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Research Article

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Association of ROS Level with Some DNA Repair Genes Polymorphisms in Type 1 Diabetes Mellitus Patients

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Abstract

The ROS is most problems in some disease and have major role disease development; DNA repair genes have been associated with different disease in addition to related with ROS, the present study aims to study ROS level with some DNA repair genes polymorphisms in patient with type 1 diabetes mellitus patients, the *OGG1 Ser326Cys* (rs1052133) and APE1 Asp148Glu (rs3136820), the results show that ROS level was significant elevation in patients 196.3600 ± 90.039 than control 95.37 ± 13.22, the genotyping of APE1 shows three genotyping (GT,GG and TT) with tow alleles (G and T), GT was low frequents in patients while TT was higher in patients than control in non-significant differences (p 0.38, 0.50) , T is more frequent in patients in addition to G was low frequent also in on significant differences (p 0.0513) in addition to deletion mutation which significant association with disease, *OGG1* show strong association with disease, all patients have AC pattern which contributed in lowering ROS level, the present study concluded that the APE1 deletion mutation association with DM and didn't relation with ROS level, *OGG1 SER326CYS (RS1052133)* strong association with DM and ROS level in type one of diabetes mellitus diseases.

Keywords: ROS • DNA repair genes • Polymorphisms • Type 1 diabetes mellitus • Nucleic acids • Patients • Diabetes • Mellitus

Introduction

The Reactive Oxygen Species (ROS) is a free radicals produced naturally in cells for involved in the some cell functions, the excessive ROS have been recorded that it's related with disease incidence and developments [1]. Diabetes mellitus found to be associated with oxidative stress imbalance and elevation of ROS, and pivotal role in DM complications [2], the excessive ROS production targeted biological molecules like proteins, nucleic acids and lipids [3].

The oxidative stress balanced in the body dependent on different factors like antioxidant capacity molecules, the stress exposure period, repair system efficiency [4], the DNA repair genes is a system consist of different enzymes and proteins contributed in the oxidative nucleotides repair, the present study deal with APE1 (Apurinic/apyrimidinic endonuclease 1) and *OGG1* (8-oxoguanine-DNA glycosylase 1) genes, both genes belong to base excision repair system which contributed in the rapier of oxidative DNA damage [5,6].

Diabetes Mellitus (DM) is one of the most important health problems in last decades in the world, the association between oxidative stress and diabetes mellitus have been proved [7]. The results of DNA damage is 8-oxo dG that is found in high percentages in DM patients [8]. Type 1 of diabetes mellitus characterized by insulin deficiency also recorded high percentages of ROS and the long periods of excessive free radicals exposure may be causes mutation in DNA repair genes [1].

Methodology

Type 1 diabetes mellitus patients attended to the Margan Hospital City were enrolled in present study, FBG, BMI, duration of disease, ROS were detection using classical lab tests, DNA was extracted from whole blood then APE1 Asp148Glu (rs3136820) polymorphism using PCR-CTTP 5′-CCT ACG GCA TAG GTG AGA CC; R1:5′-TCC TGA TCA TGC TCC TCC-3′;

F2: 5′-TCT GTT TCA TTT CTA TAG GCG AT; R2: 5′-GTC AAT TTC TTC ATG TGC CA. Three bands amplifying a 236 bp, 167 bp and a 360 bp band corresponded to the T allele, G allele and common band respectively. *OGG1 SER326CYS (RS1052133)* was amplified using PCR-SSCP [9,10]. *OGG1 SER326CYS (RS1052133)* F- GGTGGCCCTAAAGGACTCTC, R-AAGGTGCTTGGGGAATTTCT. Data were analysis using t test and odd ratio with CI95% at P value 0.05.

Results

The aim of this study was to study association ROS and tow DNA repair genes in diabetes mellitus type 1 patients, the results show the mean of ages were 49.2400 ± 12.650, 33.2414 ± 11.55 for patients and control, the BMI kg/m^2 were 31.07 ± 6.346, 27.3407 ± 3.744 for patients and control, the fasting blood glucose was higher in patients 196.36 ± 90.0 than control 95.37 ± 13.224, also ROS higher in patients 196.3600 ± 90.039 than control 95.37 ± 13.22, all previous variables were significant differences between patients and control (Table 1).

