The Relationship Between the Peroxisome Proliferator-Activated Receptor Gamma 2 Gene Polymorphism, Lipids and Adipokines in Patients with Major Depression

Majör Depresyonlu Hastalarda Peroksizom Çoğaltıcı-Aktive Edici Reseptör Gama 2 Gen Polimorfizmi, Lipidler ve Adipokinlerle İlişkisi

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ABSTRACT Objective: Peroxisome proliferator-activated receptor gamma (PPARγ), lipids, lipoproteins, and adipokines have recently been shown to be associated with psychiatric diseases. Our major aim is to investigate the contribution of the PPARγ gene polymorphism, adipokines, lipids, and lipoproteins to the development of major depression. **Material and Methods:** The frequency of Pro12Ala in exon 2 and C478T in exon 6 of the PPARγ gene, lipids and adipokines in major depression (n = 78) and control subjects (n= 64) were analyzed. Genotypes of PPARγ gene polymorphisms were examined. Serum leptin, adiponectin, and resistin were studied by enzyme-linked immunosorbent assay (ELISA). Serum apo A1, apo B, and Lp(a) levels were determined by immunonephelometry. Serum total cholesterol, triglyceride, HDL-cholesterol and LDL-cholesterol levels were analyzed by enzymatic methods. **Results:** The genotypes of exon 2 and exon 6 distribution did not differ between the control subjects and patients with major depression. Frequencies of genotypes of Pro12Ala, and Ala12Ala in exon 2 in overweight and obese patients with major depression were higher than those of overweight and obese controls. C478T polymorphism was highest in overweight and obese patients with major depression. Pro12Ala and Ala12Ala genotypes in exon 2 of PPARγ gene in patients were found to be associated with triglyceride and HDL-cholesterol. There were significant differences regarding glucose, total cholesterol, LDL-cholesterol, apo B, Lp(a), adiponectin and resistin levels between patient and control subjects. **Conclusion:** PPARγ exon gene polymorphisms, alterations in lipid profile and adipokines may be associated with the development of major depression.

Key Words: Adipokines; lipids; major depressive disorder;single nucleotide polymorphisms; PPAR gamma

ÖZET Amaç: Peroksizom çoğaltıcı-aktive edici reseptör gama (PPARγ), lipidler, lipoproteinler ve adipokinlerin son yıllarda psikiyatrik hastalıklarla ilişkili olduğu gösterilmiştir. Çalışmadaki temel amacımız,majör depresyon gelişimine PPAR gama gen polimorfizmi, adipokinler, lipidler ve lipoproteinlerin katkısını araştırmaktır. **Gereç ve yöntemler:** Majör depresyonlu 78 ve kontrol grubundaki 64 kişide adipokinler, lipidler ve PPARγ geninin ekzon 6 kısmında C478T ve ekzon 2 kısmında ise Pro12Ala'nın sıklığı analiz edildi. PPAR gama gen polimorfizminin genotiplendirilmesi incelendi. Serum leptin, adinopektin ve resistin düzeyleri ELISA yöntemiyle çalışıldı. Serum apo A1, apo B ve Lp(a) seviyeleri immünonefelometri ile ölçüldü. Serum total kolesterol, trigliserid, HDL-kolesterol, LDL- kolesterol seviyeleri enzimatik metodlarla analiz edildi. **Bulgular:** Ekzon 2 ve ekzon 6 dağılımı, kontrol ve majör depresyon vakalarında farklılık göstermedi. Ekzon 2'deki Pro12 Ala ve Ala12Ala genotiplerinin sıklıkları, majör depresyonu olan kilolu ve obez hastalarda, majör depresyonu olmayanlara göre daha yüksekti. C478T polimorfizmi majör depresyonlu kilolu ve obez hastalarda en yüksek düzeyde bulundu. Hastaların PPAR gama geni ekzon 2'deki Pro12Ala ve Ala12Ala genotipleri trigliserid ve HDL ile ilişkili bulundu. Hasta ve kontrol gruplarında glukoz, total kolesterol, LDL-kolesterol, apo B, Lp(a), adiponektin ve resistin seviyeleri açısından anlamlı bir ilişki bulundu. **Sonuç:** PPAR gama ekzon gen polimorfizmleri, lipid profilinde ve adipokinlerdeki değişiklikler majör depresyon hastalığının gelişimiyle ilişkili olabilir.

