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Evaluation of CDKAL1 and TCF7L2 Serum level in a Sample of Iraqi Type 2 Diabetes Mellitus Patients.

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Abstract

Background. Diabetes Mellitus (DM) is a multifactorial disorder with a complex of signs and symptoms. Recent evidence suggests that *CDKAL1* and *TCF7L2* play important roles in glucose metabolism and insulin secretion, making them potential biomarkers for T2DM development. **Aim.** The current study aimed to investigate the association of CDKAL1 and TCF7L2 serum levels with increased incidence of type 2 diabetes mellitus in Iraqi patients. **Methods.** A case–control study was conducted on 200 participants, including 100 patients diagnosed with T2DM and 100 apparently healthy controls. Demographic and clinical parameters such as sex, age (classified into three groups), body mass index (BMI), fasting blood glucose (FBG), and HbA1c (%) were recorded. Serum levels of CDKAL1 and TCF7L2 were measured using the enzyme-linked Immunosorbent assay (ELISA). **Results.** Significant differences were observed between patients and controls regarding age, age groups, BMI, FBG, and HbA1c ($p < 0.001$), while no significant difference was found in sex distribution. The mean serum level of CDKAL1 was significantly higher in T2DM patients (3.07 ± 0.89) compared to controls (1.11 ± 0.18) ($p < 0.001$). Likewise, TCF7L2 serum levels were markedly elevated in patients (2278.0 ± 533.2) versus controls (832.4 ± 91.7), showing a highly significant difference ($p < 0.001$). **Conclusion.** Elevated serum levels of CDKAL1 and TCF7L2 are strongly associated with T2DM in Iraqi patients, suggesting their potential role as promising biomarkers in the development and progression of type 2 diabetes mellitus.

Keywords: *CDKAL1*, *TCF7L2*, Type 2 diabetes mellitus
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Introduction

Diabetes Mellitus (DM) is a multifactorial disorder with a complex of signs and symptoms. Diabetes is a systemic disease with chronic hyperglycemia, which results in damage, dysfunction, and failure of various organs after a certain period including eyes, kidneys, nerves, and cardiovascular system (1, 2). Diabetes mellitus (DM) is a chronic metabolic disease with hyperglycemia resulting from insufficient secretion of insulin and/or resistance to insulin peripheral actions or both (3). The two major classes of DM are insulin-dependent DM and type 2 (non-insulin-dependent) DM; however, there are other types also exist (4). Transcription Factor 7 Like 2 (TCF7L2) and Cyclin‑dependent kinase 5 regulatory subunit‑associated protein 1 ‑ like 1 (*CDKAL1*) are essential proteins in consideration of diabetes. The

TCF7L2 gene is a transcription factor that affects the expression of several genes; it thus performs various functions within the cell. *TCF7L2* gene is found on chromosome 10 q 25. 2–q25. 3 and consists of 19 exons (5). Being a member of the TCF family, the *TCF7L2* gene possesses a bipartite transcription factor to get involved in the regulation of various biological pathways, including the wingless-type MMTV integration site family (Wnt signaling pathway) [6]. TCF7L2 protein acts as a transcription factor that, in humans, is encoded by the *TCF7L2* gene. The TCF7L2 protein contains 619 amino acids and its molecular mass is 67,919 Dalton. The TCF7L2 protein plays crucial roles in various physiological processes and is involved in regulating zonal metabolic pathways in the liver, contributing to nonalcoholic fatty liver disease development (7). *CDKAL1*, standing for Cyclin‑dependent kinase 5 regulatory subunit‑associated protein 1 ‑ like 1, is a gene that was newly discovered through GWAS as a predisposition gene for T2DM in white European and Asian populations and it is located on chromosome 6p22.3 (7). This gene codes the CDKAL1 protein which might control its own activity; in turn *CDKAL1* is involved in insulin synthesis— hence affecting other processes related to the functioning of insulin-secreting β-cells forming the pancreatic gland (8). Understanding the roles of CDKAL1 and TCF7L2 in diabetes is essential for unraveling the molecular mechanisms underlying the disease and developing targeted therapeutic interventions. The present study aims to investigate the importance of CDKAL1 and TCF7L2 as proteins in increase diabetes mellitus type 2 incidence in a sample of Iraqi patients.

