome, and *from this point of view*, a high TG level is considered to be an important risk factor for asymptomatic ION. Furthermore, *the TC level* after steroid *therapy* tended to be higher in patients with asymptomatic ION. *However*, the levels of high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were not correlated with asymptomatic ION. As described previously, the TC level after 1 month of steroid treatment was significantly higher in patients with asymptomatic ION. Our data are similar to those reported previously [46]. In the early phase, lipids—especially TG—play an important role in the development of ION in patients with SLE. HMG-CoA reductase inhibitors (statins) have been widely used for the treatment of dyslipidemia as well as for prevention of *ischemic heart disease*. *According to* a chicken model, Wang et al. suggested that lovastatin prevented steroid-induced ION [47], and a study by Nishida et al. using a rabbit model also *revealed* that pitavastatin had a similar effect [48]. In humans, it has been reported that the incidence of osteonecrosis was decreased by 1% by administration of statins in a study of 284 patients with various disorders (excluding SLE) who received glucocorticoid treatment [49]. We used pravastatin, pitavastatin, lovastatin, and atorvastatin for prevention of ION, but no such preventive effect was observed [32]. Until now, no randomized controlled trial has been reported to successfully prevent steroid-induced ION. In patients with SLE, treatment with statins alone is insufficient for prevention of ION.

## 8. Prevention of osteonecrosis

In patients at risk of osteonecrosis, several factors are controllable, and thus prevention is the best approach. Hyperlipidemia and DM should be managed appropriately and alcohol consumption minimized [42]. Smoking should also be avoided, if possible [50]. The dosage of glucocorticoid should be minimized as far as possible, as described previously. Statins may help to protect against osteonecrosis. One database review found that only 1% of 284 patients developed ION after treatment with statins before glucocorticoid use. In renal transplant recipients, among 338 patients who were treated with statins, 15 (4.4%) developed ION and among 2543 patients who were not treated with statins, 180 (7%) patients developed ION [49]. Antioxidant agents have been shown to inhibit osteonecrosis in animal models [51]. Further accumulation of similar studies is needed to clarify the preventive effect of statins against SLE-associated ION.

## 9. Treatment of ION

The management of ION is usually determined by the degree of femoral head involvement. If the subchondral shell remains intact, there is still a possibility of healing, but if collapse occurs, healing is impossible. If the necrotic area is small and there are no symptoms, ION



should be followed up because some cases may spontaneously progress over time. If femoral head ION is diagnosed early, core depression is a commonly used form of prophylactic surgery to prevent the development of arthritis. One study has demonstrated long-term spontaneous repair of osteonecrotic lesions during low-dose glucocorticoid therapy [52]. Conservative treatment of ION involves limiting the degree of weight-bearing on the hip joint in conjunction with analgesia. In general, simple observation may be considered for asymptomatic lesions. Symptomatic lesions will likely progress to collapse, and if observation is chosen, the next joint-preserving procedure should be considered. Various forms of medication have been tried. BP is regularly used for prevention of insufficiency fractures, and several studies have shown that alendronate can reduce pain and slow the progression of collapse [53–55]. Treatment with BP is effective before subchondral collapse, but after subchondral collapse, the effects of treatment for inhibiting destruction of the femoral head are limited. Lipid-lowering agents, especially statins, are hypothesized to have a protective effect against ON. The prevalence of a clinically significant antiphospholipid profile is approximately 20% in SLE patients, and these antiphospholipid antibodies are believed to contribute to ION through hypercoagulation. Accordingly, anticoagulation therapy has been tried for prevention of ION in SLE patients, and warfarin has been modestly beneficial in this respect. One study of 60 SLE patients receiving prednisolone at more than 40 mg/day found that treatment with warfarin significantly reduced the onset of ION [31]. Among various physical modalities, extracorporeal shockwave therapy, hyperbaric oxygen, and pulsed electromagnetic therapy have yielded encouraging results, but further large prospective studies will be necessary to confirm these effects. Surgical treatments to prevent joint destruction include hip arthroplasty, core decompression, osteotomy, and vascularized bone grafting. Core decompression is commonly performed as prophylactic surgery for pre-collapse osteonecrosis of the femoral head. This decreases intramedullary pressure within the femoral head and neck, and has been postulated to improve blood circulation to the femoral head. Core decompression is often combined with bone grafting to help regenerate healthy bone and support cartilage at the hip joint. Bone grafting involves transplantation of healthy bone tissue to an area of the body where it is needed. Another option that has had some degree of success is harvesting and *in vitro* culture of autologous mesenchymal stem cells and their re-implantation into the core decompression site [56–58]. Long-term studies to confirm the success of this approach are still underway. Hip arthroplasty is the most commonly performed procedure for post-collapse lesions of the femoral head. Recent mid- and long-term studies have yielded satisfactory results [59]. Transtrochanteric anterior rotational osteotomy moves the symptomatic portion of the antero-superior femoral head out of the weight-bearing dome, enabling the normal posterior aspect of the head to bear weight, thus helping to preserve the joint [60]. These procedures have yielded favorable success rates, but are associated with a moderate risk of non-union. Vascularized fibular grafting is a more complex procedure in which a segment of bone is taken from the fibula of the patient, along with the arterial and venous blood supply. This is then transplanted into a hole created in the femoral neck and head. Vascularized fibular grafting has yielded successful outcomes in patients with precollapse lesions and moderate success in those with postcollapse lesions [61]. Additionally, use of autogenic or allogeneic cortical bone grafts and cancellous bone grafts has yielded good results for the treatment of precollapse and/or early precollapse osteonecrotic lesions of the femoral head.

