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ORIGINAL ARTICLE

ABCB1 Gene Polymorphism: Relation to Risk of Femoral Head Osteonecrosis in Systemic Lupus Erythematosus Patients.

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ABSTRACT

Background: Osteonecrosis (ON) is a known complication of SLE affecting patient's life. Aim of the work was to find out the association between polymorphism of *ABCB1* gene and susceptibility to osteonecrosis of femoral head (ONFH) in SLE patients.

Subjects and methods: A case control study was done on 93 subjects who were divided into 3 groups: Group I: 31 SLE patients with ONFH, Group II: 31 SLE patients without ONFH, Group III: 31 matched healthy volunteers as a control group. ONFH was identified and staged by MRI. Genotyping of *(C3435T)* polymorphism was done by polymerase chain reaction restriction fragment length (PCR-RFLP) for all subjects.

Results: No statistically significant difference (P≥ 0.05) between the studied groups regarding genotypes frequency. However the percentage of genotype *CC* and genotype *CT* were more in group I (32.3%, 29%) and in group II (32.3%, 38.7%) than in controls (22.6%, 25.8%) respectively. Percentage of genotype *TT* was more in controls (51.6%) than in group I (38.7%) and in group II (29%). No statistically significant difference (P≥ 0.05) between groups regarding alleles frequency; however, allele *C* percentage was more in group I (46.8%) and in group II (51.6%) than in controls (35.5%), and allele *T* percentage was more in controls (64.5%) than in group I (53.2%) and in group II (48.4%).

Conclusions: No statistically significant difference between the studied groups regarding genotypes and allele frequencies; *ABCB1*gene polymorphisms *C3435T* do not increase susceptibility to ONFH in SLE patients, but future large scale studies among Egyptian patients are recommended.

Key words: *ABCB1*, Polymorphism, Osteonecrosis of femoral head, SLE.

INTRODUCTION

Systemic lupus Erythematosus (SLE) is an autoimmune disorder caused by loss of tolerance to self-antigens, production of autoantibodies and deposition of complement-fixing immune complexes in different tissues **[1].** It affects predominantly women, primarily during the reproductive age, with a lower ratio seen before puberty and a decline later in life. Female-to-male incidence ratio is 6.2:1 and a female-to-male prevalence ratio is 10.1:1**[2]**.

Musculoskeletal manifestations of SLE are diverse including arthralgia, synovitis, myositis, myopathy

and avascular necrosis of bone which occur at variable frequency at various stages of the disease **[3].**

Osteonecrosis (ON) is caused by lack of blood supply to a part of bone that contributes to bone necrosis and collapse. The prevalence of ONFH is unclear, although statistics indicate that the incidence is between 10,000 and 20,000 new cases each year in the US, with a smaller fraction being idiopathic. ONFH has been associated with a wide variety of autoimmune conditions, including SLE and antiphospholipid syndrome. It also associated with infections and immunodeficiencies, such as human immunodeficiency virus (HIV) **[4]**. SLE is considered as a well-known cause of ONFH, and occurs in around 10% of SLE patients **[5], [6]**

Several causes such as thromboembolism, fat embolism, thrombophilia, hypofibrinolysis, intramedullary hemorrhage, vasculitis and increased bone marrow pressure which correlated to corticosteroid-induced osteonecrosis, contribute to ON in these patients **[7].**

Recently gene polymorphism and non-coding RNA are believed to act as critical regulators in the development of ONFH**.** Among these genes ATP-binding cassette subfamily B member 1 (*ABCB1*) gene which serves as a tumor suppressor **[8]**.

ABCB1 also called P-glycoprotein 1 (P-gp) gene, multidrug resistance gene 1 (*MDR1*) or CD243 which is located on 7q21.1 in human chromosome and contains 28 exons **[9].** P-gp is a protein encoded by *ABCB1* gene, it actively pumps substrates entering cells, like chemicals and drugs to protect cells from the damage of poisons and metabolites **[10],** so it is correlated with the metabolism and transformation of multiple drugs, human tolerance to drugs, and human susceptibility to different diseases **[11]**. SLE is one of autoimmune diseases in which P-gp level is elevated with active SLE when compared with SLE patients in clinical remission **[12]**. Additionally, there is relationship of P-gp and ONFH risk, the increased P-gp activity indicating low risk for ONFH **[13]**.

ABCB1 gene has several single nucleotide polymorphisms (SNPs) which could regulate expression level of P-gp **[14].** In our study, we selected one SNPs *(C3435T)* in *ABCB1* gene and analyzed the association of genotyping and allele frequency of *C3435T* polymorphism with ONFH susceptibility in SLE patients.