Materials and methods

Study Subject

A case-control study of 200 subjects (100 patients and 100 controls) was conducted. The present investigation was duly permitted and approved by the Human Ethics Committee of the College of Science at Baghdad University (No. CSEC/0524/0043). The one hundred T2DM patients were selected from people attending the National Center for Diabetes/ Mustansiriyah University/ Baghdad / Iraq. Both groups are divided into (50 males and 50 females) . The patients included in this study met the diagnostic criteria for T2DM as outlined by the American Diabetes Association (ADA). The American Diabetes Association (ADA) standard was used to categorize T2DM, Hemoglobin A1c (HbA1c) levels above 6.5% are indicative of Diabetes, whereas levels ranging from 5.7% to 6.4% indicate pre-diabetes. Test results below 5.6% are considered normal. Fasting blood glucose (FBG) levels of 120 mg/dl (7.0 mmol/l) or higher means that the patient has diabetes mellitus (1). In addition, Sex, Age, and body mass index (BMI) were also enrolled in the study.

Blood Collection

Blood samples (5 ml) were collected from each subjects and after that, subjected to centrifugation at a speed of 3000 revolutions per minute for duration of fifteen minutes at ambient temperature, resulting in the separation of the serum and transferred into another plane tube and stored at – 20 ˚C. Glycated hemoglobin (HbA1c %) was calculated by using (the Boditech kit, Korea) and fasting blood glucose (FBG) test using (Biosystem kit, Spain) (9).

Assessment of Human TCF7L2 and CDKAL1 Serum Level

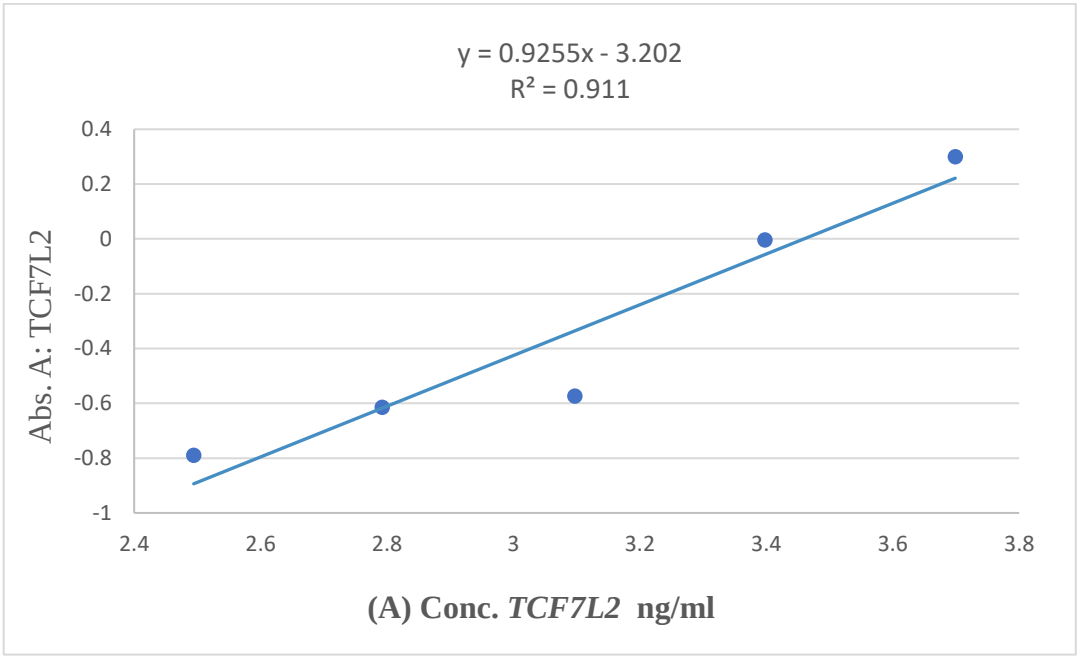
The levels of TCF7L2 and CDKAL1 were assessed in the serum of T2DM patients and healthy controls by using enzyme-linked immune sorbent assay (ELISA) kits. (BioSource Inc., United States, United States) (TCF7L2 / Catalog Number: MBS2883541), (CDKAL1 /Catalog Number: MBS7249153). In this work, the quantitative sandwich enzyme immunoassay method was used as the approach. The micro-ELISA plate provided in the kit has been pre-coated with an antibody specific to Human TCF7L2 and CDKAL1. Standards and samples were added to the microtiter plate wells with a biotin-conjugated polyclonal antibody preparation specific for TCF7L2 and CDKAL1, and Avidin conjugated to Horseradish Peroxidase (HRP) was added to each microplate well and incubated. Then, a Tetra-methyl-benzidine (TMB) substrate solution is added to each well. Only those wells that contain TCF7L2 and CDKAL1, biotin-conjugated antibody and enzyme-conjugated Avidin will exhibit a change in color. The enzyme-substrate reaction is terminated by adding a stop solution, and the color turned yellow. The optical density (OD) was measured spectrophotometrically at a wavelength of 450 nm. The concentration of TCF7L2 and CDKAL1 in the samples is then determined by comparing the O.D. of the samples to the standard curve. For each serum TCF7L2 and CDKAL1, standard solutions were prepared according to the manufacturer's instructions, and presented as follows:

- TCF7L2: (0, 312, 625, 1250, 2500, and 5000) pg/ml.
- CDKAL1: (0.000, 0.500, 1.000, 2.500, 5.000 and 10.000) pg/ml.

