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ORIGINAL RESEARCH

Association between leptin gene rs7799039 polymorphism and lipid profile changes induced by isotretinoin treatment in acne patients

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Introduction: Isotretinoin, a vitamin A-derived medication, is one of the effective treatments for severe acne. However, in a fraction of patients, this treatment causes significant adverse effects. Leptin is a pro-inflammatory cytokine that plays a role in apoptosis of adipose cells and sebaceous lipid metabolism. Thus, genetic polymorphisms in the leptin (*LEP*) gene may modulate the response to isotretinoin therapy. Here, we explore the contribution of rs7799039 polymorphism of the *LEP* gene in the adverse effects of the oral isotretinoin therapy among acne patients.

Materials and methods: Clinical parameters were obtained from 200 patients before and after isotretinoin treatment for acne. In addition, circulatory lipid profile and aspartate transaminase (AST) and alanine aminotransferase (ALT) enzymes from acne subjects before and 1 month after oral isotretinoin treatment were also measured.

Results: An association between the rs7799039 polymorphism and the following lipid parameters: high-density lipoprotein (HDL) at baseline and after treatment, HDL % change, low-density lipoprotein % change and total cholesterol % change ($P < 0.05$). In addition, there was an association between the *LEP* polymorphism and higher AST and ALT at baseline and after treatment ($P < 0.05$).

Conclusion: In conclusion, rs7799039 *LEP* polymorphism might modulate lipid parameters and liver enzymes, but not other major side effects of oral isotretinoin therapy.

Keywords: leptin, isotretinoin, acne, polymorphism, side effects

Introduction

Acne vulgaris is a prevalent inflammatory disease of the human sebaceous follicle that affects the young patients.[1,2] It has an estimated prevalence of 70%–90%, and severe acne can affect up to 12% of the adolescent population.[3,4] Acne greatly impacts the quality of life of severely affected individuals as it has been shown to be associated with lesions that mostly occur on the face with the potential for permanent scarring.[5]

The most potent treatment of acne includes the use of isotretinoin.[6] Typically, 1–2 months of isotretinoin therapy is required for an effect to be observable.[7] Isotretinoin achieves its efficacy by interfering with several cellular processes such as division, growth, survival, differentiation and apoptosis.[8] Among the suggested anti-acne effects of isotretinoin are substantial decrease in sebum production, reduction of comedogenesis and suppression of inflammation.[9,10] However, isotretinoin therapy is associated with many side effects that may limit its usage. The major adverse event of isotretinoin is teratogenicity.[11] Other adverse effects include skeletal and mucocutaneous changes where isotretinoin causes myalgia, arthralgia, skin and nostrils dehydration,

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leading to nose bleeding and cracked lips.[12] Other less common side effects include headache, fatigue and hair loss.[13] It also causes psychiatric adverse effects, including mood swings, depression, psychosis, aggressiveness and tendency to commit suicide.[14] It was also found that isotretinoin has a negative impact on lipid profile and liver function.[6,15] The side effects of isotretinoin therapy vary among individuals, and their possible modulation by genetic background in patient samples still needs investigation.[16]

It is known that one of the mechanisms by which isotretinoin exerts its activity is by increasing the leptin levels during and after therapy.[17] Leptin, which is encoded by *LEP* gene,[18] is an important adipokine that plays important roles in appetite pathway[19] and energy expenditure via the regulation of lipid and sugar metabolism.[20,21] Literature also showed that leptin protein is elevated during skin diseases, which suggests a role for leptin in immune network and body defenses.[22,23] Thus, collectively previous data suggest a possible role for leptin in mediating some of the effects of isotretinoin.

Among *LEP* gene polymorphisms is rs7799039. The clinical significance of this polymorphism is well documented as it was associated with higher risk of several diseases including malnutrition inflammation syndrome,[24] obesity[25] and metabolic syndrome.[26] In addition, rs7799039 was associated with blood lipid levels among Southern Chilean population,[27] dyslipidemia in patients using atypical antipsychotic agents and lipid profile modulation induced by soluble fiber intake.[28,29] In the current study, we examined the impact of leptin gene polymorphism (rs7799039) on lipid profile alterations as adverse effects of isotretinoin in acne patients.

