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ORIGINAL PAPER

Multifocal osteonecrosis related to corticosteroid: ten years later, risk of progression and observation of subsequent new osteonecroses

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Abstract
Purpose No study has reported the risk of other site osteonecroses after the diagnosis of multifocal osteonecrosis related to corticosteroids in patients who continue this corticosteroid treatment. An analysis of the time-course to other sites of osteonecrosis, as well as the effects of underlying corticosteroid risk factor on the evolution of asymptomatic lesions at the time of diagnosis, is presented.
Methods Two hundred patients were followed prospectively every year during a minimum ten years with a radiograph if a joint became symptomatic. In absence of evidence of osteonecrosis on radiographs of a symptomatic or non-symptomatic joint (hips, shoulders, knees, ankles), patients had an MRI performed at the most recent follow up. The average duration of follow-up after inclusion of the patient in the study was 15 years (range 10–20).
Results Of the 200 patients followed for an average of 15 years (minimum 10 years, maximum 20 years), 35 patients developed new osteonecrosis lesions during the period of study. Asymptomatic lesions became symptomatic and a high number of collapse was observed resulting in 258 arthroplasties (187 hips, 51 shoulders, 20 knees) at the most recent follow up.
Conclusion The continuation of peak doses (>200 mg) of corticosteroids predicted (p=0.04) occurrence of new lesions and the continuation of corticosteroids without peak dose was a risk for quicker progression to collapse.

Keywords Multifocal osteonecrosis · Hip osteonecrosis · Shoulder osteonecrosis · Knee osteonecrosis · Talus osteonecrosis

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Introduction

Osteonecrosis is a clinical entity usually known as affecting the femoral head, but it may also affect other sites of the skeleton. There are two types of bone osteonecrosis: the intramedullary (or metaphyseal) osteonecroses which are often silent, and those epiphyseal where the subchondral plate is involved in sub-articular or para-articular sites. The latter gradually collapse and become painful, finally leading to joint destruction. For this reason the early diagnosis and treatment is very important. When osteonecrosis (ON) extends to three or more separate anatomical sites, it is termed multifocal osteonecrosis [1, 2] and the effect on the patient is proportionately greater. Corticosteroid administration, connective tissue disorders, dysbarism, hemoglobinopathies, arteritis/vasculitis, pancreatitis, Gaucher's disease, and alcohol are strong correlations with multifocal osteonecrosis.

In those patients in whom osteonecrosis is steroid-induced there is evidence [3] that the number of affected sites is related to the dose of steroids which has been given. However, the risk of developing other osteonecrosis on the contralateral side [2, 3] or on other sites after the diagnosis of multifocal

osteonecrosis among these patients when they continue their corticosteroid treatment remains poorly understood. In particular no study has reported other sites osteonecroses occurring after the diagnosis of multifocal osteonecrosis related to corticosteroids in patients. It is likely that the true incidence is in fact much greater than these statistics reflect, because not all cases of ON progress to arthroplasty and some lesions are asymptomatic. Also, risk factors associated with disease progression have not been defined and the risk of disease developing in a previously asymptomatic joint after the onset of symptomatic disease is unclear. Estimates are that approximately 50 % of patients with ON require a major surgical procedure (arthroplasty) within three years of the diagnosis [4] for one site, but the risk is unknown in multifocal osteonecrosis.

Therefore we performed an analysis of the time course to other sites of osteonecrosis, of symptoms and number of arthroplasties performed during ten years as well as the effects of underlying continuing corticosteroid risk factor in this population with multifocal osteonecrosis.

