The Association of Single Nucleotide Polymorphism in SLC30A8 Gene with Type 2 Diabetes Mellitus in AL-Najaf Population.

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Abstract
Background: Diabetes mellitus is a collection of chronic endocrine disorders marked by persistent hyperglycemia caused by insulin production, insulin action, or both. The importance of insulin as an anabolic hormone leads to a metabolic deficit in carbs, lipids, and proteins. Various genome-wide association studies have identified several single nucleotide polymorphisms associated with type 2 Diabetes, as they were found to alter lipid metabolism, insulin secretion, glucose metabolism, and insulin receptor signaling, and the rs13266634 found in (the solute carrier family 30 member 8) SLC30A8 gene is one of the consistently reported risk factor single nucleotide polymorphism for type 2 Diabetes Study Objective: To verify the association of SLC30A8 gene single nucleotide polymorphisms and the risk of occurrence of type 2 Diabetes mellitus in AL-Najaf population and explore the role of SLC30A8 gene on insulin secretion. Methods: This case-control study enrolled 100 type 2 Diabetes mellitus patients and 100 controls who fulfilled the inclusion criteria. Blood samples were collected from all participants and were used for the rs13266634 single nucleotide polymorphism genotyping by Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) technique. Outcomes: Two-hundred case-control studies with 100 cases and 100 controls were included for SLC30A8 and type 2 Diabetes mellitus. The comparison of results of parameters (fasting blood glucose, homeostatic model insulin resistance) exhibited significant ($p<0.0001$) increases in the patient's group when compared with the group of controls. The comparison of results of insulin values in the patients group ($P=0.103$) insignificant decrease with respect to the controls group. Genotyping result of single nucleotide polymorphism (rs13266634 C/T) of Type 2 Diabetes mellitus as well as control persons under the co-dominant model showed that patients of heterozygous genotypes (CT) significantly elevated (OR = 2.56, 95% CI = 1.33 - 4.67, P = 0.0049) with respect to the control group. The dominant model indicated that patients of (CT+TT) genotypes increased significantly (OR=1.87, CI 95%=1.04 - 3.30, P=0.0434) with respect to the controls, and the single nucleotide polymorphism (rs13266634 C/T) of SLC30A8 not associated with of phenotypic parameter analysis. Conclusion: The rs13266634 is single nucleotide polymorphism significantly associated with type 2 Diabetes mellitus susceptibility among AL-Najaf Population and this gene not associated with insulin level, fasting blood glucose, and homeostatic model insulin resistance. Recommends: A large sample size is required to investigate the correlation between rs13266634 SNP of SLC30A8 gene and occurrence of disease and further studies in the future should be done on different SNPs of SLC30A8 gene in AL_Najaf population. These studies can discover which SNPs are more common in this governorate that involved in the pathogenesis of T2DM.
Keywords: SLC30A8 gene, single nucleotide polymorphism, Type 2 diabetes mellitus

1. Introduction

Diabetes mellitus is a collection of chronic endocrine disorders marked by persistent hyperglycemia caused by insulin production, insulin action, or both. The importance of insulin as an anabolic hormone leads to a metabolic deficit in carbs, lipids, and proteins. These metabolic disorders are caused by low insulin levels and/or insulin resistance in target tissues, primarily skeletal muscles, adipose tissue, and to a lesser extent, liver, at the level of insulin receptors, signal transduction systems, and/or effector enzymes or gene (Kazi et al .,2019).

The major DM types are as follows:

1.Type 1 diabetes mellitus (T1DM) is a chronic autoimmune illness defined by elevated blood glucose levels (hyperglycemia) caused by insulin insufficiency caused by the death of pancreatic islet cells (Katsarou et al. ,2017).

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2. Type 2 diabetes (also known as non-insulin dependent diabetes) is defined by a dysregulation of carbohydrate, lipid, and protein metabolism, which can be caused by decreased insulin production, insulin resistance, or a combination of the two (Reed et al., 2021).