The linear regression equation between the standard curve and the concentration of the corresponding sample was calculated according to standard concentrations and O.D values of samples. Calculation of the sample results were done after finished the procedures. Figure (1) showed the Standard curves of both TCF7L2 and CDKAL1.

Statistical Analysis

Analysis of data was carried out using the available statistical package of SPSS-26 (Statistical Packages for Social Sciences- version 26) [10], and WinPepi software. Data were presented in simple measures of frequency, percentage, mean, standard deviation, and median (minimum-maximum values). For quantitative variables (FBS, HbA1c, serum TCF7L2, and CDKAL1 levels), normality tests for the data were tested and were given a standard deviation and mean for a level. Significant differences between medians were assessed by the nonparametric tests (Mann-Whitney and Kruskal-Wallis) with probability value < 0.05 was considered significant, for each analytic.



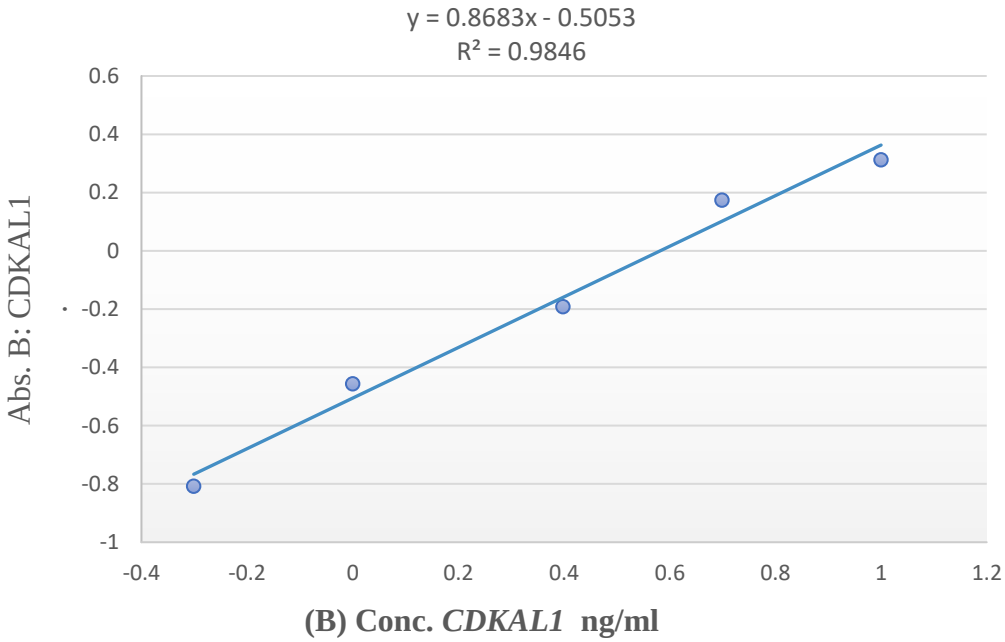


Figure (1): Standard curves of A) TCF7L2, B) CDKAL1, which generated by Excel Software.

Results

Demographic data

The results revealed the (mean± S.D.**)** of sex, age, age groups, BMI, FBG, and HbA1c % levels. The collected data were 50 male and 50 female, 56.3±7.9 years old, 31.4±5.4 kg/m2, 199.78±84.76 mg/dl and 9.08±1.72 % for the diabetic patients, respectively, and 50 male and 50 female, 45.0±12.6 years, 28.5±4.1 kg/m2, 100.04±16.67 mg/dl and 5.41±0.24 % for the controls, respectively. as shown in Table (1).

Table (1): Demographic characteristics of Type 2 diabetes mellitus patients and healthy control.

Characteristic		Group		p-value
		Controls N=100	Patients N = 100	
Sex	male	50	50	N. S
	female	50	50	N. S
Age Group	<50 years	62 (62.0)	16 (16.0)	<0.01*
	50-60 years	25 (25.0)	54 (54.0)	
	>60 years	13 (13.0)	30 (30.0)	
	mean± S.D.	45.0±12.6	56.3±7.9	
BMI (kg/m²)	mean± S.D.	28.5±4.1	31.4±5.4	<0.001***
FBG (mg/dl) N.R. (80-120 mg/dl)	mean± S.D.	100.04 ±16.67	199.78 ±84.76	<0.001***
HbA1C (%) N.R. (<5.7%)	mean± S.D.	5.41±0.24	9.08±1.72	<0.001***

N. S= non-significant, N.R. = Normal rang , Percentage , S.D. = Standard Deviation, p-value= Probability value, *= Significant (<0.01), *= Highly significant(<0.001).**

The subjects were divided into three groups according to Age: (<50) years, (50-60) years and (>60) years. In these age categories, the prevalence of cases was 16 (16%), 54 (54%) and 30 (30%) respectively. In contrast, According to Table 1, there were 62 (62%), 25 (25%) and 13 (13%) control participants for the same age groups, respectively.

