VITAMIN D RECEPTORS GENES POLYMORPHISMS AND OXIDATIVE DNA DAMAGE AMONG KURD PATIENTS WITHTYPE 2 DIABETES, KURDISTAN REGION (IRAQ)

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ABSTRACT

Background: Although the relationship between vitamin D deficiency and oxidative DNA damage has been previously reported, few studies have examined vitamin D receptor (VDR) gene polymorphisms for association with the risk of DNA damage. This study aimed to identify vitamin D receptor genotypes in patients with type 2 diabetes and healthy subjects, as well as identify the relationship with oxidative DNA damage.

Methods: The study enrolled 162 subjects, 96 with type 2 diabetes and 66 healthy individuals were randomly selected to participate in prospective genotype detection by standard polymerase chain reaction methods and restriction fragment length polymorphism (PCR-RFLP). The polymorphism of FokI and BsmI genes and its association with DNA damage were determined. The main outcome measures were oxidative DNA damage marker including serum 8-hydroxy 2-deoxy guanosine (8-OHdG) and 25 hydroxy vitamin D [25(OH) D].

Results: Notable statistical significance exists in the frequency of genotype and allele of FokI (VDR 2228570 C>T) in patient group (OR 9.7, P=0.01) compared with the healthy individual group. No significant difference was found in the patient group (OR 0.74, p=0.66) in the frequency of genotype and allele of BsmI (VDR 1544410 A>G.). The frequency allele carrier of the (VDR 2228570) C allele was higher in the patients sub- group with high DNA damage than in the healthy individuals (OR=1.22, CI=0.02-18.9, p= 0.70). The frequency allele carrier of the (VDR 1544410) G allele was also higher in the patients sub-group with a high level of DNA damage than in the healthy individuals (OR=1.38, CI=0.13-16.8, p=0.57).

Conclusion: Our results suggest a significant relationship between DNA damage and the gene polymorphism FokI (VDR 228570 C>T) CC and its allele C among diabetic patients. Additionally, our results suggest that the high prevalence of FokI (VDR 228570 C>T) polymorphism among patients group may be a genetic marker of susceptibility for diabetes in our population.

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Keywords: 8-OHdG, FokI gene, BsmI gene, Vitamin D receptor gene, vitamin D deficiency, Type 2 diabetes.

Patients with type 2 diabetes mellitus and vitamin D deficiency promote a great intensive to study the extent of DNA damage and factors affecting this health problem in the community. Vitamin D is involved in DNA damage as well as in DNA repair and found to be a potential contributing cause of many diseases[1,2]. Adequate levels of vitamin D may be beneficial in maintaining DNA integrity[3], whereas its deficiency may increase DNA damage[4]. In addition, much is known

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about the association between vitamin D and oxidative stress in cell culture and animal studies[5].

There is a general agreement that strand breaks in DNA and base modification is caused by reactive oxygen species (ROS), through activate nuclear transcription factor (NF)-κB,, including oxidation of guanine residues (most potential base in DNA molecule) to 8-hydroxy-2'deoxyguanosine (8-OHdG), a marker that is frequently detected and studied DNA damage in tissue[6].

It has been shown that vitamin D is essential in maintaining genome stability and inadequate vitamin D is associated with increased frequencies of chromosomal aberrations DNA strand break and other metabolic abnormalities[7].

Numerous polymorphisms of VDR genes have been identified at chromosome 12q113.1, of these FokI (T/C rs2228570), BsmI (G/A rs 1544410), ApaI (G/T rs7975232), and TaqI (T/C rs731236) which are located in exon 2, intron 8, and exon 9, respectively. These genes may have an influence on insulin secretion and sensitivity[8].

Vitamin D/Vitamin D receptor associations may in turn negatively impact patient diabetes and result in frequent DNA damage[9]. Although some studies have identified positive effects of vitamin D intake on levels of DNA damage4, little research has been demonstrated the association between VDR polymorphisms with the risk of DNA damage.

The purpose of this study isto identify vitamin D receptor genotypes among Kurd patients with type 2 diabetes and healthy subjects, as well as identify the relationship with DNA damage.

METHODS

The study was conducted in Duhok Diabetes Center, Duhok, Kurdistan Region, Iraq; between October 2017 and May 2018. The medical ethics committee of Duhok College of Medicine and Duhok General Directory of Health approved the study, and informed consent was obtained from all participants. Participants were instructed to visit the Lab-Department of Clinical Biochemistry at Azadi Teaching Hospital; controls were also instructed to attend the same place in the morning after overnight fasting for 12-14 hours.

