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Original Paper

Evaluation of the ATP-binding cassette transporter A1 (ABCA1) in Iraqi individuals with pre-existing and newly diagnosed type 2 diabetes

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ABSTRACT

ATP-binding cassette transporter A1 (ABCA1) is a crucial protein that helps promote cholesterol efflux and HDL synthesis. ABCA1 defects can cause type 2 diabetes, insulin resistance, and difficulties with fat metabolism. The aims of this study were to establish blood ABCA1 levels in Iraqi patients with recent-onset type 2 diabetes and prediabetes and to evaluate their correlations with clinical and metabolic characteristics and smoking status. In this case-control study, serum ABCA1 levels were measured in prediabetes (n = 40), newly diagnosed type 2 diabetes (n = 56), and control groups (n = 40). Samples collected from January 15, 2024, to November 5, 2024, were used to measure diabetes parameters and lipid profiles. As a result, newly diagnosed type 2 diabetes showed a slight but statistically insignificant reduction in serum ABCA1 levels compared with prediabetes and controls. LDL-C, VLDL-C, total cholesterol, and triglycerides were inversely correlated with ABCA1 in patient groups. ABCA1 correlated positively with HDL in patients with newly diagnosed diabetes mellitus but negatively in those with prediabetes. All groups had significantly lower ABCA1 levels according to smoking status. The negative correlation between HOMA-β and ABCA1, along with the positive correlations between HOMA-IR and insulin and ABCA1 concentration, reveal the role of these factors in pancreatic function. The main conclusion is that smokers with prediabetes or newly diagnosed diabetes mellitus showed decreased ABCA1 levels, suggesting a complex regulatory system involving genes, metabolism, and environmental factors.

Keywords: *ABCA1, Diabetes mellitus, Insulin resistance, Lipid, Newly diagnosed*

1 INTRODUCTION

Diabetes, or diabetes mellitus (DM), is a hyperglycemic metabolic disorder characterized by inadequate insulin production, insulin resistance, or a combination of the two. It is classified into several types [1]. The worldwide incidence of diabetes is projected to reach 629 million individuals by 2045 [2]. Dyslipidemia, a recognized risk factor for coronary heart disease, is also being investigated as an important contributor to diabetes mellitus complications [3]. Dyslipidemia is defined as elevated blood levels of triglycerides and cholesterol, accompanied by reduced levels of high-density lipoprotein (HDL). Approximately 70% of all patients with diabetes are susceptible to dyslipidemia [4]. Dyslipidemia is particularly common among patients with poorly controlled diabetes.

ATP-binding cassette transporter A1 (ABCA1) is a pivotal protein expressed in the gastrointestinal tract, liver, adipose tissue, and immune cells, and is essential for lipid transport and cholesterol homeostasis, both of which are closely associated with glucose metabolism and

diabetes [5]. The ATP-binding cassette (ABC) transporter superfamily is a large protein family of transmembrane ATP-binding proteins that use ATP hydrolysis to transport diverse substances, including metabolites, lipids, cytotoxins, and drugs, across the cell membrane [6]. ABCA1 is approximately 149 kb in length and contains 50 exons encoding an integral membrane protein with a molecular weight of 240 kDa and 2261 amino acids [7]. ABCA1 is predominantly located in the cell membranes of the liver, macrophages, and intestines. Its primary function is to export free cholesterol and phospholipids to apolipoprotein A-I, thereby initiating HDL formation [5, 8].

ABCA1 forms a channel for lipid transport from the inner to the outer membrane via an ATPase-dependent mechanism. This process facilitates the movement of cholesterol, phospholipids, and other lipophilic compounds across cell membranes [9]. This protein regulates cellular lipid homeostasis; consequently, ABCA1 dysfunction results in cholesterol accumulation within cells, particularly in macrophages, leading to cellular foam formation and atherosclerosis [5, 10]. Research suggests that reduced ABCA1 expression in pancreatic beta cells impairs insulin production [11]. ABCA1 dysfunction leads to cholesterol accumulation within beta cells, thereby altering their function and impairing glucose responsiveness. Consequently, ABCA1 deficiency may contribute to the onset of type 2 diabetes. This defect also causes elevated cholesterol levels in macrophages, exacerbating low-grade inflammation and contributing to insulin resistance [6].

