Research Article

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Association between polymorphisms of DNA repair genes and risk of type 2 diabetes mellitus in the Turkish population

Türk Populasyonunda DNA Tamir Genleri Polimorfizmleri ve Tip 2 Diabetes Mellitus Riski Arasındaki İlişki

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Abstract

Objectives: DNA repair mechanisms work insufficiently in T2DM patients and hyperglycemia seen in diabetes disturbs the oxidant-antioxidant balance thus cause oxidative damage on DNA. The effects of the DNA repair genes' have not yet been investigated on diabetes. The aim of this study was to investigate the association between *APE1* Asp148Glu and *XPG* Asp1104His polymorphisms with T2DM in the Turkish population.

Material and methods: Sixty-five T2DM patients and 54 healthy individuals were included to this study as control. The polymerase chain reaction-restriction fragment length polymorphism techniques were used.

Results: When the study groups were compared, serum HDL-cholesterol levels were found statistically elevated in the controls. Once the *APE1* Asp148Glu polymorphism distribution between the patient and control groups was investigated, the Glu/Glu genotype ratio was found significantly higher in the control group. Furthermore, the Asp/Glu genotype and the Asp allele prevalences were observed to be higher in the patient group. Also, patients with the Asp/Asp genotype had higher serum HDL-cholesterol levels than the others.

Conclusion: Despite the small number of subjects included, it could be interpreted that the Glu allele of the *APE1* Asp148Glu polymorphism might be protective against and the Asp allele may be contributing to the development of diabetes.

Keywords: Type 2 diabetes mellitus; *APE1*; *XPG*; Polymorphism; PCR-RFLP.

Özet

Amaç: T2DM hastalarının DNA tamir mekanizması düzgün çalışmamaktadır ve diyabette görülen hiperglisemi, organizmanın oksidan-antioksidan dengesini bozarak DNA'da oksidatif hasarlara sebep olmaktadır. DNA tamir genlerinin etkileri bugüne kadar diyabette çalışılmamıştır. Bu çalışmanın amacı, Türk toplumundaki T2DM'li hastalarda *APE1* Asp148Glu ve *XPG* Asp1104His polimorfizmlerinin ilişkisini incelemektir.

Gereç ve Yöntem: Çalışmamıza 65 T2DM hastası ve kontrol grubu olarak da 54 sağlıklı birey dahil edildi. Polimorfizmlerin belirlenmesinde Polimeraz Zincir

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Reaksiyonu (PZR), Restriksiyon Parça Uzunluk Polimorfizmi (RFLP) teknikleri kullanılmıştır.

Bulgular: Serum HDL-kolesterol düzeyi bakımından gruplar karşılaştırıldığında hasta grubuna göre kontrol grubunda serum HDL-kolesterol düzeyinin istatistiksel olarak arttığı belirlenmiştir. Hasta ve kontrol grupları arasında *APE1* Asp148Glu polimorfizmi genotip dağılımları incelendiğinde kontrol grubunda Glu/Glu genotipi taşıma oranının, hasta grubuna göre anlamlı olarak yüksek olduğu tespit edilmiştir. Hasta grubunda ise Asp/Glu genotipi ve Asp alleli tasıma oranının kontrol grubuna göre istatistiksel olarak arttığı gözlemlenmiştir. Ayrıca hasta grubunda Asp/Asp genotipi taşıyan bireylerde taşımayanlara göre serum HDL-kolesterol düzeyi anlamlı olarak yüksek olarak bulunmuştur.

Sonuç: Çalışmamıza dahil edilen örnek sayısı az olmasına rağmen, *APE1* Asp148Glu polimorfizmi için Glu allelinin koruyucu olabileceğini ve Asp allelinin ise diyabet gelişiminde rol oynayabileceğini söyleyebiliriz.

Anahtar Kelimeler: Tip 2 diabetes mellitus; *APE1*; *XPG*; Polimorfizm; PCR-RFLP.