Various genome-wide association studies (GWAS) have identified several single nucleotide polymorphisms (SNPs) associated with T2DM (Imamura et al., 2021), as they were found to alter lipid metabolism, insulin secretion, glucose metabolism, and insulin receptor signaling, and the rs13266634 found in the SLC30A8 gene is one of the consistently reported risk factor SNP for T2DM.The SLC30A8 (solute carrier family 30 member 8) gene is found at 8q24.11 on the long (q) arm of human chromosome 8. The zinc transporter protein member-8 (ZnT-8) gene encodes a 369-amino-acid protein (Thirunavukkarasu et al., 2019)

Classification of diabetes mellitus include type-1cause the destruction of pancreatic b-cells by autoimmune cells causes this type of diabetic (Bhatty et al., 2020) , type -2 the most common kind of diabetes is T2DM, which accounts for more than 90% of all cases (Duarte-Díaz et al., 2022), gestational diabetes was described as glucose intolerance that manifests itself during pregnancy, without distinguishing between cases where glucose intolerance existed prior to pregnancy and those where it manifested itself concurrently with pregnancy (Yujing., 2021) ,and other type of diabetes mellitus are linked to monogenic deficiencies in b-function, also known as monogenic defects of the b-Cells (Gilor et al. ,2016).Iraq is a multi-ethnic country with a population of 40,222,493 million people in 2021. The entire adult population is 19,914,400 million, including 1,505,000 million adults suffering from diabetes (Falih et al., 2021).

In type 2 diabetes, there is a strong inheritable genetic link; having type 2 DM relative particularly first degree relatives significantly increase the risk of acquiring type 2 DM (Virginia et al., 2022).

SLC30A8 (The zinc transporter protein member-8 (ZnT-8) gene encodes a 369-amino-acid protein. ZnT-8 regulates zinc homeostasis in pancreatic beta cell and is essential for the stability, storage, and release of insulin and other genes that have role on type 2 diabetes (Blumer et al. ,2022) . Obesity (an independent risk factor for type 2 diabetes) is also significantly inherited (Ligthart et al., 2021).

Pathophysiology of T2DM is the result of two metabolic disorders: insulin resistance (Stožer et al., 2022), b-dysfunction(Mao et al., 2022).

Gene report that the solute carrier family 30 member 8 (SLC30A8) gene located on the chromosome 8q24.11, contains 13 exons encoding 369 amino acids (Li et al., 2018) ,The total length of the SLC30A8 gene is 226,442 bases (Abu Seman et al. ,2015).

Approved symbol: SLC30A8 (www.ncbi.nlm.nih.gov.2022)

Approved name: solute carrier family 30 member 8 (www.ncbi.nlm.nih.gov.2022)

GENE type: protein coding (www.ncbi.nlm.nih.gov.2022)

HGNC ID: 20303(www.ncbi.nlm.nih.gov.2022)

Chromosomal location: 8q24.11 (www.ncbi.nlm.nih.gov.2022)

Gene ID: 169026 (www.ncbi.nlm.nih.gov.2022)

OMIM: 611145 (www.omim.org)

Organism: Homo sapiens (www.ncbi.nlm.nih.gov.2022)

Previous studies of SLC30A8 gene polymorphism in relevance to type 2 diabetes mellitus the common alleles of SNPs, rs13266634(C/T), and other SNPs in the SLC30A8 gene are found to confer the risk susceptibility in T2DM. According to Egyptian Populations previous study, the risk of SLC30A8 polymorphism and T2DM patients than control (Awadallah et al., 2020).

Genome-wide association studies (GWAS) in Japan population involving type 2 diabetes and SLC30A8 gene have been published (Horikawa et al., 2008) .

Numerous of study that associated with development of impaired glucose level and insulin resistance by effect on b-cell and made that occur so, according to the study in Moscow, Russian Federation that given information about the associated the SNP (rs13266634) with (CC + CT) genotype of SLC30A8 gene with development of T2DM (Nikitin et al., 2017) by effect on insulin secretion because The protein of the SLC30A8 gene plays a direct role in the maturation and secretion of insulin granules and impairment of the transformation of proinsulin into insulin. (Dunn .,2005).

Study objective: To verify the association of SLC30A8 gene single nucleotide polymorphisms and the risk of occurrence of type 2 diabetes mellitus in AL-Najaf population and explore the role of SLC30A8 gene on insulin secretion in type 2 diabetes patients.

Hypothesis of the study: The Association of single nucleotide polymorphism in SLC30A8 gene with type 2 diabetes mellitus in AL-Najaf population.

2. Materials and Methods

Study design: A case-control study has been utilized on 200 participants. They were divided into two groups, type 2 diabetic patients (100) and a healthy individual group (100). The period of the study was from November 2020 till November 2022.The study was done in the Postgraduate Laboratory Department of Biochemistry/University of Kufa/Faculty of pharmacy.

Patients group: with 100 T2DM patients, the ages ranged from 20- 66 year with a M±SD of 49.41 ± 9.43 year. They were selected from the Diabetes Center in Teaching Hospital (AL-Sadder) in Al-Najaf Al-Ashraf, province. They have been observed and diagnosed by specialist physicians for the measures of inclusion.

Inclusion criteria: include, patients with T2DM

and The level of fasting blood sugar was 7.0mmol/l (> 126 mg/dl) with diabetes manifestation of (nocturia, polyuria, weight decrease and polyphagia).

Exclusion criteria: include, Patients with T1DM, T2DM on antihyperlipidemic therapy, patients have other diseases as cardiovascular diseases, kidney dysfunction patient, cancer patients, hypertension patients and glucocorticoid dependency,also patient with thyroids and patients take insulin therapy .

Control group of 100 volunteers include the ages ranged from 22-67 year with a M±SD of 46.5 ± 11.67 year. They were relatives, friends, and medical staff. Any participant who had a disease, for instance DM, hypertension, heart disease, cardiovascular disease, renal disease, or other persons suspected to have any diseases had been excluded from the current study.

The Ethical Committee Approval : Approval from the Ethical Committee (in the Faculty of Pharmacy /Kufa University) was taken for the protocol of the study.

Samples collection: after an overnight fast, each participant had a blood sample of five milliliters collected via a peripheral vein puncture. Two components of the blood sample were separated. Part one involved placing 3ml of blood in a plain tube and allowing it to coagulate for around 15 minutes at 37°C before centrifuging it for 10-15 minutes at 2000 xg. The collected sera were separated and stored at -20°C for phenotypic parameter assessment. That include fasting blood glucose, insulin level, and then, homeostatic model insulin resistance . Part two was a tube containing two milliliters of blood mixed with EDTA for gene analysis.

Genotype measurements: DNA is extracted from blood using a DNA purification kit (Addbio). SLC30A8 polymorphisms (rs13266634) were genotyped using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), then cheeked on an agarose gel using electrophoresis linked to the PCR product. In addition, each SNP's amplification technique was carried out using appropriate primers and master mixture. Furthermore, restriction enzyme types (Promega kit) were used to digest the PCR results, and the digested products were extracted on a 2 percent agarose gel.

Statistical analysis: The student t-test was used to examine the differences in means (mean ± SD) between the healthy individuals and patients group, also Mann Whitney test used for not normally distributed data and explained with median (Q1, Q3). Using (SPSS.v.25.0 software) SPSS Inc. Chicago, IL, the mean levels of each characteristic via genotype were compared using the Student t-test and ANOVA. The chi-square test was also used to examine categorical data (alleles and genotypes). A significance level of less than 0.05 was used in all statistical analyses. Multinominal logistic regression analysis for verifications of genotype and frequencies of allele impact on T2DM via several inheritance models, such as a recessive, co-dominant, dominant, and additive model, as well as the Allelic model, SPSS.v.25.0 software was used. The results were expressed as a P-value, an odds ratio (OR), and a confidence interval (CI 95%).

3. Study results

Table 1: phenotype parameters values of T2DM and control groups.

Parameters	T2DM group (N=100)	control group (N=100)	P value
NO (M/F)	(60/40)	(42/58)	
Age (years), Mean ± SD	49.41 ± 9.43	46.5 ± 11.67	0.06
FSG (mg/dl), median (Q1, Q3)	153.5 (128,186.8)	85 (75,90)	<0.0001****
Insulin (µU/L), median (Q1, Q3)	9.35 (5.01, 13.65)	10.02 (6.19, 15.99)	0.103
HOMA-IR, median(Q1,Q3)	3.870 (2.27, 5.84)	1.82 (1.22, 3.05)	<0.0001****
Note: * = mean that a significant result.			

Table (1) shows that not normally distributed data (FBG, insulin, HOMA-IR) tested with mann-witney test and explained with median (Q1, Q3). The comparison of results of ages values in the patient's group versus the controls group revealed insignificant variations according to the P value (0.06). Other parameters were found to change in T2DM patients when compared with healthy individuals. Levels of FBG and HOMA-IR exhibited significant (p<0.0001) increases in the patient's group when compared with the group of controls. The comparison of results of insulin values in the patients group (P=0.103) insignificant decrease with respect to the controls group.

Table (2): DNA Purity and Concentration

	Mean±SD
DNA purity	1.98 ± 0.31
DNA concentration (µg/ml)	92.34 ± 48.75

Table (2) shows that the A260/A280 ratio was calculated to measure DNA purity and concentration. Displays the purity and concentration of the extracted DNA samples.

Table (3) shows that The results of SNP (rs13266634 C/T) of T2DM as well as control persons with numerous inheritance models are shown in table 3.4. The codominant model showed that patients of heterozygous genotypes (CT) significantly elevated (OR = 2.56, 95% CI = 1.33 - 4.67, P = 0.0049) with respect to the control group. Patients with the homozygous genotype (TT) insignificantly decreased (OR=0.97, CI 95%= 0.36 - 2.65, P=0.99) relative to the control group. The dominant model indicated that patients of (CT+TT) genotypes increased significantly (OR=1.87, CI 95%=1.04 - 3.30, P=0.0434) with respect to the controls. Recessive

model showed that patients of TT genotypes insignificantly declined (OR =0.70, 95% CI = 0.27 - 1.82, P =0.63) with respect to the controls groups. Frequency of (T) in patient group insignificantly increased (OR= 1.44, CI 95%= 0.92 - 2.27, P=0.13) with respect to the controls group

Table(3): Genotype and allele frequency results of SNP rs13266634 C/T SLC30A8 gene in T2DM and control subjects.

rs13266634 C/T	Patient group (N= 100)		control group (N= 100)		OR(CI%)	P value
	NO.	%	NO.	%		
Genotyping						
Codominant						
CC	50	42.74	67	57.26	Reference group	
CT	42	65.63	22	34.38	2.56(1.33 - 4.67)	0.0049**
TT	8	42.11	11	57.89	0.97(0.36 - 2.65)	>0.99
Dominant						
CC	50	43.70	67	56.30	Reference group	
CT+TT	50	59.26	33	40.74	1.87(1.04 - 3.30)	0.0434*
Recessive						
CC+CT	92	50.83	89	49.17	Reference group	
TT	8	42.11	11	57.89	0.70(0.27 - 1.82)	0.63
Frequency						
C	142	47.65	156	52.35	Reference group	
T	58	56.86	44	43.14	1.44(0.92 - 2.27)	0.13
Total	200		200		400	

Table (4): Results of phenotypic parameters of diabetic patients analyzed in relevance to the rs13266634 C/T under the co-dominant model.

Parameters	CC(N=50) Mean ± SD	CT(N=42) Mean ± SD	TT(N=8) Mean ± SD	P value
FSG (mg/dl)	156.4 ± 30.71	175.4 ± 49.04	160.8 ± 29.30	0.09
Insulin (µU/L)	9.870 ± 5.79	10.5 ± 5.67	7.748 ± 3.43	0.61
HOMA-IR	4.072 ± 2.40	4.76 ± 2.90	4.24 ± 2.92	0.46

Table (4) shows that analysis for FBG, insulin and HOMA-IR values was conducted by the ANOVA test in relation to genotypes of the studied SNP rs13266634 C/T of SlC30A8 gene. For the SNP rs13266634 C/T genotypes, the co-dominant model revealed insignificant relationship for phenotypic parameter analysis, means did not show significant modifications. in relevance to the rs13266634 C/T under the dominant model

Table (5): Results of phenotypic parameters of diabetic patients analyzed

Parameters	CC(N=50) Mean ± SD	CT + TT(N=50) Mean ± SD	P value
FSG (mg/dl)	156.4 ± 30.71	173.2 ± 48.22	0.05
Insulin (µU/L)	10.90 ± 4.40	11.68 ± 3.82	0.67
HOMA-IR	4.652 ± 3.89	5.244 ± 2.64	0.45

Table (5): shows that under the dominant pattern, insulin, HOMA-IR and FBG showed insignificant alterations relevant to the variant allele.

4. Discussion

Nowadays, diabetes mellitus is a disorder with multiple genetic and environmental contributing elements. The complicated illness known as type 2 diabetes mellitus (T2DM) is brought on by the combination of genetic and environmental variables. Studying the origins and effects of T2DM in humans has primarily been done to lessen its impact on the health care system because it is expensive, time-consuming, and detrimental to community vitality.

The SLC30A8 gene was identified as one of the risky T2DM genes, and as a result, its effects on T2DM risk (Du et al., 2018). However, the results are still underestimate. The potential importance of defective zinc signaling in T2DM has recently increased our understanding of the condition.

In this work, FSG parameter in this study significantly increases in patients than controls group because the amount of insulin not enough to decline high level of serum glucose and weakness of beta cell to give enough amount of insulin which means a decrease in its effectiveness. Although, beta cell work hard to secret enough amount of insulin but not enough. This study is consistent with a previous study (Mizukami and Kudoh .,2022) that explain a deficiency in b-cell production of insulin results from islet dysfunction.

The insulin level in this research insignificant value where the relationship between patients and healthy

individuals exact .The reason is that patients undergo multiple treatments mean , which in turn increase the proportion of insulin by increasing the secretion of it from beta cell to counteract the amount of glucose secreted , these treatments such as sulfonylureas , dipeptidyl-peptidase 4 inhibitors and incretin mimetics, glinides .In fact (Artasensi et al., 2020) consistent with this study, confirming that the reason for the high level of insulin in patients with type 2 diabetes is to take treatments that help in adjusting the level of insulin to meet the amount of glucose secreted. Also, these patients were diagnosed long ago with this disease, so they underwent treatment and are not at the beginning of their diagnosis. Yet, notice an increase in insulin level instead of a decrease.

Insulin resistance is evidence of the lack of insulin sensitivity and the transformation of the process from normal situation to a satisfactory condition and has many causes like excess body fat and a lack of physical activity led to general obesity which in turn leads to induce IR. This research is consistent with other studies (Abbas et al., 2020) that explain hyperglycemic condition caused by increased HOMA-IR is a significant risk factor for the development of T2DM.

The analysis of the data of SNP rs13266634 C/T under the codominant demonstrated that patients of heterozygous genotypes CT significantly elevated than controls with odds ratios of more than 1. This finding suggests that CT allele is associated with diabetes risk and or/development of T2DM in the studied sample, i.e., AL_Najaf population. The current finding is consistent with past study (Du et al., 2018) which represented that heterozygous CT genotype were at higher risk of T2DM occurrence while the patients with the homozygous genotype TT under codominant demonstrated insignificantly decreased relative to the controls group with odds ratios of less than 1 and This indicates that there is no relationship between homozygous genotype TT and development/ or risk of T2DM and this consistent with previous study (Faghih et al., 2014) shows that there is no relationship with the development of T2DM with homozygous genotype TT.

5. Conclusions

1.The rs13266634 SNP of SLC30A8 gene is implicated in the pathogenesis of T2DM in AL_Najaf population.

2. According to the allele frequency the presence of heterogeneous CT genotype responsible to develop T2DM in AL_Najaf population.

3.There is no association between rs13266634 SNP of SLC30A8 gene and fasting blood glucose, insulin level, and homeostatic model insulin resistance parameters.

6. Recommendations

1. A large sample size is required to investigate the correlation between rs13266634 SNP of SLC30A8 gene and occurrence of disease.

2. Further studies in the future should be done on different SNPs of SLC30A8 gene in AL_Najaf population. These studies can discover which SNPs are more common in this governorate that involved in the pathogenesis of T2DM.

Limitation of the study: The presented work has some restrictions. In general, the individuals' family histories were not examined in relation to their genetics. Patients with diabetes may use medications that impact IR and insulin secretory function in addition to antihyperglycaemic drugs. The length of T2DM is not taken into account, however it could be an additional component that worsens the metabolic effects of prolonged hyperglycemia.

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Conflicts of interest: Authors declare no conflict of interest.

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