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Association of ACP1 genotypes and clinical parameters in patients with metabolic syndrome*

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Aim: Acid phosphatase locus 1 (ACP1) encodes a polymorphic enzyme and has potential implications for the development of metabolic syndrome (MS) by altering insulin sensitivity. The aim of this study was to determine whether a relationship exists between ACP1 genotypes and various metabolic syndrome risk factors.

Materials and methods: We employed a PCR-RFLP based genotyping of ACP1 in a cohort of 70 patients with MS and 168 healthy individuals.

Results: When compared to controls, genotypes associated with low enzyme activity were observed at significantly lower frequencies in both sexes. Of note, high enzyme activity genotypes were more common in patients with MS when compared with medium and low enzyme activity genotypes. *A allele frequency was not different between patients and controls even considering sex; however, there was a good correlation of the presence of the allele with body composition, serum cortisol levels and suppressibility of cortisol, particularly in women with MS.

Conclusion: Our findings suggest that low enzyme activity genotypes seem to be associated with a protective effect for the development of MS. Additionally, *A allele carriage affects body composition in women but not in men, and the presence of this allele might modulate serum cortisol levels as well as its suppressibility in both sexes, in an inverse manner.

Key words: Metabolic syndrome, ACP1 genotype, clinical variables, cortisol

Metabolik sendromlu hastalarda klinik parametreler ve ACP1 genotip ilişkisi

Amaç: Polimorfik bir enzim olan asit fosfataz lokus 1 (ACP1) insülin direncini etkilemesinden dolayı metabolik sendrom (MS) gelişiminde potansiyel bir öneme sahiptir. Bu çalışmanın amacı, çeşitli metabolik sendrom risk faktörleri ile ACP1 genotip arasında bir ilişkinin olup olmadığını belirlemektir.

Yöntem ve gereç: Yetmiş MS hastası ile 168 sağlıklı kontrol grubunda ACP1 genotipi PCR-RFLP yöntemi ile araştırıldı.

Bulgular: Çalışmamızda düşük enzim aktivitesine sahip genotip sıklığının, diğer genotiplere kıyaslandığında, hasta grubunda (her iki cinsiyette) kontrol grubundan daha düşük olduğu tespit edilmiştir. Diğer yandan, yüksek enzim aktivitesine sahip genotip sıklığının, kadınlar ve erkekler ayrı ayrı karşılaştırıldığında dahi, hasta grubunda kontrol grubundan daha yüksek olduğu tespit edilmiştir. A* allel sıklığında ise, kontrol ve hasta grupları arasında cinsiyet göz önüne alındığında dahi, bir fark gözlenmemiştir; ancak MS'li kadınların çoğunda vücut kompozisyonu, serum kortizol düzeyi ve kortizolün baskılanabilirliği ile A* alelinin varlığı arasında kuvvetli bir ilişki bulunmuştur.

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Sonuç: Bu veriler düşük enzim aktivitesine sahip genotiplerin MS gelişimi için koruyucu bir etkiye sahip olabileceğini göstermektedir. A* allel taşıyıcılığı kadınlarda vücut kompozisyonunu etkilemesine rağmen erkelerde etkili değildir. Ayrıca, A* allelinin varlığı hem serum kortizol düzeyi hem de kortizolün baskılanabilirliği üzerinde, her iki cinsiyet grubunda da, zıt yönde etki gösteriyor olabilir.

Anahtar sözcükler: Metabolik sendrom, ACP1 genotip, klinik değişkenler, kortizol

Introduction

The acid phosphatase (ACP1) locus 1 encodes for a highly polymorphic cytosolic low molecular weight phosphotyrosine phosphatase (cLMWPTP), which is expressed in all human tissues (1). The enzyme activity is determined by 2 isoforms: fast (F) and slow (S), and 3 common alleles, known as *A, *B, and *C. Spencer and colleagues (2) reported correlations between ACP1 variants and enzyme activities in the following order: ACP1 *A < ACP1 *B < ACP1 *C. The *C allele of ACP1 is mostly associated with the S isoform (3). Experimental studies show that ACP1 has 2 important functions in cells, namely flavin and tyrosine phosphatase activities. The former regulates the cellular concentration of flavin adenine dinucleotide, flavoenzyme activity, and energy metabolism (4,5), while the latter modifies the glycolytic rate by controlling receptor activities (6,7).