## 10. Atypical femoral fracture

Glucocorticoid-induced osteoporosis (GIO) is an important problem in patients with SLE. BP is a key drug used for prevention and treatment of GIO. Patients with SLE often need to continue glucocorticoid and BP therapy for a long time, even if they are young. AFF has recently been recognized as a complication of long-term BP use [62, 63]. AFF is defined as a fracture located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare, as distinguished from typical femoral fracture which occurs at the femoral neck or intertrochanteric area and is related to osteoporosis [63]. Diagnosis of AFF requires the presence of four of five major features (**Table 3**).

Beaking is one of these features, and is defined as localized periosteal or endosteal thickening of the lateral cortex at the fracture site. Since cortical thickening at the fracture site characterizes stress fracture, the mechanism of AFF is considered to involve stress [63]. The age-standardized incidence rates of AFF have been reported to be 16 per 100,000 person-years for patients treated with BPs over 5 years and 133 for those treated with BPs over 10 years [62], and AFF occurs much less frequently than osteoporosis-related fractures. However, once it occurs, it takes much time to heal [64, 65], and the daily life activities of the patient are often impaired. Risk factors for AFF other than long-term BP use include glucocorticoid therapy [66, 67], complicating connective tissue disease [67], lateral bowing of the femur [68, 69], a low level of serum 25-hydroxyvitamin D [66], and female gender [70]. Glucocorticoid therapy has been reported to have an important impact on AFF [66, 67], although no significant

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To satisfy the case definition of AFF, the fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare.

In addition, at least four of the five major features must be present. None of the minor features is required but have sometimes been associated with these fractures.

### Major features

The fracture is associated with minimal or no trauma, as in a fall from a standing height or less

The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur

Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex

The fracture is noncomminuted or minimally comminuted

Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site (“beaking” or “flaring”)

### Minor features

Generalized 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 femoral diaphysis fractures

Delayed fracture healing

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**Table 3.** ASBMR Task Force 2013 Revised Case Definition of AFFs [63].

association has yet been proved in several studies [71, 72]. Girgis et al. reviewed 152 femoral shaft fractures and classified 20 of them as AFF; they concluded that the use of glucocorticoid therapy for more than 6 months was significantly associated with AFF [66]. In a fracture location-, age-, and gender-matched case-control study, Saita et al. reviewed 2238 hip and femoral shaft fractures and diagnosed 10 of them as AFF, concluding that glucocorticoid therapy and complicating connective tissue disease were significant risk factors for AFF [67]. We recently evaluated the incidence of latent femoral beaking (**Figure 2**), which may precede AFF, in 125 patients with autoimmune diseases [65 (52%) with SLE] taking BP and glucocorticoid [73].

