Predictors of Avascular Necrosis of the Hip in Emiratis Patients with Systemic Lupus Erythematosus

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Symptomatic avascular necrosis (AVN) of the hip is a known complication of systemic lupus erythematosus (SLE). Data on the prevalence of bone avascular necrosis (AVN) in Arab SLE patients are limited. We conducted a cross-sectional and retrospective case–control study on 126 SLE patients from Dubai to determine prevalence and predictors of symptomatic hip AVN. 8.7 % of our lupus cohort demonstrated evidence of symptomatic hip AVN and had longer disease duration, higher cumulative steroid dose, and received cyclophosphamide and mycophenolate mofetil more often than the SLE patients without AVN (controls). Skin manifestations, serositis, lupus nephritis, neuropsychiatric lupus, and sero-positivity for autoantibodies: anti-DNA, Anti-Sm, and antiphospholipid antibodies were higher in patients than controls. Administration of hydroxychloroquine prior to onset of AVN was less frequent in cases than controls. In conclusion, disease activity, steroids, cytotoxic drugs, and antiphospholipid antibodies are important predictors of symptomatic AVN in Emirati patients with SLE, Hydroxychloroquine may play a protective role against developing AVN in Emiratis with SLE. Controlled longitudinal studies are essential to validate these findings.

Bone avascular necrosis (AVN) is a clinical entity characterized by cellular death of bone components due to an interrupted blood supply; the affected bone segment then collapses, resulting in bone destruction, pain, and loss of joint function (Mont *et al.,* 1996). Number of factors has been implicated in the pathogenesis of bone AVN including: rapid apoptosis of osteoblasts and osteocytes (Weinstein *et al.,* 2000), increased intravascular coagulation due to generalized thrombophilia or failure of fibrinolysis (Kerachian *et al.,* 2006), and altered lipid metabolism, with the result of an excessive lipid deposition in the bone, ensuing an increase in the intraosseous pressure, which in turn impede blood flow to the affected bone segment and results in its necrosis (Hungerford *et al.,* 1985; Lausten *et al.,* 1993).

Symptomatic AVN of the hip is a frequent complication of systemic lupus erythematosus (SLE). The association between glucocorticoid and AVN is extensively described in literature (Fisher *et al.,* 1971). Different investigators have variably identified steroids and other factors to significantly influence the occurrence of AVN in lupus patients. These factors include a Cushingoid body habitus, smoking, vasculitis, Raynaud's phenomenon, arthritis, pleuritis, neuropsychiatric lupus, disease activity, cytotoxic drugs, and presence of certain auto-antibodies like anti-phospholipid (APL) and the combination of anti-Ro plus anti-RNP (Fialho *et al.,* 2007; Mok *et al.,* 1998; Mok *et al.,* 1997; Kalla *et al.,* 1986; Mont *et al.,* 1997; Watanabe *et al.,* 1997). In addition, ethnicity was shown to be an essential determinant of AVN in lupus patients (Aranow *et al.,* 1997). Since data on the occurrence of AVN in Arab patients with lupus are scarce, we conducted this study to assess the prevalence of hip symptomatic AVN and identify factors that might predict

the occurrence of AVN in Emiratis patients with SLE.

Patients and Methods

This is a cross-sectional and retrospective case–control study, which included 126 Emiratis patients with lupus, who attended the Rheumatology Clinic in Dubai Hospital between January 1st 2002 and January 1st 2008. All patients fulfilled the 1997 revised American College of Rheumatology classification criteria for SLE (Hochberg *et al.,* 1997). Patients with incomplete systemic lupus erythematosus and patients with primary antiphospholipid syndrome were excluded from the study. Access to patient's medical record was granted by Dubai Hospital ethical committee.

