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Association of the XRCC1 and XRCC3 Gene Variants with Type 2 Diabetes Mellitus

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ABSTRACT • Background and aims: Type 2 diabetes mellitus (T2DM), is the most common metabolic disease of the adult population and characterized with disorders in insulin secretion and activity. The hyperglycemia seen in T2DM leads to free radical production via glucose oxidation or other complex mechanisms and creates DNA damage. Polymorphisms of the two DNA repair genes; XRCC1 and XRCC3 were investigated for their impact on disease risk and clinical parameters of T2DM patients. **Materials and Methods:** The patient group was comprised of 34 women and 40 men, a total of 74 patients, diagnosed with type 2 diabetes. The control group was randomly selected from the population as 52 women and 50 men, a total of 102 individuals, whom did not have diabetes. In order to determine the XRCC1 Arg194Trp (C/T) and XRCC3 Thr241Met (C/T) polymorphisms, the polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) techniques were used. **Results:** Statistical analysis showed that the XRCC1 Arg194Trp and XRCC3 Thr241Met polymorphisms have no association with type 2 diabetes and its clinical parameters compared to the control group. **Conclusions:** We believe that to clarify the relationship between the XRCC1 Arg194Trp and XRCC3 Thr241Met polymorphisms and T2DM, the study should be carried on with an expanded study group.

INTRODUCTION

Diabetes mellitus (DM) is a chronic and metabolic disease described by elevated blood glucose levels. As a result of the pathological events occurring in the genetic and immune structure, the absolute or relative absence or inactivity of the insulin hormone secreted from pancreas β- cells, causes disorders in carbohydrate, protein and fat metabolisms and various events in all systems (1). One of every 30 adults is diabetic and the prevalence is expected to double by 2030. Although both types of DM are increasing, type 2 diabetes mellitus (T2DM) is the most prevalent form seen in 5-10% of the pop-

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ulation in developed countries (2). T2DM is characterized by the disorders in insulin secretion or activity and also the body becomes insensitive to the metabolic effects of insulin (3).

The molecular mechanisms that form the basis of T2DM are still unknown, yet many studies are focused on enlightening the underlying genetic abnormalities. The hyperglycemia seen in T2DM leads to free radical formation through glucose oxidation, non-enzymatic protein glycation and complex mechanisms including the polyol pathway (4, 5). The β-cells are more susceptible to oxidative stress since they contain lower levels of antioxidants compared to other tissues. Therefore oxidative stress plays an important role in diabetes development and the following complications (6). Organisms have developed several DNA repair mechanisms against certain agents to conserve the integrity of their genetic material (7). These harmful agents that cannot be removed from DNA do play a role in diabetes development. Also, the increased oxidative stress due to diabetes both worsens the prognosis and breaks the balance between oxidative stress and antioxidant mechanisms thus helping other genetic diseases to manifest (8,9). In conditions of severe DNA damage, a cell selects the apoptotic path, but in mild damage it tries to solve it using the repair mechanisms. Thus, cells vital to the immune system, such as the pancreatic β-cells, will be spared from destruction (10,11).

In Base Excision Repair (BER), where minor point damages are repaired, there is a process of recognition and removal of the single strand oxidation, alkylation, hydrolysis and deamination related damages. One of the genes coding the proteins of the BER pathway is the X-ray repair cross-complementing group 1 (XRCC1) (12). The XRCC1 gene is located on chromosome 19 region q13.2, where more than 60 single nucleotide polymorphisms (SNPs) have been identified. Due to the functional importance and high allelic frequency the most widely studied polymorphism is the Cytosine/ Thymine (C/T) transition on codon 194 leading to a arginine to tryptophane substitution (13,14).

Damages do not always occur on only a single strand of the genetic material. Oxidative stress, ionized radiation and even a normal physiologic process, somatic recombination, can damage both the strands. Double strand damages are repaired with two mechanisms, which are homologous recombination and non-homologous recombination end joining. The X-ray repair complementing group 3 (XRCC3) protein plays a role in the homolog recombination (15). The XRCC3 gene is located on chromosome 14 region q32.3 (16), where more than 100 SNPs have been reported. The most broadly studied one is the C/T transition on exon 7, codon 241 that is presented as a Thr/Met substitution (17).

Until now, the effects of different polymorphisms of several DNA repair genes have been investigated on type 2 diabetes. However, the effects of the XRCC1 Arg194Trp and XRCC3 Thr241Met gene polymorphisms have not been studied. Therefore, the effect of DNA damage repair gene polymorphisms, XRCC1 Arg194Trp and XRCC3 Thr241Met, have been investigated on type 2 diabetes mellitus patients for their relation with disease risk and clinical parameters in this study.

