ORIGINAL ARTICLE

Apolipoprotein E Gene Polymorphism, Serum Lipids, and Risk of Superficial Fungal Infections in Egyptian Patients – A Preliminary Case-Controlled Study

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Abstract

Background: Apolipoprotein E (APOE) gene isoforms have been found to affect the risk of superficial fungal infections (SFIs). However, the data only cover a few ethnicities. **Aims:** The present work intended to investigate the association of APOE gene polymorphism and serum lipids with the susceptibility of SFIs among a group of Egyptian patients. **Materials and Methods:** Standard laboratory methods were used to estimate the serum lipid profile, and polymerase chain reaction–restriction fragment length polymorphism was used to detect APOE gene polymorphism in deoxyribonucleic acid extracted from 150 SFI patients and an equal number of apparently healthy matched controls. **Results:** Serum total cholesterol, triglycerides, and low-density lipoprotein cholesterol were significantly higher in the studied patients than in controls. The APOE gene $\varepsilon 2$, $\varepsilon 4$ alleles, and $\varepsilon 3/4$ and $\varepsilon 3/2$ genotypes were significantly distributed in the patients than in the controls. APOE $\varepsilon 3/3$ genotype was predominant in dermatophytosis and tinea versicolour patients, and $\varepsilon 3/4$ genotype was predominant in candidiasis. **Conclusions:** ApoE alleles $\varepsilon 2$ and $\varepsilon 4$, and genotypes $\varepsilon 2/3$ and $\varepsilon 3/4$ are linked to SFI and may be risk factors, whereas allele $\varepsilon 3$ and genotype $\varepsilon 3/3$ may be protective for SFI in the Egyptian population studied. The lipid profile results suggest that hyperlipidemia may provide evidence for SFI pathogenesis. However; further large-scale studies are still needed to validate our results.

Key Words: *Apolipoprotein E, gene polymorphism, superficial fungal infections*

Introduction

Known for hundreds of years, superficial fungal infections (SFIs) are among the most common cutaneous infections, affecting 20–25% of the population worldwide with continuously increasing incidence.[1] They can be broadly classified into dermatophytic and non-dermatophytic infections, with a predilection for dermatophytic infections to keratinised tissues including the outermost skin layers, nails, and hair.[2]

Even so, not everyone exposed to these pathogens will become infected despite their ubiquitous prevalence Moreover, growing evidence of increasingly resistant fungal infections, including SFI, is emerging, necessitating new insights into the pathogenesis of such infections.[3,4]

The apolipoprotein E (APOE) gene located on chromosome 19 has three polymorphic variants in humans designated as ε2, ε3, and ε4, which vary from one another by the existence of either a C or T nucleotide at codons 112 and 158. The three alleles encode distinct isoforms with a wide range of structural and functional characteristics, including those related to lipid metabolism.[5] Six genotypes are created by specific combinations of the two allelic copies of each gene that each human carries (ε2/2, ε3/3, ε4/4, ε2/3, ε2/4, and ε3/4).[6,7]

The APOE gene affects the lipid profile by influencing the clearance of lipoproteins.[8] Allele ε2 is associated with lower plasma levels of low-density lipoprotein cholesterol (LDL-C). Meanwhile, the ε4 allele is associated with higher plasma levels of total cholesterol (TC), LDL-C, and very low-density lipoprotein cholesterol (VLDL-C),

Access this article online

Quick Response Code:

Website: www.e-ijd.org

DOI: 10.4103/ijd.ijd_1001_22

How to cite this article: Mustafa AI, Shams GM, Fawzy EM, Alhusseini NF, Khashaba RA, EL-Shimi OS. Apolipoprotein E gene polymorphism, serum lipids, and risk of superficial fungal infections in Egyptian patients – A preliminary case-controlled study. Indian J Dermatol 2023;68:233.

