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RESEARCH ARTICLE

LEVELS OF LIVER ENZYMES, AND SERUM LIPIDS, AND ITS ASSOCIATION WITH FEMORAL HEAD OSTEONECROSIS AFTER CORTICOSTEROID TREATMENT IN EGYPTIEN LUPUS PATIENTS.

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Abstract

Objective; to evaluate the association of liver enzymes and serum lipids levels with femoral head osteonecrosis in active SLE patients after high dose steroid treatment.

Methods; Fifty four active SLE patients aged 19-50 years, (7 men and 47 women) were included in our study. Patients were given 40-80 mg prednisolone /day, except 9 patients were treated with 1,000 mg/day for 3 days . Patients are followed immediately before starting steroid therapy, and then at 1, 2 and 3 months as regard clinical ,and laboratory variables including liver enzymes and serum lipids. Patients were classified into ONF group and non-ONF group based on MRI findings.The ONF group included 2 men and 15 women, aged 19-50 years. The non-ONF group included 5 men and 32 women, aged 22-49 years.

Results; There was non significant difference between ONF and non-ONF groups as regard total SLEDAI, ALT, AST, GGT, LDH, TC, HDLP, LDLP ,and TG after follow up at one month. At second month non significant difference was found between ONF and non-ONF groups as regard total SLEDAI, ALT, AST, GGT,and LDH while there was significant difference between ONF and non-ONF groups as regard TC,HDLP, LDLP,and TG. The same findings were present at third month .The prevalence of ONF in our patients were found to be 31% and most of the cases were detected in the second month.

Conclusion; SLE patients who developed ONF showed significant increase in levels of serum lipids, however, no increase in liver enzymes was found over three months of follow up after increasing steroid dose.

INTRODUCTION

The incidence of osteonecrosis (ON) is high in collagen diseases especially systemic lupus erythematosus (SLE)[**1]**. Risk factors for ON in patients with SLE include corticosteroid (CS) therapy, vasculitis, coagulopathy, antiphospholipid antibody, Raynaud's phenomenon and fat emboli **[2].**

The pathogenesis of steroid-induced osteonecrosis femoral head (ONF) still remain unknown. Several mechanisms have been proposed, including oxidation stress, and abnormalities in lipid metabolism coagulation, and steroid metabolism **[3]**.

Many previous studies reported the occurrence of femoral head osteonecrosis either immediately **[3]** after applying CS or increasing its dose, others documented it with long term treatment with CS [**4].**

Some studies reported that the accumulation of hepatic oxidative stress may be related to the development of ONF **[5]**. From clinical findings and animal experiments, it can be proposed that hepatic dysfunction plays an important role in the pathogenesis of ONF induced by steroids and alcohol [**6]** .
Magnetic resonance imaging (MRI) was found to be more sensitive than radiography, and computed tomography, for the detection of very early, asymptomatic ON **[7].**
The aim of our study was to evaluate the association of liver enzymes and serum lipids levels with femoral head osteonecrosis in active SLE patients after high dose steroid treatment.

Patients and methods

We evaluated a total of 54 active SLE patients aged 19-50 years, (7 men and 47 women). They were selected from the out-patients clinics and in-patients units of Rheumatology and Rehabilitation department, Zagazig University hospitals, during the period from June 2014 to June 2015. All patients satisfied The Systemic Lupus International Collaborating Clinics (SLICC) group revised SLE classification criteria **[8].** A written informed consent was obtained from every patient. All patients received high dose systemic steroid therapy due to flare of their disease . The disease activity was evaluated according to the SLE disease activity index 2000 (SLEDAI-2K) **[9]**.
The steroid dosage was increased, from low maintenance dose to 40-80 mg/day, except 9 patients were treated with 1,000 mg/day for 3 days . Exclusion criteria include patients with a history of trauma, alcoholism, sickle cell disease, pancreatitis, Gaucher disease, previous high dose corticosteroid use, pregnancy, hepatic or renal impairment, or those with antiphospholipid syndrome or concomitant rheumatoid patients were excluded. Patients are followed immediately before starting steroid therapy, and then at 1, 2 and 3 months. At each visit a complete history taking, physical examination and laboratory evaluations are carried out, including complete blood count (CBC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), blood urea nitrogen (BUN), creatinine (Cr), anti-DNA antibodies, anti-Sm antibodies and complement titer (C3, C4 and CH50), . Also, we investigated changes in serum total cholesterol (TC) levels, high-density lipoprotein cholesterol (HDLP), low-density lipoprotein cholesterol (LDLP) and serum triglyceride (TG) levels.
MRI of both hips was carried out before increasing CS dose (baseline film) then after 1, 2 and 3 months after increasing corticosteroid dose in all patients. ONF was diagnosed based on the 2001 revised criteria for classification of ON of the femoral head **[10]**.
At the end of the follow up, patients were classified into the two groups; ONF group and the non-ONF group according to MRI findings. The ONF group included 2 men and 15 women, aged 19-50 years. The non-ONF group included 5 men and 32 women, aged 22-49 years. Osteonecrotic lesions appeared well demarcated lesions , such as band-like zones of decreased signal intensity on T1 weighted, spin echo (SE) images and band-like zones of increased signal intensity on short o inversion recovery (STIR) images. MRI was conducted using a 0.5 Tesla superconductive unit (MRT-50; Toshiba, Japan). T1 weighted, SE images were obtained with repetition times (TR) of 300 to 400 ms and echo times (TE) of 18 to 40 ms. STIR images were obtained with a TR of 1500 to 3000 ms, inversion times (o) of 100 to 150 ms, and a TE of 30 to 42 ms **[11][12].**