Materials and methods

Study subjects

This was a cross-sectional study that was conducted at Dermatology Clinic of the Health Center at Jordan University of Science and Technology, King Abdullah University Hospital and Prince Hamazh Hospital in Jordan. The study was approved by the Institutional Review Board and University Research Committee. New acne patients who received oral isotretinoin treatment were recruited after obtaining written informed consent from participants/guardian. The inclusion criteria were new patients who were given oral isotretinoin therapy (40 mg/day) for at least 30 days. Lipid profile and aspartate transaminase (AST) and alanine aminotransferase (ALT) enzymes were assessed at baseline (before treatment) and at 30 days of treatment. Patients with liver or renal diseases, history of active neoplasm, recent major surgical operations, alcohol abuse or receiving treatment other than isotretinoin were excluded from the study.[30]

Data collection

Clinical data were collected from clinical case files and by interviewing the patients. The collected data included patient age, sex, body mass index, alcohol and supplement use, tobacco use and health conditions. Body mass index (BMI) was calculated based on height and weight as previously described.[31]

Blood sampling

Blood samples were drawn from subjects after fasting for 14 hours. To extract the DNA, 3 mL of blood was collected in EDTA tubes from each patient. For the analysis of biochemical markers, another 3 mL of blood was withdrawn in coagulant-free sterile tubes. Serum was immediately collected after coagulation by centrifugation and stored at −80° until used.[32]

Lipid profile and liver function tests

The blood lipid profile that included total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) was analyzed using clinical chemistry analyzers from Roche Diagnostics International Ltd (Indianapolis, IN, USA). In addition, ALT and AST liver enzyme levels were measured using the same analyzer.

DNA extraction

DNA was extracted from whole blood using a commercially available kit as indicated by supplemented manual (ZymoResearch DNA purification system; Irvine, CA, USA). Isolated DNA was stored in TE buffer in the freezer (−20°C) until used in the genotyping analysis.

Genotyping analysis

Genotyping of the rs7799039 *LEP* gene polymorphism was performed by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) using a Promega master mix (Madison, WI, USA) and C1000TM thermos cycler (Bio-Rad Laboratories, Inc, Hercules, CA, USA). In each PCR reaction, about 50 ng of DNA and 100 nM of each primer were used. Primer sequences were as follows: forward: 5′TTTCCTGTAATTTTCCCGTGA3′ and reverse: 5′AAAGCAAAGACAGGCATAAAA3′. PCR conditions were 5 minutes at 96°C followed by 34 cycles: 96°C for 30 seconds, 52°C for 45 seconds and 72°C for 45 seconds. The PCR reaction was terminated by 5 minutes at 72°C.

The amplified fragment (242 bp) was restricted with HhaI enzyme (Fermentas Canada). Restriction conditions and visualization of DNA fragments were as previously described.[32]

Statistical analysis

Data were analyzed using SPSS statistical software version 23 (SPSS, Inc, IL, Chicago, USA). Continuous variables were compared using unpaired *t*-test or ANOVA tests. Discrete variables were analyzed using the χ^2 test. The significance threshold was set at a *P*-value of <0.05.

Results

Initially, 240 patients were invited to participate in the study, of which 220 gave consent with a response rate of 91.6%. Twenty participants were excluded from the study because of missing data. Therefore, 200 patients were finally included in the study. Table 1 shows participants' demographics and their clinical measures. Most of the participants were young adults with a mean age of 23.36 years and a mean BMI of 24.07 kg/m^2; the majority of them were female (79.5%).

There was a significant increase in the lipid profile (LDL, TC, triglyceride [TG]) and liver enzymes (AST, ALT) after the initiation of the oral isotretinoin therapy when compared to the baseline ($P < 0.05$). However, the levels of HDL were significantly decreased after therapy ($P < 0.05$). The concentrations of lipids and liver enzymes measured before and after 30 days of isotretinoin therapy are given in Table 2.