Serum level of CDKAL1 and TCF7L2 proteins in studied groups:

The serum levels of CDKAL1 and TCF7L2 were measured by ELISA technique. The serum concentrations of CDKAL1 and TCF7L2 significantly influence the development of Type 2 Diabetes. The result showed that the

CDKAL1 serum level normal range (0.884 - 1.873 ng/ml), the mean serum level of CDKAL1 in patients with T2DM was (3.07±0.89 pg /ml) whereas in the control group was (1.11±0.18 pg /ml). The study found a highly significant difference in the serum levels of CDKAL1 enzyme between patients and controls in *P- value* (< 0.001). Meanwhile, TCF7L2 enzyme concentrations in the patient's serum are increased compared to controls. TCF7L2 serum level normal range (720 - 1126 ng/ml), the mean serum level of TCF7L2 in patients with T2DM was (2278.0±533.2 pg /ml) whereas in the control group was (832.4±91.7 pg /ml). According to these findings, the case group's TCF7L2 levels were considerably higher than the control group (P< 0.001), as shown in (Table 2).

Table (2): CDKAL1 Regulatory Subunit Associated Protein 1 Like 1 and Transcription Factor 7 Like 2 serum level in patients and controls

Marker	Group	N	Mean ± S.D.	N.R.	P-value
CDKAL1	**Patients**	100	3.07±0.89	0.884 - 1.873	**<0.001*** **
	Controls	100	1.11±0.18		
TCF7L2	**Patients**	100	2278.0±533.2	720 - 1126	**<0.001*** **
	Controls	100	832.4±91.7		

N.R. = Normal rang, p-value= Probability value, S.D. = Standard Deviation, *= Highly significant (<. 0.01).**

Receiver Operating Characteristic (ROC) Analysis of Data

The (ROC) curve is a tool of popular graphical for the diagnostic power evaluating of a biomarker. It provides an exhaustive look at the sensitivity trend overall cut-off and thus present information about the association between the specificity and sensitivity of biomarkers. Figure (2) presents the Receiver Operating Characteristic (ROC) analysis results for various biomarkers in distinguishing between type 2 diabetes (T2DM) patients and control subjects. Each marker's area under the curve (AUC), sensitivity, specificity, and other relevant metrics are displayed, highlighting their diagnostic performance. The value for AUC ranges from 0 to 1. and classificated into five class: AUC= 0.5 = No discrimination, AUC= 0.5-0.7 = Poor discrimination, AUC= 0.7-0.8 = Good discrimination, AUC= 0.8-0.9= Very good discrimination and, AUC= >0.9 = Excellent discrimination (11). Therefore, from the ROC results can use CDKAL1 and TCF7L2 as diagnostic biomarkers in T2DM disease.