Blood samples were collected, and the sera were separated by centrifugation using a HITACHI centrifuge (model O5P-21) at 5000 rpm for 10 minutes and collected into two tubes, one processed immediately for measuring serum 25(OH) D using clinical chemistry analyzer Cobas 6000 Roche (open, automated, discrete and random access) and the latest liquid sera were stored at -80°C for later analysis of 8-OHdG. Measurement of 8-OHdG was done using ELISA technique. The Iranpur and Esmailizadeh (2010), the method was used for extracting DNA from the whole blood; The DNA samples were checked for concentration and quality using the Nano-Drop 2000 Spectrophotometer for the amplification of the region of interest of the VDR gene (FokI, BsmI)[10].

Two Sets primers manufactured by macrogen (South Korean) and supplied lyophilized were used. Each primer stock was re-suspended in a designated volume of DW to give a final concentration of 100 pmol/ul. Agarose gel was prepared in a concentration of 2% for PCR-RFLP product of the amplified and digested amplicon.

Assessment of DNA damage based on 8-OHdG levels, a cutoff point of > 4.0 ng/ml considered high DNA damage. A cutoff

point of less than 20 ng/ml of 25(OH) D was considered a low vitamin D status.

STATISTICAL ANALYSIS:

All data were analyzed using the Statistical Package for Social Science SPSS version 18.0 computer software. Significance of association between various risk factors for categorical data was assessed by using Chi-square test for association between two groups and one way ANOVA test for association among more than two groups.

RESULTS

The sample size of 162 subjects with1.5:1 patient: healthy subject ratio results in statistical power of >90%. The overall genotype error rate between the duplicate was 1.8%. The PCR implication product of FokI gene, if the digested generate a 265 bp fragment, it is a homozygous, genotype CC (FF). If 3 fragments of 265bp, 196 bp and 69bp,it is heterozygous, the genotype is TC (fF). If there is 196-69 bp fragment, it is homogenous genotype TT (ff) (Figure 1). Regarding the BsmI gene, if the digested generate an 825 bp fragment, it is a homozygous genotype AA (BB).

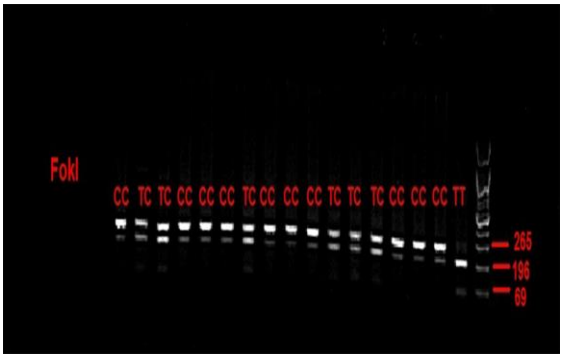

Figure 2: The Digested Results Electrophoresis (PCR-RFLP analysis of VDR gene, FokI Polymorphism on 2% Agarose Gel.)

If 2 fragments of 825 bp, 650 bp and 175 bp, it is a heterozygous genotype AG (Bb). If there is 650 bp and 175 bp Fragments, it is homogenous genotype GG (bb) (Figure2).

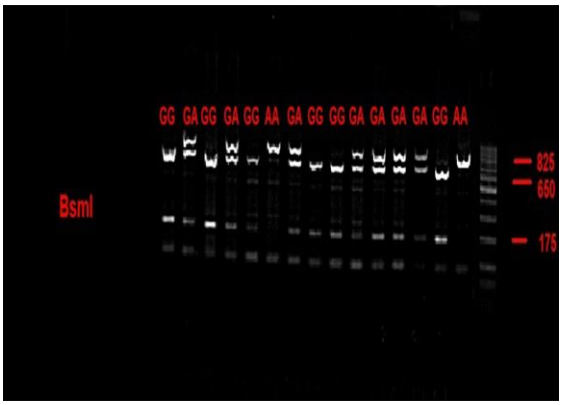

Figure 2: The Digested Results Electrophoresis (PCR-RFLP analysis of VDR Gene, BsmI Polymorphism on 2% Agarose Gel.

The frequency of VDR (FokI) gene in diabetic patients and healthy subjects are present in Table 1.