Anahtar Kelimeler: Adipokinler; lipidler; majör depresif hastalık; tek nükleotid polimorfizm; PPAR gama

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Major depression (MD) is a disorder of emotion characterized by persistent sad mood or a loss of interest or pleasure in daily activities and by a number of associated symptoms, such as weight loss or gain, loss of appetite, sleep disturbance, psychomotor retardation, fatigue and feelings of guilt.[1] Patients with recurrent type major depressive disorder had lower quality of life in terms of physical functioning, general health perception, and physical component summary score compared to patients with single episode type major depressive disorder.[2]

Peroxisome proliferator-activated receptor gamma (PPARγ) is an important transcription factor that regulates lipid and glucose metabolisms.[3] Three types of PPAR have been described up to date, and of these, PPARγ has been shown to regulate adipocyte differentiation and lipid metabolism through the activation of adipocyte-specific genes.[4] The PPARγ regulates the transcription of target genes protein by forming a heterodimer with the retinoid X receptor which then binds to specific PPARγ response elements in the promoter regions of these genes.[5] Forced expression of PPARγ leads to the differentiation of adipocytes in fibroblasts.[6] Dominant negative mutant PPARγ alleles that impair PPARγ function have provided insight into its biological function in vivo. A Pro115Gln PPARγ mutant has been reported to be related to excessive adipose tissue accumulation through an intrinsic increase in adipogenic activity.[7] Mutations in human PPARγ have been associated with severe insulin resistance, hypertension, diabetes mellitus and alterations in lipid profile, such as low levels of high-density lipoprotein cholesterol and high levels of triglycerides.[8] There are three PPARγ mRNA isoforms, PPARγ1, γ2, and γ3, generated by alternative promoter regions. PPARγ1 mRNA is found in variable amounts in all tissues, such as heart, liver, skeletal muscle and adipose tissue. PPARγ2 is expressed in adipose tissue and liver whereas PPARγ3 is confined to macrophages, colon epithelium, and adipose tissue.[9,10] PPAR γ2 contains 30 additional amino acids at its N-terminus and may confer a greater ligand-independent activation function upon this isoform. PPARγ2 expression is increased in adipose tissue taken from obese subjects, but expression in the lean subjects is reduced during weight loss.[11] A number of genetic variants in the PPARγ gene have been reported. The Pro12Ala polymorphism in PPARγ2 was first identified in 1997,[12] and the rare allele frequencies are approximately 12% in Caucasians, 10% in Native Americans, 8% in Samoans, 4% in Japanese, 3% in African-Americans, 2% in Nauruans, and 1% in Chinese.[13] At position 34, CCA-to-GCA missense mutation causes an amino acid change from a proline to an alanine at codon 12 (Pro12Ala). This exon encodes the NH_2-terminal residue that defines the adipocyte-specific PPARγ2 isoform. Functional differences are observed for this Ala variant. These differences indicate that Ala variant has a reduced affinity for the response element and a lower capacity for activating target genes.[14]

While it has long been apparent that obesity is a major risk factor for MD, it has recently been appreciated that adipose tissue, in addition to its role as an energy reservoir, modulates energy metabolism via secretion of circulating adipocytokines. The resistin, leptin, and adiponectin, which are identified as adipokins, appear to be important in regulating insulin sensitivity. Obesity, particularly visceral obesity, is associated with insulin resistance,[15] but the mechanism whereby adipose tissue modulates insulin sensitivity is controversial.[16]

Resistin is a protein produced by mature adipocytes which regulates whole-body insulin sensitivity. It is mainly expressed in visceral white fat. It was initially isolated as an mRNA whose expression is suppressed in response to rosiglitazone, PPARγ agonist that enhances insulin sensitivity.[16]

Leptin regulates the balance between food intake and energy expenditure. The plasma leptin levels are correlated with the total body fat mass.[17] Basal concentrations of leptin in the bloodstream are proportional to adipose tissue mass and hence leptin level is considered as a good marker of adipose tissue size.[18]