Our data revealed that the incidence of beaking was 8% and increased to 10% over 2 years. A case of complete AFF from the tip of the beaking occurred in one patient. The risk factors for beaking were BP therapy for a period of >4 years, age 40–60 years, and presence of diabetes mellitus [73]. Although few studies have investigated AFF in patients with SLE, the frequency of beaking in our study was thought to be higher than in conventional reports of AFF, possibly because all of the patients were taking BP (mean therapy duration  $5.1 \pm 2.7$  years) and glucocorticoid (mean dose  $10.0 \pm 3.8$  mg). Both BP and prolonged glucocorticoid therapy reduce bone remodeling [64, 74], thus, impairing the healing of microdamage occurring during normal daily life activities. BP also changes bone plasticity [75], and glucocorticoid therapy leads to a deterioration of bone quality [76]. Thus, a combination of BP and glucocorticoid therapies enhances microdamage accumulation, producing conditions in which beaking can easily occur. Generally, lateral bowing of the femur is considered to be a risk factor for AFF. Hyodo et al. indicated that



**Figure 2.** X-ray of the hip joint showing beaking (white arrow).

AFF located in the mid femur was significantly related to femoral bowing, whereas AFF in the proximal femur was related to glucocorticoid use [68]. In our previous study of patients with autoimmune diseases taking BP and glucocorticoid, the femoral beaking was mostly located at the subtrochanter, and was not related to lateral bowing of the femur [73]. Therefore, AFF and beaking in patients taking BP and glucocorticoid may generally occur irrespective of lateral femoral bowing. In order to properly benefit from BP and to minimize the risk of AFF, a BP “drug holiday” has been proposed. Postmenopausal women treated orally with BP for over 5 years can be considered for such a break in drug therapy if they have no osteoporotic fractures, their hip T score is  $>-2.5$  and their fracture risk is not high [62]. For patients with GIO, few studies have investigated the safety and effectiveness of temporary drug withdrawal, and further studies are required. Because of the high frequency of beaking in patients taking BP and glucocorticoid [73], regular femoral X-ray screening for beaking is strongly recommended for AFF prevention, and once beaking is detected, a BP drug holiday should be considered.

## 11. Conclusion

SLE is a chronic inflammatory autoimmune disease mainly affecting young women; the mortality has recently been improved by treatments including glucocorticoid therapy. However, several adverse effects of glucocorticoid may decrease the quality of life. Even though some of these adverse effects have been overcome recently, AFF and ION are still persistent problems, and further work needs to be done to alleviate them.

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## References

- [1] Boumpas DT, Chrousos GP, Wilder RL, Cupps TR, Balow JE. (1993). Glucocorticoid therapy for immune-mediated diseases: basic and clinical correlates. *Ann Intern Med.* 15;119(12): 1198–1208.