Data Symptomatic AVN of the Hip

Medical records of all patients with systemic lupus erythematosus were checked for: a history of hip joint pain, the diagnosis of AVN of the hip, date of the diagnosis of AVN, and number of hip joints affected. X-ray, and/ or MRI (for patients with normal hip X-ray) for those who had a history of hip joint pain and did not undergo radiological investigations in the past to rule concealed avascular necrosis. Since the study is a retrospective cross-sectional case control study, we validated the history of hip joint pain and the results of x-ray and MRI from all patients by direct inquiry on the last visit to our rheumatology clinic in 2007 and reviewing medical record before completing the study. We also checked the Radiology Department electronic records in Dubai Health Authority for the results of X-ray or MRI of the hip for those who stopped attending the Rheumatology Clinic or died before completing the study. We calculated the point-prevalence of AVN in Emiratis patients with SLE on December 31st 2007.

Comparisons

We stratified the patients into two subgroups: patients with AVN (cases) and patients without AVN (control). We compared the two groups with regards to patients' demographic, clinical, immunological, and therapeutic variables before the onset of AVN, and the presence of other Co- morbidities on the 31st December 2007.

Demographic Variables

Patients' age (on December 31st 2007), patients' age at the time of lupus onset, duration of lupus, gender, and present or history of smoking all were recorded.

Clinical Variables

We determined the ever presence or absence of the following clinical features (before the onset of AVN); cutaneous manifestations (malar rash, discoid rash), cutaneous vasculitis, mouth ulcers, arthritis, serositis, fever, haematologic (haemolytic anaemia or leucopenia or thrombocytopenia), renal (urinary casts and/or proteinuria), neuropsychiatric (psychosis or epilepsy or cerebral infarcts on brain MRI), and Raynaud's phenomenon from medical records, history, physical examination, and laboratory tests results. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) at a disease onset, the mean SLEDAI during follow up (the sum of SLEDAI on or around January of each year divided by the number of the years of follow up), and SLEDAI on the last visit to the Rheumatology Clinic was calculated retrospectively for all patients from medical records (Fitzgerald *et al.,* 1999). A Score of 8 or more was arbitrarily defined as active disease at the beginning of the study (Bombardier *et al.,* 1992). Admission to the intensive care unit prior to the onset of AVN was also determined from the medical records.

Immunological Variables

The following antibodies were tested in all patients:

- Antinuclear antibodies (ANA) and anti-double stranded DNA (anti-ds-DNA) were done by indirect immunofluorescent assay (IIF) using a substrate slides supplied by (Immco diagnostics-USA). The slides were analysed with Nikon epifluorscent microscope.
- Detection of autoantibodies directed against SSA (anti-Ro) SSB (anti- La), anti-Sm and anti-RNP and Scl-70 were carried out using ELISA kit provided by INOVA Diagnostics (San Diego-USA)
- Antiphospholipid antibodies (APL IgM & APL IgG) was detected by APhL IgG and IgM HRP ELISA Kit provided by Louisville diagnostics-USA.
- Lupus anticoagulant was done by the ACTICLOT® dPTT test, the kit provided by (American Diagnostica-GmbH-USA), it is intended for the qualitative diagnostic determination of LA in patient plasmas. The test may be performed using semi-automated method.

(For those who stopped attending our Rheumatology Clinic or died before 31st December 2007, medical records and laboratory data were checked for the most recent results for the above mentioned blood tests).

Therapeutic variables

Data on the current and past use of cytotoxic drugs; cyclophosphamide, azathioprine, or mycophenolate mofetil was collected from medical records. The

current or the past use of hydroxychloroquine was also recorded. The mean cumulative prednisolone dose and the maximum prednisolone dose that was taken for at least more than one month were calculated from medical records. We validated patients' compliance on medications on patients' last visit to Rheumatology Clinic before completing the study.

Co-morbidities

Medical records were checked for the diagnosis of hypercholesterolaemia, hypertension, and diabetes mellitus.