Adiponectin is an adipocyte-specific protein that sensitizes the liver and muscle to the action of insulin. It has been reported that plasma adiponec-

tin is lower in obese subjects compared to lean subjects, lower in diabetic patients compared to non-diabetic patients, and is negatively correlated with body weight, visceral fat mass, and resting insulin level. Adiponectin levels in the circulation are up-regulated by the PPARγ agonists such as rosiglitazone.[19]

Unfortunately, there no studies up date have investigated whether polymorphisms in PPARγ2 gene are associated with major depression or not. The purpose of this study is to find known polymorphisms of PPARγ2 in MD, to measure serum leptin, adiponectin, resistin, lipid and lipoprotein levels, and to determine whether there are associations among PPAR polymormhisms and adipokines.

MATERIAL AND METHODS

STUDY SETTING AND POPULATIONS

The study was carried out in the Departments of Biochemistry and Psychiatry in Faculty of Medicine, Karadeniz Technical University. The study was approved by the local ethics committee and informed consents were obtained from the participants after all procedures were fully explained. The patients between 18 and 65 years of age who accepted to participate in the study by signing up the informed consent forms were included in the study. The ones who had psychotic disorder or dementia, had a history of psychiatric disorder except major depression or used psychtropic drugs were excluded from the study. In the psychiatric examinations of the patients and the control group, Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) was used.[2] The control group was derived from the hospital staff and their relatives without any history of severe somatic disease or psychiatric disorder and accepted to participate in the study voluntarily after being informed about the aim of the study. Patient and control subjects were incorporated into the study following the examination of their medical histories. Individuals who were on medication (such as antidiabetics, antihypertensive, antilipidemics etc.) due to diabetes mellitus type 2, cardiovascular disease and other chronic diseases were excluded. Seventy eight patients diagnosed with major depression and 64 healthy controls were included in the study. All included patients and volunteers completed the study. Age, gender, and body mass index (BMI) of the all subjects were recorded. Patient group was divided into three groups with regard to BMI: (< 18.5 kg/m^2 for lean, 18.5-24.9 kg/m^2 for normally weighted, > 25 kg/m^2 for overweight and obese). There were 31 overweight and obese, 24 normal weighted, 23 lean patients. The control group was also divided into three groups; 22 overweight and obese, 20 normal weighted, and 22 lean. After an overnight fasting period, peripheral venous blood samples of the subjects were drawn into the tubes. Serum total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol levels were analyzed by enzymatic methods using Roche Diagnostics Modular DP analytic system (Germany). Serum Apo A1, apo B, and Lp(a) levels were determined by immunonephelometry (Dade Behring, BN II). Serum leptin levels were measured by Enzyme-linked Immunometric Assay (ELISA) kit (catalog no: KAP2281, BioSource International Inc., USA). Serum resistin and adiponectin levels were measured with ELISA kits according to the manufacturer's instructions (respectively, catalog no: ER1001-1, catalog no: EA2500-1, Assay Pro, USA).

Phenotypic characteristics were determined.

DNA EXTRACTION, PCR AND DNA SEQUENCING OF PPARα2 EXON 2 AND EXON 6

Pro12Ala in exon 2 and C1431T in exon 6 of the PPARγ gene were screened for the presence of polymorphisms in a total of 142 individuals. DNA was extracted from whole blood samples by using Invisorb Spin Blood Mini Kit (Catalog no: 1031100200; Berlin, Germany). Some DNA extractions have been failed for exon 6 (five subjects in MD group and one control subject). Amplifications of the PPAR γ2 exon 2 and exon 6 were performed with AmpliTaq Gold® PCR Master Mix (2X) (Applied Biosystems, California, USA) using following primers: 5'-CCAGAAAATGACAGACCTCAGACA-3' and 5'-CAGAATAGTGCAACTGGAAGAAGG-3' for exon 6.5'-GATGTCTTGACTCAT-