The results showed that rs7799039 polymorphism was associated with some lipid parameters and liver enzymes (Table 3). The CC genotype of the rs7799039 was associated with lower HDL at baseline and after treatment ($P < 0.05$) and lower HDL % change ($P < 0.05$). The same genotype was associated with lower LDL % change ($P < 0.05$) and TC % change ($P < 0.05$). For liver enzymes, the AC genotype of the rs7799039 was associated with higher ALT and AST at the baseline and after treatment ($P < 0.05$).

Table 1 Characteristics of acne patients of the current study (n = 200)

Variable	Patients, n%
Age (years; mean ± SD)	23.36 ± 6.449
Body mass index (kg/m^2; mean ± SD)	24.07 ± 3.802
Sex (male: female)	20.5: 79.5
Marital status, n (%)	
Single	158 (79.0)
Married	42 (21.0)
Smoking	
No	179 (89.5)
Yes	21 (10.5)
Most reported side effects, n (%)	
Arthralgia/myalgia	155 (77.5)
Nosebleed	159 (79.5)
Headache	149 (74.5)

Table 2 Modulation of lipid profile and liver enzymes by isotretinoin therapy (n = 200)

Parameter	Measure	Before isotretinoin therapy	After isotretinoin therapy
Lipid profile (mmol/L)	HDL	1.41 ± 0.24	1.32 ± 0.32*
	LDL	2.33 ± 0.71	2.78 ± 0.76*
	TC	4.141 ± 0.88	4.61 ± 0.97*
	TG	0.99 ± 0.57	1.32 ± 0.77*
Liver function enzymes (U/L)	AST	18.61 ± 4.97	21.71 ± 9.84*
	ALT	15.71 ± 9.01	17.73 ± 12.30*

Notes: Data expressed as mean ± standard deviation. *Significant difference ($P < 0.01$).

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride.

Table 3 The impact of rs7799039 genotypes on biochemical parameters that are modulated by isotretinoin (n = 200)

Parameter	Genotypes (mean ± SD)		
	CC	AC	AA
HDL (mmol/L)			
Baseline	1.30 ± 0.29*	1.4 ± 0.27	1.37 ± 0.31
After treatment	1.26 ± 0.31*	1.36 ± 0.28	1.33 ± 0.29
% change	−9.54 ± 1.58*	−3.03 ± 1.77$^{\$}$	−9.54 ± 1.20
LDL (mmol/L)			
Baseline	2.37 ± 0.61	2.30 ± 0.82	2.30 ± 0.62
After treatment	2.81 ± 0.70	2.80 ± 0.88	2.69 ± 0.55
% change	1.95 ± 2.08$^{\#}$	2.73 ± 2.11	2.02 ± 1.96
TC (mmol/L)			
Baseline	4.02 ± 0.85	4.24 ± 0.98	4.10 ± 0.70
After treatment	4.55 ± 0.97	4.67 ± 1.09	4.59 ± 0.63
% change	1.03 ± 1.29$^{\$}$	1.44 ± 1.42	9.92 ± 1.25
TG (mmol/L)			
Baseline	0.97 ± 0.55	1.04 ± 0.65	0.91 ± 0.40
After treatment	1.22 ± 0.71	1.45 ± 0.89	1.21 ± 0.50
% change	45.5 ± 116.9	40.6 ± 56.7	29.4 ± 44.4
AST (U/L)			
Baseline	18.40 ± 4.12	19.46 ± 6.04$^{\ell}$	17.00 ± 2.73
After treatment	20.61 ± 6.05	23.40 ± 10.0$^{\ell}$	19.72 ± 4.75
% change	1.956 ± 3.70	1.88 ± 2.52	1.28 ± 3.72
ALT (U/L)			
Baseline	15.56 ± 10.34	17.12 ± 9.35$^{\ell}$	12.68 ± 3.26
After treatment	16.9 ± 9.15	19.44 ± 9.85$^{\ell}$	15.14 ± 5.55
% change	17.41 ± 43.67	23.81 ± 50.69	14.07 ± 69.84

Notes: *CC genotype is significantly different from AC genotype. $^{\$}$A significant difference of CC genotype with AC genotype. $^{\#}$A significant difference of CC with other genotypes. $^{\ell}$A significant difference of AC genotype with other genotypes.

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride.