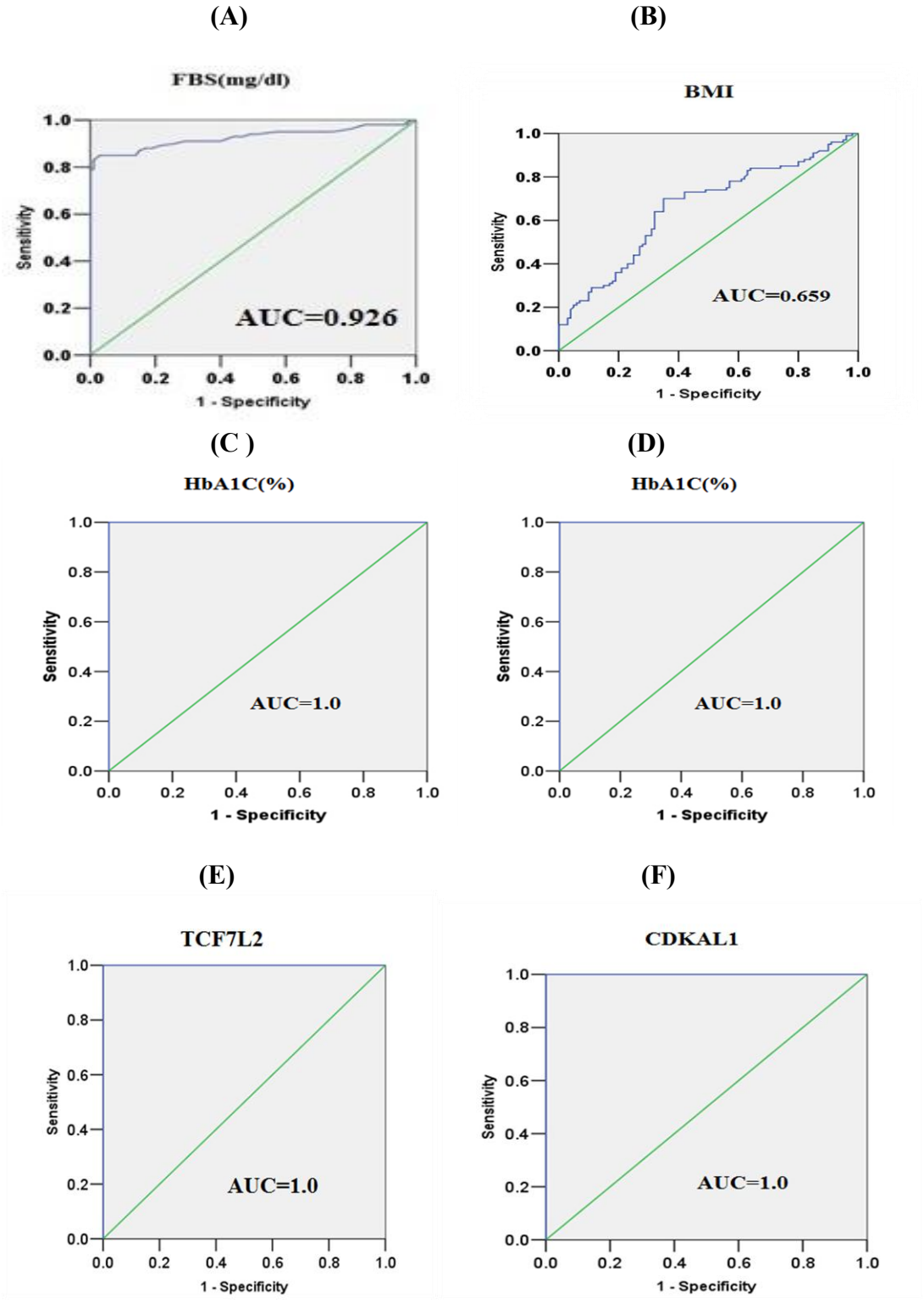


Figure (2): Clinical Diagnosis by ROC Curve to A: FBS B: BMI C: HbA1C D: TCF7L2-QTA E: CDKAL1-QTA.

Correlation Coefficient Analysis:

Table (3) showed a correlation coefficient and *p-value* between CDKAL1, TCF7L2 , and all parameters under study in patients with Type 2 Diabetes Mellitus (T2DM). In this table we notes the correlation coefficients presented in the table offer valuable insights into the relationships between various biomarkers and clinical parameters in patients with (T2DM). Understanding these correlations can elucidate underlying mechanisms and highlight potential biomarkers for disease management. The correlation coefficients from this study reinforce established research on T2DM, showing that the relationships between biomarkers such as CDKAL1 and TCF7L2, and clinical parameters like Age and HbA1C are consistent with known interactions.

Table (3): Correlation coefficient between the biomarker in patients

Correlations		Age	BMI	FBS	HbA1C	CDKAL1/ QTA	TCF7L2 / QTA
Age	**r**	1	-.377(**)	-.135	-.195	.219(*)	.115
	p		0.0001	.181	.052	.029	.256
BMI	**r**	-.377(**)	1	.074	-.060	-.075	-.170
	p	0.0001		.463	.556	.460	.093
FBS	**r**	-.135	.074	1	.622(**)	.029	-.067
	p	.181	.463		0.0001	.775	.512
HbA1C	**r**	-.195	-.060	.622(**)	1	.152	-.133
	p	.052	.556	0.0001		.130	.189
CDKAL1/ QTA	**r**	.219(*)	-.075	.029	.152	1	.213(*)
	p	.029	.460	.775	.130		.034
TCF7L2 / QTA	**r**	.115	-.170	-.067	-.133	.213(*)	1
	p	.256	.093	.512	.189	.034	

P= Probability value, r = Correlation coefficient ** Correlation is significant at the 0.01 level (2-tailed), * Correlation is significant at the 0.05 level (2-tailed).

The correlation between *CDKAL1* with *TCF7L2*.