Received: December, 2022. **Accepted:** March, 2023.

when compared to the ε3 allele.[9,10] The liver and macrophages are the main producers of APOE, which mediates cholesterol metabolism in peripheral tissues in an isoform-dependent manner.[11] It is a protein component of LDL-C, VLDL-C, and high-density lipoprotein (HDL-C) (lipoproteins), and its localisation has been demonstrated immunohistochemically in normal skin.[12] Growing evidence suggests that APOE interacts with a number of immunological processes, including reducing T cell proliferation, controlling macrophage activity, facilitating the presentation of lipid antigens to T cells, and regulating inflammation.[13,14] Microbial growth can be hindered by APOE by impeding cytokine signalling caused by pathogens.[15] de Bont *et al.*[16] suggested that the lack of APOE might make it more difficult for lipopolysaccharides to be neutralised, which would result in a granulocyte defect and explain the heightened susceptibility to candidiasis.

The association between APOE gene alleles and genotypes with skin disorders has been previously investigated. However, the studies of their association with SFI are limited to a few ethnicities.[17] Therefore, in the current work, we tried to explore the association between APOE gene polymorphism and SFI susceptibility in a group of Egyptian patients.

Materials and Methods

Study population

This study included 150 patients with SFI lesions [tinea versicolour (TVC), cutaneous candidiasis, and dermatophytic lesions]. SFI was diagnosed clinically and confirmed with microscopic examination. A control group of 150 apparently healthy subjects was enrolled. None of the participants had a history of alcohol abuse, primary or secondary hyperlipidemia, cardiovascular disease, or medications that affected lipid metabolism. The study was carried out in accordance with the Helsinki Declaration 2004, and it was approved by the local ethics committee at the Faculty of Medicine, Benha University. All subjects provided informed consent prior to participation.

Laboratory investigations

Participants were asked to fast for 12 hours after eating a standard diet and not taking any medication. Five millilitres of venous blood was obtained from each participant; 3 ml was put in a standard plain tube to separate serum for lipid profile estimation [TC, triglycerides (TGs), HDL-C, and LDL-C] using standardised enzymatic methods, and 2 ml of blood was put in a sterile ethylene diamine tetra-acetic acid vacutainer tube for further deoxyribonucleic acid (DNA) extraction.

Genotyping and polymerase chain reaction

Genomic DNA was extracted and purified using a Gene JET® Whole Blood Genomic DNA Purification Mini Kit (Thermo Scientific, Germany). The extracted DNA purity and concentration were assessed using a NanoDrop 2000™ spectrophotometer with an A260/280 ratio >1.7 considered to be qualified. The genotypes of APOE gene polymorphisms were determined by polymerase chain rection (PCR) and the restriction fragment length polymorphism (RFLP) technique. PCR was carried out using the I-Star™ Taq DNA polymerase enzyme (iNtRON Biotechnology, Korea) with the following primer pair: APOE-P1: 5′-ACA GAA CGC CCC GGC CTG GTA CAC-3′; APOE-P2: 5′-TAA GCT YGG CAC GGC TGT CCA AGG A-3 (Metabion International AG, Germany) on a Vereti thermal cycler (Applied Biosystems, USA) following the PCR conditions, with an initial DNA denaturation at 94°C for 2 min, followed by 40 cycles of denaturation at 94°C for 30 s, annealing at 68°C for 10 s, and extension at 72°C for 1 min. The amplified products were digested with the restriction endonuclease (*Hha I*) enzyme (Thermo Fisher, Germany), then separated by electrophoresis on 2% agarose gel, and visualised by ultraviolet illumination to identify the genotype. According to the size and number of separated fragments, the expected digestion products for each genotype were ε2/2: 91, 83, and 61 bp; ε3/3: 91, 61, 48, and 35 bp; ε4/4: 72, 61, 48, and 43 bp; ε2/3: 91, 83, 61, 48, and 35 bp; ε2/4: 91, 83, 72, 61, 48, and 35 bp; and ε3/4: 91, 72, 61, 48, and 35 bp. APOE genotypes were recalled by two persons independently. ε2/2, ε4/4, and ε2/4 genotypes were not detected in the studied subjects.

Statistical analysis

The collected data were processed using SPSS Version 20.0. Parametric numerical data are expressed as mean and standard deviation (SD), while non-numerical data are expressed as frequency and percentage. Shapiro test was used to determine the normality of data distribution. The Student *T* test was used to compare the means of two groups, while one-way analysis of variance (ANOVA) was used to compare the means of three groups or more, followed by the Tukey test. To investigate the relationship between two qualitative variables, the Chi-square (X^2) test was used, and when the expected count is less than 5 in more than 20% of cells, Fisher's exact test (FET) was used. Deviations from Hardy–Weinberg equilibrium (HWE) expectations were determined using the X^2 test. The odds ratio (OR) and 95% confidence interval (CI) were calculated. *P* values ≤0.05 were considered significant.

