

Detection of DNA Repair Gene (OGG1) Polymorphism and Oxidative State in Some Iraqi with Type 1 Diabetes Mellitus

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Abstract: Oxidative stress plays an important role in the pathogenesis of cardiovascular alterations observed in diabetic patients and that hyperglycemia is the causal link between diabetes and increased oxidative stress. Evidence suggests that Ser326Cys, a genetic polymorphism of (8-OxoGuanine Glycosylase 1 OGG1) is associated with coronary artery lesions in patients with diabetes mellitus type 1 however, the underlying mechanism is unclear.

Key words: OGG1, insulin-dependent diabetes mellitus, type 1 diabetes, OXDLDL, lesions, cardiovascular

INTRODUCTION

Diabetes mellitus is a metabolic disorder disease categorized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. In either case, the cause of this defect is the glucose does not enter the cells and builds up in the blood. The chronic hyperglycemia of diabetes is linked with long term damage, dysfunction and failure of different organ, especially the heart, blood vessels kidney, nerves and eyes. Also, the longer duration of diabetes is the most risk of complications which rise significantly following teens. Diabetes mellitus can be categorized into four clinical groups by American diabetes Association (ADA) and World Health Organization (WHO). There are three main types of DM are recognized type 1 DM or (IDDM), type 2 DM or (NIDDM) and Gestational Diabetes Mellitus (GDM). The fourth is from other specific types of diabetes are caused by specific genetic defects of beta cell function or insulin action, the pancreas diseases and drug or chemical induced diabetes mellitus (Han *et al.*, 2009; Saifullah and Dia'a, 2015). In type 1 diabetes onset occurs when 80-90% of pancreatic beta cells can no longer function normally. Under physiological situations, β cells sense and reply to ever changing blood glucose levels by producing insulin which acts on other tissues to stimulate glucose uptake from the blood and consequently lower blood glucose levels. Without sufficient numbers of functional β cells, insulin production come to be insufficient and

hyperglycemia ensues. In type 2 diabetes which accounts for 90-95% of those with diabetes, progresses when insulin secretion or insulin action fails. Hyperglycemia and free fatty acid consumption are among the causes for oxidative stress conditions. Hence, it may not be unexpected that diabetic subjects tend to have extra oxidative cell and organism environments than healthy subjects, viz. an increase in ROS generation. As a consequence, the accumulation of Reactive Oxygen Species (ROS) may generate additional destruction to various biological macromolecules including DNA (Evans *et al.*, 2002). The 8-OxoGuanine DNA Glycosylase1 (OGG1) is a crucial enzyme of the BER pathway and catalyzes the removal of 8-OHdG Reactive Oxygen Species (ROS) play role an increased in glucose levels that regular by 8-OxoGuanosine DNA Glycosylase 1 (OGG1) (Rains and Jain, 2011; Mclean, 2014). One of the most polymorphism in OGG1 is (Ser326Cys) which play a major roles in various disease (Wu *et al.*, 2004). This lesion is effective mutagen and can generate transversion (substitution) of C/G serine with cytosine in codon 326 which lower the activity of the DNA repair enzyme. Thus, it is accepted that oxidative stress has been approved as a major participant in the pathophysiology of diabetic complications. So, the generation of ROS is increased in types 1 of diabetes and that the onset of diabetes that is closely related with oxidative stress (Dherin *et al.*, 1999; Scott *et al.*, 2014).

MATERIALS AND METHODS

Study population: The study involved a total (100) subjects including (60) people are suffering from diabetes type 1 according to the United States Center (US) for diabetes aged between (6-40 years) and (Hassan *et al.*, 2012) non-diabetic controls aged between (10-40) years. All samples were taken from the Diabetes Center of the University of Mustansiriyah the Molecular Biology part of the study was carried out in the molecular and medical Biotechnology Research Center/Al-Nahrain University, Iraq, Baghdad. Sequencing data assay is done for Iraqi diabetes patients, by (Humanizing Genomics MacroGen Company-Korea). Detailed medical information was taken from each subject and the individuals with history of type 1 diabetes underwent clinical examination. Individuals with obesity, hypertension, smoking and chronic infections, autoimmune and renal diseases were excluded. Kits based on enzymatic methods measured serum concentrations of glucose and lipid profile. Oxid-LDL was measured by using standard Enzyme Linked Immune Sorbent Assay (ELISA) method. Hemoglobin (A1C) by kit based on non-enzymatic method and Body Mass Index (BMI) were also measured.