Table 1: FokI (VDR 2228570 C>T) Genotype and Allele Frequency in Diabetic Patients and Healthy Individuals

Genotype FOKI	Patients n(%)	Healthy individuals n(%)	OR	95%CI	p-value
CC	22 (22.9)	2 (3.1)	9.7	1.18-79.6	0.01
TC*	68 (70.8)	60 (90.9)	_	_	_
TT	6 (6.3)	4 (6.0)	1.32	0.2-8.4	0.76
P-value	0.04				
X^2	6.22				
Alleles					
C	112(58.3)	64(48.5)	1.49	1.0-29.9	0.37
T	80(41.7)	68(51.5)	0.67	0.15-13.08	0.55
****P-value***	0.02	0.73			

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The most prominent allele in the patients group was C 56(58.3%) compared to T allele 40(41.7%), P= 0.02. The frequency CI=1.0-29.9, P=0. 37).Analysis of FokI genotype frequency distribution among study subjects also revealed that the (VDR 228570 C>T) CC was the most prominent in the patients group compared with that of TT, 22 (22.9%) vs. 6 (6.3%), P=0.04. The CC genotype was significantly more frequent in the patients group than in healthy subjects (OR= 9.70, CI=1.18-79.6, P=0.01). Healthy subjects group, FokI allele carrier of the (VDR 2228570 C>T) C allele was higher in the patients group than in the healthy subjects (OR=1.49, genotype distribution frequency observations CC, TC, TT was 2(3.1%), 60 (90.9%) and 4 (6.0%).

The differences between diabetic patients and healthy subjects regarding to the frequency of the BsmI genotype and allele did not show statistical significance (Table2).

Table 2: BsmI (VDR 1544410 A>G) Genotype and Allele Frequency in Diabetic Patients and Healthy Individuals

Genotype BsmI	Patients n(%)	Healthy individuals n(%)	OR	95%CI	p-value
AA	24(25.0)	22 (33.3)	0.74	0.45-14.8	0.66
GA	38(39.6)	26 (39.4)	_	_	_
GG	34(35.4)	18(27.3)	1.29	0.46-9.5	0.68
P-value	0.64				
X2	0.88				
Alleles					
A	86(44.8)	70(53.0)	0.72	0.1-15.3	0.47
G	106(55.2)	62(47.0)	1.39	0.5-15.4	0.47
P-value	0.15	0.49			

The most prominent allele in the patients group was G 106 (55.2%) compared to A allele 86 (44.8%), P=0.15. The frequency allele carrier of the (VDR 1544410A>G) G allele was higher in the patient's group than in the healthy subjects (OR 1.39, CI=0.5-15.4, P=0. 47). Analysis of GG genotype distribution among study subjects also revealed that the (VDR 1544410 A>G) GG was the most prominent in the patients group compared with that of AA, 34 (35.4%) vs. 24 (25%), P=0.64. Healthy subject group BsmI genotype distribution frequency observations AA, AG, GG were 22 (33.3%), 26 (39.4%) and 18 (27.3%). The GG genotype was more frequent in the patients group than in healthy subjects (OR=1.29, CI=0.49-9.5, P=0.68).

The allele and genotype frequency of FokI gene in diabetic patients and healthy subjects with high DNA damage are present in Table 3.

Table 3: FokI (VDR 2228570 C>T) Genotype and Allele frequency in Diabetic Patients and Healthy Individuals with High DNA Damage.

Genotype FokI	Patients	Healthy individuals	8-OHd	G ≥ 4.0	ng/ml
	n(%)	n(%)	*OR*	*95%CI*	*p-value*
CC	20(21.7)	2(5.3)	5.45	0.01-27.7	0.71
TC	66(71.7)	36(94.7)	_		_
TT	6(6.6)	0(0.0)	_	_	_
P-value	0.11				
X^2	4.30				
Alleles					
C	106(57.6)	40(52.6)	1.22	0.02-18.9	0.70
T	78(42.3)	36(47.4)	0.82	0.59-10.7	0.72
P-value	0.15	0.73			

The frequency allele carrier of the VDR 2228570 (C allele) was higher in the patients sub-group with high DNA damage than in the healthy subjects (OR=1.22, CI=0.02-18.9, P= 0.70). The most prominent allele in the patients sub-group with high DNA damage was C, 106 (57.6%) compared to T allele 78 (42.3%), P=0.15. Analysis of FokI genotype frequency distribution among sub-groups also revealed that the VDR 228570 CC was the most prominent in patients compared with that of TT, 20 (21.7%) vs 6 (6.6%), P=0.11.

