Hip Int 2010; 20 (04): 473 - 481

ORIGINAL ARTICLE

Avascular necrosis of the femoral head in patients with Hodgkin's Disease

Raúl J. G. Renedo [1], Mario M. Sousa [2], Salvador F. Pérez [2], Juan R. Zabalbeascoa [2], Luis P. Carro [1]

[1] Facultativo Especialista Cirugía Ortopédica y Traumatología Hospital Marques de Valdecilla. Santander - Spain
[2] Facultativo Especialista Cirugía Ortopédica y Traumatología, H.U. Virgen de Rocio, Sevilla- Spain

Abstract. *Avascular necrosis of the femoral head (ANFH) is a rare complication that may occur in patients diagnosed with Hodgkin's Disease (HD), as a result of treatment. A review was made of 315 cases of HD treated with systemic chemotherapy associated with high doses of steroids and radiation therapy and 18 patients (5.71%) were found to have developed ANFH during treatment. The mean follow-up time for chemotherapy was 40 months (range 20-110 months) with an average dose of prednisone of 8.45 g (range 3.20 – 18.50). The patients were treated by simple forage, simple forage plus IES and total hip arthroplasty (THA). In 8 cases (44.44%) forage associated with IES was performed as the initial treatment option and 6 of these cases were found to be in Ficat stage II (75%), 1 was found to be in stage III (12.55%) and another in stage IV (12.5%). In 2 cases, the central decompression technique was used (Simple Forage); both were in Ficat stage II. In the other 8 cases, a total hip arthroplasty (THA) was chosen as the initial treatment option, with 3 of these patients in Ficat stage III and 5 in Ficat stage IV. The clinical outcomes (time to postoperative pain, time to radiological failure, and time to arthroplasty from the forage) following surgical management using the forage-biopsy technique with and without internal electrostimulation (IES) were recorded. We observed that treatment with Forage + IES was better than simple Forage in stages below III in patients with Hodgkin's Disease. We considered that in Ficat stage III and IV arthroplasty (THA) was the better option. Steroids do not appear to be the only factor that worsens the outcomes of the parameters tested, and, in our opinion, other associated factors exist.*

Key Words: *Avascular necrosis of the femoral head, Hodgkin's disease, Radiation therapy, Steroids*

Accepted: June 24, 2010

INTRODUCTION

Risk factors for the development of bone necrosis include injuries, haemoglobinopathies, exogenous or endogenous hypercortisolism, renal transplantation, alcoholism, pancreatitis, collagen diseases, dysbarism, Gaucher's disease, metabolic diseases, radiation and synovitis with increased intra-articular pressure (1-3). The aetiopathogenesis of avascular necrosis is currently a controversial matter. It is thought that, regardless of the aetiology, the pathological characteristics of bone necrosis are similar (4-6). Long-term administration of steroids has been related to the development of avascular necrosis, mainly of the femoral and humeral heads (7, 8). Bone necrosis induced by corticosteroids is considered to be the most common cause, with a frequency of 3-5% among adults, although it may account

for 40% of all avascular necrosis of the femoral head (ANFH) in children (9). It is estimated that the incidence ranges from 10,000 to 20,000 cases per year in the US, and it accounts for 10% of all total primary hip arthroplasties (10).
Avascular bone necrosis is a condition that may develop in patients with Hodgkin's disease who have been treated with a combination of radiation therapy and chemotherapy. Despite being a rare complication in this group of patients, ANFH is a serious cause of morbidity. It is important to recognise the symptoms and signs of avascular necrosis, as these are easily confused with lymphoma symptoms. Patients usually complain of mild to moderate pain that comes on gradually and usually starts with activity, eventually persisting even when the patient is at rest. Hobbling and non-pain gait are common symptoms. In the final phases, when the degenerative condition is advanced, it is characterised by stiffness (11).
In suspected bone necrosis, radiographs should be performed in basic antero-posterior and axial projections of both hips and other joints, for the purpose of locating injury patterns. Early diagnosis enables the use of conservative treatment which may stabilise necrosis in some cases and delay arthroplasty in others. Radiological changes may be seen up to three months after the symptoms first develop, initially with changes in density and morphology of the joints. The initial radiological findings include osteopenia, with radiolucent areas interspersed with opaque areas, corresponding to bone formation and resorption. Collapse of the subchondral trabecular bone shows a characteristic radiolucent image in the shape of a crescent. Later, in advanced stages, secondary degenerative changes occur at the joint surface, consisting of a reduction of the joint space, sclerosis, formation of subchondral cysts and marginal osteophytes (12, 13).
Magnetic resonance (MR) images are very sensitive and specific in over 95%, with a loss of the femoral head signal in T1 and, as the disease progresses, fractures of the granulation tissue and an increase of the signal and joint bleeding in T2. MR is currently considered the best imaging method for early diagnosis. Computerised tomography (CT) images make it possible to ascertain the extent, depth and location of the injury (14-16).
Technecium bone scans may be useful for early diagnosis, but with a certain degree of non-specificity, with cold areas of hypo-uptake due to cell death, alternating with warm hyper-uptake areas associated with inflammatory tissues and newly formed bone (17).