DNA isolation and determination of OGG1 genotype:

DNA was extracted from the whole blood by wizard genomic (DNA purification kit, Intron) according to the isolating genomic DNA from 200 μ L whole blood in each case. The volume of the extracted DNA solution was usually 100 μ L were stored at -20°C and use the serial replication and the varying lengths of cutting restricted DNA to investigate the genetic diversity of the gene OGG1 of all members of this study. A fragment 207 bp containing the Ser326Cys polymorphism which amplify the exon 7 region in which the Ser326Cys fragment is located. PCR amplification products were obtained using 25 μ L reactions (Template DNA 1.5 μ L, Primer Forward 0.8 μ L F, Primer Reverse 0.8 μ L R, Deionized Water 16.9 μ L PCR Master Mix 5 μ L). Thermal cycling conditions for the OGG1 were: an initial denaturation step for 2 min at 94°C , 33 cycles of denaturation for 30 sec at 94°C , primer annealing for 30 sec at 61°C and primer extension for 30 sec at 72°C , followed by a final extension step for 10 min at 72°C . The primers used for amplification of OGG1 gene exon 7 including Ser326Cys were 5'-ACT GTC ACT AGT CTC ACC AG-3' forward and 5'-TGA ATT CGG AAG GTG CTT GGG GAA T-3' reverse. (16) Simple PCR-RFLP was used to detect the Ser326Cys variant, because the C to G transversion creates a new Fnu4HI restriction site. The PCR product was digested with 2 units of Fnu4HI. The C/C homozygote is not cleaved by FNU4HI and the

single 207 bp band residues. The C/G heterozygote contains all 3 bands (100, 107 and 207 bp bands) following restriction digestion. After PCR, amplification product was digested the reaction was conducted in 10 μ L final volume at 37°C for 30 min for genotyping of studied samples, the digested fragments were electrophoresed on 4% agarose gel mixed with red stain.

Statistical analysis: The Statistical Analysis System-SAS Institute Inc. (2004) was used to detect different factors in study parameters. p-value test was applied to compare differences in clinical parameters between patients and controls. OGG1 was classified as homozygous wild type Ser/Ser, heterozygous mutant Ser/Cys. p-values were a value of ≤ 0.01 , 0.05 was considered statistically significant. Least significant difference LSD test was used to significant compare between means in this study.

RESULTS AND DISCUSSION

The results were carried out to indicate the relationships between The Diabetes Mellitus type 1 (T1DM) patients and the genotyping of OGG 1 and measurement of some clinical parameters in patients group and healthy control group. The current study includes (100) subjects (60) patients with diabetes mellitus type 1 and (Hassan *et al.*, 2012) subjects as control group.

Table 1 summarizes the anthropometric characteristics of type 1 diabetic subjects and non-diabetic controls. The difference of age was not significantly different ($p > 0.05$) in diabetic patients when compared with control group. Also, there was significant differences were observed in the values of BMI ($p = 0.0288$), the BMI for non-diabetic controls was ($p = 0.05$) when matching diabetics group but both of them in the normal range of BMI.

Table 2 Summarizes the glycemic parameters of type 1 diabetic subjects and respective non-diabetic controls. Mean blood glucose concentrations were significantly higher in type 1 diabetic than in controls. HbA1c levels were significantly higher ($p < 0.0001$) in diabetic as compared to the control group. The results show the triglyceride levels negative significant for patients as compared to the control group. Also, the results show a significant difference was observed in serum levels of Ox-LDL in diabetic and control group. The results show No significant differences were observed in serum levels of Cholesterol, HDL, LDL and VLDL.