Results

The ONF group included 2 men and 15 women, with a mean age of 37.5±9.4 years. The non-ONF group included 5 men and 32 women, with a mean age of 38.6±9.7 years. Table(1) showed non significant difference between ONF and non-ONF groups as regard the baseline clinical and laboratory variables.
Table(2) showed non significant difference between ONF and non-ONF groups as regard total SLEDAI ,ALT, AST, GGT,LDH, TC,HDLP, LDLP ,and TG after follow up at one month. Comparison between the two groups of patients after follow up at second month showed non significant difference between ONF and non-ONF groups as regard total SLEDAI,,ALT, AST, GGT,and LDH while it showed significant difference between ONF and non-ONF groups as regard TC,HDLP, LDLP,and TG (Table 3).The same findings were present at third month as shown in Table 4. The prevalence of osteonecrosis femoral head in our patients were found to be 31% and most of the cases were detected in the second month as shown in Table(5).

Table(1);The baseline clinical and laboratory variables of the study group of patients(mean ±SD);

	ONF group N=17	**Non-ONF group N=37**	**t**	**P-value**
Age(19-50 years)	**19-50 37.5±9.4**	**22-49 38.6±9.7**	**.20**	**.84**

Male/female	**2/15**	**5/32**	**Of fisher**	**.58**
BMI(kg/m²)	**21-23** **22.1±.8**	**20.5-22.8** **21.6±.9**	**.94**	**.37**
Total SLEDAI	**15-45** **30.2±10.7**	**12-42** **28.9±9.4**	**.61**	**.55**
ALT (U/L)	**20-34** **28.1±4.9**	**17-29** **27.4±4.0**	**.73**	**.50**
AST (U/L)	**19-31** **24.7±4.8**	**22-34** **25±4.2**	**1.71**	**.11**
GGT(U/L)	**25-40** **33.3±5.8**	**27-39** **31.9±3.9**	**.54**	**.59**
LDH (U/L)	**120-200** **156.1±34.1**	**125-200** **159.9±30.4**	**.73**	**.50**
TC (mg/dl)	**150-185** **160.2±14.2**	**155-190** **170.7±11.9**	**.33**	**.80**
HDLP (mg/dl)	**60-65** **62.1±1.3**	**57-64** **61.1±2.7**	**1.04**	**.22**
LDLP (mg/dl)	**70-95** **81.7±9.8**	**67-93** **78.7±9.4**	**1.06**	**.18**
TG (mg/dl)	**145-195** **166.9±19.4**	**150-190** **169.4±14.7**	**.23**	**.83**

*****P<0Table(2)** Comparison of clinical and laboratory variables between the two groups of patients after follow up at one month

	ONF group **N0=29**	**Non-ONF group** **No=25**	**t**	**P-value**
Total SLEDAI	**10-32** **21.3±9.2**	**9-34** **19.4±10.3**	**.41**	**.69**
ALT (U/L)	**23-37** **31.2±6.1**	**18-39** **29.2±4.3**	**1.33**	**.21**
AST (U/L)	**19-35** **28.6±6.1**	**21-34** **29±4.3**	**.46**	**.66**
GGT(U/L)	**29-40** **35±4.5**	**27-43** **33.6±5.2**	**.53**	**.61**
LDH (U/L)	**135-210** **169.2±32**	**125-198** **170±26.1**	**.06**	**.99**
TC (mg/dl)	**152-187** **166.1+_22.1**	**151-193** **172.2+_34.2**	**2.04**	**.09**
HDLP (mg/dl)	**50-66** **53.7+_1.1**	**48-65** **51.7+_2.27**	**1.98**	**.10**
LDLP (mg/dl)	**71-95** **90.2+_9.7**	**69-94** **84.4+_7.9**	**2.07**	**.08**
TG (mg/dl)	**144-191** **188.4+_17.9**	**152-189** **180.1+_8.9**	**1.99**	**.11**