Results

The present study included 300 subjects, including 150 patients with SFI, 62 males (41.3%) and 88 females (58.7%) with a mean age of 33.2 ± 11.0 years,

and 150 apparently healthy age- and sex-matched control subjects. Body mass index (BMI), serum TC, TGs, and LDL-C were significantly higher in patients than in control group (P < 0.001, <0.001, 0.042, and < 0.001, respectively). On the contrary, serum HDL-C was significantly lower in the patients' group (P 0.039). Among SFI patients, there were 102 patients (68%) with dermatophytosis, 36 patients (24%) had TVC, and 12 patients (8%) had candidiasis [Table 1].

TC, TGs, and LDL-C were significantly higher in patients with candidiasis and TVC infections rather than in patients with dermatophytosis (P 0.001 each). However, serum HDL-C levels did not differ between SFI clinical types (P 0.301) [Table 2].

Table 1: Basic features of studied subjects

Variable	SFI patients *n*=150	Control *n*=150	*P*
Age (years)	33.2±11.0	36.7±8.6	0.134
Gender			
Male	62 (41.3%)	66 (44%)	0.641
Female	88 (58.7%)	84 (56%)	
BMI (kg/m²)	26.8±3.2	23±2.6	**<0.001**
Lipid profile			
TC (mg/dL)	292.1±67.9	205.4±64.2	**<0.001**
TG (mg/dL)	132.4±42.6	98.4±32.7	**0.042**
HDL-C (mg/dL)	36.3±5.1	40.8±6.6	**0.039**
LDL-C (mg/dL)	232.8±62.3	153.3±50.3	**<0.001**
Duration (months)	**5.3±1.5**	-	-
Clinical types			
Dermatophytosis	102 (68%)	-	-
TVC	36 (24%)	-	-
Candidiasis	12 (8%)	-	-

Data represented as mean±SD or number (frequency). BMI=Body mass index, TC=Total cholesterol, TG=Triglycerides, HDL-C=High density lipoprotein cholesterol, LDL-C=Low density lipoprotein cholesterol, TVC=Tinea versicolor. Bold indicates a significant P

The APOE-ε3 allele was considered the reference allele among studied subjects (92.3% in controls vs 82.7% in patients). Both ε4 and ε2 alleles were significantly associated with SFI patients vs controls (11.3% vs 7.7%, P 0.046 and 6% vs 0%, P 0.0001, respectively). Regarding APOE observed genotypes, the homozygous *ε3/3* genotype was considered the reference genotype among studied subjects (84.7% in controls vs 65.3% in patients). Both ε3/4 and ε3/2 genotypes were significantly distributed in the patients compared to the control subjects (22.7% vs 15.3%, P 0.030 and 12% vs 0%, P 0.0001, respectively) [Table 3].

Significant differences were found in TC, TG, and LDL-C levels in SFI patients in association with APOE alleles and different genotypes. The highest levels of TC and LDL-C were associated with ε4 allele and ε3/4 genotype, while the highest levels of TG were associated with ε2 allele and ε3/4 genotype [Table 4].

With regard to the APOE genotype distribution among SFI clinical types, we observed that ε3/3 genotype was predominant in dermatophytosis and TVC patients (72.6% and 52.8%, respectively), while ε3/4 genotype was predominant in candidiasis patients (50%) [Table 5].