MATERIALS AND METHOD

A retrospective clinical and radiological study was performed on 315 patients diagnosed with HD and treated at the Hospital Virgen del Rocío ((HUVR) from 1998 to 2008. Eighteen of the patients (5.71%) had an associated ANFH complication.
The following were assessed: presence of symptoms and degree of activity prior to the injury; predisposing conditions or risk factors associated with developing ANFH; clinical symptoms and treatment. Data associated with the treatment of lymphoma were gathered, including the type and frequency of chemotherapy, total cumulative dose of corticosteroids and intermittent or continuous administration method. We attempted to identify all factors of comorbidity or disease associated with ANFH.
The diagnostic criteria used for ANFH were those proposed by Hungerford including radiographs (AP and axial for both hips) and MR. Radiographs were classified on the basis of the Ficat and Arlet classification (1). In all cases, the diagnosis was confirmed by histology. The Ann Arbor classification was used to establish the stage of the lymphoma.
The patients were treated by simple forage or simple forage plus IES. All patients gave their informed consent for the technique to be used.
1. Central decompression technique (Forage):
A cannulated drill was used under fluoroscopic scopic control, guided by a Kirschner needle to make a tunnel of 9-10 mm in diameter, from the base of the great trochanter to the necrotic area of the femoral head, ending 5 mm from the joint surface.
2. Forage plus IES:
The electrostimulator used was Osteogen TM by EBI, which generates a constant, direct current. The electrostimulator comprises an energy source, an anode, a cathode and a conductor. The primary objective of the implantation is to insert the cathode into the tunnel made in the area of the infarct, to perform decompression.
To evaluate the results of the technique, three parameters were defined; presence or absence of postoperative pain after forage, presence or absence of radiological failure after forage, and time from forage to conversion to arthroplasty.

Development of postoperative pain

Time in months from the procedure to the onset of clinical symptoms. This parameter demonstrates clinical failure. It is not applicable to the controls by definition, as no intervention is performed in them to stop the pain.

Conversion to arthroplasty

Time in months from the procedure or from the diagnosis in the case of controls to conversion to arthroplasty (THA). This parameter demonstrates clinical failure, determined basically by disabling pain and/or severe functional impairment.

Radiological failure

Time in months from the procedure or from the diagnosis in controls to radiological failure, where the minimum expression is considered to be the occurrence of a collapse of more than 10% of the total original surface area of the femoral head or a change, even if less than 2 mm, in the outline of the femoral head, i.e., stage IV of Steinberg classification.

The clinical outcomes were evaluated based on the criteria of Merle D´Aubigne before and after surgical treatment, depending on the degree of pain, ability to walk and mobility of the hip. The outcomes were classified based on three types, over a maximum of 18 points as follows: excellent, 15-18 points; good, 11-14 points, and poor, less than 11 points.

Finally, we compared the time to postoperative pain, time to radiological failure and time to conversion to arthroplasty after forage for the 18 patients with Hodgkin's Disease and ANFH compared to the 54 patients (84 hips) from a general series (HUVR), diagnosed with ANFH of diverse aetiology in our centre based on identical criteria (simple forage or simple forage plus IES) with a follow-up time of 51 months (12-108).

Statistical method

Kaplan-Meier

The Kaplan-Meier procedure is a method for estimating models to the event in the presence of censored cases. It is based on estimating the conditional probabilities at each time point when an event occurs and on taking the limit of the product with those probabilities to estimate the survival rate at each time point.

Log rank test

This enables the equality of the survival distributions to be compared for the different factor levels.

