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Evaluation of Retinol Binding Protein 4 Level in Iraqi Patients with Type 2 Diabetes and Pre-diabetes Status as a Predictive Factor

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Abstract

The prevalence of type 2 diabetes has doubled in recent years due to a defect in insulin production, which can develop to form diabetes complications that affect the kidneys, nerves, and eyes. As a result, early diagnosis and classification of Type II diabetes are critical to aiding physician assessments. Accordingly, the current study aimed to determine Retinol binding protein 4 (RBP4) levels in patients with T2DM and pre-DM as early predictors for disease cases. The current study included 138 subjects, divided into three groups, on the basis of FBG and HbA1c criteria, including (DM, 46 patients, pre-DM, 46 participants, and healthy subject,46 persons), when they enrolled in the National Diabetes Center-Al-Mustansiriya University. Enzyme-linked immunosorbent assays (ELISA) were used to detect the levels of Retinol Binding Protein 4 and Insulin, and spectrophotometric techniques were used to determine the levels of FBG and lipid profile. Retinol binding protein 4 results revealed significant differences (P≤0.0001) among the studied groups. Also, the insulin results showed significant differences (P≤0.0001) between the diabetic and control groups. The results of HOMA-IR showed significant differences (P≤0.0001). It also showed a lipid profile significant effect (P≤0.0022), (P≤0.0001), (P≤ 0.050) between the studied groups, except HDL that showed no significant difference(P≤.0.148). In conclusion, retinol-binding protein 4 can serve as an early indicator of T2DM, and this conclusion can be reinforced by the results of the ROC analysis, which indicated that Retinol binding protein 4 is an excellent indicator for diagnosis of the studied condition.

Keywords: Diabetes mellitus II, HOMA-IR, Insulin, Pre-diabetes, Retinol binding protein 4.

Introduction

Type 2 Diabetes (T2D) is a chronic condition that occurs when the body doesn't produce enough insulin or doesn't use insulin effectively[1-3]. The primary sign of diabetes is hyperglycemia, long-term hyperglycemia affects organ function[4,5]. Diabetic complications were investigated in numerous previous studies that include diabetic nephropathy[6], diabetes with osteoporosis[7] and diabetic with periodontitis[8]. Insufficient insulin synthesis by pancreatic cells combined with an inability of insulin-sensitive tissues to react to insulin are the two main contributing reasons[9]. Obesity represents an unhealthy excess in body fat mass that is characterized by the development of a chronic, widespread, low-grade inflammatory state. Obesity-related inflammation can affect insulin signaling in tissues that are sensitive to insulin (including skeletal muscle and Adipose tissue), which leads to insulin

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Baghdad Science Journal

resistance[10]. As a result, the global obesity pandemic is causing an important rise in the incidence of cardiometabolic diseases, such as type 2 diabetes (T2D). Obesity, overweight, and insulin resistance lead to diabetes and prediabetes[11.] Prediabetes is quite common, particularly in elder person groups and obese people. It represents a transition stage between normal glycaemia and diabetes. Prediabetes is diagnosed through laboratory measurements of fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c). The expression prediabetes is used to recognize those who are at hazard of developing diabetes in the future[12]. Prediabetes, and insulin resistance are all intimately related, as is widely known[13.] Retinol binding protein 4 (RBP4), also known as a primary retinol transporter in plasma, is principally expressed in hepatocytes and is present at relatively lesser levels in adipocytes and skeletal myocytes. RBP4 transports retinol from hepatocytes to peripheral target tissues[14]. Several studies found a connection between metabolic syndrome, cardiovascular disease, type 2 diabetes, and insulin resistance and high RBP4 levels and inflammation[15.]

The objective of this study is to estimate retinol binding protein 4 (RBP4) levels in both diabetes patients and subjects with prediabetes compared to healthy persons to know whether it can be applied as an early predictor for the studied cases.

Materials and Methods

Selection of Patients

In the current study, levels of retinol binding protein 4, and some relevant biochemical parameters were measured. All the studied samples were collected from patients in the National Diabetes Center, Mustansiriyah University, Baghdad, Iraq, where the study had been conducted. A total of 138 participants, 46 healthy individuals, 46 people with T2DM, and 46 people with prediabetes in the age range of (30-65) years were included in the study. A questionnaire was used to present the anthropometric and biochemical features of each group. Patients were divided into two groups based on their fasting blood glucose and HbA1c levels. Group 1 included 46 diabetic type 2 patients (T2DM) with FBG of more than 126 mg/dl and HbA1c of more than 6.4%. Group 2 included 46 pre-diabetic patients with FBG between 100 -125 mg/dl and HbA1c between 5.7-6.4 percent.