Material and methods

Two hundred patients were included in the study and initially evaluated at the time of presentation between 1985 and 1995. They had hip surgery related to stage II, III or IV osteonecrosis according to the Ficat and Arlet classification. The patient population consisted of 124 males and 76 females with a mean age of 39 years at the time of presentation (range, 25–55 years) and was followed until the year 2015. For all these patients the cause of osteonecrosis was related to corticosteroids. The mean body mass index of these patients was 28 kg/m² (range, 25–32 kg/m²). The diagnosis of osteonecrosis was done on MRI or radiographs. MRI of hips, shoulders, knees and ankles were obtained at the entry of the study for all the patients. Patients were followed prospectively every year with a radiograph if a joint became symptomatic. According to the number of MRIs performed in this study, MRI examinations were limited and performed as screening techniques in many joints of these patients. This limited examination consisted of T1-weighed images with the following parameters: 450–600 / 10–15 (repetition time msec / echo time msec), 5 mm thickness, 2 mm intersection gap, 38 cm field of view, 256×256 matrix. In case of osteonecrosis, the full examination consisted of additional imaging sequences: fast spin echo T2-weighed images with fat suppression. In absence of evidence of osteonecrosis on radiographs of a symptomatic joint, patients had an MRI performed. When osteonecrosis was present on a joint, the patients had an MRI performed on the contralateral joint in absence of radiological evidence of osteonecrosis as the contralateral side. The average duration of follow-up after inclusion of the patient in the study was 15 years (range, 10–20). In the absence of evidence of osteonecrosis on radiographs of a symptomatic or non-symptomatic joint (hips, shoulders, knees, ankles), patients had an MRI performed at the most recent follow-up. Radiological signs of osteonecrosis in epiphysis were sclerotic or cystic changes, crescent line, and collapse. In the metadiaphyseal area, demarcating sclerosis was considered as a radiologic sign of infarct. Because fatty marrow or mixed marrow can be found in the epiphysis of patients with sickle cell disease the diagnosis on MR imaging was only based on bandlike abnormal signals [bandlike hypointense zones on T1-weighted images and matching hyperintense zones on short tau inversion (STIR images)].

Sites of osteonecrosis were found in epiphyseal areas with or without contact with cartilage: in the proximal femoral epiphysis, in the proximal humeral epiphysis, in the distal femoral epiphysis, in the proximal tibial epiphysis, in the distal tibial epiphysis and in the talus. In the knee joint each femoral condyle and tibial plateau was considered as a different site of osteonecrosis. Osteonecrosis was also found in meta-diaphyseal areas not in contact with endosteum. This means that one knee could have two metadiaphyseal osteonecroses and four epiphyseal osteonecrosis (Fig. 1). The median interval between initiation of steroid treatment and diagnosis of multifocal osteonecrosis on MRI was 15 months (range, 6–24 months). These patients had received a mean cumulative dose of 4,067 mg±1,835 mg, a mean daily dose of 164 mg±48, a mean peak dose of 320 mg±43, with a mean duration of therapy treatment of 32 days±12 days. Among the 200 patients, at the time of diagnosis, 83 had stopped corticosteroid treatment, 58 were still receiving steroid treatment but without peak doses, and 59 were still receiving treatment with peak doses of corticosteroids.

Statistical analysis Means and standard deviations were used to characterize continuous variables. An independent samples

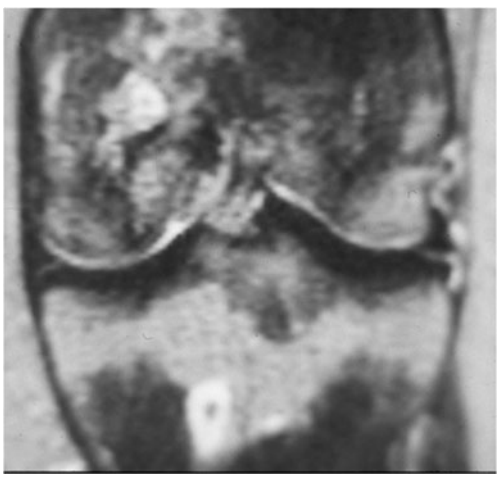

Fig. 1 Example of multi focal osteonecrosis of the knee

t-test was used for comparing means between groups. The chi-squared test or Fisher's exact test as appropriate were applied to compare the proportions between groups with p-value≤ 0.05 taken to be significant. Logistic regression models were applied to identify significant risk factors which were predictive of osteonecrosis including duration of therapy, peak, and mean daily, and cumulative methylprednisolone-equivalent doses.

Results

Prevalence of osteonecrosis at different anatomic sites

At presentation (Table 1)

Of the 200 patients found to have multifocal osteonecrosis at study entry, all the patients had hip involvement. Other sites involved included the shoulder in 70 % of patients, the knee in 60 % of patients, and the ankle in 30 % of patients. Bilateralism (as confirmed by radiographs or MRI) was common including 70 % of the hips, 62 % of the shoulders, and 45 % of the knees. Symptomatic lesions were present in 58 % of hips in 24 % of shoulders, in 19 % of the knees, and in 12 % of ankles. Among these osteonecroses, 35 % were stage I, 29 % stage II, 15 % stage III, and 21 % stage IV at presentation. The number of arthroplasties was 108 cases (88 hips, 16 shoulders, four knees).

