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Original Research Article

PPARγ Pro12Ala and C161T polymorphisms in patients with acne vulgaris: Contribution to lipid and lipoprotein profile

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ABSTRACT

Purpose: The aim of present study was to clarify the role of peroxisome proliferator-activated receptor γ (PPARγ) Pro12Ala and C161T variants in the pathogenesis of acne vulgaris (AV) and their influence on lipid and lipoprotein profile.
Methods: The present case-control study consisted of 393 individuals including 198 patients with AV (mild-, moderate-, and severe-AV) and 195 unrelated age-matched healthy individuals from Western Iran. The PPARγ Pro12Ala and C161T polymorphisms were identified using polymerase chain reaction-restriction length polymorphism method. Also, serum lipid and lipoprotein profile and fasting blood sugar (FBS) were detected in studied individuals.
Results: In women patients with AV significantly higher serum levels of FBS, total cholesterol, low density lipoprotein-cholesterol (LDL-C) and high density lipoprotein-cholesterol compared to healthy women were detected. Neither PPARγ Pro12Ala nor C161T polymorphism was associated with the risk of AV but the Pro allele was a risk factor for AV among all men and women patients ≥20 years. The variant genotype of PPARγ CG (Pro/Ala) was associated with significantly higher levels of total cholesterol and triglycerides compared to CC (Pro/Pro) genotype. We detected a significantly lower level of FBS in the presence of CT + TT genotype of PPARγ C161T compared to CC genotype. Also, carriers of PPARγ TT genotype had significantly lower serum level of total cholesterol and LDL-C compared to CC genotype.
Conclusions: Our results demonstrated the association of PPARγ Pro allele with susceptibility to AV in patients ≥20 years and the influence of PPARγ Pro12Ala and C161T polymorphisms on the lipid and lipoprotein profile.

1. Introduction

Acne vulgaris (AV) is a chronic inflammatory disease of pilosebaceous unit hair follicles in the skin that are associated with an oil gland. The clinical features of AV are seborrhea (excess grease), inflammation, abnormal follicular keratinization and various degrees of scarring [1].

The peroxisome proliferator-activated receptors (PPARs) belong to the family of nuclear hormone receptors that act as transcriptional regulators of a variety of genes including genes involved in lipid metabolism in adipose tissue, liver and skin. The main receptors involved in sebocyte biology are isoforms of PPARα and PPARγ [2]. Activation of PPARγ involves in glucose homeostasis and adipogenesis in subcutaneous fat and also regulation of lipid metabolism in adipocytes [3].

The gene of PPARγ is located at chromosomal region 3p25 [4]. The common single nucleotide polymorphism of cytosine to guanine in exon 2 of PPARγ results in a proline to alanine substitution at codon 12 (Pro12AlaC/G, rs1801282). The polymorphism modulates the transcriptional activity of the gene. The presence of Pro12Ala polymorphism is associated with reduced transcriptional activity of PPARγ [2]. In one available study the Pro12Ala polymorphism had a protective role against AV development [2].

The polymorphism of PPARγ C161T (rs3856806, His447His) at exon 6 results in a silent substitution of histidine residue [5] .There

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is no available study related to the role of this polymorphism in susceptibility to AV.

The aims of present study were to investigate the association of PPARγ Pro12Ala and C161T variants with AV and with lipid and lipoprotein profile in a population from Western Iran with Kurdish ethnic background.

2. Patients and methods

2.1. Sample

We studied 198 patients with AV (13–43 years, mean age 22.1 ± 4.7 years) consisted of 169 females and 29 males and 195 unrelated age-matched healthy individuals including 143 females and 52 males (13–33 years, mean age 22.6 ± 4.2 years, p = 0.33) without systemic and dermatologic disorders. Adult onset acne (onset ≥25 years of age) was detected in 55 patients. Among patients there were 57 patients with the age onset of AV ≤19 years old and 141 individuals with the age onset of AV ≥20 years old. Exclusion criteria for selecting patients were the presence of pregnancy or breast feeding, receiving anti-inflammatory, anti androgens, anabolic androgens, and oral contraceptive pills and the presence of systemic and autoimmune diseases. All subjects were examined by dermatologist. Patients with AV consisted of 89 individuals with mild AV, 53 subjects with moderate AV and 56 persons with severe AV. Mild AV was detected in the presence of comedones without significant inflammation and a few or the absence of papules, moderate AV was determined in the presence of comedones and significant inflammatory papules and pustules and severe AV was detected in the presence of comedones, papules and pustules and inflammatory nodules [6]. Healthy individuals were medical and paramedical students of the Kermanshah University of Medical sciences. All studied patients and healthy individuals were from the Kermanshah province in Western Iran with ethnic background of Kurds.