- [2] Zonana-Nacach A, Barr SG, Magder LS, Petri M. (2000). Damage in systemic lupus erythematosus and its association with corticosteroids. *Arthritis Rheum.* 43(8): 1801–1808.
- [3] Calvo-Alén J, McGwin G, Toloza S, Fernández M, Roseman JM, Bastian HM, Cepeda EJ, González EB, Baethge BA, Fessler BJ, Vilá LM, Reveille JD, Alarcón GS; LUMINA Study Group. Systemic lupus erythematosus in a multiethnic US cohort (LUMINA): XXIV. (2006). Cytotoxic treatment is an additional risk factor for the development of symptomatic osteonecrosis in lupus patients: results of a nested matched case-control study. *Ann Rheum Dis.* 65(6): 785–790.
- [4] Kirou KA, Boumpas DT. Dubois' lupus erythematosus and related syndrome. Wallace DJ, Hahn BH (Eds.) Saunders-Elsevier, Philadelphia. 2012. p. 597
- [5] Kalunian KC, Kim M, Xie X, Baskaran A, Daly RP, Merrill JT. (2016). Impact of standard of care treatments and disease variables on outcomes in systemic lupus erythematosus trials: analysis from the Lupus Foundation of America Collective Data Analysis Initiative. *Eur J Rheumatol.* 3(1): 13–19.
- [6] Moroni G, Quaglini S, Gallelli B, Banfi G, Messa P, Ponticelli C. (2007). The long-term outcome of 93 patients with proliferative lupus nephritis. *Nephrol Dial Transplant.* 22(9): 2531–2539.
- [7] Abeles M, Urman JD, Rothfield NF. (1987). Aseptic necrosis of bone in systemic lupus erythematosus. Relationship to corticosteroid therapy. *Arch Intern Med.* 138(5): 750–754.
- [8] Koo KH, Kim R. (1995). Quantifying the extent of osteonecrosis of the femoral head. A new method using MRI. *J Bone Joint Surg Br.* 77(6): 875–880.
- [9] Landmann J, Renner N, Gächter A, Thiel G, Harder F. (1978). Cyclosporin a and osteonecrosis of the femoral head. *J Bone Joint Surg Am.* 69(8): 1226–1228.
- [10] Mont MA, Hungerford DS. (1995). Non-traumatic avascular necrosis of the femoral head. *J Bone Joint Surg Am* 77(3): 459–474.
- [11] Moskal JT, Topping RE, Franklin LL. (1997). Hypercholesterolemia: an association with osteonecrosis of the femoral head. *Am J Orthop.* 26(9): 609–612.
- [12] Oinuma K, Harada Y, Nawata Y, Kobayashi K, Abe I, Kamikawa K, Moriya H. (2000). Sustained hemostatic abnormality in patients with steroid-induced osteonecrosis in the early period after high dose corticosteroid therapy. *J Orthop Sci.* 5(4): 374–379.
- [13] Ichiseki T, Matsumoto T, Nishino M, Kaneuji A, Katsuda S. (2004). Oxidative stress and vascular permeability in steroid-induced osteonecrosis model. *J Orthop Sci.* 9(5): 509–515.
- [14] Iuchi T, Akaike M, Mitsui T, Ohshima Y, Shintani Y, Azuma H, Matsumoto T. (2003). Glucocorticoid excess induces superoxide production in vascular endothelial cells and elicits vascular endothelial dysfunction. *Circ Res.* 92(1): 81–87.