Statistical Analysis

The prevalence of symptomatic AVN of the hip in Emiratis with SLE was calculated using Microsoft Excel. All mean values were expressed as mean ± standard error of the mean (SEM). The distribution of each continuous variable was examined statistically for normality. Variables normally distributed were compared using Student t-test. In contrast, variables not normally distributed were compared using the Mann–Whitney test. We used 2×2 tables to calculate the odds ratio (OR) and the confidence interval (CI) of different clinical, immunological, and therapeutic variables. Fisher's exact test was used to assess the statistical significance of the recorded OR, a two-sided P <0.05 were considered to be significant. All statistical analyses were performed using GRAPHPAD PRISM 5 software (Graph Pad Software, San Diego, CA, USA).

Results

Characteristics of the Population before Stratification

A total of 126 Emiratis with lupus patients was enrolled in the study. The mean patients' age on 31st December 2007 was 35.1±0.9 years, the mean age at disease onset was 28.6±0.94 years, and the mean disease duration was 6.6±0.5 years. Of the 126 SLE patients, 121 were females (96.0%). The mean SLEDAI at baseline was 17.3±0.8, the mean SLEDAI during follow up was 6±0.58, and on the last visit to our clinic was 4.5±0.56. The clinical and immunological characteristics of the studied population are summarized in Table 1.

Table1. Frequency (%) Of Clinical and Immunologic Manifestations in 126 Emirati's with Systemic Lupus Erythematosus.

Manifestations	Frequency (%)
Malar rash	69
Discoid lupus	14.3
Oral ulcers	26.9
Arthritis	87.3
Serositis	19
Renal	48.4
Neuropsychiatric	15
Haematologic	61.1
Raynaud's Phenomenon	8.7
Anti-DNA	84.9
ANA	98.4
Anti-Sm	22.2
Anti-RNP	35.7
Anti-Ro	51.6
Anti-La	21.4
Anti-Cardiolipin IgM	20.6
Anti-Cardiolipin IgG	17.5
Lupus anticoagulant	15
Anti-Cardiolipin syndrome	14.3

AVN Data

Hip joint status was verified in 119 of 126 patients who were still under our follow up until 31st December 2007. Six patients died before 31st December 2007 and one stopped attending our clinic since April 2006. Review of medical records and Radiology Department database has helped us in identifying hip status for the remaining seven patients.

Prevalence of AVN on 31st December 2007

The prevalence of AVN in our lupus cohort was 8.7% (11 patients). Ten out of eleven patients with AVN were females. 45.4% (5 patients) had symptomatic AVN at both hip joints. Another 45.4% underwent total hip replacement. 36.3% (4 patients) were found to have symptomatic AVN at other skeletal sites than the hip. On average AVN occurred 6.6±1.5 years after the diagnosis of lupus.

Comparison

We compared the demographic, clinical, immunological, and therapeutic variables of 11 lupus patients with AVN of the hip with 115 lupus patients without AVN of the hip. On comparison, patients with AVN had longer disease duration (11.7±1.6 years vs. 6±0.49 years, *P*<0.0001) than patients without AVN. Otherwise; the two groups were comparable with regards to patients' age, age at the time of onset of lupus, and disease activity at baseline (Table 2).

Table 2. Characteristics of SLE Patients with and without Avascular Necrosis of the Hip Bone

Variables	AVN (11)	Non-AVN (115)	*P*-value
Mean age ± SEM (years)	35.4±1.8	35 ±1	NS
Mean age ± SEM at diagnosis of lupus (years)	23.6±2.2	29 ±1	NS
Mean disease duration ± SEM (years)	11.7±1.6	6± 0.49	<0.0001
Females (%)	90.9	96.5	NS
SLEDAI at baseline ± SEM	21.7±2.3	16.9±0.8	NS

SEM= Standard Error of the Mean, NS= Non significant, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

Interestingly, the occurrence of discoid lupus (OR= 2.5, CI: 1.2-5.1, *P*<0.05), cutaneous vasculitis (OR= 2.7, CI: 1.4-5.3, *P*<0.004), serositis (OR= 2.7, CI: 1.4-5.3, *P*<0.004), lupus nephritis (OR=3.0, CI: 1.7-5.4, *P*<0.0003), neuropsychiatric lupus (OR=3.5,CI: 1.7-6.9, *P*<0.0005), and the proportion of patients with active disease during follow up (OR=2, CI: 1.0-3.7, *P*<0.05) was higher in the cases than in the control group. Table 3 shows the frequency of clinical variables observed in lupus patients with AVN and lupus patients without AVN.