2 MATERIALS AND METHODS

A case-control study was designed and conducted in this work at Al-Imam Al-Kadhim Teaching Hospital and the Department of Biochemistry and Chemistry, College of Medicine, Al-Nahrain University, Baghdad. Sample collection took place between January 15, 2024, and November 5, 2024. Patients were selected based on specific criteria according to the World Health Organization (2011) diagnostic criteria for type 2 diabetes mellitus: Pe-DM HbA1c values between 5.7% and 6.4% and fasting plasma glucose (FBS) levels of 100–125 mg/dL. In contrast, newly diagnosed diabetes mellitus had HbA1c ≥6.5% and fasting plasma glucose ≥126 mg/dL. This study included 40 apparently healthy controls and 96 patients aged 38–64 years. Samples were randomly collected from patients and controls attending the hospital's Diabetic Consultation Unit. Questionnaires were used to collect information from both the control and case groups. The medical history of each participant, including age, sex, smoking status, and any additional comorbidities, was documented. Individuals with chronic liver disease, thyroid disorders (hyperthyroidism or hypothyroidism), malignancies, age ≥70 years or ≤30 years, cardiovascular diseases, vascular conditions (such as stroke), infections, or emergency conditions were excluded from the study.

2.1 Study examinations

2.1.1 Clinical assessment

This study evaluated body mass index (BMI) by measuring participants' height and weight; BMI was calculated as mass in kilograms divided by height in meters squared, following the technique previously described [11]. Insulin resistance was measured using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), calculated by multiplying fasting plasma insulin (μU/mL) by fasting plasma glucose (mg/dL) and then dividing by 405 [12]:

HOMA-IR = (fasting insulin (μU/mL) × fasting glucose (mg/dL)) / 405

The Homeostasis Model Assessment of β-cell function (HOMA-β) was employed to evaluate insulin-secreting β-cell function in the pancreas and was calculated using the following equation [12]:

HOMA-β = (20 × fasting insulin (μU/mL)) / ((fasting glucose (mg/dL) / 18) - 3.5)

2.1.2 Sample collection

Blood samples were collected from each participant after a 10-12 h fast. The collected blood volume was 5 mL and was obtained using disposable syringes while the subject was seated. The collected blood was preserved in two sterile tubes: a gel tube and an EDTA tube for HbA1c analysis. Samples were collected in the morning between 08:00 and 10:00 AM. The blood was permitted to coagulate at 37 °C for 10-15 min and then centrifuged at 2000 × g for 10-15 min. The serum was divided into two samples and preserved at -20 °C. Serum samples from patients and controls were used to evaluate ABCA1 concentration, fasting blood sugar (FBS), and lipid profiles, including total cholesterol, triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and very low-density lipoprotein cholesterol (VLDL-C).

2.1.3 Estimation of plasma abca1 concentration levels

ABCA1 levels were assessed using a Quick Step Human ATP-binding cassette transporter A1 enzyme-linked immunosorbent assay (ELISA) kit (Sunlong Biotech, Cat. No. QS0314Hu, Beijing, China), following the manufacturer's instructions [13]. The kit was prepared in five standard concentrations: 1800, 1200, 600, 300, and 150 pg/mL (detection range of 40-2000 pg/mL). A regression model for the calibration curve was used to calculate concentrations. The R^2 value for the calibration curve was about 0.8541, with the standard curve equation y = 0.0011x + 0.5033 as shown in Figure 1, an intra-assay coefficient of variation (CV) below 10%, and an inter-assay coefficient of variation (CV) below 12%.

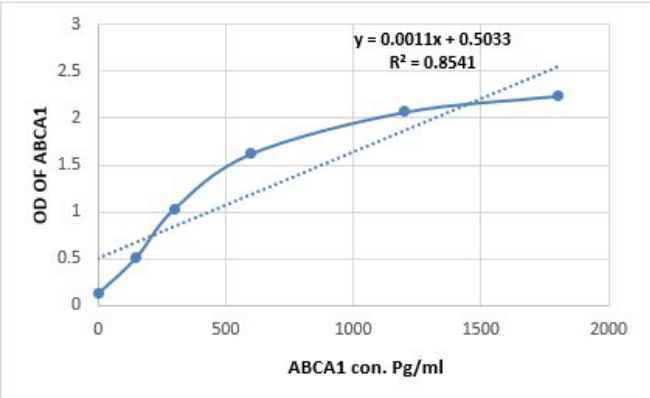

Fig. 1 Standard calibration curve for ABCA1 ELISA assay. The X axis represents ABCA1 concentration (pg/mL), and the Y axis represents the optical density (OD) measured at 450 nm. The equation of the regression line (y = 0.0011x + 0.5033) and the coefficient of determination (R^2 = 0.8541)