At the most recent follow-up (Table 2)

Of the 200 patients followed for an average of 15 years (minimum ten years, maximum 20 years), only 35 (17.5 %) patients developed new osteonecrosis lesions during the period study on a site where a contralateral lesion was present. The time between presentation and diagnosis of new osteonecrosis was within two years for 50 % of the patients and within four years for 25 % of the patients. The most common site of new osteonecrosis was the hip (25 cases) followed by proximal humerus (eight cases) and the knee (two cases).

So at the most recent follow up among these 200 patients, the occurrence of osteonecrosis was 330 hip lesions associated with 264 proximal humerus osteonecroses, 184 knee osteonecrosis, and 100 ankle osteonecrosis. The total number of osteonecrosis was 878 in these 200 patients. Bilateralism was present in 82 % of the hips, 66 % of the shoulders, 46 % of the knees, and 25 % of ankles. Symptomatic lesions were present in 100 % of hips in 70 % of shoulders, in 60 % of the knees, and in 42 % of ankles. At final followup, 15 % of these osteonecrosis were stage I, 24 % stage II, 27 % stage III, and 34 % stage IV. The number of arthroplasties was 258 cases (187 hips, 51 shoulders, 20 knees), with a regular increase of 15 new arthroplasties each year of follow up in this 200 patients' population.

Table 1 Osteonecrosis involvement at presentation

Location	Total number of patients with involvement at this site, *n* (%)	Number of patients with bilateral lesions, *n* (%)	Total number of symptomatic lesions, *n* (%)
Hip	200 (100 %)	140 (70 %)	163 (58 %)
Shoulder	140 (70 %)	124 (62 %)	60 (24 %)
Knee	120 (60 %)	90 (45 %)	34 (19 %)
Ankle	60 (30 %)	50 (25 %)	12 (12 %)

Table 2 New osteonecrosis at the most recent followup resulting in increase of bilateral lesions

Location	New osteonecrosis observed at this site, *n* (% related to 400 joints)	Number of patients with bilateral lesions, *n* (%)
Hip	25 (6.25 %)	165 (82 %)
Shoulder	8 (2 %)	132 (66 %)
Knee	2 (0.5 %)	92 (45 %)
Ankle	0 (0 %)	50 (25 %)

Evolution of multifocal osteonecrosis in the population of this series according to the corticosteroid treatment

The continuation of peak doses (>200 mg) of corticosteroids predicted (p=0.04) occurrence of new lesions. New osteonecroses occurred only when the peak doses were higher than those used at the time of the diagnosis of multifocal osteonecrosis. The continuation of corticosteroids without peak doses was not a risk (none observed) for new osteonecrosis. Evolution of asymptomatic osteonecrosis to symptomatic osteonecrosis was not related to the continuation of corticosteroid treatment. However the continuation of corticosteroids without peak dose was a risk for quicker progression to collapse (p=0.01).

Discussion

The site distribution of the osteonecrotic lesions in multifocal osteonecrosis related to corticosteroids has been documented previously by several authors [1, 3, 5]. In our study, we found a similar pattern, with a high incidence in the femoral head, knee and shoulder. But none of the previous reports mentioned evolution of asymptomatic osteonecrosis, the risk of arthroplasties or occurrence of new osteonecrosis in these

patients. This may be related to the fact that none of these studies utilized standardized prospective entrance criteria or uniform criteria to determine the timing of the osteonecrosis. In another study performed in patients with sickle cell disease [6] who are at risk for multifocal osteonecrosis it was demonstrated that about 50 % of the patients developed avascular necrosis at the second site within two years after diagnosis of avascular necrosis at the first site and 25 % of the patients developed avascular necrosis at the third site within four years after the diagnosis at the second site. But contrary to sickle cell disease where the risk factor for osteonecrosis is continuous throughout life, multifocal osteonecrosis related to corticosteroids is related to the initial treatment with steroids [7, 8], except when patients continue steroids.