Metabolic syndrome is a complex endocrine disorder and harbors potential risk for the development of coronary heart disease and type 2 diabetes. This syndrome has become increasingly common in the United States, western populations as well as Turkey (8,9). Results of the TARF (Turkish Adult Risk Factor) study have demonstrated that the frequency of metabolic syndrome (MS) is 56% in women aged between 60 and 69 (9). Although the molecular mechanism of the disease is not fully understood, insulin resistance seems to be pivotal. Because of the regulatory function of ACP1 on signal transduction by insulin, high ACP1 activity may impair glucose homeostasis through suppression of insulin action as well as decreased activity of glycolytic enzymes. Therefore, genotypic variants of ACP1 might play an important role in the regulation of insulin sensitivity via altered enzymatic activity. The aim of the present study was to determine the association of ACP1 genotypes and key clinical parameters in metabolic syndrome in a group of patients of Turkish origin.

Material and methods

Study sample

Seventy patients with a diagnosis of MS using the National Cholesterol Education Program (ATPIII) diagnosis criteria (10) were enrolled into the study. Risk factors for MS according to the criteria are abdominal obesity (men > 102 cm, women > 88 cm), high triglyceride levels (≥150 mL/dL), low HDL level (men < 40 mg/dL, women < 50 mg/dL), elevated blood pressure (systolic > 130 mmHg, diastolic > 85 mmHg), and high fasting glucose (>110 mg/dL). Age and sex matched 168 healthy individuals were used as control subjects. BMI, body fat percent, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, fasting and postprandial glucose as well as hormone levels (cortisol, suppressed cortisol, dehydroepiandrosterone (DHEA), insulin, CRP, c-peptide) were determined. The study was approved by the ethics committee of GATA Haydarpaşa Teaching Hospital.

Measurement of risk factors

Body mass index and body fat content were calculated by a TANITA body fat analyzer (Tanita Corporation, Tokyo, Japan). Blood samples were collected after 12 h fasting. Serum lipid levels were analyzed using standard procedures. LDL-C was calculated using the Friedewald formula, LDL-C = Total cholesterol – (HDL-C + 0.2 × Triglyceride). Serum insulin was determined by ELISA using commercial kits (Monobind Inc, Lake Forest, CA, USA) with an automated EIA analyzer (Bio-Rad Laboratories, Hercules, CA, USA). The standard low dose overnight dexamethasone suppression test was employed as described previously. Briefly 1 mg of dexamethasone was administered at 2300 hours. Blood samples were taken at 0800 hours the next morning and then serum cortisol levels were measured by radioimmunoassay (Amersham Pharmacia Biotech, TFB Co., Tokyo, Japan).

Genotyping

ACP1 gene represents 3 co-dominant alleles named ACP1 *A, *B, and *C (11). The alleles differ from each other by single-base substitutions located at 3 specific sites: *A and *B alleles bear 2-base substitutions, a silent C-T transition at codon 41 (exon 3), and an A-G transition at codon 105 (exon 6). *C allele is different from *A and *B alleles at codon 43 (exon 3) (12).

To evaluate ACP1 allelic variants, total genomic DNA was extracted from whole blood samples using standard phenol/chloroform/isoamyl alcohol method (13). We amplified exon 3 and exon 6 regions of ACP1 genome sequence using the PCR technique. PCR was performed in a total volume of 20 µL containing 100 ng template genomic DNA, 0.2 µM each primer, 1.5 mM $MgCl_2$, 0.2 mM dNTP, and 1 U *Taq* polymerase (Fermantase). PCR was carried out under the following conditions: denaturation at 94 °C for 5 min, followed by 35 cycles of denaturation at 94 °C for 1 min, annealing at 55 °C for 1 min, and extension at 72 °C for 1 min, with a final extension at 72 °C for 7 min. After confirmation of expected PCR fragments at 2% agarose gel, the products were subjected to restriction enzyme (RE) digestion. Table 1 represents primers and REs used for ACP1 SNPs analysis.