GGG-3' and 5'-GGAAGACAAACTACAAGAGC-3' for exon 2. The reactions were performed with an initial denaturing cycle of 10 minutes at 95°C, followed by 30 cycles of 95°C for 45s, 58°C for 60s, 72°C for 60 s, and a 7 minutes final extension at 72°C. BigDye Cycle Sequencıng v3.1 Kit (Applied Biosystems, California, USA) was used for cycle sequencing reactions. Cycle sequencing was performed for 25 cycles of 96 °C for 10 s, 50 °C for 5 s, and 60 °C for 4 min on Gene Amp PCR Systems 9700 (Applied Biosystems, California, USA) and sequencing products were purified using SEPHADEX G-50 (Sigma-Aldrich, Taufkirchen, Germany). Automated sequencing was carried out on an ABI PRISM 310 Genetic Analyzer (Applied Biosystems, California, USA). Sequencing analysis was performed with SeqScape v2.6 software (Applied Biosystems, California, USA) and BioEdit (BioEdit, Carlsbad, CA) software using mutation charts.

CC genotypes expressed in C478T polymorphism in exon 6 were evaluated as wild type, while TC was heterozygous and TT was homozygous mutant. For Pro12Ala polymorphism in exon 2, CC was revealed as wild type, GC was heterozygous and GG as homozygous mutant.

DATA ANALYSIS

The results were expressed as mean ± SD. Distribution of variables in the study groups was assessed by Kolmogorov Smirnov test. Comparisons of clinical parameters for patient and control groups were done by either unpaired t-test (normal distribution) or Mann-Whitney-U test (not normal distribution). The parameters according to subgroups (overweight and obese, normal and lean) within normal distribution were analyzed by post hoc Tukey test after one way ANOVA test, those not within normal distribution by Kruskal Wallis test. The distribution of alleles and genotypes between groups was compared using χ^2 analysis test. A value of $p < 0.05$ was considered significant.

RESULTS

Serum glucose, total cholesterol, LDL-cholesterol, apo B, Lp(a), adiponectin, and resistin levels of the patients with MD were found significantly higher compared to those of the control group (Table 1).

Table 2 shows clinical parameters within subgroups (overweight and obese, normal, lean).Glucose, total cholesterol, triglycerides, LDL-choles-

TABLE 1: The clinical and demographic characteristics of the patient and control groups.[a]

	Patient group Mean ± S.D. (Median)	Control group Mean ± S.D. (Median)	p value
n	78	64	
Gender (female / male)	62/15	35/28	
Age (years)	38 ± 11 (39)	28 ± 9 (24)	0.001
BMI (kg/m2)	24.66 ± 5.61 (24)	22.98 ± 5.55 (22)	0.033
Glucose (mmol/L)	5.34 ± 1.13 (5.80)	4.87 ± 0.52 (4.88)	0.003
Total cholesterol (mmol/L)	10.26 ± 2.09 (9.86)	9.41 ± 2.13 (9.02)	0.019
Triglyceride (mmol/L)	6.60 ± 4.04 (5.80)	6.10 ± 3.42 (4.88)	0.380
HDL-cholesterol (mmol/L)	2.90 ± 0.66 (2.88)	2.97 ± 0.83 (2.83)	0.597
LDL-cholesterol (mmol/L)	6.55 ± 1.98 (6.47)	5.85 ± 2.14 (5.52)	0.049
Apo A1 (mmol/L)	8.08 ± 1.43 (8.41)	7.93 ± 1.83 (8.05)	0.615
Apo B (mmol/L)	5.22 ± 1.55 (5.14)	4.29 ± 1.73 (4.13)	0.001
Lp (a)	19.48 ± 16.75 (9.87)	20.31 ± 15.95 (13)	0.002
Insulin (µU/mL)	7.99 ± 8.28 (5.09)	7.87 ± 11.04 (4.03)	0.135
Leptin (ng/mL)	9.22 ± 7.55 (7.23)	9.61 ± 9.08 (7.18)	0.784
Adiponectin (µg/mL)	10.27 ± 7.50 (7.67)	5.84 ± 4.07 (4.42)	0.001
Resistin (ng/mL)	2.26 ± 0.98 (2.06)	2.72 ± 1.30 (2.35)	0.022