The concentrations of insulin and retinol binding protein 4 were evaluated by using a My BioSource manufactured enzyme-linked immunosorbent test ELISA kit, USA. The levels of F.B.G., total cholesterol, triglycerides, High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL) and Very Low-Density Lipoprotein (VLDL) were measured using a Linear Chemicals S.L kit.

Exclusion Criteria

Patients with diabetic neuropathy, diabetic nephropathy, and diabetic retinopathy were excluded, as well as patients over 65 years of age. Also, patients who have been treated with insulin, non-fasting diabetic patients and chronic thyroid patients.

Inclusion Criteria

Clinical screening signals were used to determine the presence of metabolic syndrome in patients. (Lipid profile, Insulin Resistance IR, Fasting Blood Glucose FBG, HbA1c), patients with diabetes mellitus type 2, aged 30 to 65, who are also diabetic and who should be fasting according to their medical history and physical examination.

Blood Samples Collection

Five milliliters of venous blood were collected from each patient and control in serum-separating tubes. Samples of sera were obtained by centrifuging 4 ml of blood at 3000 rpm for 10 minutes after blood had been allowed to clot for approximately 30 minutes at room temperature, the obtained serum was divided between two Eppendorf tubes, and was stored at -20 ^{o}C until being used for subsequent analysis. The first section was utilized to determine (FBG, CHOL, TG, and HDL). Retinol binding protein 4 and Insulin levels in the second component, which was kept at a temperature of minus 20°C, were evaluated by ELISA kits, an enzyme-linked immunosorbent assay. Additionally, 1 ml of whole blood in EDTA tubes and analyzed for HbA1c assay.

Statistical Analyses

To categorize the influence of numerous factors on research parameters, the Statistical Analysis System-SAS (2018) program was applied. Thus, for statistical comparison between means, the Least Significant Difference (LSD) test (Analysis of

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Baghdad Science Journal

Variation, ANOVA) was employed. The ROC curve was used to assess the accuracy of markers as indicators of diabetes.

Results and discussion

Table .1 shows the values of age and BMI, WHR for all the studied groups. Age results in mean ±SD for DM2, Pre-DM, and control groups [(53.21 ±1.20) (51.00 ±1.35) (42.30 ±1.12)] respectively, the results revealed notable high differences between the DM2 groups and control groups as well as the pre-DM groups and control groups(P≤0.01). But there is no considerable variance between the DM2 and pre-DM groups, as shown in Table .1.

Table 1. Age, BMI and WHR for all the studied groups

Groups	Age (year)	BMI (kg/m^2)	Waist/Hip (WHR)	Duration of (DM/preDM)year
DM (n =46)	53.21 ±1.20 a	28.61 ±0.94 a	0.958 ±0.01 a	6.73 ±0.69
Pre-DM (n =46)	51.00 ±1.35 a	27.41 ±0.64 a	0.915 ±0.009 b	0.726 ±0.06
Control (n =46)	42.30 ±1.12 b	24.78 ±0.19 b	0.917 ±0.004 b	-
LSD	3.44 **	1.870 **	0.0262 **	1.393 **
p -value	0.0001	0.0003	0.0016	0.0001

The different letters in the same column Mean that they are differed significantly ** (P≤0.01).

The body mass index results were recorded in Table 1. The results showed mean ± SD [(28.61 ± 0.94) (27.41 ± 0.64) (24.78 ± 0.19)] of BMI in the DM, pre-DM, and control groups, showing highly significant differences among the tested groups. Both patient groups showed a significant increase (p<0.01) compared to the control group, while no significant differences were found between the patient groups themselves, as shown in Table 1.

The Waist to hip ratio results is shown in Table 1. The results showed mean ± SD [(0.958 ± 0.01) (0.915 ± 0.009) (0.917 ± 0.004)] of WHR for DM, pre-DM, and control, respectively, the result showed significant differences between DM groups and control groups in addition to DM groups and pre-DM groups, but no significant between pre-DM and control groups.