PATIENTS and METHODS

Study Groups

This study was conducted with the approval of the Istanbul Medical Faculty Ethical Committee, Istanbul University. Two study groups have been included in this study. The patient group comprised of 34 women and 40 male, a total of 74 patients, diagnosed with type 2 diabetes mellitus and who were on follow up by the Division of Endocrinology and Metabolic Diseases, Department of Internal Medicine, Istanbul Medical Faculty, Istanbul University. The control group included non-diabetic 52 women and 50 men, a total of 102, non-diabetic, healthy individuals of the Turkish population.

DNA Isolation and SNP Detection

In EDTA containing tubes, 10 ml of venous blood samples were obtained from the participants. Samples were stored at -20 °C until the genomic DNA isolation was performed using the salting out method (18). The primers used for the polymerase chain reaction (PCR) amplifications of the regions of the XRCC1 Arg194Trp and XRCC3 Thr241Met polymorphisms are given in Table 1. The reaction volumes were set for a total of 25 µl as 16.2 µl apyrogenik water, 2.5 µl $MgCl_2$ free (10X) buffer, 2.5 µl $MgCl_2$ (25 mM) buffer, 1.5 µl dNTP (10 mM), 1 µl mix of forward (10 pmol) and reverse primers (10 pmol), 0.3 µl Taq polimerase (5 U/µl) ve 1 µl 200 ng/µl genomic DNA sample. The PCR mixes were prepared on ice and in a sterile cabin.

For the XRCC1 Arg194Trp polymorphism, the PCR reaction conditions were set as following the initial denaturation of 95 ºC for 5 minutes, 95 ºC for 30 sec, 58 ºC for 45 sec and 75 ºC 45 sec for 35 cycles and a final elongation duration of 10 min at 72 ºC. Then, for the XRCC3 Thr241Met, following the initial denaturation of 95 ºC for 5 minutes, 94 ºC for 1 min, 58 ºC for 1 min and 75 ºC 1 min for 30 cycles and a final elongation at 72 ºC for 5 min. The PCR yields were controlled on 2% agarose gel electrophoresis.

In order to determine the XRCC1 Arg194Trp and XRCC3 Thr241Met polymorphisms, obtained PCR yields were digested with PvuII and Hin1II (Hsp92II) restriction enzymes, respectively. The digested yields were separated on 2% agarose gel electrophoresis and genotyped after being viewed under UV light. The obtained PCR and restriction yields and genotyping of the polymorphisms are shown in Table 1.

Statistical Analysis

The statistical analysis was performed using SPSS version 11.0 (SPSS inc. Chicago, USA). The statistical significance cutoff was taken as $p<0.05$. The distributions of the genotype and allele frequencies between study groups were evaluated using the Chi-square and Fisher's exact test. The demographic data were compared between the study groups using the Student's T and Anova tests. Allele frequencies were calculated according to the gene counting method.

RESULTS

The demographic data of the study groups is given in Table 2. There were no significant difference by means of age, gender, body mass index and smoking ($p>0.05$). Also, biochemical parameters of the study group given in Table 3 and no statistically significance was found according to lipid profiles between the patient and control groups ($p>0.05$).

The genotype and allele distributions were similar between the patient and control groups for the

Table 1 The PCR-RFLP-based assay of the XRCC1 and the XRCC3 polymorphisms

SNPs	Primers	Restriction Enzymes	Interpretation (bp)
XRCC1 Arg194Trp	F: 5′-GCCAGGGCCCCTCCTTCAA-3′ R: 5′-TACCCTCAGACCCACGAGT-3′	PvuII	CC: 485 TT: 396+89 CT: 485+396+89
XRCC3 Thr241Met	F: 5′-GGTCGAGTGACAGTCCAAAC-3′ R: 5′-TGCAACGGCTGAGGGTCTT-3′	Hin1II (Hsp92II)	CC: 456 TT: 315+131 CT: 456+315+131

(F: Forward primer, R: Reverse primer)

XRCC1 Arg194Trp polymorphism even that there were no individuals were detected to carry the TT allele in both groups (p>0.05) (Table 4). Likewise, there was no statistically significant difference for the XRCC3 Thr241Met genotype and allele distributions (Table 5).

The quantitative examinations of the demographic data for the XRCC1 Arg194Trp and XRCC3 Thr241Met genotypes in the patient group are shown in Tables 6 and 7, respectively. According to these findings no statistical significant differences were observed for either polymorphism.