[a]Statistical analysis by unpaired t test, except triglyceride, Lp(a), insulin, leptin and adiponectin by Mann-Whitney U test.
BMI: Body mass index

TABLE 2: Biochemical analysis results in overweight and obese, normal and lean patients with major depression.[c]

	Overweight and Obese n = 31 Mean ± S.D. (Median)	Normal n = 24 Mean ± S.D. (Median)	Lean n = 23 Mean ± S.D. (Median)	p value
Glucose (mmol/L)	5.84 ± 1.43 (5.38)	5.13 ± 0.91[a] (5.00)	4.88 ± 0.42[a] (4.94)	0.004
Total cholesterol (mmol/L)	11.31 ± 1.83 (11.00)	9.43 ± 1.45[a] (9.55)	9.72 ± 2.44[a] (8.83)	0.001
Triglyceride (mmol/L)	8.87 ± 4.00 (8.11)	5.50 ± 4.27[a] (4.55)	4.68 ± 1.96[a] (4.22)	0.001
HDL-cholesterol (mmol/L)	2.62 ± 0.49 (2.61)	3.02 ± 0.82 (2.94)	3.14 ± 0.57[a] (3.11)	0.009
LDL-cholesterol (mmol/L)	7.76 ± 1.77 (7.50)	5.90 ± 1.15[a] (5.72)	5.59 ± 2.15[a] (5.11)	0.001
Apo A (mmol/L)	7.86 ± 1.09 (7.94)	8.02 ± 1.95 (8.41)	8.44 ± 1.16 (8.66)	0.330
Apo B (mmol/L)	6.09 ± 1.55 (5.48)	4.62 ± 1.02[a] (4.56)	4.68 ± 1.54[a] (4.38)	0.001
Lp (a)	20.27 ± 17.16 (13)	21.54 ± 18.28 (11)	16.28 ± 14.67 (9)	0.300
Insulin (μU/mL)	9.06 ± 9.68 (6)	8.68 ± 8.58 (5)	5.82 ± 5.31 (4)	0.132
Leptin (ng/mL)	12.94 ± 8.41 (11.07)	8.03 ± 6.84[a] (5.99)	5.45 ± 4.28[a] (4.19)	0.001
Adiponectin (μg/mL)	9.59 ± 6.98 (8.09)	8.29 ± 7.50 (4.54)	13.27 ± 7.57[b] (15.42)	0.053
Resistin (ng/mL)	2.18 ± 0.99 (2.03)	2.37 ± 0.91 (2.29)	2.25 ± 1.05 (2.03)	0.775

Values are mean ± SD.

[a]Values are significantly different from those of obese ($p < 0.05$)

[b]Values are significantly different from those of normal weighted ($p < 0.05$).

[c]Statistical analysis by post hoc Tukey test after one way ANOVA, except Lp(a), glucose, insulin and adiponectin by Kruskal Wallis test

terol, apo B and leptin levels had the highest levels in overweight and obese patients with MD, whereas HDL-C levels were the lowest.

The genotypes of exon 2 and exon 6 distribution did not differ between the control group and the patients with MD (Table 3).

The frequencies of Pro12Ala (CG), and Ala12Ala (GG) genotypes in exon 2 in overweight and obese major depressive patients were higher than those of overweight and obese controls (Table 4), but there was no significant difference.

The frequencies of exon 6 genotypes of major depressive patients did not differ from those of the control group. However, T allele had the highest frequency in overweight and obese patients with MD (Table 4).

Pro12Ala (CG) and Ala12Ala (GG) polymorphisms in exon 2 of PPARγ gene were found to be associated with lipids (increased triglycerides and decreased HDL-C) (Table 5), whereas polymorphisms in exon 6 were not found to have such an association.

DISCUSSION

PPARγ plays an important role in the control of adipocyte differentiation and in the regulation of lipid and glucose homeostasis. Therefore, the PPARγ gene may regulate insulin sensitivity and resistance.[20]

Swarbrick et al. analyzed the relationship between Pro12Ala polymorphism of the PPARγ gene and combined hyperlipidemia in obese patients.

TABLE 3: Genotype distribution and allele frequency of the exon 2 and exon 6 of PPARγ2 gene in major depressive patients and control group.

