RESEARCH ARTICLE

The Excision Repair Cross-complementation Group 2 (rs1799793) Gene Polymorphism in Type 2 Diabetes Mellitus Patients

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ABSTRACT

The excision repair cross-complementation group 2 (ERCC2) or (XPD) gene encoded to protein used in bulky deoxyribonucleic acid (DNA) lesion removal from DNA, the present study used polymerase chain reaction single-strand conformation polymorphism (PCR-SSCP) to study ERCC2 polymorphism by haplotypes variations between DM2 patients and control group in addition to detect the glycemic parameters. The results show a significant increase in all glycemic parameters in the patient group except insulin resistance that significant decrease. The ERCC2 gene polymorphism shows three haplotypes (A, B and C), two patterns for patients and control observed; AC was more frequent in patients (46.34%) than control (17.24%) in significant differences (or 4.1455, $p > 0.0147$) and less frequent of ABC patterns in patients (53.65%) than control (82.75%). The polymorphism did not affect glycemic parameters. From this finding can be concluded that there was association between ERCC2 rs1799793 and DM2 but did not affect glycemic parameters.

Keywords: ERCC2 (rs1799793), Polymorphism, Type 2 diabetes mellitus.

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INTRODUCTION

The most important disease that causes an elevation of mortality rate worldwide is diabetes type 2 which is results from the combination between environmental factors and polygenic defects.[1] The lifestyle of patients and lack of commitment to a healthy diet lead to occurrence of the oxidative stress condition and thus cause complications developed with diabetes.[2]

Oxidative stress is represented by Reactive Oxygen Species (ROS), in addition to the endogenous and exogenous stress has the ability to damage DNA. There were several genes have an important role in DNA repair like nucleotide excision repair (NER).[3] ERCC2 participated in the elimination of bulky DNA lesions from DNA, where it has an important role in regulation of cell cycle, apoptosis and transcription coupled repair.[4] In a study of Hussien *et al*.,[5] found the presence of genetic instability which may result from genetic variation in the single nucleotide polymorphisms (SNPs) that will cause obstruct the repair of DNA. So, this study aimed to detect effects of polymorphisms in the ERCC2 gene in glycemic control in T2D patients.

MATERIALS AND METHODS

Study Groups

A case control study was implemented at the February-April period, included 40 T2DM patients and 30 control individuals, blood samples for glycemic and XPD gene polymorphism detection. Ethical approvals were dependent with written consent from all study contributors.

Glycemic Parameters

The Glycemic parameters included fasting blood glucose, glycated protein, insulin, insulin sensitivity and insulin resistance were detection using routine lab works.

Gene Polymorphism

The ERCC2 Asp312Asn (rs1799793) was detected by PCR-SSCP technique using F- CTGGAGACCCTGCAGAAGAC, R – CTCTGCGAGGAGACGCTATC, the PCR product was 354 bp at the annealing tm 57ºC.

Gel Electrophoresis and SSCP Technique

Agaros gel used for visualized DNA extraction and PCR products. The gene polymorphism detection by SSCP technique according to Mohcen *et al*..[6]

Data Analysis

Data represented as mean ± SE, Odd ratio (CI95%) and ANOVA one way were used to significant differences at $p < 0.05$.

RESULTS

The ERCC2gene polymorphism was detected in the present study for DM2 patients and control, three haplotypes were

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observed (A, B and C), two patterns for patients and control observed AC was more frequent in patients than control in significant differences (OR 4.1455, CI95% 1.3225–12.9937, p = 0.0147) and less frequent of ABC patterns in patients also (Table 1, Figure 1).

All parameters in the present study were significant affected by ERCC2 gene except IN, the AC haplotypes causes elevated in FBG, IN, and in addition to decreased in the IR and while slight changes between AC and ABC in control group, in general some parameters increased or decreased in patients than control according to disease effect (Table 2).