2.1.4 Evaluation of plasma parameter levels in this study

Fasting blood sugar (FBS) and lipid profiles, including total cholesterol, LDL cholesterol, VLDL-C, HDL cholesterol, and triglycerides (TG), were measured using an automated method with the ROCHE COBAS Integra 400 Plus chemistry analyzer (Roche Diagnostics, Switzerland).

2.2 Statistical analysis

The data were analyzed using one-way ANOVA to calculate the mean ± standard deviation (SD) with the Statistical Package for the Social Sciences (SPSS, version 24; IBM, Armonk, NY, USA). The chi-square test was applied to compare differences in categorical variables among the healthy control, prediabetes, and newly diagnosed diabetes groups. For continuous variables, post hoc multiple comparisons were performed using Tukey's HSD test to determine pairwise differences between groups. Correlations among variables were assessed using Pearson's correlation coefficient (r) with corresponding p-values for significance. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic performance of the biomarker. Graphs were generated using GraphPad Prism software (version 9.0.0).

3 RESULTS

The diagnostic characteristics of the control group (n = 40), prediabetic group (n = 40), and newly diagnosed diabetic group (n = 56) are shown in Tables 1, 2, and 3. These include demographic information (age, sex, and body mass index [BMI]), diabetes-related evaluations (fasting blood sugar [FBS], HbA1c, insulin levels, HOMA-IR, and HOMA-β), lipid profiles (cholesterol, triglycerides [TG], HDL-C, LDL-C, and VLDL-C), and the study biomarker (ABCA1). Table 4 presents serum ABCA1 levels among the three study groups: healthy controls, prediabetes mellitus (Pre-DM), and newly diagnosed diabetes mellitus (N-DM).

Table 1 Clinical characteristics and demographic information of the study subjects: healthy controls, prediabetes (Pre-DM), and newly diagnosed diabetes mellitus (N-DM)

Parameters	Control	Pre-DM	N-DM	P-value
Age (years) (Mean ± SD)	49.53 ± 9.951[a]	51.68 ± 11.387[a]	52.36 ± 9.120[a]	0.381
Male N (%)	16(40%) [a]	17(42.5%) [a]	26(46.4%)[a]	0.816
Female N (%)	24(60%) [a]	23(57.5%) [a]	30(53.6%) [a]	
BMI (kg/m^2) (Mean ± SD)	29.93 ± 5.68[a]	31.839 ± 5.68[a]	32.093 ± 5.85[a]	0.165

The results are presented as Mean ± SD for continuous variables (age, BMI) and as a frequency (n, %) for categorical variables (sex). A post hoc ANOVA was employed to compare continuous variables. Categorical variables are evaluated by the Chi-square test of independence. SD denotes Standard Deviation, BMI signifies Body Mass Index, N represents the number of subjects, % indicates percentage, P refers to the probability, values with the same superscript letter within a row are not significantly different ($p > 0.05$), while values with different letters indicate significant differences ($p < 0.05$).

The mean serum concentration of ABCA1 (pg/mL) was evaluated in the three study groups. In the healthy control group, the ABCA1 level was 373.58 ± 52.08. The Pre-DM group exhibited a mean of 375.15 ± 49.75, whereas the N-DM group showed a marginally lower mean of 361.95 ± 44.32. The data revealed a slight reduction in ABCA1 levels in the N-DM group compared with the other groups (Figure 2).