Table 2. shows the results for Retinol-binding protin4 and Insulin for all the studied groups, retinol-binding Protin4 data showed a significant difference (P ≤ 0.01), mean ±SD between DM, pre-DM, and control which were found to be [(21.34 ± 1.36) (15, 68 ± 0.96) (10.27 ± 0.11] respectively. Accordingly, there were highly significant differences in RBR4 among all the studied groups (P≤0.01). On another hand, insulin level results found a significant difference (P≤0.01). The Mean ± SD for DM, Pre-DM, and control were recorded to be [(4.02 ±0.20) (2.14 ±0.13), (1.838 ±0.05)], as shown in Table 2. The insulin outcomes showed highly significant differences between diabetic group (DM) and control group, as well as DM and pre-DM groups, but no significant differences between pre-DM and control groups.

Table 2. Retinol-binding protin4 and Insulin levels in all the studied groups

Groups	Retinol-binding protin4 (ng/ml)	Insulin (µu/ml)
DM (n =46)	21.34 ±1.36 a	4.02 ±0.20 a
Pre-DM (n =46)	15.68 ±0.96 b	2.14 ±0.13 b
Control (n =46)	10.27 ±0.11 c	1.838 ±0.05 b
LSD	2.703 **	0.402 **
p -value	0.0001	0.0001

The different letters in the same column Mean that they are differed significantly ** (P≤0.01).

Table 3 shows the results for FBG, HbA1c, and HOMA-IR for all the studied groups. Mean ±SD of FBG for DM, Pre-DM, and control were [(196.14 ±9.14) (114.37 ±1.10) (93.49 ±0.76)] respectively. Accordingly, the results showed highly significant differences in FBG among the three groups (P≤0.01).

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Baghdad Science Journal

Also, mean ±SD of HbA1c for DM2, pre-DM, and control were [(8.11 ±0.23) (6.02 ±0.03) (4.69 ±0.03)] respectively. Subsequently, the results showed highly significant differences in HbA1c among the studied groups (P≤0.01).

Table 3. FBG, HbA1c, and HOMA-IR values for all the studied groups

Groups	FBG (mg\dl)	HbA1c	HOMA IR
DM (n =46)	196.14 ±9.14 a	8.11 ±0.23 a	1.97 ±0.15 a
Pre-DM (n =46)	114.37 ±1.10 b	6.02 ±0.03 b	0.603 ±0.04 b
Control (n =46)	93.49 ±0.76 c	4.69 ±0.03 c	0.453 ±0.02 b
LSD	14.907 **	0.380 **	0.258 **
p -value	0.0001	0.0001	0.0001

The different letters in the same column Mean that they are differed significantly ** (P≤0.01).

The mean ± SD of HOMA-IR in DM2, Pre-DM, and control were [(1.97 ±0.15) (0.603 ±0.04) (0.453 ±0.02)] respectively. Hence, the results of HOMA IR showed higher levels in the group of patients with (DM) related to the pre-DM group and the control group, and there was a high statistical significance (P≤0.01) between the group of patients and the control group, as well as the case for the pre-DM group, but no statistical significance between the control group and pre-DM group, as shown in Table 3.

Table .4 shows the results for Lipid profile of Patient DM, Pre-DM, and control groups. The mean ±SD values of cholesterol in DM, Pre-DM, and control were found to be [(182.81 ±6.62) (191.22 ±5.33) (162.67 ±5.32)] respectively. The results showed significant variations (P≤0.01) between DM group and the control group and between the pre-DM groups with the control group, but no significance between the DM group and the pre-DM group, as shown in Table 4.

The mean ± SD values of Triglyceride patients with DM, pre-DM, and control groups were [(171.82 ±13.46) (168.56 ±11.46) (110.84 ±4.28), respectively, the results showed highly significant differences (P≤0.01) between DM2 groups, control groups and between pre-DM groups with control groups, but no significant differences between DM2 groups and pre-DM groups, as shown in Table 4.

Table 4. Lipid profile of Patient DM, Pre-DM, and control groups

Groups	Cholesterol	Triglyceride	HDL	LDL	VLDL
DM (n =46)	182.81±6.62a	171.82±13.46a	44.98 ±1.62	103.46±5.39ab	34.36 ±2.69a
Pre-DM (n =46)	191.22±5.33a	168.56±11.46a	46.87±1.96	110.63 ±4.78a	33.71 ±2.29a
Control (n=46)	162.67±5.32b	110.84 ±4.28b	49.78±1.61	94.14 ±4.21b	22.53 ±0.98b
LSD	16.201 **	29.384 **	4.864 NS	13.48 *	5.927 **
p -value	0.0022	0.0001	0.148	0.050	0.0001

The different letters in the same column Mean that they are differed significantly** (P≤0.01) *(P≤0.05)

The mean ± SD values of HDL in DM, Pre-DM, and control groups were [(44.98 ±1.62) (46.87 ±1.96) (49.78 ±1.61)] respectively, the result HDL level was lower in T2DM than in the control group, but no significant difference between three groups studied, as shown in Table 4.