Similarly, the prevalence of positive anti-DNA (OR= 3, CI: 1.4-6.6, *P*< 0.007), Anti-Sm (OR= 2.1, CI: 1.1-3.9, *P*<0.05), antiphospholipid antibodies APL-IgM (OR= 3.6, CI: 1.9-6.8, *P*<0.0001), and APL-IgG (OR= 2.7, CI: 1.4-5.3, *P*<0.004) was higher in the cases than in the control group. On the other hand, the prevalence of positive anti- Ro antibodies was lower in the cases than the control group (OR= 0.4, CI: 0.2-0.7, *P*<0.005). Otherwise, there was no significant serological difference between the two groups. Table 4 illustrates the frequency of immunologic variables seen in the two groups.

Expectedly, patients with AVN had higher mean cumulative steroid dose 34.4g±4.8 vs.16.5±1.5 g (*P*<0.0008), and higher maximum prednisolone dose per day taken for at least one month 40.5±4.3 mg/day vs. 16.5±0.9 mg/day (*P*<0.001) than the control. Furthermore, patients with AVN received cyclophosphamide and mycophenolate

mofetil more often, (OR= 9.6, CI: 5.1-18.3, *P*<0.0001) and (OR=3.5, CI: 1.7-6.9, *P*<0.0005) respectively, than the control. On the other hand, the percentage of patients who received hydroxychloroquine prior to the onset of AVN was lower in the cases than in the control group (OR= 0.45, CI: 0.25-0.8, *P*<0.02). Table 5 outlines the therapeutic variables in the two groups.

There was no significant difference between the two groups with regards to the frequency of arthritis, Raynaud's phenomenon, haematological manifestations, smoking, hypercholesterolaemia, hyper-tension, diabetes mellitus, antiphospholipid syndrome, and the proportion of patients received azathioprine.

Table 3. Comparison of the Clinical Features between SLE Patients with and without Avascular Necrosis of the Hip Bone

Clinical variables	AVN	Non-AVN	Odds Ratio (CI)	*P*-value
Malar Rash (%)	81.8	67	2.4 (1.2-4.3)	<0.05
Discoid lupus (%)	27.3	13	2.5 (1.2-5.1)	<0.05
Cutaneous Vasculitis (%)	36.4	17.4	2.7 (1.4-5.3)	<0.004
Oral ulcers (%)	36.4	26.1	1.6 (0.8-2.9)	NS
Arthritis (%)	90.9	85.4	1.5 (0.6-3.7)	NS
Serositis (%)	36.4	17.4	2.7(1.4-5.3)	<0.004
Renal (%)	72.3	46.1	3.0(1.7-5.4)	<0.0003
Proteinuria	72.3	45.2	3.1(1.7-5.7)	<0.0002
Casts	63.6	33.9	3.451(1.9-6.2)	<0.0001
Neuropsychiatric (%)	36.4	13.9	3.5(1.7-6.9)	<0.0005
Psychosis	27.3	4.3	3.5(1.9-6.7)	<0.0001
Epilepsy	9.1	10.4	0.9 (0.3-2.3)	NS
Brain Infarctions	36.4	10.4	5 (2.3-10.9)	<0.0001
Haematologic (%)	54.5	61.7	0.8 (0.4-1.3)	NS
Leucopenia	54.5	51.3	1.2 (0.7-2.0)	NS
Thrombocytopenia	9	17.4	0.5 (0.2-1.1)	NS
Haemolytic anaemia	9	7.8	1.13 (0.42-3.7)	NS
Hair loss	63.6	56.5	1.3 (0.8-2.4)	NS
Raynaud's Phenomenon	18.2	7.8	2.5 (1.0-6.1)	NS
Antiphospholipid syndrome	9.1	14.8	0.5(0.2-1.3)	NS
Active disease during follow up (%)	36.4	21.7	2 (1.0-3.7)	<0.05
Active disease on the last visit (%)	45.5	12.2	6.3 (3.0-12.8)	< 0.0001
Admission to ICU (%)	18.2	6.1	3.4(1.3-9)	< 0.02
Co morbidities				
Hypercholesterolaemia	36.4	36.5	1.1 (0.6-1.8)	NS
Hypertension	36.4	27	1.8 (0.99-3.1)	NS
DM	18.2	27	0.6 (0.3-1.2)	NS
Smoking	9	5.2	1.8(0.6-5.8)	NS