RESULTS

The patient age range at the time of diagnosis of ANFH was 34.28 years (19-60). There were 6 females and 12 males. The average body mass index (BMI) was 24.73 (18.80-32.60). The degree of activity prior to the diagnosis of ANFH was moderate to high. After receiving treatment for HD, most patients maintained their levels of previous occupational activity, with sufficient autonomy and capacity to fulfill their activities of daily life (ADL). In two patients (11.11%) necrosis of the humeral head was also diagnosed (Tab. I).

The stage of the cases according to the Ficat classification at the time of diagnosis of ANFH were distributed as follows; 8 stage II cases (44.44%), 2 stage III cases (11.11%), and 8 stage IV cases (44.44%). The predominant clinical symptom was moderate to severe pain in 85% of the cases, which appeared spontaneously and increased with movement, and recurred on examining the hip.

The mean duration of treatment with corticosteroids (prednisone) associated with the various combinations was 16 months, with a total cumulative dose of 8.45 grams (3.20-18.50 g). The mean time from the start of treatment with corticosteroids to the development of ANFH was 14 months (1-36 months). The mean time from the diagnosis of ANFH to surgery for cases treated with forage associated with IES was 6 months (2-10) and in patients treated with total hip prosthesis it was 22 months (4 -59).

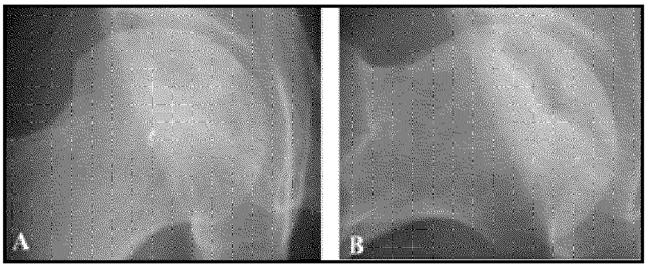
In 8 cases (44.44%) forage associated with IES was performed as the initial treatment option and 6 of these cases were found to be in Ficat stage II (75%) (Fig. 1), 1 was found to be in stage III (12.55%) and another in stage IV (12.5%). After performing the forage, the patients had no symptoms for an average of 16 months. Five patients in the group treated with forage and IES (62.50%) had radiological failure with collapse of the femoral head within an average 20 months, distributed as follows: 3 patients in stage II, and 2 patients in stages III and IV. The mean time to conversion to arthroplasty was 27 months since the forage (Tab. II).

In 2 cases, the central decompression technique was used

TABLE I - SUMMARY OF THE PATIENTS IN OUR SERIES

Patient No.	Age/ Gender	Diagnosis	Total Dose of Prednisone	Side	Forage + les	Time To xr Failure (Months)	Time Free from post-op. Pain (Months)	Time To conversion To arthroplasty (Months)	Score Pre	Score Post
1	60 V	Nodular Sclerosis IA	3.0	R	No	17	-	23	8(3-3-2)	15(6-5-4)
2	43 M	Mixed Cellularity IV	15.30	R	Yes	47	18	60	5(1-2-2)	15(5-5-5)
3	47 M	Large Cell Lymphoma	6.00	R	No	14	-	64	8(3-3-2)	13(5-5-3)
4	54 M	Nodular Sclerosis II B	18.50	L	Yes	23	23	23	5(2-2-1)	11(4-4-3)
5	19 M	Nodular Sclerosis IA	6.90	R	No	8	-	10	4(1-2-1)	16(5-5-6)
6	35 M	Mixed Cellularity IV	6.00	B	Yes	18	5	22	5(1-2-2)	9(3-3-3)
7	44 F	Nodular Sclerosis IV B	7.20	R	Yes	22	15	34	9(4-3-2)	13(4-4-5)
8	20 F	Mixed Cellularity II B	5.60	B	Yes	18	18	18	5(1-2-2)	8(2-3-3)
9	32 F	IA Mixed Cellularity	8.75	B	No	15	-	33	4(1-2-1)	12(4-3-5)
10	31 M	Nodular Sclerosis II A	7.00	L	Yes	18	12	23	9(2-4-3)	17(6-6-5)
11	26 F	Mixed Celularity I A	12.00	B	Yes	27	15	27	7(2-3-2)	14(3-6-5)
12	31 M	Nodular Sclerosis IA	9.00	B	No	18	14	29	6(2-2-2)	14(6-4-4)
13	30 F	Nodular Sclerosis I B	6.75	B	No	8	14	20	7(2-3-2)	16(5-6-5)
14	36 M	Nodular Sclerosis II B	4.70	L	Yes	20	20	20	9(3-3-3)	14(6-3-5)
15	20 M	Mixed Cellularity IV	5.60	B	Yes	18	14	18	5(1-3-1)	8(2-4-2)
16	32 F	Large Cell Lymphoma I A	8,75	B	No	39	-	110	4(1-1-2)	12(2-6-4)
17	26 M	Nodular Sclerosis II B	12,00	B	Yes	18	22	27	7(2-3-2)	14(6-4-4)
18	31 M	Nodular Sclerosis IV B	9,00	B	No	27	20	30	6(2-2-2)	14(4-5-5)