- [15] Abeles M, Urman JD, Rothfield NF. (1978). Aseptic necrosis of bone in systemic lupus erythematosus. Relationship to corticosteroid therapy. *Arch Intern Med.* 138(5): 750–754.
- [16] Dimant J, Ginzler EM, Diamond HS, Schlesinger M, Marino CT, Weiner M, Kaplan D. (1978). Computer analysis of factors influencing the appearance of aseptic necrosis in patients with SLE. *J Rheumatol.* 5(2): 136–141.
- [17] Nagasawa K, Tsukamoto H, Tada Y, Mayumi T, Satoh H, Onitsuka H, Kuwabara Y, Niho Y. (1994). Imaging study on the mode of development and changes in avascular necrosis of the femoral head in systemic lupus erythematosus: long-term observations. *Br J Rheumatol.* 33(4): 343–347.
- [18] Weiner ES, Abeles M. (1989). Aseptic necrosis and glucocorticosteroids in systemic lupus erythematosus: a reevaluation. *J Rheumatol.* 16(5): 604–608.
- [19] Massardo L, Jacobelli S, Leissner M, González M, Villarroel L, Rivero S. (1992). High-dose intravenous methylprednisolone therapy associated with osteonecrosis in patients with systemic lupus erythematosus. *Lupus.* 1(6): 401–405.
- [20] Gladman DD, Urowitz MB, Chaudhry-Ahluwalia V, Hallet DC, Cook RJ. (2001). Predictive factors for symptomatic osteonecrosis in patients with systemic lupus erythematosus. *J Rheumatol.* 28(4): 761–765.
- [21] DuBois D, DuBois EF. (1989). A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition.* 5(5): 303–311; discussion 312–313.
- [22] Garrow JS, Webster J. (1985). Quetelet's index (W/H<sup>2</sup>) as a measure of fatness. *Int J Obes.* 9(2): 147–153.
- [23] Sekiya F, Yamaji K, Yang K, Tsuda H, Takasaki Y. (2010). Investigation of occurrence of osteonecrosis of the femoral head after increasing corticosteroids in patients with recurring systemic lupus erythematosus. *Rheumatol Int.* 30(12): 1587–1593.
- [24] Mont MA, Pivec R, Banerjee S, Issa K, Elmallah RK, Jones LC. (2015). High-dose corticosteroid use and risk of hip osteonecrosis: meta-analysis and systematic literature review. *J Arthroplasty.* 30(9): 1506–1512.
- [25] Hauzeur JP, Sintzoff S Jr., Appelboom T, De Maertelaer V, Bentin J, Pasteels JL. (1992). Relationship between magnetic resonance imaging and histologic findings by bone biopsy in nontraumatic osteonecrosis of the femoral head. *J Rheumatol.* 19 (3): 385–392.
- [26] Kubo T, Yamamoto T, Inoue S, Horii M, Ueshima K, Iwamoto Y, Hirasawa Y. (2000). Histological findings of bone marrow edema pattern on MRI in osteonecrosis of the femoral head. *J Orthop Sci.* 5(5): 520–523.
- [27] Sugano N, Masuhara K, Nakamura N, Ochi T, Hirooka A, Hayami Y. (1996). MRI of early osteonecrosis of the femoral head after transcervical fracture. *J Bone Joint Surg (Br).* 78(2): 253–257.

- [28] Kubo T, Yamazoe S, Sugano N, Fujioka M, Naruse S, Yoshimura N, Oka T, Hirasawa Y. (1997). Initial MRI findings of non-traumatic osteonecrosis of the femoral head in renal allograft recipients. *Magn Reson Imaging*. 15(9): 1017–1023.
- [29] Fujioka M, Kubo T, Nakamura F, Shibatani M, Ueshima K, Hamaguchi H, Inoue S, Sugano N, Sakai T, Torii Y, Hasegawa Y, Hirasawa Y. (2001). Initial changes of non-traumatic osteonecrosis of femoral head in fat suppression images: bone marrow edema was not found before the appearance of band patterns. *Magn Reson Imaging*. 19 (7): 985–991.
- [30] Saito M, Ueshima K, Fujioka M, Ishida M, Goto T, Arai Y, Ikoma K, Fujiwara H, Fukushima W, Kubo T. (2014). Corticosteroid administration within 2 weeks after renal transplantation affects the incidence of femoral head osteonecrosis. *Acta Orthop*. 85(3): 266–270.
- [31] Nagasawa K, Tada Y, Koarada S, Tsukamoto H, Horiuchi T, Yoshizawa S, Murai K, Ueda A, Haruta Y, Ohta A. (2006). Prevention of steroid-induced osteonecrosis of femoral head in systemic lupus erythematosus by anti-coagulant. *Lupus*. 15(6): 354–357.
- [32] Kuroda T, Tanabe N, Wakamatsu A, Takai C, Sato H, Nakatsue T, Wada Y, Nakano M, Narita I. (2015). High triglyceride is a risk factor for silent osteonecrosis of the femoral head in systemic lupus erythematosus. *Clin Rheumatol*. 34(12): 2071–2077.
- [33] Ficat RP. (1985). Idiopathic bone necrosis of the femoral head. Early diagnosis and treatment. *J Bone Joint Surg Br*. 67(1): 3–9.
- [34] Gardeniers JW (1992). A new international classification of osteonecrosis of the ARCO Committee on terminology and classification. *J Jpn Orthop Assoc* 66(1): 18–20.
- [35] Bombardier C, Gladman DD, Urowitz MB, Carton D, Chang CH. (1992). Derivation of the SLEDAI. A disease activity index for lupus patients. The committee on prognosis studies in SLE. *Arthritis Rheum*. 35(6): 630–640.
- [36] Galli M, Luciani D, Bertolini G, Barbui T. (2003). Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. *Blood*. 101(5): 1827–1832.
- [37] Taraborelli M, Leuenberger L, Lazzaroni MG, Martinazzi N, Zhang W, Franceschini F, Salmon J, Tincani A, Erkan D. (2016). The contribution of antiphospholipid antibodies to organ damage in systemic lupus erythematosus. *Lupus*. 25(12): 1365–1368.
- [38] Asherson RA, Lioté F, Page B, Meyer O, Buchanan N, Khamashta MA, Jungers P, Hughes GR. (1993). Avascular necrosis of bone and antiphospholipid antibodies in systemic lupus erythematosus. *J Rheumatol*. 20(2): 284–288.
- [39] Mont MA, Glueck CJ, Pacheco IH, Wang P, Hungerford DS, Petri M. (1997). Risk factors for osteonecrosis in systemic lupus erythematosus. *J Rheumatol*. 24(4): 654–662.
- [40] Faezi ST, Hoseinian AS, Paragomi P, Akbarian M, Esfahanian F, Gharibdoost F, Akhlaghi M, Nadji A, Jamshidi AR, Shahram F, Nejadhosseini M, Davatchi F. (2015). Non-corticosteroid risk factors of symptomatic avascular necrosis of bone in