CI= Confidence Interval, ICU= Intensive Care Unit, DM= Diabetes Mellitus, NS= Non significant.

Table 4. Comparison of the Immunological Features between SLE Patients with and without avascular Necrosis of the Hip Bone

Antibodies	AVN	Non-AVN	Odds Ratio (CI)	P-value
Anti-DNA (%)	100	83.5	3 (1.4-6.6)	< 0.007
ANA (%)	100	98.3	1.2 (0.5-2.94)	NS
Anti-Sm (%)	36.4	20.9	2.1 (1.1-3.9)	<0.05
Anti-RNP (%)	36.4	35.7	1 (0.6-1.8)	NS
Anti-Ro (%)	27.3	48.7	0.4 (0.2-0.7)	<0.005
Combination of anti-RNP & anti-Ro	18.2	20	0.9 (0.4 -1.8)	NS
Anti-La (%)	18.2	21.7	0.8 (0.4-1.6)	NS
Anti-Cardiolipin IgM (%)	45.5	19	3.6 (1.9-6.8)	< 0.0001
Anti-Cardiolipin IgG (%)	36.4	16.5	2.7 (1.4-5.3)	< 0.004
Lupus anticoagulant (%)	9.1	15.7	0.5 (0.2-1.2)	NS

CI= Confidence Interval, NS= Non significant.

Table 5. Comparison of Therapeutic Variables between SLE Patients with and without Avascular Necrosis of the Hip Bone.

Drugs	AVN	Non-AVN	Odds Ratio (CI)	*P*-value
Maximum prednisolone dose taken for at least one month ± SEM (mg/day)	40.5 ± 4.3	16.5 ± 0.9	-	< 0.001
Cumulative steroid dose ± SEM (g)	34.36 ± 4.8	16.52 ±1.5	-	< 0.0008
Average number of cytotoxic drugs ± SEM	2 ± 0.34	0.7 ± 0.06	-	<0.01
Mofetil Mycophenalate (%)	36.4	13.9	3.5(1.7-6.9)	<0.0005
Cyclophosphamide (%)	72.7	21.7	9.6 (5.1-18.3)	<0.0001
Azathioprine (%)	36.4	33.9	1 (0.6-1.9)	NS
Hydroxychloroquine (%)	54.5	73	0.45(0.25-0.8)	<0.02

SEM= Standard Error of the Mean, CI= Confidence Interval, NS= Non significant.

Discussion

In the present study, we calculated the prevalence of symptomatic AVN of the hip in 126 Emiratis with lupus residing in Dubai. Furthermore, we compared the clinical, immunological, and therapeutic variables seen in lupus patients with symptomatic AVN of the hip and patients without AVN. The prevalence of symptomatic AVN of the hip in our cohort was (8.7%) which was comparable to the reported prevalence of symptomatic AVN of the hip in lupus patient from other

ethnic backgrounds (Mok *et al.,* 1998; Heimann *et al.,* 1960).

The mechanism by which SLE causes AVN is multifaceted, i.e. different factors contribute variably to the occurrence of AVN in lupus patients and these include; disease activity/ organ involvement(Nilsen *et al.,* 1977; D'Cruz *et al.,* 1998), vasculopathy (inflammatory vs. thrombotic) (Kluz *et al.,* 2007), steroid (Zizic *et al.,* 1985; Abeles *et al.,* 1978; Kaneshiro *et al.,* 2006; Weng *et al.,* 2005) and cytotoxic drugs (Calvo-Alén *et al.,* 2006; Gladman *et al.,* 2001).