Table 2 Biomarkers for diagnosing a diabetic case include healthy controls, prediabetes (Pre-DM), and newly diagnosed diabetes mellitus (N-DM). The data were analyzed using a Post Hoc ANOVA test (mean ± SD)

Parameters	Control	Pre-DM	N-DM	P-value
FBS (mg/dl)	105.173 ± 10.54^{a}	128.12 ± 37.98^{b}	224.77 ± 94.93^{c}	0.001
HbAlc (mg/dl)	5.241 ± 0.365^{a}	6.427 ± 0.63^{b}	8.71 ± 1.69^{c}	0.001
Insulin concentration (μU/ml)	4.185 ± 1.628^{a}	13.78 ± 3.96^{b}	26.185 ± 3.187^{c}	0.001
HOMA-IR	1.093 ± 0.458^{a}	4.403 ± 2.038^{b}	14.56 ± 6.499^{c}	0.001
HOMA- β	36.469 ± 14.564^{a}	100.48 ± 60.787^{b}	77.175 ± 52.629^{b}	0.001

FBS: Fasting Blood Sugar. HbA1c: Hemoglobin A1c. HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; HOMA-β: Homeostasis Model Assessment of Beta Cell Activity; P represents the probability; values with the same superscript letter within a row are not significantly different ($p > 0.05$), while values with different letters indicate significant differences ($p < 0.05$).

Table 3 lipid profile Biomarkers Level between healthy control, prediabetes (Pre-DM), and newly diagnosed diabetes mellitus (N-DM). Were analyzed using Post Hoc ANOVA test (Mean ± SD)

Parameters	Control	Pre-DM	N-DM	P-value
Cholesterol(mg/dl)	155.34 ± 27.412 a	191.177 ± 44.799 b	175.19 ± 36.49ab	0.001
LDL-C (mg/dl)	66.06 ± 19.92a	86.773 ± 27.212 b	78.29 ± 21.37ab	0.001
HDL-C (mg/dl)	47.55 ± 8.39 a	40.75 ± 8.78 b	40.37 ± 10.08ab	0.001
VLDL-C (mg/dl)	25.82 ± 18.08a	31.86 ± 15.74ab	37.77 ± 17.89 b	0.010
TG (mg/dl)	129.186 ± 90.396a	159.31 ± 78.69ab	188.85 ± 89.49 b	0.004

HDL-C indicates high-density lipoprotein, LDL-C represents low-density lipoprotein, VLDL-C indicates very low-density lipoprotein, and TG stands for triglycerides. P denotes the probability; values with the same superscript letter within a row are not significantly different ($p > 0.05$), while values with different letters indicate significant differences ($p < 0.05$)

Table 4 Serum concentrations of ABCA1 among study groups: Group 1: Healthy Control, Group 2: Pre-Diabetes, Group 3: Newly Diagnosed Diabetes were evaluated using Post Hoc ANOVA test (Mean ± Standard Deviation)

Study Groups	Serum Biomarker Level (Mean ± SD) Of ABCAl (pg/ml)	p- value
Group 1	373.58 ± 52.08a	0.376
Group 2	375.15 ± 49.75a	
Group 3	361.95 ± 44.32a	

P denotes the probability; values with the same superscript letter within a row are not significantly different ($p > 0.05$), while values with different letters indicate significant differences ($p < 0.05$)

3.1 Correlation analysis of serum levels of ATP-binding cassette transporter A1 and physiological indicators

Correlation analysis of serum levels of ATP-binding cassette transporter A1 and physiological indicators in the prediabetic and newly diagnosed diabetic groups Figure 3 illustrates the correlations between ABCA1 blood levels and several biomarkers in the Pre-DM and N-DM groups. Comparison of the correlation profiles between the Pre-DM and newly diagnosed diabetes mellitus groups revealed several differences. ABCA1 showed negative correlations with LDL-C, cholesterol, triglycerides, and VLDL-C in both groups; however, it was negatively correlated with HDL-C in prediabetes and positively correlated in newly diagnosed diabetes mellitus. The strengths of these relationships differed between groups, and the negative relationships with LDL-C and cholesterol were less pronounced in Pre-DM.