Discussion

Despite being restricted to superficial keratinised tissues, SFI elicits both humoral and cellular immune responses.[1] Apo E expression regulates lipid metabolism in the epidermis. There is growing evidence that links lipid metabolism and immunity.[18]

Our findings revealed a higher APOE ε2 allele and a lower ε3 allele frequency in the patients studied compared to matched controls, inferring that individuals who carry the APOE ε2 allele are more likely to develop SFI (P = 0.0001), while the APOE ε3 allele protects against SFI in the studied group of Egyptian patients. These findings are consistent with previous Turkish reports.[17]

Table 2: Association between the studied SFI clinical types and the other studied parameters

Variable	Dermatophytosis *n*=102	TVC *n*=36	Candidiasis *n*=12	*P*
Age (years)	30.8±12.9	33.7±15.1	52.5±2.6	**<0.001**
Gender				
Male	48 (47.1%)	12 (33.3%)	2 (16.7%)	0.069
Female	54 (52.9%)	24 (66.7%)	10 (83.3%)	
BMI (kg/m²)	26.4±3.4	27±2.2	30±2	**0.001**
Duration (months)	5±1.5	2.6±1.7	3.5±1.2	0.213
Lipid profile				
TC (mg/dL)	275.6±62.7	320.1±44.1	348±73.2	**<0.001**
TG (mg/dL)	126.8±33.2	114.5±32.2	234±70.1	**0.001**
HDL-C (mg/dL)	36.2±6	35.6±3.1	38.5±4.9	0.301
LDL-C (mg/dL)	216.6±61.2	265.6±39.2	271.5±51.1	**<0.001**

Data represented as mean±SD or number (frequency). TVC=Tinea versicolor, BMI=Body mass index, TC=Total cholesterol, TG=Triglycerides, HDL-C=High density lipoprotein cholesterol, LDL-C=Low density lipoproteincholesterol. Bold indicates a significant P

Table 3: Frequency and association between APOE gene genotypes and alleles with SFI susceptibility

Variables	SFI patients *n*=150	Control *n*=150	*P*	OR (95% CI)
Observed alleles				
ε3	124 (82.7%)	138 (92.3%)	Reference	
ε4	17 (11.3%)	12 (7.7%)	**0.046**	1.368 (1.168-1.934)
ε2	9 (6%)	0 (0%)	**0.0001***	-
HWp	0.086	0.771	-	
Observed genotypes				
ε3/3	98 (65.3%)	127 (84.7%)	Reference	
ε3/4	34 (22.7%)	23 (15.3%)	**0.030**	1.502 (1.040-2.169)
ε3/2	18 (12%)	0 (0%)	**0.0001***	-

Data represented as number (frequency). *HWp*=The *P* value of Hardy–Weinberg equation, OR=Odds ratio, CI=Confidence interval. **P*-value is obtained by FET. Bold indicates a significant *P*

Table 4: Lipid profile in SFI patients with different APOE alleles and genotypes

Lipid profile	TC	TG	HDL-C	LDL-C
APOE alleles				
ε3	246.4±96.7	112.7±81.4	35.4±6.3	191.1±92.1
ε2	241.9±78.7	215.4±129.1	37.2±3.7	187.8±81.9
ε4	339.9±73.5	109.2±66.7	36.3±4.7	267.7±59.4
P	**<0.001**	**<0.001**	0.305	**0.002**
APOE genotypes				
ε3/3	243.5±71.6	108.7±26.9	36.1±4.5	188.7±55.5
ε3/4	339.9±73.5	215.4±69.1	35.2±3.7	267.7±59.4
ε3/2	240.6±77.8	109.1±32.1	37.3±6.6	186.8±53.5
P_1	**<0.001**	**<0.001**	0.308	**0.001**
P_2	**<0.001**	**<0.001**	0.215	**<0.001**
P_3	0.839	0.972	0.345	0.888

Data represented as mean±SD. TC=Total cholesterol, TG=Triglycerides, HDL-C=High-density lipoprotein cholesterol, LDL-C=Low-density lipoprotein cholesterol (in mg/dl). P_1 is the comparison between all genotypes, P_2 is comparison between *ε3/3* and *ε3/4*, P_3 is comparison between *ε3/3* and *ε3/2*. Bold indicates a significant *P*

Table 5: Frequencies and association between observed APOE gene genotypes and SFIs

Clinical types	Dermatophytosis *n*=102	TVC *n*=36	Candidiasis *n*=12
APOE genotypes			
ε3/3	74 (72.6%)	19 (52.8%)	5 (41.7%)
ε3/4	8 (7.8%)	4 (11.1%)	6 (50.0%)
ε3/2	20 (19.6%)	13 (36.1%)	1 (8.3%)