We have shown in this study that lupus patients with AVN of the hip tend to have distinctive clinical features that separate them from lupus patients without AVN. The frequency of skin involvement, serositis, lupus nephritis, and neuropsychiatric lupus predating the onset of symptomatic AVN of the hip was higher in cases than in the control. This is coherent with other studies conducted on lupus patients of Caucasians and Chinese origin (Mok *et al.,* 1998; Cozen *et al.,* 1998; Bono *et al.,* 1999).

In lupus patients, disease activity is usually associated with disturbed lipid metabolism (Borba *et al.,* 2006), leukothrombosis (Belmont *et al.,* 1994), vasculitis (Kluz *et al.,* 2007), and venous thrombosis (Ho *et al.,* 2005); these are the same factors that impede blood circulation in the bone and consequently, influence the occurrence of AVN in patients with lupus, hence the reported association between disease activity and AVN in lupus patients (Fialho *et al.,* 2007; Nilsen *et al.,* 1977; Cozen *et al.,* 1998). Although there was no significant difference in SLEDAI at baseline between the two groups in our cohort, the proportion of patients with active disease during follow up was significantly higher in cases than in the control group, which is in concurrence with other studies (Fialho *et al.,* 2007; Nilsen *et al.,* 1977; Cozen *et al.,* 1998). Interestingly, a greater proportion of patients with AVN had an active disease during their last visit to our Rheumatology Clinic than patients without AVN; we attributed that to the inclination of physicians to keep patients with AVN on the lowest possible dose of steroid after the diagnosis of AVN.

Vasculopathy is a known pathological hallmark of SLE, it tends to be recurrent, widespread, and diverse (inflammatory and thrombotic) (D'Cruz *et al.,* 1998; Cieslik *et al.,* 2008). Furthermore, these lesions are responsible for many of the clinical features seen in lupus. Unlike systemic vasculitis (Shupak *et al.,* 1983; Lowe *et al.,* 1979) there are few case reports in the literature describing the occurrence of AVN in lupus patients with cutaneous vasculitis (Mont *et al.,* 1997; Meyers *et al.,* 2000). We have demonstrated a significant association between cutaneous vasculitis and AVN in patients with lupus, probably through occluding bone microcirculation (Shupak *et al.,* 1983).

Meanwhile, the relationship between APL antibodies and AVN in lupus patients is still controversial as some researchers have found an association between APL antibodies and AVN in lupus patients (Tektonidou *et al.,* 2003; Asherson *et al.,* 1993); others did not find such a relationship (Migliaresi *et al.,* 1994; Houssiau *et al.,* 1998; Mok *et al.,* 2000). Our study supports the presence of an association between APL and AVN in Emiratis patients with lupus, again probably through inducing thrombosis in bone microcirculation (Egan *et al.,* 1994).

Similarly, the data on the relationship between autoimmune antibodies and AVN in lupus patients is scarce. Few have found an association between the presence of the combination of anti-RNP and anti-Ro and the occurrence of AVN in lupus patients (Watanabe *et al.,* 1997); this association was not significant in our cohort. On the other

hand, we have found an association between AVN in Emiratis with lupus and anti-Sm and anti-DNA antibodies. This observation can be interpreted in the context of the reported association between the occurrence of lupus nephritis and anti-DNA and anti-Sm (Alba *et al.,* 2003). Surprisingly; we found lower prevalence of anti-Ro in patients with AVN than in patients without AVN, which we cannot explain.