systemic lupus erythematosus: a retrospective case-control study. *Mod Rheumatol.* 25(4): 590–594.

- [41] Mok MY, Farewell VT, Isenberg DA. (2000). Risk factors for avascular necrosis of bone in patients with systemic lupus erythematosus: is there a role for antiphospholipid antibodies? *Ann Rheum Dis.* 59(6): 462–467.
- [42] Sakaguchi M, Tanaka T, Fukushima W, Kubo T, Hirota Y. (2010). Idiopathic ONF multicenter case-control study group. Impact of oral corticosteroid use for idiopathic osteonecrosis of the femoral head: a nationwide multicenter case-control study in Japan. *J Orthop Sci.* 15(2): 185–191.
- [43] Noda H, Iso H, Saito I, Konishi M, Inoue M, Tsugane S, JPHC Study Group. (2009). The impact of the metabolic syndrome and its components on the incidence of ischemic heart disease and stroke: the Japan public health center-based study. *Hypertens Res.* 32(4): 289–298.
- [44] Patel A, Barzi F, Jamrozik K, Lam TH, Ueshima H, Whitlock G, Woodward M, Asia Pacific Cohort Studies Collaboration. (2004). Serum triglycerides as a risk factor for cardiovascular diseases in the Asia-Pacific region. *Circulation.* 110(17): 2678–2686.
- [45] Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, Boekholdt SM, Khaw KT, Gudnason V. (2007). Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation.* 115(4): 450–458.
- [46] Nagasawa K, Tada Y, Koarada S, Horiuchi T, Tsukamoto H, Murai K, Ueda A, Yoshizawa S, Ohta A. (2005). Very early development of steroid-associated osteonecrosis of femoral head in systemic lupus erythematosus: prospective study by MRI. *Lupus.* 14(5): 385–390.
- [47] Wang GJ, Sweet DE, Reger SI, Thompson RC. (1977). Fat-cell changes as a mechanism of avascular necrosis of the femoral head in cortisone-treated rabbits. *J Bone Joint Surg Am.* 59(6): 729–735.
- [48] Nishida K, Yamamoto T, Motomura G, Jingushi S, Iwamoto Y. (2008). Pitavastatin may reduce risk of steroid-induced osteonecrosis in rabbits: a preliminary histological study. *Clin Orthop Relat Res.* 466(5): 1054–1058.
- [49] Pritchett JW. (2001). Statin therapy decreases the risk of osteonecrosis in patients receiving steroids. *Clin Orthop Relat Res.* 386: 173–178.
- [50] Takahashi S, Fukushima W, Kubo T, Iwamoto Y, Hirota Y, Nakamura H. (2012). Pronounced risk of nontraumatic osteonecrosis of the femoral head among cigarette smokers who have never used oral corticosteroids: a multicenter case-control study in Japan. *J Orthop Sci.* 17(6): 730–736.
- [51] Mikami T, Ichiseki T, Kaneuji A, Ueda Y, Sugimori T, Fukui K, Matsumoto T. (2010). Prevention of steroid-induced osteonecrosis by intravenous administration of vitamin E in a rabbit model. *J Orthop Sci.* 15(5): 674–677.