The most prominent allele in the diabetic patients sub-group with high DNA damage was G 102 (55.5%) compared to A allele 82 (44.5%), P=0.92 (Table 4).

Table 4: BsmI (VDR 1544419 A>G) Genotype and Allele Frequency in Diabetic Patients and Healthy Individuals with High DNA Damage.

Genotype	Patients	Healthy individuals	BSMI 8-OHd	G ≥ 4.0	ng/ml
		n (%)	n(%)	*OR95%CI*	*p-value*
AA	22(24.0)	10(26.3)	0.86	0.60-13.4	0.92
AG	38(41.2)	20(52.6)			
GG	32(34.8)	8(21.1)	2.10	0.81-7.80	0.61
P-value	0.54				
X^2	1.24				
Alleles					
A	82(44.5)	40(52.5)	0.72	0.37-15.7	0.56
G	102(55.5)	36(47.5)	1.38	0.13-16.8	0.57
P-value	0.92	0.75			

The frequency allele carrier of the (VDR 1544410) G allele was higher in the patient sub-group with high DNA damage than in the healthy subjects (OR=1.38, CI=0.13-16.8, P=0.57).Analysis of BsmI genotype frequency distribution among sub-groups also revealed that the VDR 1544410 GG was the most prominent in patients compared with that of AA, 32 (34.8%) vs. 22 (24.0%), P=0.54.

For FokI polymorphism, in vitamin-D sub-group of patients, the CC genotype frequency was quite a bit higher in comparison with that of the healthy individual group, however, the increase

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was not statistically significant (OR=3.17, CI=0.05-1.9, P=0.18) (Table 5).

Table 5: FokI (VDR 2228570 C>T) Genotype and Allele Frequency in Diabetic Patients and Healthy Individuals with Low Vitamin D Status

Genotype	Patients	Healthy individuals 25(OH)D < 20ng/ml			
		n(%)	n(%)	*OR95%CI*	*p-value*
CC	8(16.7)	2(6.25)	3.17	0.05-1.9	0.81
TC	36(75.0)	28(87.5)			
TT	4(8.3)	2(6.25)	1.58	0.09-5.16	0.95
P-value	0.55				
X^2	1.08				
Alleles					
C	52(54.2)	32(50.0)	1.18	0.46-8.2	0.79
T	44(45.8)	32(50.0)	0.84	0.42-8.0	0.80
P-value	0.55	1.0			

There was none significant difference between patients with C>T and healthy subjects in the frequency of C and T allele (P=0.8). For VDR 1544410 A>G polymorphism, we observed that there was a significant difference between the low vitamin D sub-group in diabetic patients and healthy subjects (P=0.01) (Table 6).

Table 6. BsmI (VDR 1544419 A>G) genotype and allele frequency in diabetic patients and healthy individuals with low vitamin D status.

Genotype	Patients	Healthy individuals 25(OH)D < 20 ng/ml			
		n(%)	n(%)	*OR95%CI*	*p-value*
AA	6(12.5)	8(25.0)	0.67	0.8-14.8	0.70
AG	18(37.5)	16(50.0)			
GG	24(50.0)	8(25.0)	2.67	0.24-31.0	0.39
P-value	0.26				
X^2	2.71				
Alleles					
A	30(31.2)	32(50.0)	0.45	0.6-31.8	0.29
G	66(68.8)	32(50.0)	2.20	0.03-34.4	0.20
P-value	0.01	1.0			

DISCUSSION

This study is the first to examine the association of vitamin D receptor (VDR) gene polymorphism with DNA damage in Duhok population. Vitamin D receptors are widely distributed in human tissues, which is controlled vital genes related to bone metabolism, oxidative damage and chronic inflammatory diseases11. Vitamin D/ vitamin D receptors also play a role in regulating the B-cell insulin secretion12. Several polymorphisms, such as BsmI (VDR1544410A>G) and FokI (VDR 228570 C>T), have been described in the VDR genes that are able to alter the activity of VDR protein[13]. It has been demonstrated that BsmI and FokI polymorphisms are associated with type 2 diabetes mellitus, insulin secretion[14] and with metabolic changes related to obesity and oxidative damage[15]. Although the link between vitamin D deficiency and DNA damage has been previously demonstrated[16], few studies have examined VDR gene polymorphisms and its association with the risk of DNA damage[17]. Thus, this studywas conducted this study to examine the polymorphism of VDR gene (FokI and BsmI) in type 2 diabetic patients and healthy subjects.