The results demonstrate a statistically significant but weak positive correlation between CDKAL1 and TCF7L2 levels, with a correlation coefficient (r) of 0.213 and a p-value of 0.034. This suggests that while there is a slight tendency for CDKAL1 levels to increase as TCF7L2 levels rise, the relationship is not strong. The statistical significance indicated by the p-value underscores that the observed correlation is unlikely to be due to random chance, highlighting a meaningful association between these two proteins in the context of type 2 diabetes (T2DM), as shown in Figure (3).

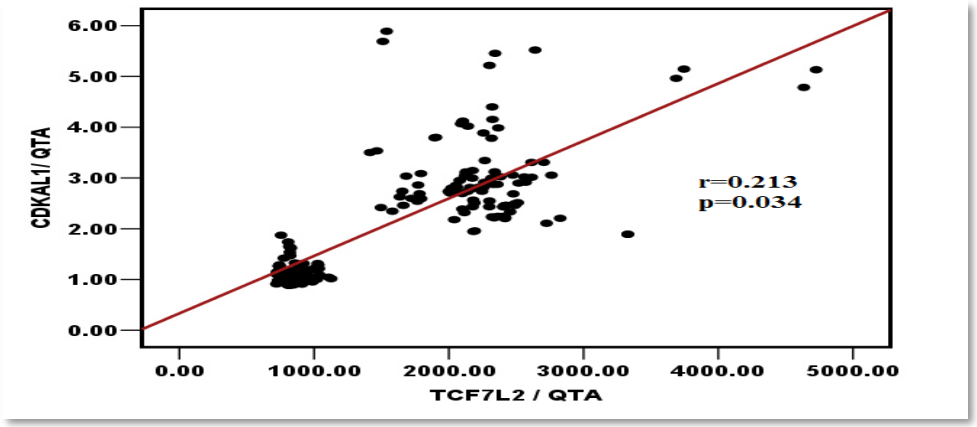


Figure (3): The correlation between CDKAL1 with TCF7L2.

Discussion

The results in (Table 1) clearly showed that the Age, BMI, FBG, and HbA1c % of T2DM patients compared with control revealed significant differences *P(<0.01)* for all age groups and highly significant *P (< 0.001)* for BMI, FBG, and HbA1c %, while no significant differences were seen with Sex between studied groups. The association of Age and body mass index (BMI) with the risk of T2DM has been examined in several studies. Abd and Al-Jumaili showed that the mean average BMI in T2DM patients and health controls were (28.69 ± 0.47) and (26.55 ± 0.46) respectively, which means that all cases under study have normal body weight and are not obese (12). Ohno *et al*., found that the risk of developing T2DM increased steeply after BMI exceeded approximately 20-21 kg/m2 (13).

Jung *et al.* analyzed data from the Korean National Health Insurance Service-Health Screening Cohort and found that being obese before the Age of 50 increased the risk of developing T2DM in the future (14). However, it is important to note that the association between BMI and T2DM may vary across racial/ethnic groups. This finding is supported by meta-analyses and population-based studies demonstrating a strong correlation between higher BMI and the prevalence of Diabetes mellitus (15, 16). Strings *et al.*, found that the association between BMI and T2DM was weaker among Black individuals, indicating that BMI may not be a reliable predictor of T2DM in this population (17).

Overall, maintaining a healthy BMI and avoiding obesity may help reduce the risk of developing T2DM, especially at a younger age. Younger Age at diagnosis of T2DM is associated with a higher risk of both Alzheimer's disease (AD) and vascular dementia (VD) (18). The risk for major diabetes complications, such as myocardial infarction, stroke, heart failure, lower extremity amputation, end-stage kidney disease, and all-cause mortality, increases exponentially with diabetes duration (19). Screening criteria for T2DM may need to be revised to include younger and leaner adults, as a non-negligible proportion of new T2DM patients are younger than 35 years and have a normal body mass index (BMI) (20). The association between obesity and T2DM is reduced with aging, indicating that the older people may gain fewer potential benefits from weight loss interventions (21).

Age is a significant factor in the incidence of Diabetes mellitus, while Sex does not show a significant relationship (22). Research by Huebschmann *et al.,* conducted a meta-analysis of BMI differences between diabetic and non-diabetic populations, highlighting higher BMI values among individuals with diabetes across various demographic groups (23). FBG and HbA1c are both important markers for assessing glycemic control in T2DM.