B = Bilateral



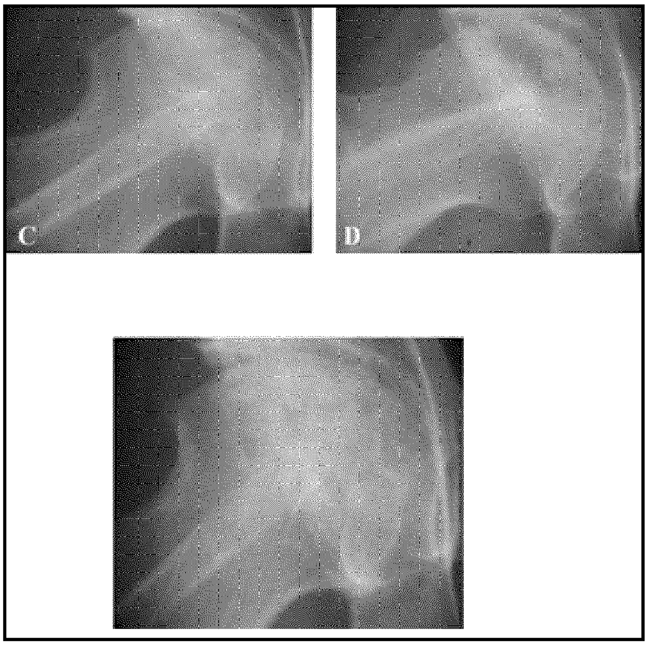


Fig. 1 - A) *and* **B)** *Antero-posterior and axial view of the hip with stage II bilateral ANFH:* **C)** *and* **D)** *Postoperative control of forage + IES at one year with no radiological necrosis progression;* **E)** *Control at 5 years with ANFH progression.*

(Simple Forage); both were in Ficat stage II at the time of surgery and were free from symptoms for 18.2 months. One patient had collapse of the femoral head (50%). The mean time to radiological failure was 11.7 months. The mean time to conversion to arthroplasty was 24.8 months since the forage.

In the other 8 cases, a total hip arthroplasty **(THA)** was chosen as initial treatment option, with 3 of these patients in Ficat stage III and 5 in Ficat stage IV.The pre-surgical score was below 9 points (range 4-9 points) in all patients. After treating the ANFH (simple forage, forage + IES or THA) the post-surgical score reached an average of 13 points (8-17) and the clinical distribution was; good in 1 case and poor in 1 case with simple forage, excellent in 2 cases, good in 4 cases and poor in 2 cases with IES, and excellent in 5 cases and good in 5 cases with THA.

The comparison of the series of patients with HD to the general series of our hospital (HUVR), shows that patients with HD had a worse prognosis in all the parameters tested; time to postoperative pain, time to radiological failure of the femoral head and time to conversion to arthroplasty.

The comparison of the results of the patients in the HD group with general series general series (HUVR) respective of the treatment applied (simple forage vs IES), it was seen that in FICAT stages I and II, the results in the time to postoperative pain and time to radiological failure of the femoral head were significantly worse in the group of patients with HD compared to the general series (HUVR) with $p< 0.005$ and $p< 0.001$, respectively. With regard to the time from forage to conversion to arthroplasty, no statistically significant differences were found. In FICAT stages III and IV we found no significant differences in postoperative pain, but there were important differences in the time to radiological failure ($p< 0.001$) (Fig. 2), and in the time from forage to conversion into arthroplasty ($p< 0.005$) (Fig. 3), which were better for the general series (HUVR). The comparison of the results of the patients treated with IES by stages shows that in FICAT stages I and II all cases except one had post-