- [52] Shigemura T, Nakamura J, Kishida S, Harada Y, Ohtori S, Kamikawa K, Ochiai N, Takahashi K. (2011). Incidence of osteonecrosis associated with corticosteroid therapy among different underlying diseases: prospective MRI study. *Rheumatology (Oxford)*. 50(11): 2023–2028.
- [53] Agarwala S, Shah S, Joshi VR. (2009). The use of alendronate in the treatment of avascular necrosis of the femoral head: follow-up to eight years. *J Bone Joint Surg Br*. 91(8): 1013–1018.
- [54] Lai KA1, Shen WJ, Yang CY, Shao CJ, Hsu JT, Lin RM. (2005). The use of alendronate to prevent early collapse of the femoral head in patients with nontraumatic osteonecrosis. A randomized clinical study. *J Bone Joint Surg Am*. 87(10): 2155–2159.
- [55] Nishii T, Sugano N, Miki H, Hashimoto J, Yoshikawa H. (2006). Does alendronate prevent collapse in osteonecrosis of the femoral head? *Clin Orthop Relat Res*. 443: 273–279.
- [56] Gangji V, Toungouz M, Hauzeur JP. (2005). Stem cell therapy for osteonecrosis of the femoral head. *Expert Opin Biol Ther*. 5(4): 437–442.
- [57] Hernigou P, Beaujean F. (2002). Treatment of osteonecrosis with autologous bone marrow grafting. *Clin Orthop Relat Res*. 405: 14–23.
- [58] Hauzeur JP, Gangji V. (2010). Phases 1–3 clinical trials using adult stem cells in osteonecrosis and nonunion fractures. *Stem Cells Int*. 2010: 410170.
- [59] Woo MS, Kang JS, Moon KH. (2014). Outcome of total hip arthroplasty for avascular necrosis of the femoral head in systemic lupus erythematosus. *J Arthroplasty*. 29(12): 2267–2270.
- [60] Atsumi T, Muraki M, Yoshihara S, Kajihara T. (1999). Posterior rotational osteotomy for the treatment of femoral head osteonecrosis. *Arch Orthop Trauma Surg*. 119(7–8): 388–393.
- [61] Malizos KN, Quarles LD, Seaber AV, Rizk WS, Urbaniak JR. (1993). An experimental canine model of osteonecrosis: characterization of the repair process. *J Orthop Res*. 11(3): 350–357.
- [62] Adler RA, El-Hajj Fuleihan G, Bauer DC, Camacho PM, Clarke BL, Clines GA, Compston JE, Drake MT, Edwards BJ, Favus MJ, Greenspan SL, McKinney R Jr., Pignolo RJ, Sellmeyer DE. (2016). Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American society for bone and mineral research. *J Bone Miner Res*. 31(1): 16–35.
- [63] Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung AM, Cosman F, Curtis JR, Dell R, Dempster DW, Ebeling PR, Einhorn TA, Genant HK, Geusens P, Klaushofer K, Lane JM, McKiernan F, McKinney R, Ng A, Nieves J, O'Keefe R, Papapoulos S, Howe TS, van der Meulen MC, Weinstein RS, Whyte MP. (2014). Atypical subtrochanteric and

diaphyseal femoral fractures: second report of a task force of the American society for bone and mineral research. *J Bone Miner Res.* 29(1): 1–23.