The frequency distribution of OGG1 gene polymorphism was represented in Table 3. Frequency of OGG1 C/C (homozygous) genotype showed (26.67%) in patients and (100%) in control. The differences were

Table 1: AGE and BMI for the patients group and control group

Parameters	Mean±SD		p-values
	Patients	Control	
Age (year)	23.59±6.48	25.63±8.19	0.3184
BMI (kg/m ²)	22.94±4.45	24.96±5.10	0.0288

Significant differences at (p = 0.05)*

Table 2: The (mean±SE) of (F.B.G, HbA1c, lipid profile and Oxd-LDL) in patients and control group

Parameters	Mean±SD		p-values	LSD
	Patients	Control		
FBG	243.42±11.51	88.95±7.38	0.0001	44.536**
HbA1C	11.14±2.45	4.98±0.34	0.0001	1.052**
Cholesterol	178.59 ±39.01	176.04±31.76	0.7780	17.906 NS
Triglyceride	83.82±48.11	108.00±60.07	0.0223	22.268*
HDL	49.09±12.81	43.40±12.33	0.0646	6.045 NS
LDL	107.55±44.56	109.13±21.81	0.8724	19.481 NS
VLDL	25.12±33.02	23.63±12.37	0.8369	14.264 NS
Ox-LDL	0.902±0.29	0.665±0.05	0.0416	0.185*

**(p<0.01), NS: Non-Significant

Table 3: Genotype distribution of OGG1 gene C/G & C/C polymorphism in healthy control and diabetic mellitus type 1 patient

Polymorphism	Patients	Control	p-values
CC	20 (26.67%)	25 (100%)	0.0001**
CG	55 (73.33%)	0 (0.00%)	0.0001**
GG	0 (0.00%)	0 (0.00%)	1.00 NS
p-values	0.0001**	0.0001**	---
Allele freq.			
C	0.63	1.00	---
G	0.37	0.00	---

**(p<0.01), NS: Non-Significant

significant (p = 0.01). The results of OGG1 heterozygous G/C genotype showed higher significantly in diabetes mellitus type 1 (73.33%) and not found in controls (0.00%). The differences were significant. OGG1 G/G genotype frequency was not found, neither in the diabetes mellitus type 1 nor controls (0.00%), consequently there was not significantly different (p>0.05) (Fig. 1 and 2).

The results show Table 5 and Fig. 3, Sequence ID: dbj|AB037881.1| and have number score (278) bits, expect 7e-71, identities 100 and gap 0% and other them (patient) appeared 99% compatibility with Homo sapiens for OGG1 type 1 gene from 322-471 number of nucleotide from gene of gene bank results as shown in Table 4 and Fig. 4, Sequence ID: dbj|AB037881.1| and have number score (147) bits, expect 1e-69, identities 99 and gap 0%. And the Fig. 4 shows sample curves that represent each of the two genotypes

Table 5 shows the mean of Duration, FBG and HbA1C statistically significant (p<0.01) while the age and BMI statistically not significant (Franz, 2000; Hajas, 2015). Also, Table 5 shows the mean of VLDL and Oxd-LDL statistically significant (p<0.05) while the Cholesterol, Triglyceride, HDL and LDL statistically not significant.

As apparent from Table 1, there were significant differences in BMI (p = 0.05) in control group when matching with diabetics group but both of them in the normal range of BMI. A decreased BMI in patient group is due to stop producing insulin hormone which is required in glucose metabolism, the major type of sugar in the blood and make the body can't use it correctly, then the calories away from the body in urine. As a result, kids and adult who develop type 1 diabetes can lose weight despite having a normal or increased appetite (Gulcin, 2012). The result shown there is any significant differences in age in control and diabetics group.

In Table 2, there was a significant increase (p<0.0001) in the mean of fasting serum glucose levels of patients compared to control, this agrees with previous studies (Haifa *et al.*, 2014; Al-Naama *et al.*, 2011; Hamad *et al.*, 2010). Elevated F.B.G is due to insulin hypo secretion in DM1 patients, this insufficient secretion cannot compensate with nutritional needs for patients, decreases the shifting of extracellular glucose to intracellular storage in the form of macromolecules (such as glycogen, fats and protein) and because patient eating un healthy food or lack of commitment to patient treatment therefore blood glucose elevated high F.B.G.