In agreement with previous studies (Mok *et al.,* 1998; Heimann *et al.,* 1960; Zizic e*t al.,* 1985; Abeles *et al.,* 1978; Houssiau *et al.,* 1998), the cumulative steroid dose and the maximum steroid dose taken for at least one month were strong predictors for AVN in Emiratis patients with lupus. The mechanism of how steroid induces avascular necrosis in lupus patients remains to be elucidated. Probably, this is due to the effect of steroid on altering lipid metabolism systemically through the inhibition of hepatic cytochrome P450 3A (Abeles *et al.,* 1978) giving rise to a fatty liver (Weng *et al.,* 2005; Wen *et al.,* 1998; Wang *et al.,* 1978). Alternatively, via inhibiting lipid metabolism in the bone marrow; by shifting the differentiation of marrow stromal cells to adipocytes (Yin *et al.,* 2006), and inhibiting the differentiation and function of osteoblasts (Hernigou *et al.,* 1999; Hernigou *et al.,* 1997), resulting in excessive fat accumulation within the head of femur and thus raises intraosseous pressure within the head of femur, which in turn, impedes blood flow within the head of femur (Li *et al.,* 2005) and leads to avascular necrosis. Indeed, bone histomorphometric studies have shown an increase in fat deposition in the head of femur in patients with steroid induced avascular necrosis (Motomura *et al.,* 2005). Conversely, several studies conducted on animals have shown the deleterious effect of high dose steroid on blood flow to the head of femur, the significance of these observations to the occurrence of AVN in lupus is yet to be determined (Drescher *et al.,* 2004).

Cytotoxic drugs are often given to lupus patients with systemic involvement. There are several reports on the association between cytotoxic drugs and AVN in patients with lupus (Calvo-Alén *et al.,* 2006; Gladman *et al.,* 2001); our findings support these previous reports. Whether cytotoxic drugs are confounding factors for disease severity or whether there is an underlying mechanism explaining (Wang *et al.,* 1986) the association between cytotoxic drugs and AVN in lupus patients is yet to be determined.

On the other hand, patients with AVN were less exposed to hydroxychloroquine prior to the onset of AVN than patients with normal hip joints. Owing its anti-inflammatory (Fox *et al.,* 1993), anti-thrombotic (Ernst *et al.,* 1984), anti-platelets (Espinola *et al.,* 2002), and lipid lowering effect (Wallace *et al.,* 1990), it is expected that hydroxychloroquine helps in preventing AVN in lupus patients. However, the data on the relationship between hydroxychloroquine and AVN in lupus patients is still controversial. While some have demonstrated the protective effect of hydroxychloroquine against developing AVN in lupus patients (Mok *et al.,* 1998) others were not able to do so (Calvo-Alén *et al.,* 2006).

Despite the described association between hypercholesterolaemia and idiopathic AVN was demonstrated in a number of studies (Moskal *et al.,* 1997), the effect of hypercholesterolaemia on the occurrence of AVN in lupus patients is still unclear. While some have found an association between hypercholesterolaemia and AVN in lupus patients (Ono *et al.,* 1992; Nagasawa *et al.,* 2005), others (Prasad *et al.,* 2007), and the data from our cohort showed no difference in the occurrence of hypercholesterolaemia between the cases and control group. Our work could be criticized of being a cross-

sectional i.e. we probably missed the rise in cholesterol level prior to the onset of AVN. However, there are several factors frequently influence the serum cholesterol level in patients with lupus including disease activity (Borba *et al.,* 2006), antibodies (Lopez *et al.,* 2006), lupus complications (Appel *et al.,* 1985), and medications (Petri *et al.,* 1994), hence the observed discrepancy between the studies with regards to the effect of hypercholesterolaemia on the occurrence of AVN in lupus patients.

We intentionally did not study the interaction between risk factors and their effect on the occurrence of AVN because our sample size was too small for an accurate stepwise regression analysis (Tabachnick *et al.,* 2001).

In conclusion, disease activity, steroids, cytotoxic drugs, and antiphospholipid antibodies are the important predictors of symptomatic AVN of the hip in Emiratis patients with lupus. Probably, hydroxychloroquine plays a protective role against developing AVN in Emiratis patients with lupus. Certainly, larger controlled and longitudinal studies are needed to confirm these findings in Emiratis with lupus.

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