We used *Hfa I* and *Taq I* REs to detect SNPs in C/T transition at codon 41 (exon 3) and A/G transition at codon 105 (exon 6), respectively. Table 1 shows expected DNA fragments after RE digestion. Briefly, 10 µL of each amplicon was fully cleaved by specific REs at 65 °C for 1 h according to manufacturer's instruction. Digested products were run with electrophoresis on 2% agarose gel matrix. Determination of ACP1 genotypes was carried out by using Table 2.

Statistical evaluation

Chi-square analyses, followed by Fisher's exact test wherever required, were used to compare the frequencies of ACP1 genotypes between patients and healthy controls. The test was also applied for identifying the deviations from the Hardy-Weinberg proportion. Two-tailed Student's t-test and one-way ANOVA test were used to compare clinical parameters and ACP1 genotypes. Following clinical variables were taken into consideration: age, sex, weight, body mass index (BMI), total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, fasting, postprandial glucose, CRP, body fat percentage, waist-hip ratio (WHR), and systolic and diastolic blood pressures. Circulating hormone levels (cortisol, suppressed cortisol, dehydroepiandrosterone (DHEA), insulin, and C-peptide) were also compared with ACP1 genotypes. ACP1 genotypes were analyzed in 3 ways. Firstly, ACP1 genotypes were grouped according to enzyme activity; low-activity genotypes (*A/*A,*A/*B), medium-activity genotypes (*B/*B,*A/*C), and high-activity genotypes (*B/*C,*C/*C). Secondly, we grouped ACP1 genotypes according to *A allele carriers (*A*A, *A*B, *A*C) vs. non*A carriers (*B*B, *C*C, *B*C). Finally, ACP1 genotypes were designated as low-activity genotypes (*A/*A,*A/*B) vs. medium-high activity genotypes (*B*B, *A*C, *B*C, *C*C). Odds ratios with 95% confidence intervals were given wherever appropriate. A difference was considered significant when $P < 0.05$. SPSS 11.0 was used for all analyses.

Results

When we analyzed the ACP1 genotypes according to *A allele carriage and low-activity ACP1 genotypes vs. medium and high-activity ACP1 genotypes (without considering sex), we did not find any statistical significance with A allele carriage; however, we noted a striking difference between ACP1 enzyme activity genotypes in MS patients and controls. Table 3 shows the distribution of ACP1 genotypes in relation with enzyme activities (low, medium, and high) and the presence of *A allele in the genotype. The locus, for both patients and controls, showed a generally good fit to the Hardy-Weinberg equilibrium. ACP1 *A/*A and *A/*B genotypes, which are associated with low enzyme activity, displayed a significantly lower frequency than the control group when compared with other genotypes (medium and high activity) ($P = 0.001$). On the other hand, *B/*C and *C/*C genotypes, which are associated with higher enzyme activity, were found at a significantly higher frequency than the control group when compared with other genotypes (low and medium activity) ($P = 0.0001$).

Table 1. Primer sets and restriction enzymes (RE) used for ACP1 SNPs analysis.

Target amplification	Nucleotide sequence 5'-3'	PCR product (bp)	Type of RE	RFLP fragments (bp)
Exon 3	AGGCCAACCTGAACTCCTCTG CCTGTCTTGCTTTATGGGCT	342	*HfaI*	254, 88
Exon 6	TTCAGAACACCCTAGCAGATG TTGCAAAACCTGCATAACAA	300	*TaqI*	199, 101

Table 2. Detection of ACP1 genotype using PCR-RFLP.

ACP1 Genotype	Exon 3 (codon 41) *Hfa I* Restriction	Exon 6 (codon 105) *Taq I* Restriction
AA	Presence	Presence
AB	Heterozygote	Presence
AC	Heterozygote	Heterozygote
BB	Absence	Presence
BC	Absence	Heterozygote
CC	Absence	Absence

Table 3. Distribution of ACP1 genotype and association with enzyme activities and *A allele carriage.