Several studies have investigated the relationship between FBG and Hba1c. Al-kenane *et al.* found that the mean levels of HbA1c and F.B.G showed a highly significant difference between patients and control group (HbA1c: 7.96 ±0.21,5.06 ±0.11, F.B.G: 7.91 ±0.16,4.79 ±0.04, respectively) (24). Studies by Al-Ahmer and Al-Waely have emphasized the significant difference in FBS concentrations in type 2 diabetes patients aged 50-60, with a higher concentration of 180 mg/dl in those aged 50-60, and 154.9 mg/dl in those aged less than 50. However, there was no significant difference in HbA1C concentrations among the same age group (25). Hassan *et al.* showed that the levels of FBG and HbA1c increased in T2DM patients than in healthy controls. with significant differences ($p<0.05$) (26). Glycemic control, as measured by HbA1c levels, is important in reducing the probability of harmful cardiovascular events in individuals diagnosed with T2DM and coronary heart disease (CHD)(27). HbA1c is a key marker used to manage blood glucose levels in individuals diagnosed with T2DM (28, 29).

It is a form of hemoglobin that represents the blood glucose level over some time (30). Previous research, such as that conducted by Wang *et al.,* has consistently demonstrated elevated FBG levels in individuals diagnosed with diabetes compared to non-diabetic control subjects. This supports the significant difference observed in FBG levels between patients and controls in the present study (31). Similarly, studies by Shaalan *et al.,* have emphasized the importance of HbA1C as a reliable indicator of glycemic control, with elevated HbA1C levels associated with increased risk of diabetes-related complications (15). Al-Attaby and Al-Lami observed elevated FBG and HbA1c levels in T2DM patients than controls (32).

The findings of the current study align closely with numerous previous studies investigating the relationship between FBG and hemoglobin A1C (HbA1C) levels in patients with DM. The data clearly show that serum levels of both CDKAL1 and TCF7L2 are significantly elevated in patients with diabetes compared to control subjects. The high statistical significance (*p-value <0.001****) strongly suggests that these differences are not due to random variation but rather are associated with the disease state. For CDKAL1, the serum level in patients is nearly three times higher than that in the control group. For TCF7L2, the serum level in patients is almost three times higher than that in the control group. These findings highlight the potential of these proteins as biomarkers for diabetes, with TCF7L2 showing a broader range and higher absolute values, which might imply its stronger association or higher detectability.

The following research investigations and these results are in agreement with recent studies in the same field. Recent research has confirmed the significant role of *CDKAL1* and *TCF7L2* in the pathophysiology of diabetes. Studies have demonstrated that CDKAL1 variants are associated with impaired insulin secretion and an increased risk of type 2 diabetes. For instance, a survey by Krentz *et al.,* 2020 found that *CDKAL1* expression is significantly higher in individuals with type 2 diabetes, correlating with the findings in this study where serum

levels were elevated in diabetic patients. The elevated levels of CDKAL1 observed in this study align with its known role in insulin regulation and its association with β-cell dysfunction in type 2 diabetes. In a study by (33), they showed *CDKAL1* falls into the class of genes evidently linking to T2DM since it impinges on the functional activity of pancreatic beta cells, and insulin release. *TCF7L2* is widely recognized as one of the strongest genetic risk factors for type 2 diabetes. Research by Florez *et al.,* 2017 has shown that TCF7L2 variants significantly increase the risk of type2 diabetes by affecting insulin secretion and glucose metabolism. The high serum levels of TCF7L2 in diabetic patients observed in this study are consistent with these findings, supporting the role of TCF7L2 in the disease's development and progression. TCF7L2, a protein with a primary function as a Wnt signalling pathway transcription factor, has been identified as a major gene predisposing individuals to T2DM with antagonistic effects on the biology of adipose tissue and systemic metabolism (34). AUC of 0.926 indicates that the fasting blood sugar (FBS) mark is highly discriminative to differentiate between T2D patients and controls with a sensitivity and specificity of 100% at a cut-off value of 140.1. This means that FBS is so dependable in diagnosing T2D. In contrast, however, FBS levels are expected to be within normal ranges among controls' data; this strongly proves its diagnostic significance in relation to other works in the literature who always consider it as one of the most critical markers for diabetes diagnosis (American Diabetes Association, 2020).

Body Mass Index (BMI), on the other hand, exhibits a moderate AUC of 0.659, with a cut-off value of 25.0, achieving 65.7% sensitivity and 100% specificity. This moderate AUC reflects BMI's limited role as a standalone diagnostic tool for T2D, although it remains a significant risk factor. This finding is consistent with studies such as those by Abdullah et al. (2010), which highlight the importance of considering BMI in conjunction with other markers for a more accurate diagnosis. The HbA1c levels demonstrate an outstanding AUC of 1.000, with sensitivity and specificity both at 100% for a cut-off value of >5.9%. This perfect score underscores HbA1c's critical role in monitoring long-term glucose control in T2D patients. This aligns with extensive research, including Nathan *et al*. (2007), which positions HbA1c as a gold standard for diabetes management. TCF7L2 occupied a significant AUC of 1.000 ($p<0.0001$). At the cut-off value of >1126.442 ng/ml, the specificity and sensitivity were 100.00% and 100.00%, respectively as shown in Figure (2 D). The ROC curve in T2DM patients revealed that CDKAL1 occupied a significant area under curve (AUC), which was 1.000 ($p<0.0001$). At a cut-off value of >1.873 ng/mL, the specificity and sensitivity of CDKAL1 were 100.00% and 100.00%, respectively as shown in Figure (2 E). Serum levels of TCF7L2 have been implicated in various metabolic conditions.