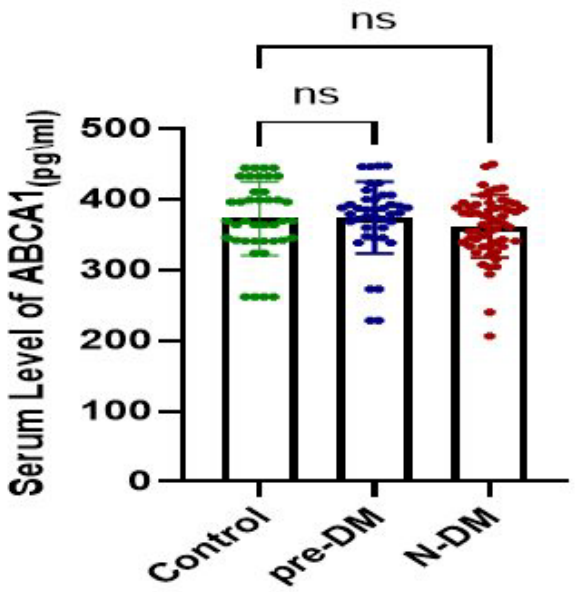

Fig. 2 Mean levels of ABCA1 (Pg/ml) in subjects' groups: Healthy Control, Pre-Diabetes (Pre-DM), Newly Diagnosed Diabetes (N-DM) were evaluated using Post Hoc ANOVA test (Mean ± Standard Deviation), ns: non-significant

Regarding insulin resistance and beta cell function (HOMA-IR, HOMA-β, and insulin concentration), both groups showed low correlations with ABCA1, although the direction and strength varied to some extent. The positive correlations with insulin concentration and HOMA-IR were more pronounced in the newly diagnosed diabetes mellitus group than in the prediabetes group. The weak negative correlation between HOMA-β and ABCA1 in Pre-DM was reversed in N-DM. Overall, the correlation patterns between ABCA1 and the studied biomarkers differed between Pre-DM and N-DM partici-

pants. Disturbances in glucose metabolism may influence the relationship between ABCA1 and various metabolic indicators. Variations in the direction and magnitude of correlations, particularly with HDL-C and insulin-related measures, may help elucidate the mechanisms underlying diabetes development.

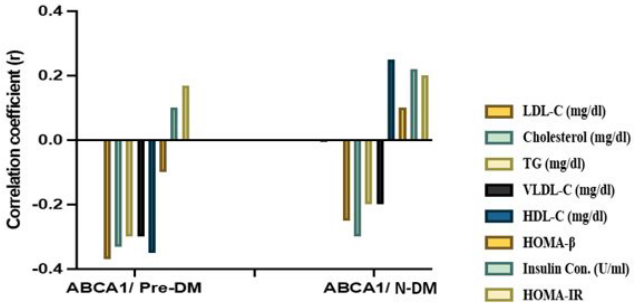

Fig. 3 The correlation coefficient (r) between Serum Levels of ATP cassette Transporter A1 (ABCA1) and biomarkers among the prediabetes (Pre-DM) group and the newly diagnosed diabetes (N-DM) group. LDL-C represents low-density lipoprotein, TG stands for triglycerides, VLDL-C indicates very low-density lipoprotein, and HDL-C indicates high-density lipoprotein, insulin con. Represent insulin concentration.

3.2 Relation of serum ABCA1 levels with smoking condition between study groups

Relation of serum ABCA1 levels with smoking status between study groups The relationship between smoking status and serum ABCA1 level (pg/mL) was assessed within each study group, as shown in Table 5. Serum ABCA1 levels were compared between participants who reported no smoking ("No") and those who reported smoking ("Yes") in each group. The results indicated statistically significant differences across all three groups, with the "No" category consistently showing higher ABCA1 levels than the "Yes" category.

In Group 1 (healthy controls), the "No" subgroup (n = 24, 60%) had a higher mean ABCA1 level (387.36 ± 53.87 pg/mL) than the "Yes" subgroup (n = 16, 40%), which had a mean of 351.69 ± 43.83 pg/mL (p = 0.028). In Group 2 (Pre-DM), the difference was more pronounced: participants in the "No" subgroup (n = 26, 65%) exhibited a mean ABCA1 level of 399.26 ± 26.87 pg/mL, whereas those in the "Yes" subgroup (n = 14, 35%) demonstrated a reduced mean of 328.41 ± 53.54 pg/mL (p = 0.001). In Group 3 (newly diagnosed DM), a similar trend was observed, with the "No" subgroup (n = 24, 42.9%) showing higher ABCA1 levels (384.36 ± 30.76 pg/mL) than the "Yes" subgroup (n = 32, 57.1%), which had a mean of 345.14 ± 45.85 pg/mL (p = 0.0012).