ACP1 enzyme activity	ACP1 Genotype	Case N (%)	Control N (%)	OR 95%CI	P value
Low	AA, AB	21 (30)	90 (53.6)	0.371 (0.205-0.673)	0.001
Medium	BB, AC	34 (48.6)	72 (42.9)	1.259 (0.720-2.203)	0.475
High	BC, CC	15 (21.4)	6 (3.6)	7.364 (2.723-19.915)	<0.001
Total		70 (100)	168 (100)		
**A carrier genotype*		32 (45.7)	93 (55.4)		
*Non-*A carrier genotype*		38 (54.3)	75 (44.6)	0.679 (0.388-1.189)	0.201
Total		70 (100)	168 (100)		

To determine which of the clinical characteristics of MS patients are sex dependent, we analyzed all clinical parameters in men and women separately. We detected difference in age, weight, total cholesterol, WHR, body fat percentage, suppressed cortisol, CRP, and c-peptide (Table 4). Accordingly, gender dependent variations in these distinct clinical parameters were correlated with ACP1 genotypes.

With regard to the association between MS and ACP1 genotypes in males and females, the frequency of *A allele carriers were 42% (n = 19) and 54% (n = 41) in men (P = 0.260) and 52% (n = 13) and 56% (n = 48) in women (P = 0.821) from patient and control groups, respectively. On the other hand, when we analyzed the difference between low enzyme activity genotype and medium-high enzyme

Table 4. Characteristics of patients with MS.

Parameter	Women (n = 25)	Men (n = 45)	P value
Age (years)	42.2 ± 8.6	31.1 ± 9.1	<0.001
Weight (kg)	100.6 ± 17.5	124.2 ± 17.9	<0.001
BMI (kg/m^2)	40 ± 7.2	40.2 ± 4.8	0.931
Total cholesterol (mg/dL)	226.4 ± 37.3	208.1 ± 35	0.045
HDL-C (mg/dL)	41.1 ± 7.1	38.6 ± 11.7	0.328
LDL-C (mg/dL)	132.3 ± 26.2	120.9 ± 31	0.155
Triglycerides (mg/dL)	282.2 ± 152	270 ± 124	0.731
Fasting glucose (mg/dL)	141 ± 44	133.7 ± 45	0.524
Nonfasting glucose (mg/dL)	192.9 ± 53	172.3 ± 74	0.234
Waist-hip ratio	0.889 ± 0.08	1.025 ± 0.05	<0.001
Systolic blood pressure (mmHg)	156.6 ± 18	150.8 ± 15.5	0.172
Diastolic blood pressure (mmHg)	96.4 ± 9.3	97.1 ± 7.8	0.734
Body fat (%)	46.5 ± 6.4	36.9 ± 6.4	<0.001
Insulin (μU/mL)	26.7 ± 16.3	33.7 ± 19.9	0.098
Cortisol (μg/dL)	14.1 ± 6.3	16.6 ± 5.7	0.093
Sup cortisol (μg/dL)	1.58 ± 0.9	2.8 ± 2.7	0.039
DHEAS (ng/mL)	279 ± 62	312 ± 100	0.145
CRP (mg/dL)	5.8 ± 1.7	6.8 ± 2.2	0.053
C-peptide (ng/mL)	4.2 ± 1.2	5.5 ± 2.4	0.015

P values were obtained by unpaired Student's t-test.

activity genotypes in males and females separately low activity genotype carriers were 29% (n = 13) and 53% (n = 40) in men (P = 0.014) and 32% (n = 8) and 54% (n = 46) in women (P = 0.071) among cases and controls, respectively.

We also evaluated the relationship between serum lipid parameters, various hormones, and *A allele carriage in men and women (Table 5). Although we did not find any difference in serum lipid levels, there was a significant association between weight, BMI,

Table 5. Comparison of clinical parameters with ACP1 genotypes according to A-carriers vs. non-A carriers in men and women with MS.