Introduction

Diabetes mellitus (DM) develops due to insulin insufficiency, effects of altered insulin activity or both, and is defined as a metabolic disorder characterized with disrupted glucose tolerance and hyperglycemia [1]. Type 2 diabetes mellitus (T2DM) is the most common among all types of diabetes and as a result of the variety of the factors seen in phenotype, it is considered as a heterogenic disease [2]. Since its prevalence is rapidly rising worldwide, T2DM has become the most significant and formidable health problem of the 21st century [1].

The chronic hyperglycemia seen in T2DM leads to an increase in reactive oxygen species (ROS) and/or a reduction in antioxidant defense, meaning additional oxidative stress that induces oxidative damage on biomolecules such as lipids, proteins and DNA [3, 4]. Some complications of diabetes have been associated with increased activity of lipid peroxidation due to free radicals and accumulation of lipid peroxidation products [5]. DNA damage is a major reason for cellular functional disturbances and cell death, which plays an important part in the pathogenesis of diabetic complications [3]. Certain oxidative damages are highly associated with a considerable decrease in the antioxidant levels of the patient and the up regulation of the DNA damage as a result of pro-oxidants. Thus, this situation leads to attenuation in the efficiency of DNA repair mechanisms and increases the risk of cancer development [4, 6].

It has been shown that the DNA repair mechanisms of type 2 diabetes patients do not work properly. The increase of oxidative stress levels and also the decrease in the efficiency of DNA repair in T2DM both has significant contributions to neoplastic transformation [7]. The oxidative DNA damage encountered in diabetes is generally repaired by the base excision repair (BER) mechanisms, in which *APE1* plays a vital role. The *APE1* gene is located on chromosome 14q11.2-q12 where 18 polymorphisms have been described so far. Among these polymorphisms the most studied is the thymine to guanine transversion Asp148Glu polymorphism [8]. Moreover, disorders in nucleotide excision repair (NER) mechanism have also been shown in cancers of type 2 diabetes patients [9]. With its endonuclease activity, Xeroderma pigmentosum G (*XPG*) plays a key role in the restoration of the DNA helix structure in NER. The *XPG* gene is located on chromosome 13q22 and the ASP1104His polymorphism on exon 15 is associated with cancer development [10].

Recent studies on *APE1* and *XPG* have mostly focused on a probable genetic susceptibility to cancer development yet their relation with diabetes has not been studied. In this study, the aim was to investigate the association between the *APE1* Asp148Glu and *XPG* Asp1104His gene polymorphisms with T2DM.

Materials and methods

Study group

This study was conducted with the approval of the Istanbul Medical Faculty Ethical Committee, Istanbul University. Study group comprised of 65 patients (35 women, 30 men) diagnosed with T2DM and in follow up by the Division of Endocrinology and Metabolic Diseases, Department of Internal Medicine, Istanbul Medical Faculty, Istanbul University and 54 healthy individuals (11 women, 43 men).

DNA isolation and SNP detection

Blood samples were obtained from the participants in EDTA containing 10 mL tubes and stored at –20°C until the DNA isolation step that was performed using the salting out method [11]. The specific primers shown in Table 1 were used to amplify the *APE1* Asp148Glu and *XPG* Asp1104His polymorphisms gene regions for the PCR method. The PCR reaction volume was set as 25 μL as 1 μL DNA sample of 50–100 ng, 2.5 μL dNTP (100 μ/mL), 2 μL $MgCl_2$ (25 mM/mL), 1 μL each primer and 0.5 μL Taq polymerase (5 U/μL),

Table 1: PCR-RFLP-based assay of *APE1* Asp148Glu and *XPG* Asp1104His polymorphisms.

SNPs	Primers	Restriction enzymes	Interpretation (bp)
APE1 Asp148Glu	F: 5′-CTGTTTCATTTCTATAGGCTA-3′ R: 5′-AGGAACTTGCGAAAGGCTTC-3′	FspBI (BfaI)	AA: 164 GG: 144+20 AG: 164+144+20
XPG Asp1104His	F: 5′-GACCTGCCTCTCAGAATCATC-3′ R: 5′-CCTCGCACGTCTTAGTTTCC-3′	Hin1II (NlaIII)	GG: 271 CC: 227+44 GC: 271+227+44

F, Forward primer; R, reverse primer.