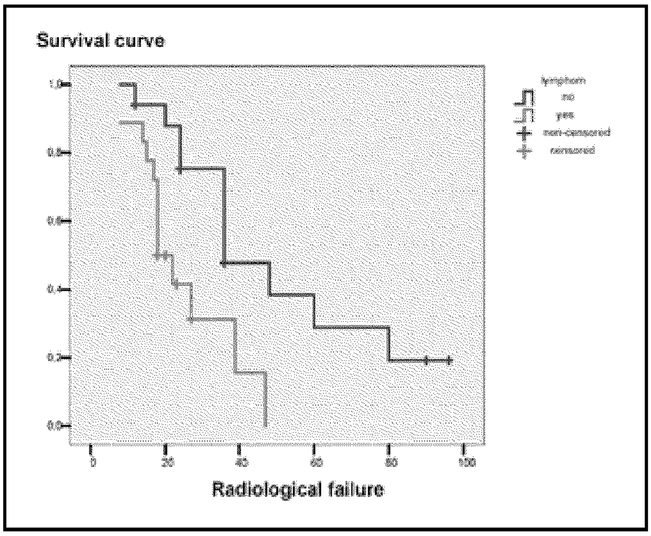


Fig. 2 - *Time to radiological failure in simple forage.versus.forage plus electrostimulator in stages III and IV of patients with HD as compared to the general HUVR series.*

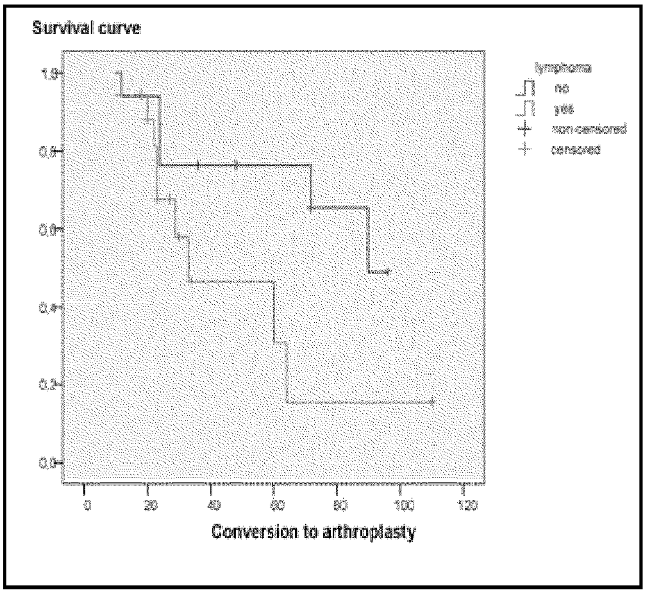


Fig. 3 - *Time to radiological failure in arthroplasty conversion in simple forage versus forage plus electrostimulator in stages III and IV of patients with HD as compared to the general HUVR series.*

operative pain, but in the general group (HUVR) no patients had postoperative pain ($p < 0.001$). With regard to radiological failure, we found statistically significant differences on comparing the survival functions of the lymphoma group with the rest of the general series (HUVR) favourable to it ($p < 0.001$). The number of conversions to arthroplasty could not be compared due to the small number of cases in both groups, and only six cases of lymphoma was converted into arthroplasty and one from the general group. We found no statistically significant differences in stages III and IV in the parameters tested.

The comparison of the results of the patients in the HD group treated with IES vs those treated with simple forage in the general series (HUVR) shows statistically significant differences in radiological failure in FICAT stages I and II favourable to the group treated with simple forage in the general series (HUVR) ($p < 0.005$). Similarly, the comparison of the results of the patients in the HD group treated with IES vs those treated with simple forage in the general series (HUVR) for FICAT stages III and IV shows no statistically significant differences in the parameters tested.

An analysis was made of the patients in the general series (HUVR) taking steroids for other causes, representing a total of 23 patients, with 6 cases due to kidney transplant, 8 cases due to chronic bronchitis, 5 cases due to leukaemia and 4 cases due to other causes. Significant differences were present to comparison of the series of patients with HD in FICAT stages I and II, but they were not significant for time to conversion to arthroplasty, or time to postoperative pain, but were significant for time to radiological failure of the femoral head. In stages III and IV, the differences seen for postoperative pain were not significant. Statistically significant differences were found in the time to radiological failure ($p < 0.001$) and in the time to conversion to arthroplasty in which the general series (HUVR) had better results ($p < 0.005$).