Research has shown that TCF7L2 plays a crucial role in Type 2 Diabetes (T2D) and nonalcoholic fatty liver disease (NAFLD) (35), with TCF7L2 polymorphisms associated with an increased risk of T2D (36), and negatively regulating beta cell survival and function in diabetes (37). Additionally, TCF7L2 has been linked to muscle atrophy in conditions like cancer cachexia, where its repression can prevent muscle loss and restore muscle mass (38). Studies have also highlighted the importance of TCF7L2 in regulating zonated metabolic pathways in the liver, impacting fibrosis development and cholesterol accumulation (35). Therefore, monitoring serum levels of TCF7L2 could provide valuable insights into the

pathophysiology of metabolic disorders and potentially serve as a biomarker for disease progression and therapeutic interventions. The analysis reveals that Age exhibits a significant negative correlation with Body Mass Index (BMI) ($r = -0.377$, $p < 0.001$), indicating that BMI tends to decrease with advancing age. This finding is consistent with recent literature suggesting that older individuals often experience a reduction in BMI due to changes in body composition, such as reduced muscle mass and alterations in metabolic rate (39). Such changes are critical as they influence diabetes risk and management strategies. In addition to BMI, Age shows positive correlations with CDKAL1/QTA ($r = 0.219$, $p = 0.029$) and CDKAL1/Folding ($r = 0.217$, $p = 0.030$). The *CDKAL1* gene is associated with insulin secretion and glucose metabolism.

The positive correlation with Age suggests that the impact of this genetic marker on diabetes risk may evolve throughout an individual's life, possibly due to age-related changes in insulin sensitivity and β-cell function. This is supported by recent research that highlights how CDKAL1 variants affect glucose metabolism and insulin secretion, with age-related factors influencing these effects (40). The significant positive correlation between Fasting Blood Sugar (FBS) and HbA1C ($r = 0.622$, $p < 0.001$) underscores the close relationship between these two biomarkers of glucose homeostasis. FBS measures current glucose levels, while HbA1C reflects average glucose levels over the previous two to three months. The strong correlation between them validates the use of HbA1C as a reliable indicator of long-term glycemic control, aligning with established research on its role in monitoring chronic glucose levels (41). Regarding Immune markers, CDKAL1/QTA is positively correlated with TCF7L2/QTA ($r = 0.213$, $p = 0.034$). Both CDKAL1 and TCF7L2 are well-recognized for their roles in T2DM risk.

The observed correlation suggests that these markers may interact in contributing to diabetes pathogenesis through their effects on insulin secretion and glucose metabolism (31, 42). The correlations observed in this study align well with current scientific understanding of diabetes biomarkers. The negative correlation between Age and BMI and the positive correlations involving CDKAL1 and TCF7L2 reflect established aspects of diabetes research. Recent studies emphasize that *CDKAL1* and *TCF7L2* are critical in T2DM risk through their impact on insulin secretion and glucose metabolism. For instance, *CDKAL1* is known to alter insulin production, while *TCF7L2* affects glucose metabolism and insulin sensitivity (40, 42).

The correlation observed in this study, though weak, aligns with the understanding that T2DM is a multifactorial disease influenced by various genetic and environmental factors. The weak correlation coefficient suggests that while CDKAL1 and TCF7L2 levels are related, they are not strongly predictive of each other. This could be due to the involvement of multiple interacting pathways and regulatory mechanisms in the pathogenesis of T2DM. Both proteins are critical in the disease's development, but their relationship is not strictly linear, indicating that other factors may also play significant roles in determining their levels.

Conclusion

In this study suggest that an elevated BMI is linked to diabetes prevalence. And important markers for assessing glycemic control in T2DM. Also, highly significant difference in BMI indicates an association between elevated BMI and diabetes prevalence. FBG and HbA2c are both

important markers for assessing glycemic control in T2DM. The possibility of using the CDKAL1 and TCF7L2 proteins as a biomarker for T2DM. may highlight the need for collaborative efforts, larger sample sizes, comprehensive meta-analyses, and further research is needed to elucidate the specific mechanisms underlying this association.

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