Table 5 Lipid profile Biomarkers Level between healthy control, prediabetes (Pre-DM), and newly diagnosed diabetes mellitus (N-DM). Were analyzed using Post Hoc ANOVA test (Mean ± SD)

Study Groups	N %	Serum Biomarker Level of ABCA1 (pg/ml) (Mean ± SD)	P-Value
Group 1			
No	24 (60%)		0.028*
Yes	16(40%)		
Group 2			
No	26 (65%)		0.001**
Yes	14 (35%)		
Group 3			
No	24 (42.9%)		0.0012**
Yes	32 (57.1%)		

*The probability was *: significant at P ≤ 0.05, **: highly significant at P ≤ 0.005*

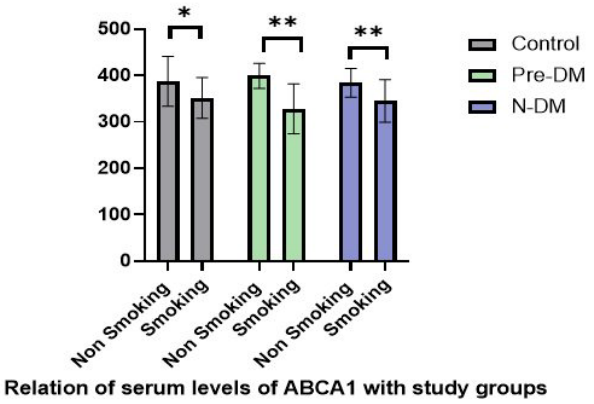

Fig. 4 The relation between ABCA1 serum levels and the smoking state, Mean levels of ABCA1 (Pg/ml) in subjects' groups: Healthy Control, Pre-Diabetes (Pre-DM), Newly Diagnosed Diabetes (N-DM) were evaluated using T test (Mean ± Standard Deviation), was *: significant at p = 0.05, **: significant at p = 0.01

3.3 Receiver operating characteristic (ROC) curve

Receiver operating characteristic (ROC) curve diagnostic efficacy of serum ABCA1 levels in distinguishing prediabetic patients from healthy controls. Table 6 shows the diagnostic performance of serum ABCA1 levels in distinguishing prediabetic patients from healthy controls. The area under the curve (AUC), optimal cut-off,

sensitivity, specificity, and related ROC metrics indicate the ability of this biomarker to differentiate between the groups, as shown in Figure 5. The table presents the AUC, threshold, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The AUC for ABCA1 was 0.530, reflecting a poor capacity to distinguish between the groups. Using Youden's index, the computed cut-off value for ABCA1 was 368.45 pg/mL, with a sensitivity of 72.73% and a specificity of 45.45%. At this threshold, the PPV was 57.14% and the NPV was 62.5%.

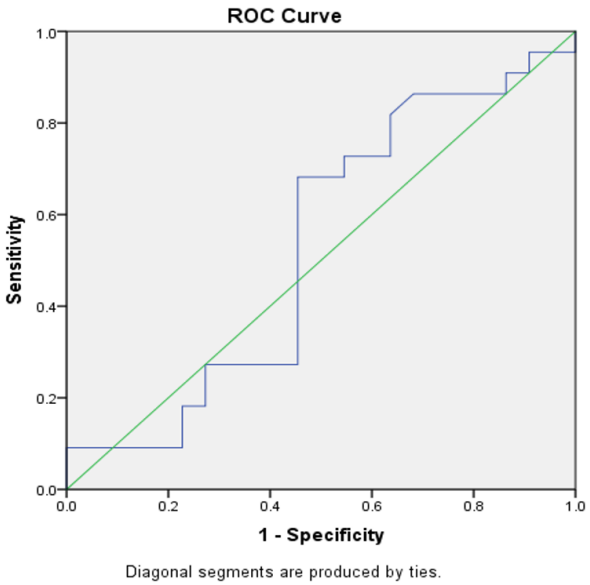

Fig. 5 ROC curves of ATP cassette Transporter A1 (ABCA1) serum levels among the Pre-Diabetes group to analyze the optimal diagnostic points for predicting such cases, compared to the control group