SUBJECTS AND METHODS

Study Design and Setting: This case control study was approved by the Local Research Ethical Committee of Zagazig University, with accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki 1964) for studies involving humans. The study was carried out in Rheumatology and Rehabilitation Department in cooperation with Medical Biochemistry and molecular Biology Department, Zagazig University Hospitals on 93 subjects after taking a written informed consent from all participants for ethical consideration. The subjects were divided into 3 groups:

I.Group I: 31 SLE patients with ONFH**.**

II.Group II: 31 SLE patients without ONFH**.**

III.Group III: 31age and sex matched apparently healthy volunteers who served as a control group.

Inclusion criteria: All patients were above 16 years old, and classified according to the systemic lupus international collaboration clinics (SLICC) classification criteria **[15]**. This part was deleted

Patients with any history of hip trauma, previous thrombosis, coagulation disorder, lipid profile abnormality before diagnosis of SLE were excluded. Other Connective tissue diseases as RA, scleroderma, mixed connective tissue disease, overlap syndrome and Behcet's disease, Other chronic diseases such as, renal failure on dialysis, viral hepatitis, cancers, HIV and alcohol consumption or tobacco use before onset of the disease, were excluded from the study.

Tools and instruments used in data collection: Data collected from patient history obtained from medical records of SLE patients followed up in our department, complete examination, and investigations.

Operational steps: History taking with special emphasis on symptoms of ON (groin pain, hip pain radiating to the knee especially with weight bearing with or without stiffness, limping)

- Complete clinical examination, including local examination of locomotor system, all joints of the body were examined, with special concern on hip joints.
- Laboratory investigations: complete blood picture, C3 and C4, kidney function tests, creatinine clearance, protein in 24-hour urine collection, complete urine analysis, antinuclear antibody (ANA), anti-double stranded DNA (Anti-dsDNA) antibodies titre and Antiphospholipid antibodies: lupus anticoagulant (LA) and anticardiolipin ACL.
- MRI on femoral head was done for all patients bilaterally according to **Steinberg et al. [16]**, MRI was done in the sagittal, coronal, and axial planes and includes T1-weighted and T2-weighted sequences. Staging was done using MRI Ficat and Arlet classification **[17].**
- Peripheral venous blood (EDTA anticoagulation) samples were gathered from all subjects for *ABCB1* polymorphism *(C3435T)* analysis.

-DNA extraction & genotype analysis *(C3435T):* DNA was extracted from whole blood using "blood mini kit "QIAamp DNA" (QIAGEN, GmbH, Hilden, Germany)" and stored at -80 °C. DNA was obtained from peripheral leukocytes using a salting out procedure. The presence of the *(C3435T, rs1045642)* variant was identified by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) **[18]**. PCR was performed in a final volume of 25 µl containing 2 µl (30 ng) of genomic DNA, 0.2 µmol/l of each primer and 10 µl of Taq PCR Master Mix (BIORON). The primer sequences were*:* (TTGATGGCAAAGAAATAAAGC; CTTACATTAGGCAGTGACTCG). PCR amplification consisted of three steps: denaturation at 94°C for 90 s, annealing at 54°C for 60 s and extension at 72°C for 90 s over 30 cycles. A negative control was included in each experiment. Amplified DNA fragments (206 bp) were cut by restriction enzyme MboI (New England Biolabs). For 16h at 37°C, The genotypes were identified by electrophoresis of DNA fragments generated after digestion (two bands of 130 and 76 bp for *3435CC*, one band of 206 bp for *3435TT* and three bands of 206bp, 130 bp and 76 bp for heterozygous *3435CT* genotype). The DNA fragments were separated according to size by electrophoresis on 2% agarose gel and observed by ethidium bromide staining.

Statistical analysis: Data were analyzed by the Statistical Package for Social Science (SPSS) version 20 (SPSS, Inc., Chicago, IL, USA). Quantitative data were presented as mean, standard deviations, median and ranges; qualitative data as number and percentage. Comparison between 2 groups with qualitative data was done by Chi-square test and/or Fisher exact test only when the expected count in any cell found <5. Comparison between 2 groups with quantitative data and parametric distribution was done by Independent t-test while nonparametric data was done by Mann-Whitney test.