DISCUSSION

Hyperglycemia is the main symptom of Diabetes mellitus which is results from the deficiency of insulin completely or partially and\or the dysfunction of pancreatic β-cell.[7] Oxidative stress developed according hyperglycemia condition and insulin resistance causes many of diabetic complication as a result of the accumulation of ROS where increasing the levels of free radicals lead to damage of DNA and mitochondrial DNA.[8,9] The DNA repair its damaged via genes have the ability to repair these damages such as Xeroderma pigmentosum complementation group D (XPD) gene using pathway of NER which is accomplished the repair by the combination between XPD and groups of DNA repair enzymes. The Activity of XPD and its expression is depending on insulin where the activation of insulin receptors leads to control XPD expression at the level of mRNA and protein.[10] The results of the current study show that the ERCC2gene polymorphism has three haplotypes (A, B and C), two patterns for patients and control observed AC was more frequent in patients than control in significant differences and less frequent of ABC patterns in patients also and the glycemic controls are significantly affected by ERCC2 gene except IN, the AC haplotypes causes elevated in FBG, IN, and in addition to decreased in the IR and while slight changes between AC and ABC in control group. Several studies indicated the polymorphism in ERCC2 gene and found that the presence of two polymorphisms ERCC2 Asp312Asn and ERCC2 Lys751Gln and the Asp312Asn polymorphism is the more frequent. The transition of amino acid substitution aspartic acid to asparagine at codon 312 of exon 10 of ERCC2 cause function, loss of SNP and thus diminish in DNA repair.[11] In a study of Merkel and his colleagues[12] found that the elevation of blood glucose to the toxic levels have the ability to diminish regulate insulin-dependent DNA repair. In another study detected ERCC2 Lys751Gln Lys/Gln genotype in T2D patients, which found it was more prevalent in the patient group and concluded that this genotype lead to reduce repair of DNA and thus it associated with the development of diabetes.[13] Other studies indicate another genotype of ERCC2

Table 1: Genotyping of ERCC2 (rs1799793) gene in study groups

Genotyping	*Patients*	*Control*	*Odd ratio*	*p-value*
ABC	22 (53.65)	24 (82.75)	4.1455 1.3225 to 12.9937	0.0147
AC	19(46.34)	5(17.24)		

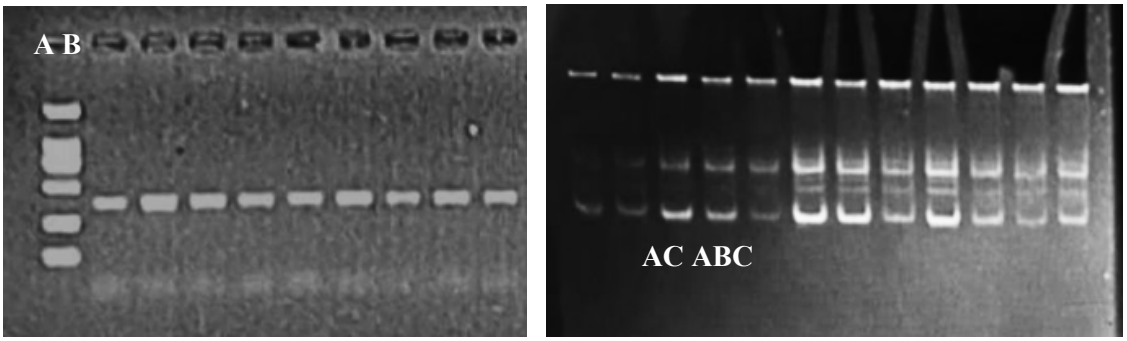

Figure 1: the amplification products of ERCC2(rs1799793), A one band has 354 bp, B the SSCP electrophoresis patterns AC and ABC patterns for patients and control

Table 2: The ERCC2 genotyping impact in study variables

Study variables	*Patient*		*Control*		
	ABC	*AC*	*ABC*	*AC*	*p-value*
FBG	217.40 ± 25.60a	233.26 ± 23.340a	93.75 ± 2.81bc	95.80 ± 8.163c	0.000
HbA1c	8.60 ± .398a	8.54 ± 0.424a	5.10 ± 0.071bc	5.32 ± 0.195c	0.000
IN	3.68 ± 0.5844	4.1853 ± 0.70942	2.56 ± 0.204	2.3710 ± 0.44	0.078
IR	1.54 ± 0.24ad	2.1528 ± 0.364d	0.58 ± 0.052b	0.54 ± 0.088ab	0.000
IS	0.38 ± 0.014ace	0.3718 ± 0.016c	0.42 ± 0.009be	0.43 ± .020e	0.005

Different later refer to significant between groups at p-value less than 0.05

in diabetic patients and investigate that Cys/Cys genotype was more prevalent in patients and associated with elevation of blood glucose and body mass index and it more associated with the development of coronary artery disease in diabetic patients while the Ser/Ser genotype decrease in patient with glucose intolerance.[14-18] From this finding can be concluded that there was association between ERCC2 rs1799793and DM2 but didn't effect by glycemic parameters. It needs more investigations to prove the effect of other factors related to DM in the DNA repair gene polymorphism.

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