3.4 Receiver operating characteristics (roc) curve

Table 7 presents diagnostic accuracy metrics for serum ATP-binding cassette transporter A1 (ABCA1) levels in distinguishing the newly diagnosed diabetes mellitus group from healthy controls. The AUC for ABCA1 was 0.420, indicating poor diagnostic precision in differentiating between the two groups. Using Youden's index, the optimal cut-off value was 343 pg/mL, yielding a sensitivity of 69.64% and a specificity of 31.82%. The positive predictive value (PPV) and negative predictive value (NPV) at this threshold were 72.22% and 29.17%, respectively, as illustrated in Figure 6.

Table 6 AUC, optimal threshold, Sensitivity, and specificity of Serum Levels ATP cassette Transporter A1 (ABCA1) among Pre-DM Group and Healthy Control

Cut-off point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden's index	AUC
368.45	72.73%	45.45%	57.14%	62.5%	0.182	0.530

The test result variable ABCA1 pg/ml shows fewer than 1 tie between the positive actual state group and the negative actual state group. PPV denotes Positive Predictive Value, NPV signifies Negative Predictive Value, and AUC refers to the area under the curve. The cutoff value, determined using Youden's index, is calculated as Sensitivity + Specificity – 1. Specificity and Sensitivity are derived from the coordinates of the curve.

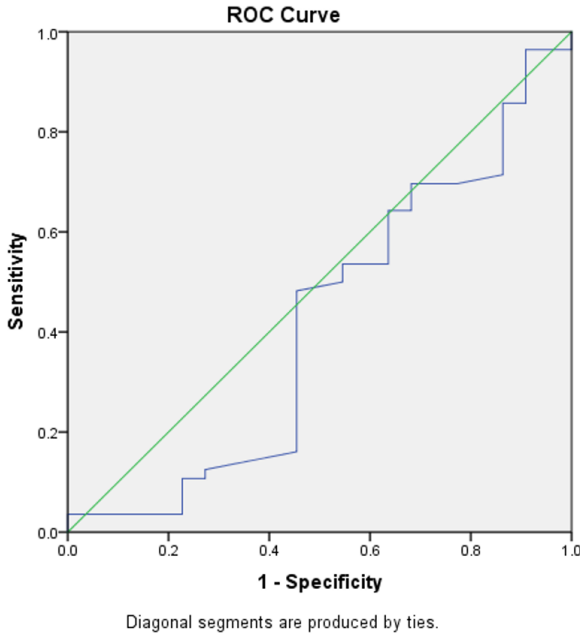

Fig. 6 ROC curves of ATP cassette Transporter A1 (ABCA1) serum levels among the newly diagnosed Diabetes group to analyze the optimal diagnostic points for predicting such cases compared to the control group

Table 7 AUC, optimal threshold, Sensitivity, and specificity of Serum Levels ATP cassette Transporter A1 (ABCA1) among the newly diagnosed DM Group and Healthy Control

Cut-off point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden's index	AUC
343	69.64%	31.82%	72.22%	29.17%	0.01461	0.420

The test result variable ABCA1 pg/ml shows fewer than 1 tie between the positive actual state group and the negative actual state group. PPV denotes Positive Predictive Value, NPV signifies Negative Predictive Value, and AUC refers to the area under the curve. The cutoff value, determined using Youden's index, is calculated as Sensitivity + Specificity -1. Specificity and Sensitivity are derived from the coordinates of the curve.

4 DISCUSSION

Diabetes mellitus (DM) is an irreversible chronic disease. According to the WHO (2024), approximately 537 million adults currently have diabetes. Experts predict that the figure will reach 643 million in 2030 and 783 million in 2045 [1, 14]. It is therefore essential to understand the underlying causes (etiology) of the disease to prevent complications and progression to end-stage disease through early detection. It is also essential to identify high-risk populations who may benefit from early therapy [15]. The current study assessed serum ABCA1 levels in Iraqi individuals categorized as prediabetes (Pre-DM), healthy controls, and newly diagnosed DM. ABCA1 levels were slightly lower in newly diagnosed DM patients compared with pre-DM and healthy individuals. Correlation analysis showed a negative relationship between ABCA1 and atherogenic lipids, with different HDL-C correlations between the Pre-DM and newly diagnosed DM groups. Recent data have confirmed the key role of ABCA1 in regulating total cholesterol homeostasis, which is crucial for maintaining insulin sensitivity. Dysregulation of ABCA1 inhibits reverse cholesterol transport, thereby increasing fat accumulation and insulin resistance, a major component of DM progression. Compromised ABCA1 function in pancreatic beta cells obstructs insulin secretion and impairs glucose homeostasis, supporting ABCA1's physiological significance beyond lipid transport [16, 17].