1.5 µL 10X DNA Taq PCR buffer and 16.5 µL apyrogenic water. The PCR mix was prepared on ice and in a sterile cabin. The PCR reaction for *APE1* Asp148Glu was set as 95°C for 30 s, 52°C for 45 s and 75°C for 45 s for 35 cycles following the 95°C for 2 min initial denaturation and a final elongation step as 72°C for 5 min. For the *XPG* Asp1104His polymorphism 94°C for 1 min, 62°C for 1 min and 72°C for 1 min for 35 cycles following the 95°C for 5 min initial denaturation and a final elongation step as 72°C for 10 min. The PCR yields were controlled on 3% agarose gel electrophoresis. In order to determine the *APE1* Asp148Glu and *XPG* Asp1104His poly morphisms the PCR yields were digested with FspBI (BfaI) and Hin1II (NlaIII) restriction enzymes, respectively. The digested yields were separated on 3% agarose gel electrophoresis and genotyped after being viewed under UV light. Used primers and restriction enzymes and obtained PCR and restriction yields are given with their lengths and which genotype they correspond to in Table 1. The genotyping for *APE1* Asp148Glu was evaluated as, AA for Asp/Asp, GG for Glu/Glu and AG for Asp/Glu, and for *XPG* Asp1104His GG for Asp/Asp, CC for His/His and GC for Asp/His.

Statistical analysis

The statistical analysis was performed using SPSS version 11.0 (SPSS Inc. Chicago, USA). For the determination of the distribution of the prevalence of the alleles between groups the Chi-squared (χ^2) and Fisher's test were used. The demographical data was compared using Student's t-test and one way ANOVA. Allele frequencies were determined using the gene counting method. Values of $p < 0.05$ were considered statistically significant.

Results

The mean age of the 65 patients included in this study were 59.93 ± 13.97 and the 54 healthy controls were 54.83 ± 10.88, which was compatible. When the serum HDL-cholesterol levels were compared, it was found higher in the control group than the patient group (p = 0.001, 95%CI = 3.51–11.97). The demographic data is given in Table 2.

Table 2: Demographic details of the study groups.

Demographic parameters	Control (n: 54)	Patient (n: 65)
Age (years)	54.83 ± 10.88	59.93 ± 13.97
Gender (F/M)	11/43	35/30
Body mass index (kg/m^2)	26.33 ± 3.77	28.25 ± 8.36
Triglyceride (mg/dL)	174.6 ± 112.47	152.22 ± 73.85
Total cholesterol (mg/dL)	198.98 ± 46.14	187.25 ± 69.45
HDL-cholesterol (mg/dL)	41.47 ± 8.05$_a$	33.72 ± 12.25
LDL-cholesterol (mg/dL)	129.73 ± 42.39	113.41 ± 39.81
VLDL-cholesterol (mg/dL)	31.58 ± 17.89	32.02 ± 18.97
Blood glucose level (mg/dL)	–	218.4 ± 115.26
HbA_{1c} (%)	–	24.2 ± 8.73
Insulin (mU/mL)	–	13.44 ± 10.43
C-peptide (ng/mL)	–	5.32 ± 5.71
Folate (ng/mL)	–	7.3 ± 3.29
B12 (pg/mL)	–	514.1 ± 403.19

[a]p: 0.001, 95% CI: 3.51–11.97.

The mutant *APE1* Asp148Glu Glu/Glu genotype was not encountered in the patient group thus the Glu/Glu genotype is found statistically higher in the control group (p = 0.007, 95% CI = 0.80–0.97). Also, the Asp/Glu genotype (p = 0.005, χ^2 = 8.005, OR = 2.904, 95% CI = 1.375–6.133) and the Asp allele (p = 0.007, 95% CI = 0.80–0.97) were found more common in the patient group (Table 3).

Table 3: The *APE1* Asp148Glu genotype/allele distributions in the patient and control groups.