	Men			Women		
Parameters	A-carrier	Non-A	P	A-carrier	Non-A	P
Weight (kg)	124.7 ± 23.5	123.6 ± 12.5	0.870	93.4 ± 15.5	108.4 ± 16.7	**0.029**
BMI (kg/m^2)	40.8 ± 6.1	39.6 ± 3.6	0.396	36.8 ± 5.8	43.5 ± 7	**0.017**
Total cholesterol (mg/dL)	203.8 ± 33	212.2 ± 37	0.483	235.9 ± 40	216.1 ± 31.9	0.19
HDL-C (mg/dL)	37.5 ± 15.8	39.4 ± 8	0.611	41.9 ± 7	40.3 ± 7.3	0.575
LDL-C (mg/dL)	120.3 ± 30	121.4 ± 32	0.911	129.8 ± 24.3	134.6 ± 28.7	0.684
Triglycerides (mg/dL)	269 ± 124	272 ± 126	0.945	328.6 ± 171	232 ± 116	0.115
Fasting glucose (mg/dL)	127.3 ± 48	138 ± 44	0.432	147.4 ± 49.3	133.9 ± 38.2	0.456
Nonfasting glucose (mg/dL)	185.5 ± 74	162 ± 75	0.313	202.9 ± 62	181 ± 40	0.325
Waist-hip ratio	1.03 ± 0.05	1.02 ± 0.04	0.560	0.88 ± 0.06	0.90 ± 0.09	0.604
Systolic blood pressure (mmHg)	153 ± 16	149 ± 15	0.366	157.7 ± 23.3	155.4 ± 13	0.769
Diastolic blood pressure (mmHg)	98 ± 8.5	96.5 ± 7.3	0.570	93.5 ± 10.8	99.6 ± 6.2	0.101
Body fat (%)	38.7 ± 8.3	35.6 ± 4.3	0.111	43.9 ± 4.4	49.2 ± 7.1	**0.033**
Insulin	32.4 ± 20.5	33 ± 18.4	0.928	25.1 ± 15.6	17.6 ± 5.1	0.619
Cortisol	15.1 ± 5.7	17.6 ± 5.6	0.159	14.2 ± 5.8	13.9 ± 7	0.907
Suppressed cortisol	1.82 ± 1.6	3.4 ± 3.1	0.057	1.97 ± 0.9	1.20 ± 0.7	**0.037**
DHEAS	282.7 ± 96	334 ± 101	0.094	302.5 ± 58	254.4 ± 60	0.054
CRP	6.5 ± 2.2	7 ± 2.3	0.406	5.77 ± 2	5.86 ± 1.4	0.901
C-peptide	5.4 ± 2.9	5.5 ± 2	0.928	4.13 ± 1.2	4.28 ± 1.2	0.769

P values were obtained by unpaired Student's t-test.

and % body fat in women. Female non-A carriers had higher weight (P = 0.029), BMI (P = 0.017), and body fat percentage (P = 0.033) but lower suppressed cortisol (P = 0.037) and DHEAS (P = 0.054) levels. Of note, most of the non-*A allele carriers were associated with higher BMI (P = 0.035) (Table 6). In men, all lipid parameters and body compositions displayed similar values with respect to the genotypes. On the other hand, there was a negative correlation with a modest significance for suppressed cortisol (P = 0.057) and DHEAS (P = 0.094) levels among non-A carriers. Non-*A allele carrier men had higher suppressed cortisol and DHEAS levels. On the other hand, when we analyzed possible correlations between clinical parameters and genotypes according to low vs. medium-high enzyme activity genotypes of ACP1 in men and women separately, the only correlation was between the cortisol level and the genotype. Patients with low enzyme activity genotype had lower cortisol level (13.7 ± 6 μg/dL vs. 17.7 ± 5 μg/dL) compared to high and medium activity genotypes (P = 0.035). These differences were not observed in the control group.

Further analysis of the data from the control group (n = 96, 37 men, 59 women) revealed that only one clinical parameter was associated with the ACP1 genotype. Of note, cholesterol levels were significantly lower in A-allele carriers as well as low enzyme activity genotype in men (182.2 ± 32 mg/dL vs. 205 ± 28 mg/dL) (P = 0.047), but not in women.

Discussion

To the best of our knowledge, this is the first study to demonstrate that DHEAS, cortisol, and suppressibility of cortisol levels are influenced by ACP1 genotypes in patients with MS. Although the frequency of *A allele is not different between patients and controls from both sexes the presence of the allele appears to be associated with some of the clinical parameters of MS. We also found that suppressed cortisol and, in part, circulating DHEAS levels are negatively correlated with the ACP1 genotypes in men and women. Non-*A allele genotypes are associated with reduced cortisol suppressibility as well as low DHEAS levels but increased BMI and % body fat in women, whereas these genotypes are associated with increased suppressibility of cortisol and higher circulating DHEAS levels with no apparent effect on body composition in men. On the other hand, frequency of low enzyme activity genotype is very rare in MS patients. Cortisol levels also appear to be affected by low enzyme activity ACP1 genotypes in men. Moreover, cholesterol levels are significantly lower in A-allele carriers and low enzyme activity genotype in healthy men (182.2 ± 32 mg/dL vs. 205 ± 28 mg/dL) (P = 0.047), but not in healthy women.