Data represented as number (frequency). TVC, tinea versicolour

It is possible that the APOE protein, through immunomodulatory and anti-microbial effects, contributes to the pathogenesis of SFI. APOE affects both innate immunity and acquired immunity *in vitro*.[18] It has been demonstrated that lipoproteins can modulate the growth of microorganisms like Candida albicans by interfering with the interaction between lipopolysaccrides and cytokine-producing cells.[19-21] Similar to Gram-negative bacteria and their lipopolysaccharide component, viable Candida cells and their cell wall components have the ability to stimulate the synthesis of pro-inflammatory cytokines *in vitro*.[22,23] Mice lacking APOE, a protein crucial for neutralising lipopolysacharides, were found to be incredibly susceptible to various microorganisms.[15,16] Granulocytes' ability to phagocytose appears to be lessened in APOE-deficient mice.[24]

Our findings regarding lipid parameters in both APOE ε4 and ε2 carriers were in line with previous published reports.[25,26] Environmental factors, genetics, and exercise appear to have a greater impact on high HDL-C levels than APOE genotypes. However, the small sample size and the inclusion of only one ethnic group limited the study's generalisability. Lipid transport and catabolism in APOE ε2 carriers are markedly slower than in APOE ε3 and ε4 carriers due to APOE ε2's lower receptor binding affinity. Due to the structural difference between APOE ε2 and 3 isoforms, APOE ε2 isoform has a significantly reduced ability to bind to the LDL family of receptors, with metabolic sequalae, particulary type III hyperlipoproteinemia.[27,28]

Additionally, current results reavealed a significantly higher distribution frequency of genotype ε2/3 in the studied group of Egyptian patients as compared to matched control subjects (*P* 0.0001). The genotype ε2/3 has been linked to a substantial imbalance in the lipid metabolism.[29-31] Also, we found a higher prevalence of ε4 allele and ε3/4 genotype in the patient group compared to controls, indicating that the ε4 allele is related to an increased risk of SFI. Similar results have been reported in Turkish patients.[17] The APOE ε4 allele is typically associated with lipid disorders.[32-34] Lipid imbalances have been linked to the pathogenesis of SFI, and dyslipidemia has been found to be more common in those patients.[20,35-37]

The current study found that patients with candidiasis and TVC infections had significantly higher TC and LDL-C levels (*P* 0.031 and 0.024, respectively), while serum TG and HDL-C did not differ significantly among patients with

different clinical types (*P* 0.091 and 0.681, respectively). Hyperlipoproteinemia has been shown to have a determinal impact on the progression of an acute disseminated Candida albicans infection.[20,36,37] Lipids presumably provide growth factors required for replication of the organisms. Cultures of Malassezia furfur are best achieved with a solid medium supplemented with a lipid source.[21,38] These results agreed with those of Framil *et al*.[39] However, Tursen *et al*.[17] and Nowrozi *et al*.[40] observed that there was no correlation between the incidence of TVC and hypercholesterolemia or hypertriglyceridemia.

Current findings support the implication of APOE gene polymorphism to the pathogenesis of SFI and may make it possible to successfully develop anti-SFI therapies that specifically target the APOE gene and its properties, particularly in resistant or recurrent cases. Even though APOE is not specifically targeted, it is likely that APOE genotype influences the therapeutic responses to a number of potential anti-SFI therapies. Therefore, when developing preventive and curative therapies for SFIs, patient stratification by APOE genotype should be taken into account for both treatment regimens and outcome measures.

Limitations

The limitations of the current study are the relatively small sample size due to the higher cost of molecular studies with limited self-funded research and the recruitment of subjects from a single centre. Furthermore, our findings may be the result of genetic–environmental interactions that we did not investigate.

Conclusions

Our findings show that the APOE ε2/3 and ε3/4 genotypes as well as allele ε2 are associated with the increased risk of SFIs in Egyptians, whereas allele ε3 and genotype ε3/3 may have a protective role. APOE ε4 was linked to higher TC and LDL-C levels. Large-scale studies are necessary to verify the relation between APOE polymorphisms and SFI susceptibility. It will be beneficial to define the function of APOE as a potential therapeutic target by conducting similar research on various ethnic groups.

Acknowledgment

We are extremely grateful to all volunteers who took part in this study and the research team who collected the data.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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