RESULTS

deleted part There was no statistically significant difference (P≥ 0.05) between the three studied groups regarding demographic characteristics and special habits, ensuring homogeneity of the studied groups **(Table 1).**

Regarding antiphospholipid antibodies there was statistically significant difference (P< 0.05*) between SLE with ONFH and SLE without ONFH groups regarding APL LA, while there was no statistically significant difference (P≥ 0.05) between both groups regarding APL ACL **(Table 2).**

Regarding genotypic analysis, there was no statistically significant difference (P≥ 0.05) between the three studied groups regarding genotypes frequency; however, the percentage of genotype *CC* and genotype *CT* were more in SLE with AVN group (32.3%, 29%) and in SLE without AVN group (32.3%, 38.7%) than in controls (22.6%, 25.8%) respectively. Percentage of genotype *TT* was more in controls (51.6%) than in SLE with ONFH group (38.7%) and in SLE without ONFH group (29%). There was no statistically significant difference (P≥ 0.05) between the three studied groups regarding alleles frequency; however, allele *C* percentage was more in SLE with ONFH group (46.8%) and in SLE without ONFH group (51.6%) than in controls (35.5%), and allele *T* percent was more in controls (64.5%) than in SLE with ONFH group (53.2%) and in SLE without ONFH group (48.4%) **(Table 3).**

Regarding relation between MRI grading of ONFH in group I and genotyping, there was no statistically significant association (P≥0.05) between genotypes and ONFH grading among the SLE with ONFH group **(Table 4)**.

Table (1): Demographic characteristics and special habits among the studied participants (n=93).

Variables	SLE with ONFH (n=31)	SLE without ONFH (n=31)	Controls (n=31)	P value
Age (years) mean± SD Range	 34.55±9.2 18 – 75	 33.68±8.5 19 – 50	 30.77±9.2 18 – 50	 [a]0.229
Sex: No (%) Female Male	 23 (74.2%) 8 (25.8%)	 26 (83.9%) 5 (16.1%)	 24 (77.4%) 7 (22.6%)	 [b]0.640
Smoking: No (%) +ve -ve	 6 (19.4%) 25 (80.6%)	 1 (3.2%) 30 (96.8%)	 5 (16.1%) 26 (83.9%)	 [c]0.134
Alcohol: No (%) +ve -ve	 0.0 (00%) 31 (100%)	 0.0 (00%) 31 (100%)	 0.0 (00%) 31 (100%)	 -

[a] One-Way ANOVA Test

[b] Chi square test (X^2)
[c] Fisher exact test
ONFH: osteonecrosis of femoral head

Table (2): Comparison between SLE with ONFH and SLE without ONFH groups regarding antiphospholipid antibodies (n=62).

Variables	SLE with ONFH (n=31) No (%)	SLE without ONFH (n=31) No (%)	[a]Test	P value
APL LA				
+ve	17 (54.8%)	6 (19.4%)	8.363	0.004*
-ve	14 (45.2%)	25 (80.6%)		
APL ACL				
+ve	13 (41.9%)	7 (22.6%)	2.657	0.103
-ve	18 (58.1%)	24 (77.4%)		

[a] Chi square test (X^2)
APL: antiphospholipid. LA: lupus anticoagulant ACL: anticardiolipin.

Table (3): Comparison between the three studied groups regarding Genotypes and Alleles frequencies (n=93).

Variables	SLE with ONFH (n=31) No (%)	SLE without ONFH (n=31) No (%)	Controls (n=31) No (%)	P value
Genotype				
CC	10 (32.3%)	10 (32.3%)	7 (22.6%)	P1=0.559
CT	9 (29%)	12 (38.7%)	8 (25.8%)	P2=0.108
TT	12 (38.7%)	9 (29%)	16(51.6%)	P3=0.554
Alleles				
C	29(46.8%)	32 (51.6%)	22 (35.5%)	P1=0.201
T	33(53.2%)	30 (48.4%)	40 (64.5%)	P2=0.070
				P3=0.281

P1: Chi square test of significance between SLE with ONFH and Controls, P2: Chi square test of significance between SLE without ONFH and Controls, P3: Chi square test of significance between SLE with ONFH and SLE without ONFH.
Allele is one of a pair of alternative form of a gene, where two alleles make one genotype, so the total numbers of alleles are 62 in each group.

Table (4): Relation between genotypes frequency and MRI grading of ONFH among the SLE ONFH group (n=31).