	Major depressive patients		Control group	
Genotype	n	%	n	%
Exon 2				
CC	65	83.34	54	84.37
CG	11	14.10	10	15.62
GG	2	2.56	0	0
Allele				
C	141	90.39	118	92.18
G	15	9.61	10	7.81
Exon 6				
CC	58	79.45	46	73.02
CT	0	0	0	0
TT	15	20.54	17	26.98
Allele				
C	116	79.45	92	73.02
T	30	20.54	34	26.98

Data were compared between groups by $\chi 2$ test ($p > 0.05$ for all).

TABLE 4: Genotype distribution and allele frequency of the exon 2 and exon 6 of PPARγ2 gene in subgroups of major depressive patients and control group.

	Major depressive patients						Control groups					
Genotype	overweight and obese n	%	normal n	%	lean n	%	overweight and obese n	%	normal n	%	lean n	%
Exon 2												
CC	24	77.42	22	91.66	19	82.60	20	90.91	15	75	19	96.36
CG	5	16.13	2	8.33	4	17.39	2	9.09	5	25	3	3.63
GG	2	6.45	0	0	0	0	0	0	0	0	0	0
Allele												
C	53	85.48	46	95.83	42	91.31	42	95.45	35	87.5	41	93.18
G	9	14.52	2	4.17	4	8.69	2	4.55	5	12.5	3	6.82
Exon 6												
CC	20	71.42	17	85	21	84	14	70	17	77	15	72
CT	0	0	0	0	0	0	0	0	0	0	0	0
TT	8	28.57	3	15	4	16	6	30	5	23	6	28
Allele												
C	40	71.43	34	85	42	84	28	70	34	77.27	30	71.43
T	16	28.57	6	15	8	16	12	30	10	22.73	12	28.57

Data were compared among groups by $\chi 2$ test ($p > 0.05$ for all).

TABLE 5: Relationships of lipids and adipokins with PPARγ2 exon 2 polymorphism.

	All Patients		
	CC (n = 65) Mean ± SD (Median)	CG + GG (n = 13) Mean ± SD (Median)	Pa value
Total cholesterol (mmol/L)	10.11 ± 2.00 (9.86)	10.72 ± 2.5 (9.94)	0.740
Triglycerides (mmol/L)	6.27 ± 4.22 (5.11)	7.94 ± 2.33 (7.94)	0.004
LDL-cholesterol (mmol/L)	6.50 ± 1.77 (6.38)	6.77 ± 2.77 (7.00)	0.876
HDL-cholesterol (mmol/L)	2.94 ± 0.61 (2.88)	2.5 ± 0.55 (2.55)	0.049
Apo A (mmol/L)	8.16 ± 1.38 (8.44)	7.66 ± 1.33 (7.44)	0.319
Apo B (mmol/L)	5.05 ± 1.44 (5.01)	5.51 ± 1.88 (5.97)	0.101
Lp (a)	19.63 ± 16.18 (12.10)	18.82 ± 19.80 (9.75)	0.228
Insulin (μU/mL)	8.15 ± 8.72 (5.08)	7.16 ± 5.78 (5.28)	0.901
Leptin (ng/mL)	9.05 ± 7.80 (6.22)	10.07 ± 6.38 (9.23)	0.271
Adiponectin (μg/mL)	10.72 ± 7.79 (7.67)	8.02 ± 5.57 (7.38)	0.494
Resistin (ng/mL)	2.30 ± 0.99 (2.08)	2.09 ± 0.91 (1.97)	0.576

[a]Statistical analysis by Mann-Whitney U test.