Discussion

In this study, the roles of the rs7799039 *LEP* gene polymorphism and how it might modulate isotretinoin response in acne patients were explored. The results showed an association between rs7799039 and lipid parameters such as HDL at baseline and after treatment, HDL % change, LDL % change and TC % change in isotretinoin-treated acne patients. In addition, there was an association between *LEP* polymorphism and higher AST and ALT at baseline and after treatment.

Previous literature has shown an altered lipid composition and an increase in the excretion of sebum by sebaceous glands during the development of acne[10] and skin inflammation.[33] Leptin is known as a pro-inflammatory player in sebaceous glands since sebocytes respond to leptin stimulation with pro-inflammatory changes leading to subsequent increases in the level of inflammatory markers including cytokines.[34] In addition, a previous investigation has shown that retinoids modulate the expression of leptin in adipocytes.[35,36]

The present results showed elevations of TC, TG, AST and ALT levels and decreases in HDL level in acne patients treated with isotretinoin. Such changes have been reported in previous investigations and pointed to increasing risks of cardiovascular complications, hyperlipidemia and the metabolic disorders of isotretinoin therapy.[36,37]

The results showed an association between the rs7799039 CC genotype and lower HDL at baseline, lower HDL % change, lower LDL % change and lower TC % change after acne treatment. Thus, the rs7799039 polymorphism of *LEP* gene may be related to lipid profile before and during isotretinoin treatment. The impact of polymorphisms in *LEP* gene and leptin receptor on lipid profile has been shown by previous studies.[38–41] In addition, polymorphisms in *LEP* gene have been shown to modulate the responses to therapeutic agents. For example, a study that was conducted on diabetic patients who were on atorvastatin showed that individuals with GG or GA genotype of *LEP* 2548 had significantly higher levels of LDL compared to AA genotype of *LEP* 2548 after treatment.[31] Similarly, *LEP* 2548 polymorphism has been shown to modulate lipid profile in obese adult population.[40] These findings are in the same line with the present results that rs7799039 polymorphism of *LEP* gene might affect the lipid profile in acne patients treated with isotretinoin. The mechanisms by which rs7799039 polymorphism modulates isotretinoin lipid profile side effects require further investigations. However, rs7799039 was associated with changes in leptin level.[38,42] For example, a study that was conducted on overweight and obese children showed significantly higher leptin levels in rs7799039 AA genotype compared with other genotypes.[38] In addition, AA genotype was associated with higher risk of malnutrition inflammation syndrome,[24] obesity[25] and metabolic syndrome.[26] On the other hand, the CC genotype has been shown to be associated with dyslipidemia in patients using atypical antipsychotic agents.[29] Finally, rs7799039 is known to impact body weight,[27,43] susceptibility to diseases[26,44–46] and response to treatments.[47]

For liver enzymes, the AC genotype of the rs7799039 was associated with higher ALT and AST at baseline and after treatment. As the impact of isotretinoin on liver function is well documented,[6,9,12,48] the current findings suggest a role for the rs7799039 polymorphism in modulating liver functions induced by isotretinoin treatment. The rs7799039 polymorphism was associated with hepatocellular carcinoma.[44] Similarly, an association between polymorphisms in the leptin receptor gene and hepatocellular carcinoma has been documented.[49] The role of genes involved in the leptin pathway in modulating liver functions requires further investigations.

The abovementioned findings are a first step toward further investigations of the long-term lipid complications of isotretinoin therapy and how such complication might be modulated by genetic variations among patients.[36,50,51] The link between isotretinoin therapy complications and genetic background of patients might improve the management of short-term and long-term side effects of isotretinoin use.

Among the limitations of the present study is that it did not cover all common polymorphisms of *LEP* gene and their relationships with isotretinoin treatment. In addition, other cytokines such as adiponectin might also modulate response and side effects of isotretinoin. Therefore, future studies could confirm present findings in other populations or on other *LEP* polymorphisms. Furthermore, the effect of multiple dosing levels or total cumulative dose of isotretinoin per month and variation in BMI over treatment period would also be the future directions for this line of research.

Conclusion

In conclusion, rs7799039 *LEP* polymorphism might modulate lipid parameters, but not major side effects of oral isotretinoin therapy.

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Disclosure

The authors report no conflicts of interest in this work.

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