In addition to its concentration, ABCA1 malfunction also affects HDL-C function. In type 2 diabetes mellitus (T2DM), ABCA1-mediated cholesterol export capacity (CEC) via nascent HDL-C particles is reduced by approximately 23%, possibly due to lower SERPINA1 levels [18]. Despite unchanged HDL-C levels, this dysfunction may elevate cardiovascular risk [19]. In people with dyslipidemia, ABCA1 shows an inverse relationship with LDL and total cholesterol, consistent with reduced cholesterol efflux capacity [20, 21].

Importantly, smoking was strongly associated with lower ABCA1 levels in all groups. With the most significant impact in newly diagnosed DM, smokers showed lower ABCA1 levels than nonsmokers. Oxidants and inflammatory chemicals in cigarette smoke may impede ABCA1 expression through oxidative stress and inflammatory pathways, including NF-kB and MAPK signaling [22, 23]. The gradient observed from healthy controls to newly diagnosed DM suggests metabolic dysfunction, probably caused by the combined effects of hyperglycemia, insulin resistance, and inflammation [24, 25]; this may exacerbate the damaging impact of smoking on ABCA1. Particularly in those with diabetes or at high risk, quitting smoking is essential to preserve ABCA1 activity and lower cardiovascular morbidity; therefore, these results emphasize the importance of smoking cessation.

The ROC analysis indicated that the area under the curve (AUC) was low: 0.420 between the control and newly diagnosed DM groups, and 0.530 between the prediabetic and control groups. These data showed that ABCA1 levels alone are not a valid diagnostic marker, as they cannot distinguish between conditions. According to established guidelines, AUC values between 0.5 and 0.7 indicate weak discrimination. Consequently, the results of this study indicate that ABCA1 is not a dependable solitary biomarker for diagnosis. However, ABCA1 levels can still contribute to diagnostic accuracy when combined with other biomarkers, underscoring the need for further research to assess their role in early T2DM diagnosis [25].

Genetic variants in ABCA1, including C69T, have been associated with an increased risk of T2DM in several populations, particularly in Asia and the Middle East. A meta-analysis indicated that individuals possessing the C allele have a 1.4–1.7 times elevated risk of developing T2DM [26, 27]. A Saudi cohort study of prediabetes similarly linked the C69T mutation to dysglycemia [28]. Although genotyping was not conducted in this investigation, preliminary findings from an independent Ph.D. thesis (Albaidhani, unpublished data) concerning the same ABCA1 variant indicated a possible influence of this polymorphism in our local community. These observations substantiate the concept that serum fluctuations in ABCA1 levels may reflect underlying genetic dysregulation contributing to metabolic abnormalities in early T2DM.

Study Limitations: Several limitations apply to this study. The limited sample size may limit the generalizability of the results to a larger population. Second, genotype identification was not performed and remains under investigation. Finally, unmeasured confounding variables, including dietary habits, physical activity, and other lifestyle factors, may have influenced the reported associations.

5 CONCLUSION

ABCA1 demonstrated limited efficacy for early diabetes detection; however, its levels were significantly

lower in smokers than in nonsmokers across all groups, suggesting a modifiable risk factor. These findings, supported by initial genetic data, highlight the need for further, larger investigations to elucidate the role of ABCA1 in diabetes development and its interactions with lifestyle factors.

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Data availability

N/A

DECLARATIONS

Conflict of interest

The authors declare that they have no conflict of interest.

Consent to publish

N/A

Ethical approval

The study protocol was approved by the local ethics committee Institutional Review Board (IRB) approval number (91 on 23/1/2024), and all participants provided written informed consent prior to enrollment.

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