APE1 Asp148Glu	Control (n: 54)		Patient (n: 65)	
	n	%	n	%
Asp/Asp (AA)	28	51.9	24	36.9
Asp/Glu (AG)	20	37	41	63.1$_b$
Glu/Glu (GG)	6	11.1$_a$	0	0
Asp$^+$	48	88.9	65	100$_c$
Glu$^+$	26	48.1	41	63.1

[a]p: 0.007, 95% CI: 0.80–0.97.
[b]p: 0.005, χ^2: 8.005, OR: 2.904, 95% CI: 1.375–6.133.
[c]p: 0.007, 95% CI: 0.80–0.97.

Table 4: Demographic data on *APE1* Asp148Glu genotypes and lipid profiles.

Groups	Patient (n: 65)			Control (n: 54)		
***APE1* genotypes**	**Asp/Asp (n: 24)**	**Asp/Glu (n: 41)**	**Glu/Glu (n: 0)**	**Asp/Asp (n: 28)**	**Asp/Glu (n: 20)**	**Glu/Glu (n: 6)**
Triglyceride (mg/dL)	159.33±81.98	147.70±69.12	0	171.79±134.54	164.20±79.54	211.83±91.12
Total cholesterol (mg/dL)	188.14±53.63	186.71±78.42	0	192.83±42.95	200.40±53.39	220.00±39.4
HDL-cholesterol (mg/dL)	38.10±13.06[a]	31.15±11.15	0	42.79±6.54	40.47±11.00	38.67±3.67
LDL-cholesterol (mg/dL)	120.74±45.91	109.09±35.78	0	129.62±43.69	126.00±41.34	139.50±45.78
VLDL-cholesterol (mg/dL)	31.86±16.39	32.13±20.69	0	28.58±18.87	33.40±16.56	39.0±17.1

[a]p: 0.05.

Table 5: The *XPG* Asp1104His genotype/allele distributions in the patient and control groups.

***XPG* Asp1104His**	**Control (n: 54)**		**Patient (n: 65)**	
	n	**%**	**n**	**%**
Asp/Asp (GG)	31	57.4	36	55.4
Asp/His (GC)	18	33.3	28	43.1
His/His (CC)	5	9.3	1	1.5
Asp$^+$	49	90.7	64	98.5
His$^+$	23	42.6	29	44.6

According to our findings, it can be said that carrying the Asp genotype may be a risk factor for diabetes development. Once the study groups were compared for *APE1* Asp148Glu polymorphism genotype distribution and lipid profiles, the Asp/Asp carriers in the patient group had significantly higher HDL-cholesterol levels ($p=0.05$). Since there were no patients carrying the Glu/Glu genotype, it could not be evaluated (Table 4).

There was no significant difference between the patient and control groups in terms of *XPG* Asp110His poly morphism genotype distribution (Table 5). The association between the serum lipid profiles and *XPG* Asp1104His polymorphism genotypes in the patient and control groups are shown in Table 6. In the control group, Asp/Asp genotype carriers had higher HDL-cholesterol levels than the His/His carriers ($p=0.025$, 95% CI = 1.29–18.11). There was only a single patient carrying a His/His genotype thus it could not be statistically evaluated.

Discussion

T2DM arises due to the gradual loss of pancreatic β cell function where the insulin hormone is secreted to balance the insulin resistance that leads to hyperglycemia [12]. Recent studies have shown that the increase in free radicals and the decrease in the antioxidant potential, which result with cellular oxidative damage, are associated with DM [3]. In the case of hyperglycemia, it is indicated that ROS production increases depending on the –OH radical formation, the result of glucose auto-oxidation [13]. High ROS production and accumulation leads to oxidative stress, therefore disrupts the physiologic function and the structure of the cellular biomolecules, and also impairs cell viability and functioning [12]. Oxidative stress debilitates the antioxidant mechanism of the body and in consequence causes DNA damage, lipid peroxidation and protein modifications. Subsequently, it leads to diabetes, atherosclerosis, chronic inflammation, cardiovascular diseases, cancer, and neurological diseases like Alzheimer's and Parkinson's [14]. As an important part

Table 6: Demographic data on *XPG* Asp1104His genotypes and lipid profiles.