There were significant differences in the PPARγ2 Pro12Ala polymorphism and allele in lipid profile in obese carriers.[11]

Memisoglu et al. studied the relationships between PPARγ Pro12Ala genotype and BMI according to dietary fat intake. They proposed that the relationship between dietary fat intake and plasma lipid concentrations differed according to PPARγ genotype. Their findings suggest that plasma total and HDL-cholesterol levels may need to be taken into account in PPARγ genotype analysis.[21]

Tai et al. investigated the association of C1431T and Pro12Ala polymorphisms at the PPARγ locus with plasma lipids and insulin resistance-related variables, according to diabetes status, in an Asian population. They found a decreased risk of diabetes in carriers of the T allele of the C1431T polymorphism in exon 6 of the PPARγ gene in the whole Singapo-

rean population, and that was stronger in Indians. Conversely, this association was not found for the Pro12Ala polymorphism. These observations suggested that this variant could be a marker for a relevant functional mutation.[22]

We tried to show an association between PPAR gene polymorphism and MD, two emtities that had been found to be associated with obesity.[23] In the present study, there was no evidence suggesting Pro12Ala (CG) polymorphism as a predisposing factor for MD. In addition, allele frequencies were similar in the obese and lean patients. However, differences were observed between polymorphic genotypes (CG + GG) for triglyceride and HDL-cholesterol in major depressive patients compared to normal genotypes (CC). Valve et al. found that Ala12Ala genotype was associated with increased BMI, fat mass, and waist and hip circumferences when compared to obese women (n = 141) with the Pro12Ala or Pro12Pro genotypes.[24] Deeb et al. (n = 973) found that Ala/Ala individuals had considerably higher HDL cholesterol and lower triglyceride concentrations on follow-up than did Pro/Pro and Pro/Ala patients.[25] Swarbrick et al. showed that obese Pro/Ala and Ala/Ala patients had lower concentrations of HDL-cholesterol and a trend toward higher concentrations of triglycerides than did obese Pro/Pro patients.[11]

In vitro studies have shown that the Ala12 variant of the PPARγ gene is less effective for activating target genes, one of which is the lipoprotein lipase (LPL) gene. Both chylomicrons and VLDLs are initially metabolized by LPL, which hydrolyzes triglycerides, releasing fatty acids, chylomicron remnants, and LDL cholesterol. Alterations in the blood lipid profile are seen in heterozygous lipoprotein lipase deficiency, an effect which is more pronounced in obese individuals.[11]

In Meirhaeghe et al's. study (n = 839), polymorphic alleles were associated with increased body weight, BMI, waist circumference and an atherogenic lipid profile.[26] Their results were similar to our findings, but lipid association included cholesterol and its derivative (LDL-C) as well. They suggest that genetic variability of PPARγ2 affects body weight control and lipid homeostasis in humans. On the other hand, they do not support a significant role for the PPARγ2 Pro12Ala polymorphism in the etiology of non-insulin-dependent diabetes mellitus. Several studies suggest that PPARγ has a direct effect on leptin gene transcription. For instance, the pharmacological activation of PPARγ by thiazolidinediones in animal models and in cell culture studies results in down-regulation of leptin gene expression.[27,28] Meirhaeghe et al. showed that variability within the PPARγ gene locus in obese subjects was associated with circulating leptin levels and might modify the relationships between leptin levels and adipose tissue mass.[26]

In our study, serum leptin levels of the lean and normal weight patients were lower than the overweight and obese patients ($p< 0.05$). Further epidemiological and genetic studies of the PPARγ gene polymorphisms are needed to improve our understanding of the complex regulatory mechanisms governing leptin expression by adipocytes and their importance in obesity.

Resistin has been proposed to be a connecting link between obesity and insulin resistance in rodents.[29] Although several studies have investigated its role in MD[30] and obesity,[31] there are not many reports in relation to MD. In this study, we investigated the effect of Pro12Ala and C478T SNPs on plasma resistin levels in major depressive disorders. Although higher levels of resistin have been recently found to be positively associated with insulin resistance,[32] we did not observe any difference in resistin levels in subjects classified according to BMI. Haseeb et al. showed that plasma resistin levels were not associated with metabolic syndrome. They found that the C1431T SNP was associated with higher levels of plasma resistin.[33]

CONCLUSION

Polymorphisms found in the present study were not associated with MD. On the other hand, , insignificant differences may be due to a small number of pattients and also small number of patients in the subgroups. Only 7% of obese patients had homozygous SNP (Ala12Ala), while overweight and obese

subjects in control group did not have it at all. All the adipokines and lipid parameters were found to be associated for MD patients, especially for overweight and obese patients with MD.

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