Categories	Control	DM type 1	P value
Age	33.2414 ± 11.55934	49.2400 ± 12.65003	0
BMI kg/m^2	27.3407 ± 3.74448	31.0764 ± 6.34624	0.01
FBG	95.3793 ± 13.22447	196.3600 ± 90.03975	0
ROS	25.8552 ± 7.74383	48.4042 ± 1.23339	0

Table 1. The statics analysis of age, BMI, FBG and ROS levels in study groups.

Tow DNA repair gene polymorphisms were studied in present research included APE1 and *OGG1 SER326CYS (RS1052133)*, (Figure 1) show amplification products of PCR-CTTP of APE1 and PCR-SSCP of *OOG1*, the APE1 genotyping show that about 28% of patients were suffered from

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deletion mutation in this gene while 3.33% was observed in control group in significant differences (p 0.029), three genotyping (GT,GG and TT) were observed with tow alleles (G and T), GT was low frequents in patients while TT was higher in patients than control in non-significant differences (p 0.38, 0.50) , T is more frequent in patients in addition to G was low frequent also in on significant differences (p 0.0513) present finding pointed that deletion mutation was strong related with DM type 1 (Figure 1, Table 2).

Geno-typing	Patients	Control	Odd ratio	P value
Deletion	7(28%)	1(3.33%)	11.2778 (1.2796 to 99.3984)	0.0291
GT	3(12%)	16(64%	2.0513 (0.4110 to 10.2378)	0.3811
GG	4(16%)	5(20%)		
TT	11(44%)	8(32%)	1.7188 (0.3472 to 8.5081)	0.5069
G	0.31	0.448	1.7806 (0.9967 to 3.1813)	0.0513
T	0.69	0.551		

Table 2. The APE 1 Asp148Glu (rs3136820) gene genotyping in study groups.

Figure 1. APE1genotyping using PCR- CTTP, lanes 1,2,8,9,11 and 12 deletion mutation, lanes 3,4,6,10,13,15 TT genotype, lanes 5,7 GG genotype and lanes 14 GT genotype. 70V, 20 mA, 0.5X TBE, and 1% agaros for 40 min.

The *OOG1* genotyping was explained in Figure 2 and Table 3, genotyping show three haplotypes, A, B, C in three patterns (ABC, AC and C), all patients have AC patterns while control groups show low frequent of AC and high frequent of ABC in significant differences (p 0.002, 0.001) the present results show strong association *OGG1 SER326CYS (RS1052133)* gene polymorphisms with DM type1.

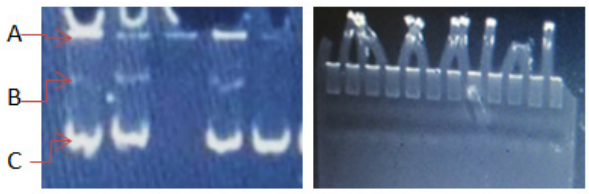

Figure 2. The haplotypes patterns of OGG1 SER326CYS (RS1052133) gene in study group, left haplotypes A, B and C , right show the AC pattern, SSCP with 40% polyacrylamide, 70 V, 0.5 X TBE for 80 min.

Haplo-types patterns	Patients	Control	Odd ratio	P value
ABC	0	19(63%)	86.4783 4.7955 to 1559.4807	0.0025
AC	25 (100%)	2(6.66%)	193.8	0.001
C	0	9(30%)	8.5024 to 4417.3955	

Table 3. The OGG 1 gene Haplotypes patterns in study group.

The association of APE1 and *OGG* genes polymorphisms with ROS was investigated in present study, the genotyping of APE 1 didn't effect in the ROS level in patients and control (p 0.96, 0.89) but significant difference were observed between patient and control which have same genotyping (p 0.00, 0.00, 0.03 and 0.00) for deletion mutation, TT, GG, and TG respectively (Table 4), the *OGG1* also didn't effect in ROS level because of one heliotyping was appeared in present study, significant elevation observed in patients than control which have AC patterns.