- [64] Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY. (2005). Severely suppressed bone turnover: a potential complication of alendronate therapy. *J Clin Endocrinol Metab.* 90(3): 1294–1301.
- [65] Kondo N, Yoda T, Fujisawa J, Arai K, Sakuma M, Ninomiya H, Sano H, Endo N. (2015). Bilateral atypical femoral subtrochanteric fractures in a premenopausal patient receiving prolonged bisphosphonate therapy: evidence of severely suppressed bone turnover. *Clin Cases Miner Bone Metab.* 12(3): 273–277.
- [66] Girgis CM, Sher D, Seibel MJ. (2010). Atypical femoral fractures and bisphosphonate use. *N Engl J Med.* 362(19): 1848–1849.
- [67] Saita Y, Ishijima M, Mogami A, Kubota M, Baba T, Kaketa T, Nagao M, Sakamoto Y, Sakai K, Homma Y, Kato R, Nagura N, Miyagawa K, Wada T, Liu L, Matsuoka J, Obayashi O, Shitoto K, Nozawa M, Kajihara H, Gen H, Kaneko K. (2015). The incidence of and risk factors for developing atypical femoral fractures in Japan. *J Bone Miner Metab.* 33(3): 311–318.
- [68] Hyodo K, Nishino T, Kamada H, Nozawa D, Mishima H, Yamazaki M. (2017). Location of fractures and the characteristics of patients with atypical femoral fractures: analyses of 38 Japanese cases. *J Bone Miner Metab.* 35(2):209–214.
- [69] Saita Y, Ishijima M, Mogami A, Kubota M, Baba T, Kaketa T, Nagao M, Sakamoto Y, Sakai K, Kato R, Nagura N, Miyagawa K, Wada T, Liu L, Obayashi O, Shitoto K, Nozawa M, Kajihara H, Gen H, Kaneko K. (2014). The fracture sites of atypical femoral fractures are associated with the weight-bearing lower limb alignment. *Bone.* 66: 105–110.
- [70] Beaudouin-Bazire C, Dalmas N, Bourgeois J, Babinet A, Anract P, Chantelot C, Farizon F, Chopin F, Briot K, Roux C, Cortet B, Thomas T. (2013). Real frequency of ordinary and atypical sub-trochanteric and diaphyseal fractures in France based on X-rays and medical file analysis. *Joint Bone Spine.* 80(2): 201–205.
- [71] Giusti A, Hamdy NA, Dekkers OM, Ramautar SR, Dijkstra S, Papapoulos SE. (2011). Atypical fractures and bisphosphonate therapy: a cohort study of patients with femoral fracture with radiographic adjudication of fracture site and features. *Bone.* 48(5): 966–971.
- [72] Warren C, Gilchrist N, Coates M, Frampton C, Helmore J, McKie J, Hooper G. (2012). Atypical subtrochanteric fractures, bisphosphonates, blinded radiological review. *ANZ J Surg.* 82(12): 908–912.
- [73] Sato H, Kondo N, Wada Y, Nakatsue T, Iguchi S, Fujisawa J, Kazama JJ, Kuroda T, Nakano M, Endo N, Narita I. (2016). The cumulative incidence of and risk factors for latent beaking in patients with autoimmune diseases taking long-term glucocorticoids and bisphosphonates. *Osteoporos Int.* 27(3): 1217–1225.

- [74] Teitelbaum SL. (2012). Bone: the conundrum of glucocorticoid-induced osteoporosis. *Nat Rev Endocrinol.* 8(8): 451–452.
- [75] Tjhia CK, Odvina CV, Rao DS, Stover SM, Wang X, Fyhrie DP. (2011). Mechanical property and tissue mineral density differences among severely suppressed bone turnover (SSBT) patients, osteoporotic patients, and normal subjects. *Bone.* 49(6): 1279–1289.
- [76] Peel NF, Moore DJ, Barrington NA, Bax DE, Eastell R. (1995). Risk of vertebral fracture and relationship to bone mineral density in steroid treated rheumatoid arthritis. *Ann Rheum Dis.* 54(10): 801–806.

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