Groups	Patient (n: 65)			Control (n: 54)		
***XPG* genotypes**	**Asp/Asp (n: 36)**	**Asp/His (n: 28)**	**His/His (n: 1)**	**Asp/Asp (n: 31)**	**Asp/His (n: 18)**	**His/His (n: 5)**
Triglyceride (mg/dL)	153.07±76.21	155.09±71.37	61	151.40±91.48	209.56±143.39	179.75±68.71
Total cholesterol (mg/dL)	196.0±83.43	176.30±45.81	168	194.24±47.16	207.88±46.19	193.0±45.92
HDL-cholesterol (mg/dL)	32.07±11.83	35.65±12.97	39	43.2±9.06[a]	40.75±3.02	33.5±11.61
LDL-cholesterol (mg/dL)	116.19±42.68	109.63±37.29	116	128.68±48.92	132.25±35.49	126.25±29.31
VLDL-cholesterol (mg/dL)	33.46±22.07	31.01±14.27	12.20	29.72±18.04	34.0±19.45	33.5±11.67

[a]p: 0.025, 95% CI: 1.29–18.11.

of the BER mechanism, the *APE1* enzyme repairs the oxidized and alkalized DNA's 3′-hydroxylation damage by producing normal 3′-hydroxyl groups. Although there are 18 polymorphisms identified in *APE1*, the most widely studied is the Asp148Glu (T1349G) (rs3136820) [15]. In many different ethnic groups, the association between the *APE1* Asp148Glu polymorphism with numerous cancer types has been studied. Gu et al. [15], in their meta-analysis including 27 studies showed that it might be a risk factor for cancer development. In other studies, the *APE1* Asp148Glu polymorphism was shown to be a possible risk factor for urinary cancers, hepatocellular carcinoma and breast cancer [16–18]. Migraine, myocardial infarction and Parkinson's disease have also been associated, however, no association was found between Alzheimer's disease and the *APE1* Asp148Glu polymorphism [19–22].

In this study, the Glu/Glu genotype of the *APE1* Asp148Glu was not encountered in the patient group, therefore, due to this absence its prevalence seems significantly higher in the control group. The Asp/Glu genotype and the Asp allele carriers were higher in the patient group than the controls. Expanding the study population will clarify the data for the evaluation of the Asp allele as a risk factor for diabetes development. Patients with the Asp/Asp geno type were found to have significantly higher HDL-cholesterol levels than the controls. No other studies have been found investigating an association between type 2 diabetes and/or lipid profiles and the *APE1* Asp148Glu polymorphism, which makes this study the first.

One of the SNPs found in *XPG* is the *XPG* Asp1104His polymorphism identified as the guanine to adenine transition, which results with the coding of the amino acid histidine instead of aspartic acid [23]. *XPG* Asp1104His polymorphism have been previously investigated in various cancers such as gastrointestinal cancers, head and neck cancer and leukemia. There was no association found with leukemia, yet it was indicated as a risk factor especially for larynx cancer in the Asian population [24–26]. In a meta-analysis of eight studies and another of 17 studies, the *XPG* Asp1104His polymorphism was shown not associated with breast cancer [27, 28]. In an additional meta-analysis it was indicated as a risk factor for melanoma [29]. Moreover, the *XPG* Asp1104His polymorphism has also been shown to have a positive association with Parkinson's disease yet none with coronary artery disease [21, 30].

In this study, no significant relation was found with the *XPG* Asp1104His polymorphism between the study groups. Once the *XPG* genotypes and lipid profiles were evaluated, the Asp/Asp genotype carriers were observed to have significantly higher HDL-cholesterol levels than the His/His genotype carriers. No other studies have been found showing a relation between the *XPG* Asp1104His polymorphism and type 2 diabetes and/or lipid profiles. The limitation of this study is the small number of the study groups and it will be carried out further with a larger study group for greater statistical significance.

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Conflict of interest statement: The authors declare that they have no conflict of interest.

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