Genotyp-ing	Control	Patients	P value
APE1 Asp148Glu (rs3136820)			
Deletion	25.3200 ± 0.00	48.2291 ± 1.00846	0
TT	25.0588 ± 4.64372	48.4351 ± 1.48170	0
GG	31.7800 ± 13.25504	48.8375 ± 0.648	0.039
TG	24.3407 ± 6.60116	48.4133 ± 1.55577	0
	0.898	0.966	
OGG1 SER326CYS (RS1052133)			
ABC	26.6083 ± 8.63134	0	-
AC	19.9150 ± .68589	48.4042 ± 1.23339	0
C	25.6689 ± 6.43240	0	-
P value	0.525	-	

Table 4. The impacts of APE1 and OGG 1 gene polymorphisms in the ROS levels in study groups.

Discussion

The diabetes mellitus is chronic disorder and most health problem in last decades on the world, its characterized by deficiency in insulin secretion or uptake by cells or both [11], investigation found that the elevation in free radicals was associated with DM, also decline in the antioxidant enzyme activity [12,13]. In present study free radicals levels were increased in type 1 of DM and this elevation may be because the hyperglycemic enhanced excessive free radicals production by four ways, first; increase the ratio between of rate G3P oxidation/1,3-DPG which resulted from glycolysis elevation, following by redox imbalance which resulted from increased NADH/NAD+ratio, second; accumulation the sorbitol and fructose by activation sorbitol pathway that lead to lowering in GSH and increased in the ration of NADH/NAD+, third; the glucose autoxidation causes production different types of free radicals, finally; formation of AGEs that upon interacting with RAGEs formation oxidative stress resulted from protein glycation [14].

The present study focused on the APE1 and *OOG1* as a result of their role in the oxidative damage rapier of DNA, the previous studies pointed to APE1 gene polymorphism in some diseases like diabetes mellitus type 2, cancers types [15-17]. There were no previous information's about association APE1 with type 1 of DM, the relation of APE1 is associated with ROS elevation level Regardless of the type of disease, studies deal with APE1 gene polymorphisms in numerous diseases found elevation in ROS level because the activation of APE1 enzyme dependent on the ROS level [18,19]. Also it's related with mitochondrial stress [20]. The APE1 gene polymorphisms didn't significant association with DM type1 but significant association with deletion mutation. In general the TT allele has been found to be associated with disease but in non-significant association.

The *OGG1 SER326CYS (RS1052133)* found to be strong association with DM type 1 disease, one Pattern (AC) with tow haplotypes (A,C) fond in disease while other pattern that fond in the control group didn't observe, the *Ser326Cys* is the more SNP was studied in investigations because it causes lowering enzyme function represented by helps in cleavage of the glycoside bond [21]. The *OGG1 SER326CYS (RS1052133)* polymorphisms play major role in some diseases pathogenesis like DM type 2 [18,22]. Other study elucidated no association with DM [23].

Conclusion

The Reactive Oxygen Species (ROS) is a free radicals produced naturally in cells for involved in the some cell functions, the excessive ROS have been recorded that it's related with disease incidence and development. Diabetes mellitus found to be associated with oxidative stress imbalance and elevation of ROS, and pivotal role in DM complications, the excessive ROS production targeted biological molecules like proteins, nucleic acids and lipids.

The present study focused on the APE1 and *OOG1* as a result of their role in the oxidative damage rapier of DNA, the previous studies pointed to APE1 gene polymorphism in some diseases like diabetes mellitus type 2, cancers types. There were no previous information's about association APE1 with type 1 of DM, the relation of APE1 is associated with ROS elevation level Regardless of the type of disease, studies deal with APE1 gene polymorphisms in numerous diseases found elevation in ROS level because the activation of APE1 enzyme dependent on the ROS level. Also it's related with mitochondrial stress. The APE1 gene polymorphisms didn't significant association with DM type1 but significant association with deletion mutation. In general the TT allele has been found to be associated with disease but in non-significant association. The aim of this study was to study association ROS and tow DNA repair genes in diabetes mellitus type 1 patients, the results show the mean of ages were for patients and control, the BMI kg/m^2 were for patients and control, the fasting blood glucose was higher in patients than control also ROS higher in patients than control, all previous variables were significant differences between patients and control. The diabetes mellitus is chronic disorder and most health problem in last decades on the world, its characterized by deficiency in insulin secretion or uptake by cells or both investigation found that the elevation in free radicals was associated with DM, also decline in the antioxidant enzyme activity.

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