*****P<0.001; **P<0.01; *P<0.05**

Table(3) Comparison of clinical and laboratory variables between the two groups of patients after follow up at second month

	ONF group No=15	**Non-ONF group** No=25	**T**	**P-value**
Total SLEDAI	**10-27**	**9-25**	**.21**	.84

	18.1±5.3	17.3±6.1		
ALT (U/L)	**25-35** 31.7±3.7	**19-38** 27.3±6.9	**1.44**	.18
AST (U/L)	**18-33** 35.7±5.9	**20-36** 33.8±4.6	**1.06**	.31
GGT(U/L)	**28-43** 35.7+_5.9	**27-41** 33.8+_4.6	**1.00**	.34
LDH (U/L)	**145-200** 170.8±24.2	**136-208** 178.3±2.5	.54	.56
TC (mg/dl)	**230-260** 220.5±19.7	**190-200** 194.9±14.1	**4.45**	.01*
HDLP (mg/dl)	44,1±11.6	63.5±13.4	**22.4**	.00*
LDLP (mg/dl)	**100-180** 124,4±12.6	**90-110** 95.7±16.4	**23.7**	.00*
TG (mg/dl)	**205-240** 210.5±13.2	**190-205** 196.4±3.4	**4.5**	.00*

*****P<0.001; **P<0.01; *P<0.05**

Table(4) Comparison of clinical and laboratory variables between the two groups of patients after follow up at three month

	ONF group **No=15**	**Non-ONF group** **No=39**	**T**	**P-value**
Total SLEDAI	**10-23** **17.1±5.1**	**5-18** **15.3±4.9**	**1.66**	**.15**
ALT (U/L)	**24-39** **32.7±6.3**	**19-35** **29.9±5.9**	**1.53**	**.15**
AST (U/L)	**18-34** **26.7±6.1**	**20-38** **28.4±6.8**	**.81**	**.44**
GGT(U/L)	**29-45** **37.3±6.3**	**24-46** **36.4±6.8**	**.52**	**P=.81**
LDH (U/L)	**160-208** **185.4+_18.2**	**150-200** **173.2+_18.2**	**.96**	**.36**
TC (mg/dl)	**240-270** **257.9+_12.1**	**195-210** **202.7±6.4**	**10.6**	**.00***
HDLP (mg/dl)	**25-32** **28.3+_2.8**	**50-65** **57.7±6.4**	**10.4**	**.00***
LDLP (mg/dl)	**185-200** **193.8+_6.4**	**95-120** **106.9±79.5**	**18.7**	**.00***
TG (mg/dl)	**200-240** **220.2+_15,2**	**185-215** **201.5+_11.5**	**2.42**	**.04**

*****P<0.001; **P<0.01; *P<0.05**

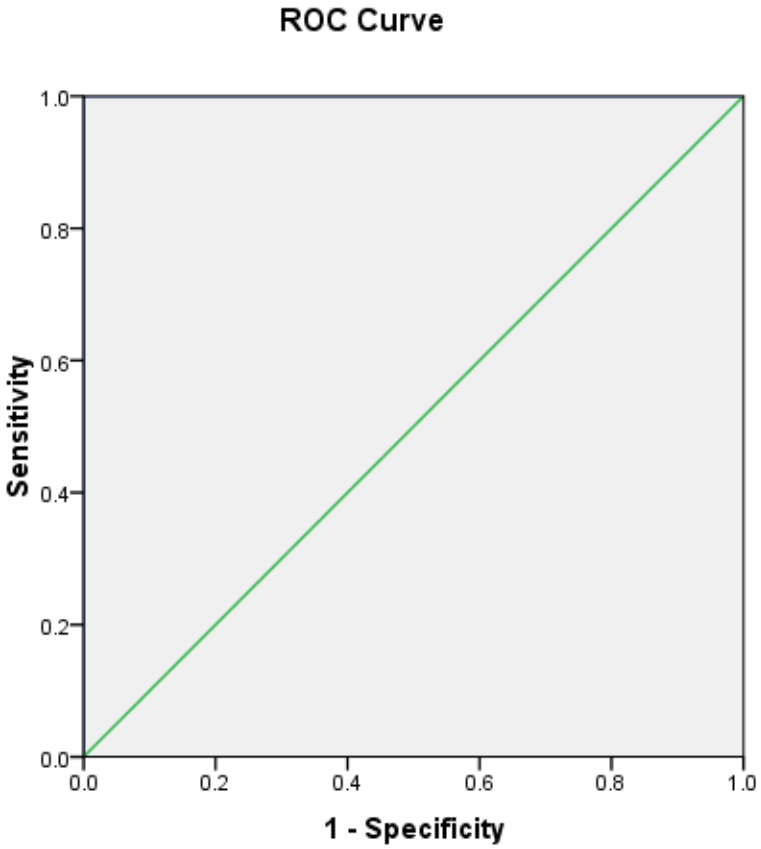
Table(5) MRI findings over the follow up period in ONF group