ONFH Grade	Genotype CC (n=10) No (%)	Genotype TT (n=12) No (%)	Genotype CT (n=9) No (%)	[a]X^2	P value
Grade II (n=15)	7 (46.7%)	5 (33.3%)	3 (20%)	5.92	0.205
Grade III (n=9)	3 (33.3%)	4 (44.5%)	2 (22.2%)		
Grade IV (n=7)	0.0 (00%)	3 (42.9%)	4 (57.1%)		

DISCUSSION

The age of our patients was ranged from (18-75) in SLE with ONFH group, (19-50) in SLE without ONFH group and (18-50) in control group, with no significant difference between SLE groups**.** This result is in agreement with the findings of other studies like **Zhang et al [19], Kuroda et al [20], Yang et al [21], and Tse and Mok [22]**.
On the other side **Hamza et al [23], Sayarlioglu et al [24], Kwon et al [25], and Faezi et al [26]**found that SLE patients with AVN were younger, however **Ghaleb et al [27]**stated that SLE patients with AVN were significantly older.
There was no significant difference among groups regarding sex, alcohol intake and smoking; this was in agreement with **Tse and Mok [22]** who found no difference between groups in sex and alcohol intake. While **Chen et al [28]** found that excess alcohol consumption and smoking were associated with AVN group; this may be due to small number of smokers and no alcohol intake at all among our patients.

There was statistically significant difference among groups regarding positive lupus anticoagulant antibodies (LA) with higher frequency in ONFH group**.** This was in contrast to **Al Saleh et al [29]** who found APL LA was not associated with ONFH while ACL IgG and IgM were more associated with ONFH group. This may explained by the theory of hypercoagulability in Patients with APS with ACL and LA antibodies, which considered a trigger of ONFH in SLE patients, On the other hand **Tse and Mok [22]** and **Sayarlioglu et al [24]** showed no significant association with antiphospholipid antibodies and ONFH.

There was no statistically significant difference between SLE with ONFH group and SLE without ONFH group regarding genotypes and alleles frequency. This result was similar to **Yang and Xu [30]** results, as no significant association was expressed between *C3435T* variant and ONFH risk. In contrast to our results, **Zhang et al [31]** found that *C3435T* polymorphism significantly decreased the risk of ONFH under *TT* vs *CC* genotype and *T* vs *C* allele. So the variant *C3435T* in the *ABCB1* gene may offer protection against the attack of ONFH and the risk of ONFH was reduced to less than one third in carriers with *TT* genotype of *C3435T* polymorphism compared with wild homozygote carriers. Other studies of **He and Li [32]** and **Zhang et al [14]** found the same results with different odds ratios.

Studies on steroid-induced necrosis of femoral head (SONFH), **Xue et al [33]**, **Yang et al [34]** and **Zhang et al [35]** reported that, there were significant correlations between *rs1045642* mutant and SONFH in the prednisone-use and methylprednisolone/prednisone-use populations. Also **Li et al [36]** demonstrated that the *ABCB1* polymorphisms *rs1045642* significantly reduced the risk of SONFH.

Also **Zhou et al [37]** found that *ABCB1 rs1045642 C>T* polymorphisms increased the risk of ONFH under the allele mode. This finding also presented by **Gong et al [38],** who confirmed that the *C* allele increased osteonecrosis risk compared with the *T* allele and *TT* genotype and *ABCB1 C3435T* polymorphisms may be risk factors for osteonecrosis**.**

Our results found no significant difference between SLE patients and controls, this was in agreement with **Gonzalez et al [39]** found no statistically significant differences in allelic and genotypic frequencies between SLE and healthy subjects. Also **Wang et al [40]** analysis for *rs1045642* polymorphism revealed no differences in allele and genotype distribution frequencies between cases and controls. This suggests that the *ABCB1* polymorphisms do not directly interfere with SLE susceptibility, and its polymorphisms are not risk factors for the development of the diseases.

With regard to discrepancies among these studies, possible reasons might be different ONFH types and genotyping methods, various criteria for the selection of cases and controls, as well as potential effects of other genetic, environmental, and demographic factors. Also gene-environment interaction was not incorporated in our study.

This study had some limitations that included relatively small sample size, single place and the data couldn't be generalized as the study design was institutional based and not community based. Also we investigated only one SNP and more polymorphisms loci involved in the pathogenesis of ONFH may help us comprehensively understand the molecular mechanism of the disease.

CONCLUSIONS

No statistically significant difference between the studied groups regarding genotypes and allele frequencies; *ABCB1*gene polymorphisms *C3435T* do not increase susceptibility to ONFH in SLE patients, but future large scale studies among Egyptian patients are recommended**.**

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST:

The authors report no conflicts of interest.

All authors have approved the final article.

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