More ever, we intended to investigate the association of VDR gene polymorphism [FokI (VDR 228570 C>T), Bs mI (VDR1544410A>G)] with the level of DNA damage in type 2 diabetic patients and healthy subjects.

The present study demonstrates the genetic contribution of VDR gene polymorphisms for diabetes. The study found that the frequency of FokI 2228570 CC genotype was significantly higher in the group of diabetes than in a healthy group and confirmed a significant relationship between polymorphism of VDR 2228570 CC genotype and allele C with DNA damage. Further, the frequency of BsmI genotype and allele did not show significant differences between diabetic and healthy group. This was consistent with other studies[18]. In a study from Saudi Arabia, it has been reported that no association was noticed between VDR BsmI polymorphism and gestational diabetes mellitus in the Saudi population. The gene frequency, allele frequency and carriage rate of the VDR polymorphism BsmI did not differ between patients and controls with no significant association with any clinical parameters[19].

Similarly, to that reported in the previous study conducted in type 2diabetic Egyptian patients, we found that the frequency allele carrier of the VDR 2228570 (C allele) was higher in diabetic patients with high level of DNA damage than in healthy subjects, but the frequency of the BsmI genotype and allele did not show any significant differences between the two groups[20]. Vitamin D receptor (VDR) gene variants may contribute to the development of diabetes mellitus. Ban Y, et al, have reported that BsmI increased susceptibility for type 1 diabetes[21]. In contrast, our results did not showed any significant differences between patients group and healthy individuals. However, analysis of genotype frequency distribution among the studied subjects revealed that the (VDR 228570 C>T) CC was the most prominent one for FokI and (VDR1544410A>G) GG for BSMI and both were more frequent in the patients group than in healthy individuals. In this study we found that the genotypes and their combinations in alleles may confer increased susceptibility to diabetes in association with increased DNA damage.

CONCLUSIONS

Our results suggest a significant relationship between DNA damage and the gene polymorphism FokI (VDR 228570 C>T) CC and its allele C among diabetic patients. Additionally, our results suggest that the high prevalence of FokI (VDR 228570 C>T) polymorphism among patients group may be a genetic marker of susceptibility for diabetes in our population.

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ثوختة

وةرطريَن ظيتامين (د) و زرارىَ DNA لدةف نةخوشيَن كورد ييَن شةكرىَ ذجورىَ دووىَ

ثيَشةكى: سةرةراى كو ثةيوةندى دناظ بةرا زرارا DNA و ظيتامين (د) هاتية خواندن بةرى نوكة. كيَم ظةكولينا ثشكنينا جورين جيني ييَن وةرطريَن ظيتامين (د) كرية ئو ثةيوةنيين وىَ دطةلمةترسيا زرارباونا DNA. ئارمانجا ظىَ ظةكولينىَ ئةوة بو دةستنيشانكرنا جورين جينى يين ظيتامين (د) لدةف نةخوشئن شةكرىَ ذجورىَ دووىَ و ثةيوةندييِن وىَ دطةل زرارباونا DNA.

ريَكيَن ظةكولينىَ: ظىَ ظةكولينىَ 162 كةس بخوظة طرتن ذوانا 96 كةسا ئيشا شةكرىَ هةبوو ذجورىَ دووىَ و 66 كةس دساخلةم بوون هاتبونة هةلبذارتن بشيوةيةكىَ سةربةخو بو بةشداريكردن دظىَ ظةكولينيَدا ذبو ديتنا جورين جيني بريكا (PCR-RFLP). هةمة جوريا جينى هاتنة دةستنيشانكرن و ثةيوةندييِن وىَ دطةل زرارباونا DNA. ثيظةرين دةرئةناجميَن سةرةكى دظىَ ظةكولينيَدا هيمايىَ زرارباونا DNA بخوظة طرتبو (8-OHdG) دطةل ئاستىَ ظيتامين (د) دناظا خوينيدا (25 (OH)D).