	ONF group **N=15**	**P-value of one sample**
MRI at baseline	**0**	
MRI at the first month	**1(6.7)**	**.45**
MRI at the second month	**8(53.3)**	**.00***
MRI at the third month	**6(40.0)**	**.00***

P sample of mc nemar test

The incidence of on at 1st month =1.9%

The incidence rate of on at 2nd month =(15.1)
The incidence rate of on at 3rd month =(13.3)
The prevalence rate of on at the 3 month =27.8%



The cut off percentage of change of the lipid profile =19.6%
The sensitiy=88.0%
Specificity =79.4
Ppv=78.6
Npv=88.5

Discussion

Osteonecrosis of the femoral head is frequently complicated with secondary osteoarthritis and walking impairment due to collapse of the femoral head.The precise etiology of this disorder still remain unclear.

One study reported that systemic CS administration contributed to ON femoral head in 51% of cases, and particularly SLE at 31%, followed by polymyositis/dermatomyositis at 6% **[13].**

In this study, we investigated the association between levels of liver enzymes and serum lipids, and occurrence of ON of the femoral head after CS dose is increased from a maintenance dose to a high dose in patients with active SLE using MRI. We followed 54 active SLE patients as regard liver enzymes and serum lipids and MRI was done for both hips before increasing CS dose then after 1, 2 and 3 months after increasing corticosteroid dose in all patients. Patients were classified into ONF group and the non-ONF group according to MRI findings.

The incidence of osteonecrosis in SLE patients varies among different studies ranging from 6 percent in one study **[2]** to 37 percent in another study **[15]** while in our study it was found to be 31 percent.

The findings of one study suggested that ON was detected in SLE within the first month of treatment with high dose corticosteroid **[7]**. Another study concluded that the highest dose corticosteroid administered within 4 months, total cumulative prednisolone dose and cytotoxic treatment were significantly associated with the etiology of ON in SLE **[2]**.

Agreeing with these findings our results showed that most of the cases of ONF occurred in the first three months after increasing corticosteroid dose.

Our study showed non significant difference between ONF and non-ONF groups as regard, ALT, AST,GGT,and LDH after follow up at the first, second, and third month

In this we agreed with one study in which cases of recurring SLE were given high corticosteroid dose after maintenance low dose and found no difference between ONF and non- ONF group as regard AST, and ALT **[1]**.

While we disagreed with a study that showed reduced AST and ALT levels and increased LDH and GGT. This study conducted a retrospective observational review of autoimmune patients including not only SLE but also Mikulicz disease, microscopic polyangitis, adult Still's disease and others **[3]**.This difference can be explained by the patients other than SLE included in his study.

It was reported that statins can help to prevent osteonecrosis in an animal model **[16]**, as well as in humans **[17]**, indicating that a lipid abnormality might be involved in onset of osteonecrosis. However, in another clinical study, anti-hyperlipidemia therapy had not been shown to prevent osteonecrosis**18]**.

In the present study we investigated serum lipids and found that there was significant difference between ONF and non-ONF groups as regard TC,HDLP, LDLP,and TG at the second and third month of follow up .

These findings agree with the results of one report that found that TC levels were significantly higher in the ONF group after the CS dose was increased with no significant difference was seen between subjects who received statin and those who did not **[1].**

Our results disagree with that of another study found no significant difference in total cholesterol levels between the ONF and non-ONF groups **[3]**.This may be because his study was a retrospective observational review including not only SLE patients but also other autoimmune patients who received high-dose systemic steroid therapy. But we agreed in finding a significant difference between the two groups in the change in TG levels .

In conclusion, in the present study, SLE patients who developed ONF showed significant increase in levels of serum lipids, however, no increase in liver enzymes was found over three months of follow up after increasing steroid dose.This suggest that lipid abnormality has role in pathogenesis of ONF in SLE patients and proper control can be helpful for its prevention.

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