DISCUSSION

Treatment of Hodgkin's disease is one of the greatest advances of modern cancer therapy. The mortality rate for HD in adults has fallen due to the excellent results achieved with modern radiation therapy and an effective combination chemotherapy. It is estimated that 90-95% of patients treated with radiation therapy and /or chemotherapy survive after 10 years and 75-80% of patients show no relapse (18).

TABLE II - RESULTS AFTER PERFORMING FORAGE + IES

Stage	Nº. Patients	Free From Post-Op. Pain	Without Xr Failure	Conversion To Arthroplasty	Mean Follow-Up Time (Months)
II	6/ 8 (%)	5 (62,5%)	2 (25%)	3 (37,5)%	25
III	1/8 (%)	0%	0%	1 (100%)	27
IV	1/8 (%)	0%	0%	1 (100%)	52

However, these excellent results are not free from complications related to the treatment administered. The complications with the greatest clinical impact are the development of a second tumour, cardio-respiratory complications, infertility and immune system and bone disorders. In this respect, the most important bone damage is femoral and humeral bone necrosis. It seems reasonable to consider that bone necrosis occurs when a number of aetiological factors coincide in patients with a certain degree of vulnerability or susceptibility to suffer this disease (19, 20).

ANFH is a rare treatment complication in patients with Hodgkin's disease. According to current literature, the prevalence ranges from 1.6% to 10.5% in patients surviving for more than 5 years. In our study, this value is slightly higher, 5.7%. The mean follow-up time in our study was 40 months. If the study had lasted longer, the bone necrosis rate might have been higher, though it is true that ANFH is usually diagnosed over an average of 2 years from the start of treatment with corticosteroids in patients with HD and in our series, this time was 14 months on average.

The obvious implication of corticosteroids on the development of ANFH is clear, based on evidence provided by literature. Pietrogrande and Mastromarino were the first to discover this association in 1957 (21). Long-term administration of corticosteroids included in multi-chemotherapy regimes is known to be a potential cause leading to the development of ANFH if used at high doses over a long period of time. Today, this is the most widely accepted hypothesis as the main cause of ANFH in patients with Hodgkin's disease, the causal effect of radiation therapy being questionable (22, 23). In this regard, it is thought that a potential disorder occurs in lipid metabolism, with fat embolisation and blood coagulation disorders leading to vascular blockage in the small subchondral arteries and the ensuing bone necrosis associated with the inhibition of angiogenesis due to the effect of steroids (24, 25). These changes are quite clear in patients undergoing transplants, who receive high doses of steroids and immunosuppressants throughout their lives (26, 27). Steroids reduce the blood flow to the affected bone, and induce apoptosis of osteoblasts and osteocytes in experimental models (28, 29).

The risk of adverse events to occur with the administration of glucocorticoids usually increases with the treatment length or frequency of administration, and to a lesser degree, with the dose. However, ANFH may develop with the short-term use of high doses (starting treatment) and with longer use. There is no dose or exposure time for corticosteroids that predicts the development of bone necrosis, but some authors have suggested that the association with prednisone doses of over 30-40 mg per day is sufficient to cause these lesions (30). Our experience leads us to think that a cumulative dose of the steroids included in anticancer therapies are a factor that puts young patients at a high risk of developing ANFH.

The time from the occurrence of radiological changes to the clinical symptoms in our study population (14 months) is comparable to other series. The symptoms may develop within a period of a few weeks to a few months after taking steroids.

The use of an electrostimulator (IES) for the femoral head as a treatment method combined with forage is aimed at reducing intrabone pressure in the femoral head, restoring an efficient microcirculation to relieve pain and delay disease progression. In spite of the small number of cases, we observed that treatment with Forage + IES was better than simple Forage in stages below III, although it is true that the results of the Hodgkin lymphoma series are worse than those of the general series (HUVR) about the outcomes of the study parameters, time to postoperative pain, time to radiological failure of the femoral head, time to conversion to arthroplasty, We considered that in Ficat stage III and IV arthroplasty (THA) was the best treatment option.