In Table 2, the study shows positive significance (p = 0.0001) in the mean of glycosylated hemoglobin in patients compared with control. This results agree another with researchers in which parameters associated with higher levels of HbA1c. (Belfort *et al.*, 2010; Saifullah and Dia'a, 2015). Some study's finding indicate that diabetic patients are at extremely high risk of cardiovascular complications than normal people. This implies that such patients are at risk of early diabetic complications, accelerated atherosclerotic disease and also increased cardiovascular disease risk (Al-Naama *et al.*, 2011). Also, found that the increased level of glycosylated hemoglobin in the diabetic patients is directly proportional to the blood glucose level. This suggests the increase in oxidative stress due to hyperglycemia (Sarlund *et al.*, 1987).

Also, in in Table 2 insignificant increments were seen in serum levels of Cholesterol, HDL, LDL and VLDL. The results of Cholesterol is agree with the study (Sarlund *et al.*, 1987) who found that no significant differences was obtained in the level of serum cholesterol in diabetic and non-diabetic patients with increase duration of disease. The observation that diabetic with type 1 have a less atherogenic standard lipid profile, especially with respect to triglyceride and HDL cholesterol levels, this finding is matching with that

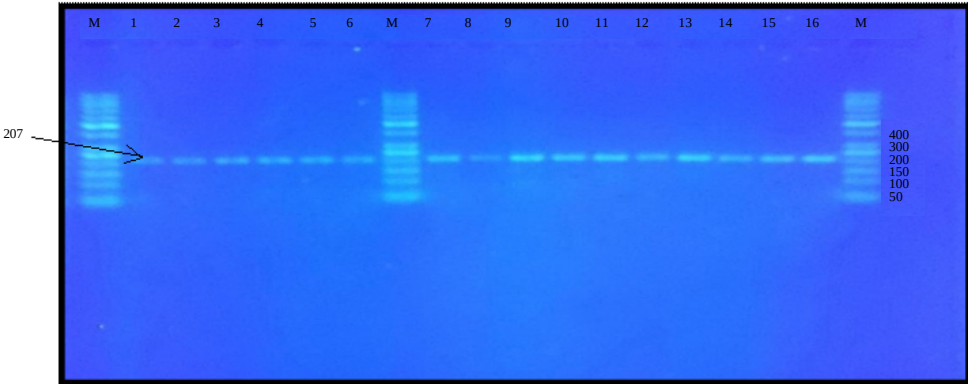


Fig. 1: A representative PCR analysis of OGG1 polymorphism. OGG1 genes PCR product resolved by (2%) agarose gel electrophoresis (1.5 h/70 v). Amplified DNA in a 207 bp fragment, Lane M, DNA molecular weight marker. Lane (1-6), negative control. Lane (7-16) is samples

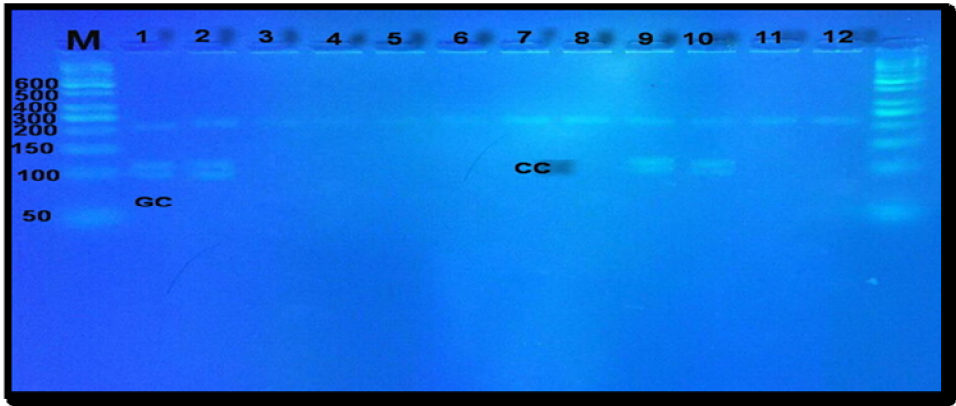


Fig. 2: Photograph of the PCR products of the OGG1 gene after FUNHI enzyme digestion and electrophoresis at 4% agarose gel (2.5 h/70 v). Lane: (3, 4, 5, 6, 7, 8, 11, 12) homozygous (CC-207 pb), lane (1, 2, 9, 10) heterozygous (CG-100, 107 and 207 bp)