Table 2 Demographic details of the study groups

Demographic Parameters	Control (n: 102)	Patient (n: 74)
Age (year)	55.96±10.13	58.82±9.44
Gender (F/M)	52/50	34/40
Smoking (%) (Yes/No)	26.5/73.5	28.4/71.6
Body mass index (kg/m^2)	28.05±5.98	28.43±4.88

n: Number of individuals

Table 3 Biochemical parameters of the study groups

Biochemical Parameters	Control (n:102)	Patient (n: 74)
Triglyceride (mg/dl)	174.77±106.66	203.76±206.7
Total cholesterol (mg/dl)	193.57±41.792	192.97±59.4
HDL-cholesterol (mg/dl)	43.491±9.41	39.21±21.61
LDL-cholesterol (mg/dl)	119.80±38.25	114.25±35.96
VLDL-cholesterol (mg/dl)	31.53±16.99	34.19±14.84
Blood glucose level (mg/dl)	-	166.18±152.55
HbA1c (%)	-	9.69±9.87
Folate (ng/ml)	-	7.77±3.15
B12 (pg/ml)	-	562.63±450.71
White blood cell	-	8.65±3.36
Hemoglobin	-	11.34±2.11
Hematocrit	-	33.75±6.06
Platelet	-	277.94±135.4

n: Number of individuals. HDL: High density lipoprotein. LDL: Low density lipoprotein. VLDL: Very low density lipoprotein. HbA1c: Hemoglobin A1c.

Table 4 Genotype distributions of the XRCC1 Arg194Trp polymorphism between the study groups

	Control (n: 102)		Patient (n: 74)	
XRCC1 Arg194Trp	n	%	n	%
CC	87	85.3	64	86.5
CT	15	14.7	10	13.5
TT	0	0	0	0
C allele	189	92.65	138	93.24
T allele	15	7.35	10	6.76

Table 5 Genotype distributions of the XRCC3 Thr241Met polymorphism between the study groups

	Control (n: 102)		Patient (n: 74)	
XRCC3 Thr241Met	**n**	**%**	**n**	**%**
CC	27	26.5	29	39.2
CT	67	65.7	38	51.4
TT	8	7.8	7	9.5
C allele	121	59.31	96	64.86
T allele	83	40.69	52	35.14

n: Number of individuals.

Table 6 Comparison of the demographic data against the XRCC1 Arg194Trp genotypes in the patient group

Demographic and Biochemical Parameters	CC	CT	TT
Body mass index (kg/m^2)	28.53±5.22	27.92±2.5	-
Total cholesterol (mg/dl)	192.66±61.21	195±48.91	-
Triglyceride (mg/dl)	209.03±220.02	170±78.95	-
HDL-cholesterol (mg/dl)	39.30±22.95	38.6±10.36	-
LDL-cholesterol (mg/dl)	113.38±33.63	119.72±50.12	-
VLDL-cholesterol (mg/dl)	34.28±14.77	33.66±16.1	-
HbA1c (%)	22.55±80.18	8.69±2.8	-
Blood glucose level (mg/dl)	172.27±154	64.7±87.49	-

HDL: High density lipoprotein. LDL: Low density lipoprotein. VLDL: Very low density lipoprotein. HbA1c: Hemoglobin A1c.

Table 7 Comparison of the demographic data against the XRCC3 Thr241Met genotypes in the patient group

Demographic and biochemical parameters	CC	CT	TT
Body mass index (kg/m^2)	28.65±5.30	28.30±4.49	28.13±6,01
Total cholesterol (mg/dl)	195.76±81.17	195.89±37.92	165.57±48,53
Triglyceride (mg/dl)	208.10±183.22	205.18±240.24	178±79.77
HDL-cholesterol (mg/dl)	38.90±11.19	36.39±10.44	58.5±68.63
LDL-cholesterol (mg/dl)	107.13±36.92	121.55±34.61	102.40±35.37
VLDL-cholesterol (mg/dl)	35.55±16.17	33.06±13.97	34.97±15.80
HbA1c (%)	11.60±15.61	28.73±100.43	8.78±2.49
Blood glucose level (mg/dl)	156.84±143.75	172.26±163.89	162.28±139.98

HDL: High density lipoprotein. LDL: Low density lipoprotein. VLDL: Very low density lipoprotein. HbA1c: Hemoglobin A1c.