Age is a factor to be considered, since many studies have established an association between ANFH and young patients, due to the fact that the number of glucocorticoid receptors decreases with age in humans. Other data conditioning the incidence of ANFH is gender, with a predominance of males of 8/1. These differences were not observed in our series, which was 2/1 for males, although it is true that this could be due to the small number of patients in the sample.

The role played by radiation as a causal agent is not clearly established in literature. Although the patients received radiation therapy treatment with the field of radiation being the pelvis, the absorption of radiation by the bone appears to be less than that of the adjacent soft tissues, and so we consider that radiation is an aetiological mechanism that is less important than corticosteroids. Radiation therapy could cause damage to the arteries, including regeneration and subsequently, thickening of the intima, causing the semi-blocking of the vessels. This depends on several factors, such as the total radiation dose received, the distribution over time, the size of the radiation field and, of course, the individual susceptibility of each patient. In 1986, Rossleigh raised the issue that corticosteroids alone are not the only aetiopathogenic factor in the development of ANFH, attributing it to the synergic effect induced by steroids with radiation therapy and cytotoxic agents (31). We should say that the development of ANFH in patients who have only received radiation therapy (including the femoral head) is rare, which supports the theory of the multi-causal effect.

However, a clear aetiological relationship could not be established to have caused the ANFH conditions identified in any of our patients. The comparison of the final results in the different groups and stages shows that steroids do not appear to be the only factor that worsens the results of the parameters tested, namely time to postoperative pain, time to radiological failure of the femoral head, time to conversion to arthroplasty, shown in the group of patients with HD compared to the rest of the general ANFH series. We believe that there must be other related factors that cause the results to be worse, such as the HD itself, individual susceptibility, associated morbidity, the volume of the initial infarct and other cytotoxic elements that favour bone resorption as opposed to bone formation. It must noted that none of our patients had worked in professions with a risk of traumatic events to shoulders or hips and they had not developed any fractures or injuries at this level, or had any other risk related factors such as alcoholism or drug-addition, collagen disorders, pancreatitis or metabolic disorders.

The author or one or more of the authors have received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this article.
The author or one or more of the authors have received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this article. In addition, benefits have been or will be directed to a research fund, foundation, educational institution, or other non-profit organisation with which one or more of the authors are associated.

Address for correspondence:
Raúl Javier García Renedo
Hospital Marques de Valdecilla
Avd. Marqués de Valdecilla s/n
39008 Santander (Cantabria)
España
rjgarciarenedo@hotmail.com

REFERENCES

1. Ficat R. Idiopathic bone necrosis of the femoral head. J Bone Joint Surg 1985; 67; 3-13.
2. Mankin H. Nontraumatic necrosis of the bone (osteonecrosis). N Engl J Med 1992; 326; 1973-9.
3. Varoga D, Drescher W, Pufe M, Groth G, Pufe T. Differential expression of vascular endothelial growth factor in glucocorticoid-related osteonecrosis of the femoral head. Clin Orthop Relat Res 2009; 467: 3273-82.
4. Park J, Jun J, Kim. Osteonecrosis of the hip in patients with aplastic anemia. J Korean Med Sci 2002; 17; 806-10.
5. Yoghida T, Kanayama Y. Okamura M. Long term observation of avascular necrosis of the femoral head in systematic lupus erythematosus; an MRI study. Clin Exp Rheumatol 2002; 20: 525-30.
6. Motomura G, Yamamoto T, Miyanishi K, Kondo K, Hirota Y, Iwamoto Y. Risk factors for developing osteonecrosis after prophylaxis in steroid-treated rabbits. J Rheumatol. 2008; 35: 2391-4.
7. Trombolini V, Capua A, Pompili E. Avascular necrosis of the femoral head after treatment Hodgkin´s disease. Acta Oncol 1992; 31: 64-5.
8. Koo KH, Kim R, Kim YS, Ahn IO, Cho SH. Risk Periods of developing osteonecrosis of the femoral head in patients on steroid treatment. Clin Rheumatol 2002; 21: 299-303.