Written informed consent was obtained from all studied individuals. The study was approved by the Ethics Committee of Kermanshah University of Medical Sciences and was in accordance with the principles of the Declaration of Helsinki II.

2.2. Biochemical analysis

The serum levels of fasting blood sugar (FBS), triglycerides (TG), cholesterol, low density lipoprotein-cholesterol (LDL-C) and high density lipoprotein-cholesterol (HDL-C) were measured using the Bionic Diagnostic Kits (Iran) by the Mindrey BS-480 chemistry analyzer.

2.3. Genotyping

DNA was extracted from venous blood obtained from each individuals using standard procedure of phenol–chloroform [7].

The PPARγ Pro12Ala (C/G) gene variants were detected by polymerase-chain reaction (PCR) – restriction fragment length polymorphism (RFLP) using the forward primer of 5′-GCCAATT-CAAGCCCAGTC-3′ and the reverse primer of 5′-GATATGTTTGCA-GACAGTGTATCAGTGAAGGAATCGCTTTCCG-3′. The 270-bp PCR product was digested with BstU I restriction enzyme. In the presence of C allele (wild type) the 270-bp fragment remains intact while C to G substitution at nucleotide 34 results in creating a BstU I restriction site and the PCR product digests to two fragments of 227-bp and 43-bp [8].

The polymorphism of PPARγ C161T was studied by PCR-RFLP using the forward primer of 5′ −CAA GAC AAC CTG CTA CAA GC −3′ and the reverse primer of 5′ −TCC TTG TAG ATC TCC TGC AG −3′. In carriers of the wild type allele the 200-bp fragment of PCR-product is digested to two fragments of 120-bp and 80-bp by the restriction enzyme of Pml1 but in carriers of mutant allele only one fragment with 200-bp is produced [9].

2.4. Statistical analysis

The allelic frequencies were calculated by the chromosome counting method. The frequency of genotypes and alleles of PPARγ Pro12Ala and PPARγ C161T in patients were compared to controls using chi-square test. Odds ratios (OR) were calculated as estimates of relative risk for disease and 95% confidence intervals (CIs) obtained by SPSS logistic regression. The correlation values of biochemical data with the studied polymorphisms between groups were calculated using independent-sample *t*-test and ANOVA analysis. Statistical significance was assumed at the p value of <0.05. The statistical package for social sciences (SPSS) logistic regression (SPSS, Inc., Chicago, IL) version 16.0 was used for the statistical analysis.

3. Results

Demographic and biochemical characteristics of patients and controls according to the gender have been compared in Tables 1 and 2. As indicated in Tables 1 and 2 both groups were age- and body mass index (BMI)-matched (p > 0.05). A significantly higher concentration of FBS was detected in women patients (80.3 ± 10.3 mg/dl, p = 0.02) compared to women in control group (76.4 ± 17.7 mg/dl). Also, comparing women indicated significantly higher levels of serum cholesterol (134.8 ± 32 mg/dl, p = 0.004), HDL-C (50.3 ± 13.1 mg/dl, p < 0.001) and LDL-C (78.2 ± 26.7 mg/dl, p = 0.004) in patients compared to those in controls (124.3 ± 28.1, 41.8 ± 9.8 and 69.8 ± 21 mg/dl, respectively) (Table 1). However, among men only serum cholesterol concentration was significantly higher in controls (140.2 ± 31.6 mg/dl, p = 0.039) than patients (125.9 ± 24.6 mg/dl) (Table 2).

Distribution of PPARγ Pro12Ala genotypes was in Hardy-Weinberg equilibrium in patients ($\chi^2 = 1.98$, p > 0.1). Also,

Table 1
Characteristics of women in studied groups

Variables	Patients with AV (n = 169)	Controls (n = 143)	P value
Age (years)	22.1 ± 4.7	22.6 ± 4.2	0.33
BMI (Kg/m^2)	23.3 ± 6.7	22.6 ± 4	0.28
Systolic blood pressure (mmHg)	99.5 ± 12.6	99.4 ± 13.3	0.94
Diastolic blood pressure (mmHg)	70.9 ± 9.5	72.8 ± 10.6	0.11
FBS (mg/dl)	80.3 ± 10.3	76.4 ± 17.7	0.02
Cholesterol (mg/dl)	134.8 ± 32	124.3 ± 28.1	0.004
TG (mg/dl)	82.1 ± 50.4	79.6 ± 38.8	0.63
HDL-C (mg/dl)	50.3 ± 13.1	41.8 ± 9.8	<0.001
LDL-C (mg/dl)	78.2 ± 26.7	69.8 ± 21	0.004

AV: acne vulgaris; FBS: fasting blood sugar; TG: triglycerides; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol.