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Detection of TAFI 1040C>T rs1926447 Gene Polymorphism in Type 2 Diabetes Mellitus Iraqi Patients

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P A P E R I N F O

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A B S T R A C T

In Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage. Thrombin-Activatable Fibrinolysis Inhibitor(TAFI) is a protein that plays a major role in regulating the analysis of blood clots, It is involved in the fibrinolysis process. The study was designed to study the change concentration of TAFI, Insulin, HOMA-IR, and lipid profile in the T2DM patient in addition to studying the TAFI 1040C>T SNP (rs1926447) gene polymorphism with the development of T2DM complication. Genome study doing by restriction fragment length polymorphism PCR (RFLP-PCR). These parameters included the evaluated of glucose metabolic characteristics (FSG, insulin, HbA1C, HOMA-IR, lipid profile). The expected frequencies, calculated under the assumption of no association, were 47.61for CC, 60.03, CT, and 9.61for TT. TC genotype does not appear a statistically significant linkage to the rise risk of thrombosis, OR(3.272) is and CI (0.4173 to 1.4498), p-value <0.0002 was associated with an increased danger of the thrombosis to three times. frequency of C allele among cases is 43.5%, but it is 69% among controls. Frequency T allele was among cases is 56.5%, whereas it is 31% among controls. The findings of this investigation revealed that there was significant link between the TAFI 1040C>T polymorphism and T2DM complication in Iraqi patients. However, we recommend conducting the study in a larger sample and different sexes to confirm our findings.

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1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex illness in which genetics and environmental factors both play important roles in disease etiology. Diabetes causes chronic hyperglycemia, which causes organ malfunction, mainly in the eyes, kidneys, nerves, heart, and blood vessels. T2DM is known by the failure of pancreas cell's to generate enough insulin hormone to preservation blood sugar levels under control (Hong et al., 2022). The reason causing T2DM includes a combination between a genetic predisposition and environmental factors systemic insulin resistance, (Javeed & Matveyenko, 2018).

T2DM patients suffer diabetic neuropathy after being diagnosed, but 25% of them will suffer it after obtaining the disease for at least 25 years (Al-Attaby & Al-Lami, 2019). Diabetes has a severe impact on the retina, causing diabetic retinopath DR, a degenerative condition that is the leading cause of blindness in diabetics.(Atwany et al., 2022). Diabetes problems primarily affect the coronary arteries, peripheral arteries ,macrovascular complications , and cerebrovasculature. Atherosclerotic causing plaque in the vasculature providing blood to the heart, brain, limbs, and other organs is related with early macrovascular disease. Late-stage macrovascular disease results in full occlusion of these arteries, rising risk of myocardial infarction(MI), stroke, claudication, and gangrene. Cardiovascular disease (CVD) is the leading cause of morbidity and death in diabetic people(Low Wang et al., 2016). Disorders fibrinolysis and Coagulation are well-known consequences of T2DM .In addition, they contribute to a rise in macrovascular consequences such myocardial infarction and ischemic stroke(Rattanawan et al., 2018). TAFI synthesized by the liver and megakaryocytes(MKs) as a propeptide. Besides, it is a zinc-dependent metallocarboxypeptidase, constraction of 423 a.a. when the 22 amino acid signal peptide is removed, the 56 kD a proenzyme containing 401 a.a is secreted into the blood stream(Totoki, 2020). TAFI construction from

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401 amino acids is divided into two chains. The first chain has 92 a.a. form the activation peptide, while another chain has 309 amino acids form the catalytic domain (Marx et al., 2008). The other known names: procarboxypeptidase R procarboxypeptidase U (CPU); procarboxypeptidase B (PCPB) and conceder carboxypeptidases are enzymes that hydrolyze C-terminal peptide bonds (Khamsehnejad et al., 2019) found in plasma and major role that controls fibrinolysis by decreising the quantity of fibrin accessible for fibrinolysis by tissue plasminogen activator (t-PA)(Mosnier et al., 2001). TAFI encoding by CPB2, The human (Carboxypeptidase B2 by the Human Genome Organization (HUGO), and is located on chromosome 13 (13q14.11. The gene spans 48 kb of genomic DNA, and has 11 exons and 10 introns(Bouma & Mosnier, 2003) . TAFI encoding by CPB2, The human (Carboxypeptidase B2 by the Human Genome Organization (HUGO), and is located on chromosome 13 (13q14.11. The gene spans 48 kb of genomic DNA, and has 11 exons and 10 introns (Rizzo, 2014), (Boffa et al., 1999). The polymorphisms of TAFI Ala147Thr or 505G/A (rs3742264), Thr325Ile or 1040C/T (rs1926447),+1542C/G (rs940) and +1583T/A (rs1087) have been reported to be associated with TAFI levels(Rattanawan et al., 2018). The higher levels of TAFI are associated with a high risk for arterial thrombosis and recurrent events in patients with an ischemic stroke.

2. MATERIALS AND METHODS

One hundred patient spacemen were taken from the Diabetes and Endocrinology Center at Sadr Medical City in Najaf, Iraq, following the acquisition of the required official approvals. Information. The individuals that took part in the study ranged in age from (35-55) , 48.3000±12.20242. Body mass index BMI (kg/m^2) measurement by height, weight, 5 ml of divided into container. 2ml was placed in an EDTA tube and free zed to deep freeze at -20C for genotyping analysis while 3ml was placed in plane tube. Insulin concentration was calculated by “enzyme-linked immunosorbent assay” (ELSA) and then Insulin resistance was as calculated.

Genome Study We employed RELP to analyze DNA, which is a fundamental concept in the study that includes fragmenting of DNA samples using a especial restriction enzyme restriction, enzyme that detects and cut DNA at a specific short sequence. The lengths of these DNA fragments are subsequently separated using agarose gel electrophoresis(Promega). The number of cleavage sites present in the DNA sequence is represented by the number of bands seen on the gel. Program Information for TAFI 1040 C>T SNP condition initial denaturation 95 C^o: 5 min 5 cycle, denaturation95 C^o: 0.50 s, Annealing55 C0.50 s, and Extension72 C^o go to 2 loop 35:1.0 min 3.5 cycle for 36X . Final Extension 72C^o: 07.00 min 3.5 cycle. To perform the amplification reaction, 1 µl of extracted DNA was taken , 10 NEBUffer 5µl 1X, Restriction Enzyme(SPeI-HF) 1µl 10 units, and Nuclease- free Water 50µl. : Primers sequence of TAFI obtain from (ElDanasori et al., 2018).

2. 1. Statistically Study

Case-control study was applied. The statistical analysis in this study involved several methods and software. Continuous variables were expressed as mean ± standard deviation. The difference in means between patient (T2DM) and the healthy group was determined using the (Student's t-test with the SPSS v.26.0 software) and MedCalc software .The Hardy-Weinberg equation was used to mathematically measure the relationship between genotypes and allele frequency. The data were expressed in terms of odds ratio (OR), confidence interval (CI%), chi-square, and p-value.

3. RESULTS

Case control study was applied in this study that included 200 volunteers. (100 T2DM patients do not suffer from any complication and disease duration less than five years, with the age range 35-55 years, and 100 healthy subjects as a control group Table 1.

TABLE1. Phenotyping of T2DM patients and the control group

Parameter	**T2DM Patients**	**Control**	**P-Value**
NO. of F/M	100(58/ 42)	100(48/52)	------
Age/Y	48.030±10.479	35.500±9.853	0.000
Height (m^2)	1.7111±.270	1.6858±.098	0.342
Wight(Kg)	71.9300±10.995	76.2347±12.974	0.000
BMI Kg/ m^2	26.53705±3.152	26.7353 ± 3.547	0.000
SBP(mmHg)	132.80±18. 09	125.49±4.01	0.063
DBP(mmHg)	81.29 ±10.48	83.15±2.44	0.086
Onset diseases (Y)	2.9293±1.597	--------------------	----------

BMI, body mass index, SBP (systolic blood pressure), DBP (diastolic blood pressure), F (female), and M (male) are all significant at the 0.05 level when comparing the patient and control groups**..**

With a statistical significance of less than (P<0.001) for each age, weight, and BMI, respectively, Table 1 demonstrated statistically significant associations and is one of the indicators linked to the indications of type 2 diabetes, the worldwide rise in the incidence of obesity has coincided with a rise in the prevalence of type 2 diabetes. However there are no statistically differences (p>0.05) height, SBP and DBP (Alberti et al., 2004).

TABLE 2. Compare between T2DM patients and control group mean± SD

C>T 1040	Cases N=100	Controls N=100	OR	95%CI	P-value
CC	21	59	0.184	0.098 to 0.345	< 0.000
TT	34	21	1.938	1.027 to 3.6556	0.041
TC	45	20	3.272	1.745 to 6.137	0.0002
Allele Frequencies					
C	43.5%	69%	0.3459	0.2296 to 0.5211	< 0.0001
T	56.5%	31%			

FSG: fasting serum glucose, HOMO-IR: Homeostatic Model Assessment for Insulin Resistance, TG: Triglyceride, HDL:high-density lipoprotein, LDL: low-density lipoproteins, and vLDL: very low-density lipoprotein) The practical part of the present study involved estimating the necessary biochemical parameters, which may be demonstrated. These parameters included the evaluated of glucose metabolic characteristics (FSG, insulin, HbA1C, HOMA-IR, lipid profile. When comparing the T2DM patients to the healthy control groups, the study's most evident conclusion was the significant increase in HOMA-IR. Table 2 shows that cholesterol values in T2DM patients are higher than those of healthy control groups and this result corroborates with the previous studies(Silva et al., 2018). TG values of T2DM patients were higher than those of control groups with a statistically significant increase (213.53±22.49, 107.08±16.93) respectively. HDL-C values of diabetic T2DM patients are lower than those of control with a statistically significant increase (42.76 ± 9.11, 57.73±17.03)(Shahwan et al., 2019). The LDL-C values of T2DM patients are higher than those of control with a statistically significant increase (193.929±27.10, 87.052±25.00)(Mohd Yasir Khan, Sultan Alouffi, Mohd. Shahnawaz Khan, Fohad Mabood Husain, Firoz Akhter, 2020). VLDL-C values of T2DM patients are higher than those of control with a statistically significant increase(42.70±8.49, 29.60 ±7.27)(Krentz, 2003). The Present study reveals significant differences in the TAFI levels between groups.

3.1. Genotyping Study

Current fending showed the association between the TAFI 1040 C>T genetic variant and the risk of a specific condition (diabetes complication). TC genotype did not show a statistically significant association with the risk of thrombosis, as the (OR) 3.272 is and CI (0.4173 to 1.4498), p-value <0.0002 is associated with a statistically significant increased risk of the thrombosis to three times. The C allele frequency among cases is 43.5%, while 69% among controls. The T allele frequency among cases is 56.5%, while it is 31% among controls Table 3

TABLE 3. Distribution TAFI Gene 1040 C/T(rs1926447) Polymorphism Genotype in T2DM and Control Subject

Recessive Mode					
Genotype	Cases N=100	Control N=100	OR	95%CI	P-value
CC+CT	66	79	0.5160	0.2736 to 0.9734	0.041
TT	34	21			
Dominant Mode					
Genotype	Cases N=100	Control N=100	OR	95%CI	P-value
CC	21	59	0.1847	0.0989 to 0.345	<0.000
TT+CT	79	41			

According to Table 4's recessive mode analysis, people with the CC+CT genotype are less likely to get sick than those with the TT genotype. The OR for the recessive mode is 0.5160. The p-value associated with the odds ratio is 0.041, which is less than the conventional significance level of 0.05

TABLE 4: Apply HWE for Polymorphism TAFI Gene 1040 C/T(rs1926447)

Variables	T2DM Patients	Control	P-Value
FSG mg/dl	228.65 ± 35.92	94.2600 ±8.06491	0.000
Insulinµ	33.34±10.55	8.32±3.20	0.000
HbA1C%	8.452±1.2993	4.50±.5.73	0.000
HOMA-IR	18.19±6.49	1.94 ±0.82	0.000
Lipid profile			
Cholesterol mg/dl	264.10±28.33	171.05±17.62	0.000
TG mg/dl	213.53±22.49	107.08±16.93	0.000
HDL-C mg/dl	42.76 ± 9.11	57.73±17.03	0.000
LDL-C(mg/dl)	193.929±27.10	87.052±25.00	0.000
vLDL-C(mg/dl)	42.70±8.49	29.60±7.27	0.000
TAFI Pg/ml	396.95 ±163.02	286.65±87.83	0.011

Table 5 shows the actual and predicted genotype frequencies for a particular genetic variation. Twenty people have the TT genotype, twenty-one have the CT genotype, and fifty-nine have the CC genotype. The anticipated frequencies, calculated under the assumption of no association, were 47.61for CC, 60.03, CT, and 9.61for TT.

TABLE 5. Pearson correlation between TAFI Gene 1040 C/T(rs1926447) and another biochemical parameters

Variables	Groups			
	T2DM Patients		control	
	r	p	r	p
Insulin µU/ml	0.272**	0.006	0.051	0.617
FSG mg/dl	0.202*	0.044	0.084	0.407
HbA1c	0.805**	0.000	0.113	0.262
HOMA-IR	0.378**	0.000	0.182	0.070
Cholesterol mg/dl	0.695**	0.000	0.097	0.336
TG mg/dl	0.376**	0.000	0.024	0.812
HDL-c mg/dl	-0.657**	0.000	-0.055	0.588
LDL-c mg/dl	0.694**	0.000	0.136	0.179
vLDL-C mg/dl	0.376**	0.000	0.063	0.536

4. DISCUSSION

The practical part of the present study involved estimating the necessary biochemical parameters by which may be demonstrated the metabolic disorders. These parameters included the measurement of glucose metabolic characteristics (fasting blood glucose, fasting insulin, and Homeostatic Model Assessment for Insulin Resistance HAMA- IR) (Mansour et al., 2022). Furthermore, the study is highly statistically significant, which is consistent with earlier research that has found out that patients who were overweight and had higher BMI values had a higher chance of developing diabetes than participants who were healthy.(Anakök et al., 2022). Obesity is an indicator of body fat(Reis et al., 2009), which can be estimated by measuring body mass index (BMI) and waist circumference (WC) (Dhurandhar, 2022).

Insulin resistance levels were represented by the HOMA-IR. HOMA-IR values in the healthy and T2DM patients groups were mean± SD (1.94 ± 0.82), and (18.19±6.49) respectively. Result had shown Insulin levels in T2DM patients group were higher than those in control group and the difference was statically significant(p-value<0.05). Insulin is the primary regulator of glucose and lipid homeostasis; it increases the absorption of glucose into striated muscles and adipocytes and decreases blood glucose levels by blocking hepatic gluconeogenesis and glycogenolysis. Moreover, it stimulates the breakdown of circulating lipoproteins by inducing lipoprotein lipase activity in adipocytes, boosts triglyceride production in the liver and adipose tissues, and enhances glucose absorption into striated muscles and adipocytes. Circulating glucose levels remain elevated when adipose, muscle, and liver cells fail to respond appropriately to insulin, which destabilizes the feedback system. Table 2. demonstrated that T2DM patients' cholesterol levels are statistically significantly higher than those of healthy control groups, which is consistent with earlier research.(Tham et al., 2023). Cholesterol metabolism is altered in diabetic states. There are three causes of the rise in cholesterol in T2DM patients increased glycation of cholesterol-rich lipoproteins, an insulin-resistant state that is mainly present in overweight type 2 diabetic patients, and changes in insulin secretion which depends on the clinical T2DM(Khan et al., 2020).

The present study found triglyceride values of T2DM patients were higher than those of control groups with a statistically significant increase. This result agrees with the results obtained by several studies (213.53±22.49, 107.08±16.93) respectively. HDL-C values of diabetic T2DM patients are lower than those of control with a statistically significant increase(42.76±9.11,57.73±17.03)Table 3.3(Shahwan et al., 2019). The LDL-C values of T2DM patients are higher than those of control with a statistically significant increase (193.929±27.10, 87.052±25.00). Diabetes is associated with quantitative changes in the amount of circulating lipids notably an increase in triglycerides, elevated LDL and a reduction in HDL-C (Femlak et al., 2017). In our study TT was significant with T2DM patient 34% with TT whereas, 21% of control group have this polymorphism. There is ongoing research into the relationship between TAFI and maternal thrombophilia or hypo fibrinolytic gene variations, and new data indicates that thrombophilic circumstances may worsen the prothrombotic state in type 2 diabetes. These thrombophilic disorders may affect the fibrinolysis clot's function and lead to inadequate advancement of diabetic complications. Stronger evidence of a connection between plasma TAFI levels and cardiovascular disease(Tregouet et al., 2009). TAFI levels were discovered to be connected to an increased risk of ischemic stroke. Based on the information in Table4, it appears that the CT genotype is associated with an increased risk of developing the T2DM complication . In the context of the chi-square analysis and the observed genotype frequencies, the CT genotype is overrepresented among the cases compared to the expected frequencies. This suggests that individuals with the CT genotype might be at a higher risk of developing the thrombosis in future in patient with T2DM. Depended on Table 5, TAFI levels in plasma have been linked to an approximately fourfold increase in the incidence of acute coronary artery disease (CAD). Endothelial functional thromboresistance is lowered in diabetes patients. (Thomas & Iyngkaran, 2020). A prethrombotic condition is caused by increased intravascular thrombin production, decreased fibrinolytic capacity, and hyperactive platelets.

5. CONCLUSION

The current study showed a high and statistically significant correlation between diabetes TAFI, insulin, and HOMA-IR, while the study found a correlation between 1040 C/T (rs1926447) polymorphism and development risk T2DM complications in Iraqi patients. Based on this information, we recommend that a more comprehensive study of different ethnic groups to be conducted and that it has to be conducted with more numbers. Type 2 diabetes has a high linkage with thrombosis, along with the result of damage to cell endothelial and oxidative proteins, and it is associated with hypofibrinolysis via increased TAFI level, which increases with diabetes duration.

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