ئةنجام: ريَذا بةربةلاظبونا جورىَ جيني و ئةليلىَ (C>T) rs2228570 بشيوةكىَ بةرضاظ هاتة ديتن لدةف نةخوشين شةكرةهةموار كردن دطةل مروظين ساخلةم (OR 9.7, P=0.01) بةلىَ جياوازى نة بشيوةيةكىَ بةرضاظبو سةبارةت ريَذا بةربةلاظبونا جورىَ جيني و ئةليلىَ (A>G) rs1544410. ريَذا بةربةلاظبونا هةلطرىَ جورىَ جينى و ئةليلى (C)rs2228570 ثتر بوو لدةف نةخوشيَن شةكرىَ يين ريَذا زرارا DNA ياوان يا بلند هةموار كردن دطةل كةسيَن ساخلةم (OR=1.22, CI=0.02-18.9, p= 0.70). ريَذا بةربةلاظبونا هةلطرىَ جورىَ جينى و ئةليلى (G)rs1544410 ديسان ثتر بوو لدةف نةخوشيَن شةكرىَ يين ريَذا زرارا DNA ياوان يا بلند هةموار كردن دطةل كةسيَن ساخلةم (OR=1.38, CI=0.13-16.8, p=0.57).

دةرئةنجام: ئةنجاميَن ظةكولينامة ثيشنياردكةت كو ثةيوةنديةكا بةرضاف يا هةى دناظبةرا زرارباونا DNA و هةبونا جوريَن جينى ييَن جورة وجور CC (C>T rs228570 و ئةليلىَ وىَ (c) لدةف نةخوشين شةكر هةى. ديسان, ئةنجاميَن ظةكولينامة ثيشنياردكةت كو بلندبونا ريَذا بةربةلاظبونا جورىَ جينى و ئةليلى rs228570 (C>T)لدةف نةخوشيَن شةكر هةى هيمايةكىَ مةترسيدارىَ جينية بو توشبون ب نةخوشيا شةكرىَ لدةف هاولاتيان ل دةظةرامة.

الخلاصة

مستقبلات فيتامين (د) والتلف التأكسدي للحمض النووي
لدى الكورد المصابين بمرض السكري من النوع الثاني في اقليم كردستان العراق

الهدف: على الرغم من ان العلاقة بين فيتامين (د) والتلف التأكسدي للحمض النووي تم دراستها سابقاً، قلة من الدراسات فحصت تعدد اشكال الجينات لمستقبلات فيتامين (د) وعلاقتها مع خطورة تلف الحمض النووي. هدفت هذه الدراسة إلى تحديد الأنماط الوراثية لمستقبلات فيتامين (د) لدى مرضى السكري من النوع الثاني والاشخاص الاصحاء وتحديد علاقتها مع التلف التأكسدي للحمض النووي.

طرق البحث: تضمنت هذه الدراسة 162 شخصاً، 96 منهم مرضى لديهم مرض السكري من النوع الثاني و66 اشخاص أصحاء تم اختيارهم عشوائياً للمشاركة في هذه الدراسة المحتملية لاكتشاف تعدد الجينات بطريقة (PCR–RFLP). تم تحديد تعدد أشكال الجينات الـrs2228570 وrs1544410 وعلاقتها مع التلف التأكسدي للحمض النووي مقاييس النتائج الرئيسية تضمنت مؤشر التلف التأكسدي للحمض النووي (8–OHdG) ومستوى فيتامين (د) في الدم [25(OH) D].

النتائج: وجدت نسبة انتشار الشكل الجيني والاليل (C>T) rs2228570 بشكل ملحوظ احصائياً في مجموعة المرضى مقارنة بمجموعة الاشخاص الاصحاء (OR 9.7, P=0.01) لكن الاختلاف لم يكن ملحوظا إحصائياً بالنسبة لنسبة انتشار الشكل الجيني والاليل (A>G) rs1544410. نسبة انتشار حامل الاليل rs2228570C كان أعلى في مجموعة المرضى الذين لديهم تلف الحمض النووي عالي مقارنة مع الاشخاص الاصحاء (OR=1.22, CI=0.02–18.9, p= 0.70). نسبة انتشار حامل الاليل rs1544410(G) كان أيضاً اعلى في مجموعة المرضى الذين لديهم تلف الحمض النووي عالي مقارنة مع الاشخاص الاصحاء (OR=1.38, CI=0.13–16.8, p=0.57).

الاستنتاج: نتائجنا اقترحت بأن هناك علاقة ملحوظة بين تلف الحمض النووي وتعدد الاشكال الوراثي للجينات rs228570 (C>T) واليلها (c) لدى مرضى السكري. إضافة إلى ذلك اقترحت أيضاً نتائجنا بأن نسبة الانتشار العالية لتعدد الشكل الجيني rs228570(C>T) لدى مرضى السكري قد يكون عامل خطورة وراثي لاحتمالية الاصابة بالسكري في المجتمع.

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