Homo sapiens mRNA for OGG1 type 1g, partial cds Sequence ID: [dbj|AB037881.1|](#)

Score	Expect	Identities	Gaps	Strand
278 bits(150)	7e-71	150/150(100%)	0/150(0%)	Plus/Plus
Query 21 CAGACTCCACCCTCCTACAGGTGCTGTTTCAGTGCCGACCTGCGCCAATCCCGCCATGCTC 80				
Sbjct 322 CAGACTCCACCCTCCTACAGGTGCTGTTTCAGTGCCGACCTGCGCCAATCCCGCCATGCTC 381				
Query 81 AGGAGCCACCAGCAAAGCGCAGAAAGGGTTCCAAAGGGCCGGAAGGCTAGATGGGGCACC 140				
Sbjct 382 AGGAGCCACCAGCAAAGCGCAGAAAGGGTTCCAAAGGGCCGGAAGGCTAGATGGGGCACC 441				
Query 141 CTGGACAAAGAAATTCCCCAAGCACCTTCC 170				
Sbjct 442 CTGGACAAAGAAATTCCCCAAGCACCTTCC 471				

Fig. 3: Sequencing of OGG1 gene, for cases of (healthy control and patient), obtained from Gene Bank. Query represents of sample; Subject represent of database of National Center Biotechnology Information (NCBI)

Score	Expect	Identities	Gaps	Strand
272 bits(147)	1e-69	149/150(99%)	0/150(0%)	Plus/Plus
Query 20 CAGACTCCACCTCCTACAGGTGCTGTTTCAGTGCCGACCTGCGCCAATGCCGCCATGCTC 79				
Sbjct 322 CAGACTCCACCTCCTACAGGTGCTGTTTCAGTGCCGACCTGCGCCAATCCCGCCATGCTC 381				
Query 80 AGGAGCCACCAGCAAAGCGCAGAAAGGGTTCCAAAGGGCCGGAAGGCTAGATGGGGCACC 139				
Sbjct 382 AGGAGCCACCAGCAAAGCGCAGAAAGGGTTCCAAAGGGCCGGAAGGCTAGATGGGGCACC 441				

Fig. 4: Sequencing of OGG1 gene, for cases of (patient), obtained from Gene Bank. Query represents of sample; Subject represent of database of National Center Biotechnology Information (NCBI).

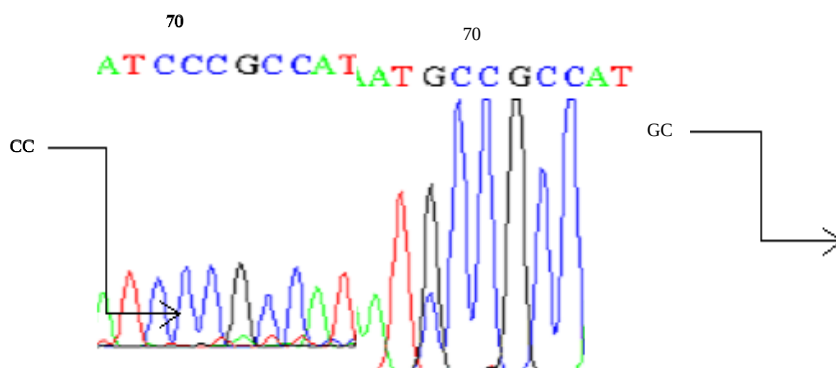


Fig. 5: Nucleotide sequence chromatogram representing two genotype of OGG1 gene. The left arrow is a C/C homozygote and the right arrow down is a G/C heterozygote

Table 4: Sequencing ID in gene bank, score, expects and compatibility of DNA sequences obtained

Organism	Sequence ID	Score	Expect	Identities (%)	No.of nucleotide	Type of sample
Homo sapiens	dbj AB037881.1	150	7e-71	100	322-471	Patient and control
Homo sapiens	dbj AB037881.1	147	1e-69	99	322-471	Patient

Table 5: Effect of Polymorphism of OGG1 gene in (Age, BMI, duration, FBG, HbA1C, lipid profile and Oxd-LDL) for diabetic mellitus type 1 patients