As most of the patients in the study had undergone radiographs [9, 10], bone scintigraphy and occasionally computed tomography in the course of the underline disease, diagnosis and management, we avoided more irradiation exposure. MRI examinations were limited and performed as screening techniques in many joints of these patients. This MR imaging sequence is fast and low cost. The authors acknowledge that small osteonecrosis may have been missed with this technique; furthermore, even if hips, shoulders and ankles of the patients were evaluated with MRI, other asymtomatic joints may not have been evaluated and therefore unidentified lesions in other sites may be present. Whole-body MR imaging examination with a moving table is now available in modern scanners and this will offer a more comprehensive and extensive modality in the diagnostic evaluation [11, 12] of patients with osteonecrosis.

Our results suggest that among patients with multifocal osteonecrosis related to corticosteroids, contrary to patients with sickle cell disease, those with joints without MRI evidence of ON at the time of presentation have a low risk of developing other disease sites during the ensuing years, except if the peak doses of corticosteroids are continued with higher doses. This means that probably all the present lesions have occurred at the same time or in a short period of time. Conversely, our data suggest also that those patients with MRI evidence of ON at the time of presentation, regardless of the presence of symptoms or continuation of corticosteroids, are extremely likely to progress to symptomatic disease in the succeeding few years and to be treated with arthroplasties.

In conclusion, this study provides important insight into the natural history of multifocal osteonecrosis related to corticosteroids. At the time of presentation of patients with multifocal osteonecrosis, MRI of hips, shoulders, knees and ankles should be obtained at the entry of the study for all the patients even if joints are asymptomatic. If there is no evidence of ON on MRI, the probability of occurrence of ON in these joints during the next several years is low even if patients continue to receive steroid treatment without peak doses. Conversely, if in the absence of symptoms there is plain radiographic or MRI evidence of ON in some sites, the probability of rapidly developing subsequent symptomatic ON is high, with progression to stage III or IV according to the classification of Arlet and Ficat. This means a risk of having several arthroplasties for these young patients if the diagnosis is not performed early enough to allow conservative treatment.

References

1. Collaborative Osteonecrosis Group (1999) Symptomatic multifocal osteonecrosis: a multicenter study. Clin Orthop 369:312–326
2. Hernigou P, Lambotte JC (2000) Bilateral hip osteonecrosis: influence of hip size on outcome. Ann Rheum Dis 59:817–821
3. Zhang NF, Li ZR, Wei HY, Liu ZH, Hernigou P (2008) Steroid-induced osteonecrosis; the number of lesions is related to the dosage. J Bone Joint Surg (Br) 90-B:1239–1243
4. Mont MA, Jones LC, Hungerford DS (2006) Nontraumatic osteonecrosis of the femoral head: ten years later. J Bone Joint Surg Am 88-A:1117–1132
5. LaPorte DM, Mont MA, Mohan V, Jones LC, Hungerford DS (1998) Multifocal osteonecrosis. J Rheumatol 25:1968–1974
6. Flouzat-Lachaniete CH, Roussignol X, Poignard A, Mukasa MM, Manicom O, Hernigou P (2009) Multifocal joint osteonecrosis in sickle cell disease. Open Orthop J 3:32–35
7. Drescher W, Schneider T, Becker C et al (2001) Selective reduction of bone blood flow by short-term treatment with high-dose methylprednisolone: an experimental study in pigs. J Bone Joint Surg (Br) 83-B:274–277
8. Drescher W, Weigert KP, Bünger MH et al (2004) Femoral head blood flow reduction and hypercoagulability under 24 h megadose steroid treatment in pigs. J Orthop Res 22:501–508
9. Kang JS, Moon KH, Kwon DG, Shin BK, Woo MS (2013) The natural history of asymptomatic osteonecrosis of the femoral head. Int Orthop 37:379–384
10. Yu T, Xie L, Zhang Z, Ke X, Liu Y (2015) Prediction of osteonecrosis collapse of the femoral head based on the proportion of the proximal sclerotic rim. Int Orthop 39:1045–1050
11. Mankin HJ (2007) Pathophysiology of osteonecrosis. Semin Arthroplast 18:170–174
12. Sugano N, Nishii T, Shibuya T, Nakata K, Masuhara K, Takaoka K (1997) Contralateral hip in patients with unilateral nontraumatic osteonecrosis of the femoral head. Clin Orthop 334:85–90