DISCUSSION

Diabetes mellitus is a metabolic disease characterized by high blood sugar (hyperglycemia) developed due to the partial or complete absence of insulin. T2DM is the most common type of diabetes and although almost all the patients have a family history, the disease has not yet been explained with a single genetic mechanism (19). Owing to the gene-environment interactions some polymorphisms found in DNA repair genes cause a promotion in disease tendencies since they affect the capacity of DNA repair. Impairments in the XRCC1 and XRCC3 increase genetic instability and susceptibility to DNA damaging agents (20).

In this study, the prevalence of the XRCC1 Arg-194Trp (C/T) and the XRCC3 Thr241Met (C/T) polymorphisms and their impacts on T2DM development was investigated. This study, which was conducted on a Turkish population, is the first to focus on this hypothesis. According to the demographic data collected the study group, comprised of 74 patients and 102 controls, no statistically significant difference was observed in terms of age, gender, smoking status, body mass index and lipid profile distributions. Since there are no other studies directed to the XRCC1 Arg194Trp polymorphism and a T2DM patient group for comparison to this study, the disease mechanism was attempted to be comprehended based on the other studies related to the XRCC1 Arg194Trp polymorphism and other patient groups or another polymorphism associated with T2DM.

The effect of the XRCC1 Arg194Trp polymorphism on patients of glaucoma with open angle have been investigated and no connection was found. On the other hand, the XRCC1 399 Arg/Gln polymorphism was indicated as a risk factor for the development of glaucoma with open angle (21). The role of the XRCC1 399 Arg/Gln polymorphism on T2DM and diabetic nephropathy was studied and no significant relation was observed (22, 23). However, Narne et al., suggested that the XRCC1 399 Arg/Gln polymorphism increases the risk of diabetic nephropathy (24). According to the findings of a study, where 207 prostate cancer patients and 235 healthy controls were included, it was reported that the Arg194Trp polymorphism decreased the risk of the disease's development (25). In the study that Deligezer et al., conducted on Turkish breast cancer patients and controls to investigate the effects of the Arg194Trp and Arg399Gln polymorphisms, because both the alleles showed similar frequency in both groups, they concluded that there were no associations between these XRCC1 variants and breast cancer development (26). Moreover, in the study of Demokan et al., on XRCC1 Arg194Trp polymorphism of 95 patients of head and neck cancer, no significant association was found (27). Again, in a study of Duman et al., on 73 Turkish chronic lymphatic leukemia patients, the allele frequency was found similar with the control group (28). While the mutant allele frequency was found to be 4-5% by Deligezer et al., (26) in both study groups, it was 1.37% in the patient group and there were no mutant allele carriers in the control group in the Duman et al. study (28).

In this study, the allele frequencies for the XRCC1 Arg194Trp polymorphisms were detected to be similar between the patient and control groups. Thus, compatible with the three other studies conducted on the Turkish population by Deligezer et al., Demokan et al. and Duman et al., the protective effects observed in other populations have not been seen and no statistical significances have been encountered. Moreover, the Trp/Trp genotype frequency is quite low in the Turkish population. There were no homozygous mutant allele carriers in either study group of this study.

So as to elucidate the function and molecular mechanisms of the polymorphisms of the XRCC and the other related BER components, the study group should be expanded and meticulous studies should be carried out.

The other polymorphism of this study, the XRCC3 Thr241Met, showed no statistical significance between the study groups in terms of genotype and allele distributions. Furthermore, the genotype distributions did not show any associations with any of the demographic criteria.

In a study on 160 acute myeloid leukemia (AML) patients and 161 controls, the XRCC3 Met/Met was shown to increase the risk of AML 2 fold (29). Similarly, in a study on 140 colorectal cancer patients and 280 controls, both heterozygous and homozygous mutant genotype increased the risk of colorectal cancer 3 fold (30). Sangrajrang et al., (31)

investigated the association between the XRCC3 Thr241Met polymorphism and breast cancer in a Thai population and found an association with the Met allele. In addition, Narter et al., (32) evaluated the relation between the XRCC3 Thr241Met polymorphism and bladder cancer. They found that the XRCC3 T allele distribution had a significant difference between the study groups and the mutant allele created protection against the risk of bladder cancer development by 4.87 fold.

There were no other studies in the literature that investigated the relationship between the XRCC1 Arg194Trp and XRCC3 Thr241Met polymorphisms and type 2 diabetes mellitus and/or lipid profiles in the Turkish population. Thus our study is the first to focus on the mentioned polymorphisms in such a group and we believe that it might be a data source for the further studies.

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

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