Parameters	Mean±SD		p-values	LSD
	CC	CG		
Age (year)	22.03 ± 1.80	24.94±1.63	0.2340	4.848 NS
BMI (kg/m ²)	23.47±0.66	23.66±0.71	0.8460	1.947 NS
Duration (year)	3.11±0.79	8.75±1.11	0.0014	3.363**
FBG	172.55±15.33	248.34±20.76	0.0053	52.49**
HbA1C	7.54±0.70	11.25±0.54	0.0002	1.856**
Cholesterol	175.32 ±5.32	185.71±6.79	0.2400	17.51 NS
Triglyceride	95.64 ±10.60	91.94±6.89	0.7660	24.726 NS
HDL	47.14±2.20	50.47±2.14	0.2830	6.135 NS
LDL	109.97±4.13	108.65 ±8.84	0.8970	20.233 NS
VLDL	19.55±2.11	33.28±7.18	0.0450	11.675*
Oxd-LDL	0.638±0.01	1.192±0.14	0.0025	0.339**

(p<0.05)*, (p<0.01) **, NS: Non-Significant

identified by the study (Taskinen, 1992) previous data in adults. In general, lipid concentrations were shown to be antiatherogenic in adults with type 1 diabetes who had optimal glycemic control or intensive insulin treatment. Moreover another study observed diabetics type 1

with good blood glucose control show relatively normal lipid concentrations including cholesterol levels (Guy *et al.*, 2009). Whereas another studies and our results are incompatible with researchers who explained a high prevalence of hypercholesterolemia in type-1 DM (Masram *et al.*, 2012; Ladeia *et al.*, 2006). The result of serum high-density lipoprotein HDL-C is agreement with the findings of other studies (Masram *et al.*, 2012; Rahma *et al.*, 2006; Torres-Tamayo *et al.*, 1997).

They found a decrease in HDL-C in type-1 diabetics as compared to control is insignificant indicating HDL metabolism is not much disturbed in type-1 diabetes mellitus. Also, it has been shown that HDL-C level is inversely correlated with the degree of risk for coronary heart disease caused by atherosclerosis. Although, most studies of lipid in children with type 1 diabetes have shown rise in cholesterol and triglycerides, particularly with poor metabolic control, results for HDL-C have been conflicting. These results are agreement with the findings of other studies (Rahma *et al.*, 2006; Belfort *et al.*, 2010).

As well the result of serum Low Density Lipoprotein LDL is agreement with the findings of other studies (Taskinen, 1992; Guy *et al.*, 2009). Generally, concentrations of lipid were shown to be antiatherogenic in adults with type 1 diabetes who had optimal glycemic control or intensive insulin treatment. However, the lack of abnormal lipid levels does not exclude the possibility of compositional changes that may be atherogenic, essentially among those with poor glycemic control (James and Pometta, 1990).

Some investigators have found LDL cholesterol concentration in the plasma is measured by the balance between LDL production rates and the LDL removal from the plasma which is frequently dependent on the action of LDL receptors. In most clinical situations, slow LDL removal, instead of increased production rates is the cause of hypercholesterolemia (Vinagre *et al.*, 2007).

Nonetheless, in a recent study by Feitosa *et al.* (2013) who explained that the increase in LDL removal was compensated by increased LDL production. Also, the result of serum very low-density lipoprotein are in agreement with Daneman *et al.* (1982) who state that in type 1 diabetes the major abnormality of plasma lipoprotein is increased the level of VLDL. Significant increase in VLDL-C in diabetic patients may due to impaired lipoprotein lipase-mediated VLDL removal from plasma in duration of diabetes.

Our results are agreement with the findings of other studies elevated levels of serum Oxd-LDL in older age with longer duration of diabetes may be more important determinants of preclinical atherosclerosis than short duration (Hamad *et al.*, 2010).

Another study evaluates the relationship between ages, inflammatory and oxidative stress related markers with functional and compositional changes of the arteries in the asymptomatic persons (Hassan *et al.*, 2012).

They found that (Oxd-LDL) levels were higher in diabetic group as compared to healthy controls and correlated significantly with BMI but not with traditional lipid parameters, age, gender or smoking status. Also, they found the factors that may promote LDL oxidation in diabetic patients contain antioxidant deficiencies, increased production of reactive oxygen species and protein glycation (Matsumoto *et al.*, 2004).