Elevated blood lipid levels were previously reported to be associated with non-*A-allele carriers in obese, but not lean post-menopausal women in the United States (14). This study also revealed a positive correlation between BMI and serum triglyceride levels in non-*A allele carriers but not in *A-allele carriers among obese subjects. These findings suggest that *A allele may be partially protective against MS development in obese individuals. Interestingly, our data indicate a positive correlation between BMI and the enzyme activity genotypes only among women, but not in men. On the other hand, we did not detect any correlation between lipid levels and ACP1 genotype in patients with MS. Although one might take into account the variable impact of genotypes

Table 6. Relationships between ACP1 genotypes (A-carrier vs. non-A carrier) and BMI in women.

ACP1 genotypes	BMI (kg/m^2)	P value	Range of BMI			Total n	P value
			30-35 (n)	35-40 (n)	>40 (n)		
A carrier	36.8 ± 5.8		6	4	3	13	
Non-A	43.5 ± 7	0.017	2	2	8	12	0.035

in different populations, larger cohorts are needed to elucidate the clinical significance of ACP1 genotypes on both sexes.

The relationship between fasting glucose levels and ACP1 genotype was previously studied in healthy adults from Italy (15). This study not only revealed that fasting glucose concentration was significantly higher in medium-high activity genotype than in low activity genotype in Italian men but also found a statistically significant increase in serum glucose concentration with advancing age. However, we did not observe this in our healthy controls but we found that cholesterol levels were significantly higher in non-*A allele carriers and medium-high activity ACP1 genotypes in men. Of note, the difference was not detected in all MS patients when sex was not considered separately.

There are some reports indicating that elevated serum cortisol levels are associated with MS (16,17). Cortisol is known to potentiate insulin resistance in MS (18). On the other hand, increased cortisol is an important risk factor for cardiovascular diseases. We think that our findings are interesting because they suggest a positive correlation between serum cortisol levels and ACP1 genotype in MS. Based on our data, one can envisage that non-*A allele genotype may affect circulating cortisol levels in men although further clinical and experimental studies are warranted to elucidate the mechanisms linking ACP1 activity and insulin resistance.

Bottini et al. (19) investigated the correlation between ACP1 genotypes and the age at onset of type 1 diabetes in children and adolescents and reported that medium and high activity genotype affects the age of onset and probably also sex ratio in type 1 diabetes. Hence, they suggested that sex hormones might modulate the susceptibility to type 1 diabetes. Our findings about gender difference in distribution of ACP1 genotype in MS support the modulator role in tendency to diabetes-related diseases of sex hormones.

Previously, a negative correlation between ACP1 and glucose levels has been suggested in type 1 and 2 diabetes (20,21). Low activity genotypes are associated with lower glucose levels in type 2 diabetes, but higher glucose levels in type 1 diabetes. A vast number of regulator molecules involved in glucose homeostasis might be a possible explanation for this observation (22). Likewise, we did not observe any correlation between ACP1 genotypes and serum glucose levels in MS patients and controls.

Conclusions

In summary, low-enzyme activity genotype of ACP1 appears to be associated with a protective effect against weight gain, increasing BMI, and body fat percentage in MS patients. Serum cortisol levels and suppressibility of this hormone could be possibly modulated by ACP1 genotypes, potentially linking the ACP1 locus with the development of insulin resistance in metabolic syndrome. In support of this, a recent study has revealed that ACP1 might be a strong regulator of glucose levels and insulin sensitivity in a murine model of obesity (23). Further studies are needed to elucidate the role of ACP1 genotypes in mediating the development of metabolic syndrome, a potential life-threatening disorder afflicting increasing numbers of individuals worldwide.

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