9. Vail TP, Covington DB. The incidence of osteonecrosis. En: Urbaniak JR, Jones JP. Osteonecrosis. Am Acad Orthop Surg 1997; 2: 213-24.
10. Mont MA, Hungerford DS. Non traumatic avascular necrosis of the femoral head. J Bone Joint Surg Am 1995; 77: 459-74.
11. Koo KH, Kim R, Kim YS, et al. Risk period for developing osteonecrosis of the femoral head in patients on steroid treatment. Clin Rheumatol 2002; 21: 299-303.
12. Kramer J, Scheurecker G, Scheurecker A, Stöger A, Huber A, Hofmann S. Femoral head necrosis. Radiologe 2009; 49: 410-8.
13. Wu Z, Yan X, Liu Z, Pan S, Cao X. Avascular necrosis of the femoral head: MR imaging with radiological and histological correlation. Chin Med J (Engl) 1998; 111: 599-602.
14. Takao M, Sugano N, Nishii T, Sakai T, Nakamura N, Yoshikawa H. Different magnetic resonance imaging features in two types of nontraumatic rabbit osteonecrosis models. Magn Reson Imaging 2009; 27: 233-9.
15. Basset LW, Gold RH, Reicher M. Magnetic resonance imaging in the early diagnosis of ischemic necrosis of the femoral head. Clin Orthop 2004; 418: 34-40.
16. Mitchell MD, Kundel HL, Steinberg ME, Kressel HY, Alavi A, Axel L. Avascular necrosis of the hip: comparision of MR, Ct and scintigraphy. AJR Am J Roentgenol 1996; 147; 67-71.
17. Sakai T, Sugano N, Nishii T, Miri H, Ohzono K. Bone scintigraphy screening for osteonecrosis of the hip in patients with non-traumatic osteonecrois of the femoral head. Skeletal Radiol 2003; 31; 650-5.
18. Fridrichova M, Dienstbier Z, Loucka M, Skala E, Blomannová E. Results of the monitoring the group of patients treated for the Hodgkin disease in the period of 1971 to 1996. Part 1: long-time survival in dependence of the clinical stage of the disease. Klin Onkol 2008; 21: 110-5.
19. Maurizi Enrici R, Anselmo AP, Ostti MF. Acute nonlymphocytic leukemia : onset after treatment for Hodgkin´s disease. Ann Heamatol 1997; 74: 103-10.
20. Maurizi Enrici R, Anselmo AP, Ostti MF. Analysis of the risk of solid tumor following Hodgkin´s disease. Haematologica 1997; 82: 52-63.
21. Pietrogrande V, Mastromarino R. Osteopatia da prolongato trattamento cortisonico. Orthop Traumatol Oggi 1957; 25: 791-810.
22. Patel B, Richards SM, Rowe JM, Goldstone AH, Fielding A. High incidence of avascular necrosis in adolescents with acute lymphoblastic leukaemia: a UKALL XII analysis. Leukemia 2008; 22: 308-12.
23. Virik K, Karapetis C, Droufaku S. Avascular necrosis of bone: the hidden risk of glucocorticoids used as antiemetic in cancer chemoterapy. Int J Clin Pract 2001; 55: 344-5.
24. Tektonidou MG, Malagari K, Vlachoyiannopoulos PG. Asymptomatic avascular necrosis in patients with primary antiphospholipid syndrome in the absence of corticosteroid use: a prospective study by magnetic resonance imaging. Arthritis Rheum 2003; 48: 732-6.
25. Smith DW. Is avascular necrosis of the femoral head the result of the inhibitation of angiogenesis? Med Hypotheses 1997; 49: 497-500.
26. Cruess RL. Cortisone-induced avascular necrosis of the femoral head. J Bone Joint Surg Br 1977; 59 :308-17.
27. Eberhardt AW, Yeager-Jones A, Blair HC. Regional trabecular bone matrix degeneration and osteocyte death in femoral of glucocorticoid-treated rabbits. Endocrinology 2001; 142: 1333-40.
28. Weinstein RS, Nicholas RW, Manolagas SC. Apoptosis of osteocytes in glucocorticoid-induced osteonecrosis of the hip. J Clin Endocrinol Metab 2000; 85: 2907-12.
29. Boss JH, Misselevich I. Osteonecrosis of the femoral head of laboratory animals: the lessons learned from a comparative study of osteonecrosis in man and experimental animals. Vet Pathol 2003; 40: 345-54.
30. Naráez J, Narváez JA, Rodríguez Moreno J, Roig-Escofet D. Osteonecrosis of the knee; differences among idiopathic and secondary types. Rheumatology 2000; 39; 982-9.
31. Rossleigh MA, Smith J, Stradu DJ, Engel JA. Osteonecrosis in patients with malignant lymphoma: a review of 31 cases. Cancer 1986; 58: 112-6.