Presently, much attention has been focused on the Ser326Cys polymorphism exon 7 in the OGG1 gene sequences and in exploring the correlation between this polymorphism and susceptibility to diabetes type-1. The observed Ser/Ser, Ser/Cys genotype frequencies were 26.67, 73.33%, respectively Table 3 and the Cys/Cys genotype frequency was not found, neither in the diabetes mellitus type 1 nor controls 0.00%. The serine

(wild-type) and cysteine (variant) allele frequencies were 0.63 and 0.37, respectively. The genotype and allele frequencies obtained from diabetic patients did not differ significantly from those found in control subjects with the OGG1 Ser326Cys polymorphism. In Table 4, the sequencing of amplified product of OGG1 gene from (healthy and patient) out of them appeared 100% compatibility and other them (patient) appeared 99% compatibility with homo sapiens for OGG1 type 1 gene. In recent years, there were many studies showed the important role of OGG1 gene polymorphism in various diseases including cancers risk. This study follow another researches demonstrated the correlation of genetic polymorphism of OGG1 with many disease diabetes mellitus type 2, cancer (Hassan *et al.*, 2012; Hara *et al.*, 2014; Karahalil *et al.*, 2008).

This present study demonstrate that significant differences in the mean of OGG1 polymorphism in diabetes mellitus type 1 patient with respect the two different type of polymorphism occurs in patients (CC, GC). There are undoubted experimental and clinical proofs that long term of duration and hyperglycemia would be generate ROS, that is increased in both types of diabetes and that the onset of diabetes is closely related with oxidative stress Superko *et al.* (2002). Our results in DM1 found the role of hyperglycemia in production of ROS, it has been proposed that long duration of DM1 and hyperglycemia can produce chronic oxidative stress by the glucose oxidation pathway leading to an excess in mitochondrial superoxide production, which can inhibit expression of the 8-OxoG-DNA Glycosylase1 (OGG1), one of the key repair enzymes for DNA oxidative damage (Halliwell, 2012). ROS cause strand breaks and base modifications in DNA including the oxidation of quinine residues to 8-hydroxy-2-deoxyguanine (8-OHdG) (Bruner *et al.*, 2000).

This lesion is effective mutagen and can generate transversion (substitution) of C/G serine with cytosine in codon 326 which lower the activity of the DNA repair enzyme (Takezaki *et al.*, 202).

Moreover, the results revealed that there were no different in cholesterol, triglyceride, HDL and LDL concentrations appear with polymorphism of OGG1 with respected that patients shows only the two genotypes C/G and C/C. The C/C genotype almost in patient with short duration and the G/C exactly in patients with long time of diabetes, moreover the difference in the level of VLDL and Oxd-LDL thought to have an effect on oxidative stress that lead to this polymorphism.

VLDL passed through the bloodstream and it is converted to LDL, therefore, it is a precursor of LDL (60). After that the oxidation of LDL occurs as soon as

the LDL cholesterol particles in the body react with free radicals. Then, Oxd-LDL itself becomes more reactive with the surrounding tissues which can produce tissue and DNA damages (Kato *et al.*, 2009).

Therefore, elevated level of C/G compared to C/G results from the effect of ROS play role of oxidation of LDL and created polymorphism. Genetic alterations in OGG1 are thought to influence the development of oxidative stress and thus, contribute to the pathophysiology of many diseases including cancer and diabetes, although many sequence variants within the OGG1 gene have been identified.

The main focus has been on the Ser (326) Cys variant, since a number of epidemiological studies have related the Ser (326) Cys polymorphism with many types of cancer including kidney, colon and lung cancer (Melmed *et al.*, 2011; Nix, 2009; Polonsky, 2012).

Other study found that OGG1 Ser326Cys gene polymorphism was correlated with the coronary artery lesions in patients with diabetes mellitus and the G/G genotype was indicated to have a greater effect on the severity of coronary artery lesions.

CONCLUSION

The study revealed that the OGG1 could have an important role in the development of type 1 diabetes also, ROS have an essential function that is impact on fat indicators was shown in the Oxd-LDL.

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