The mean ±SD values LDL of patients with DM, pre-DM, and control group were [(103.46 ±5.39) (110.63 ±4.78) (94.14 ±4.21)] respectively, as shown in Table 4. The result of LDL level was lower in the control group than in the DM group. We found significant changes (P≤0.05) between DM and control groups and between pre-DM and control groups, but no significant differences between the DM and pre-DM groups, as shown in Table 4.

The mean ±SD values of VLDL in DM, Pre-DM, and control were [(34.36 ±2.69) (33.71 ±2.29) (22.53 ±0.98)] respectively. The results showed significant changes (P≤0.01) between DM group and control groups and between the pre-DM group with control groups, but no significant between DM group and pre-DM group, as shown in Table 4.

The Receiver Operating Characteristics Curve (ROC)

The ROC test for the Retinol-binding protin4 marker showed very clear cut-off value (>11.13) with AUC

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Baghdad Science Journal

of 0.991, sensitivity of 0.967 and 0.065 1-specificity that indicates Retinol-binding protein- 4 is considered as an excellent diagnostic marker as shown in Table 5 and Fig. 1.

Table .5 ROC data for Retinol-binding protin4

Characteristics	Test Result Variables
Retinol-binding protin4 ng/ml	> 11.13
Asymptotic Sig.[b]	0.001
Std. Error[a]	0.005
Sensitivity	0.967
1-Specificity	0.065
AUC (95% CI)	0.991 (0.981- 1.000)

CI: Confidence Interval, AUC: Area Under Curve.

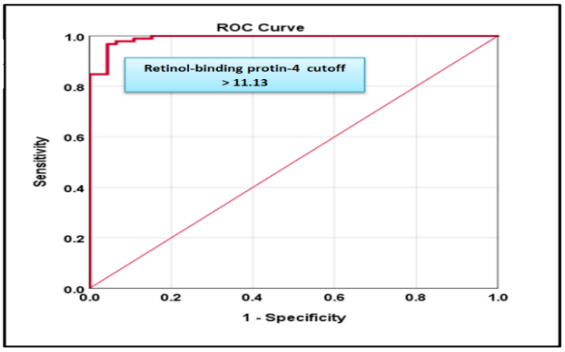

Figure1. ROC of Retinol-binding protin4

ROC test for insulin marker exhibits clear cut-off value (> 2.68) with AUC of 0.946, 0.935 sensitivity and 0.152 1-specificity that indicates Insulin is considered as an excellent diagnostic marker, as shown in Table 6 and Fig. 2

Table 6. ROC data for Insulin

Characteristics	Test Result Variable
Insulin µu/ml	< 2.68
Asymptotic Sig.[b]	0.001
Std. Error[a]	0.020
Sensitivity	0.935
1-Specificity	0.152
AUC (95% CI)	0.946 (0.907- 0.985)

CI: Confidence interval, AUC: Area under curve

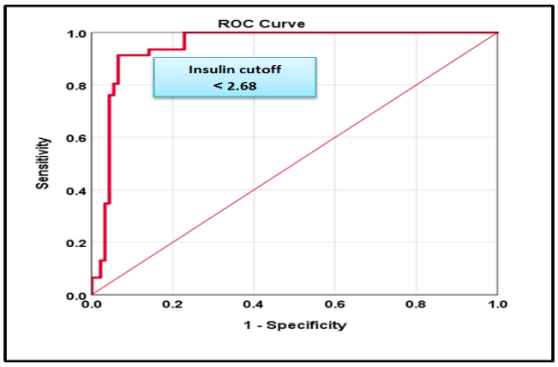

Figure 2. ROC of Insulin

ROC test for HOMA-IR markers showed very clear cut-off value (>0.467) with AUC of 0.903, 0.902 of sensitivity and 0.261 1-specificity that indicates HOMA IR is considered as an excellent diagnostic marker, as shown in Table 7 and Fig. 3

Table 7. ROC data for HOMA-IR

Characteristics	Test Result Variable
HOMA IR	> 0.467
Asymptotic Sig.[b]	0.001
Std. Error[a]	0.026
Sensitivity	0.902
1-Specificity	0.261
AUC (95% CI)	0.903 (0.852- 0.954)

CI: Confidence interval, AUC: Area under curve.

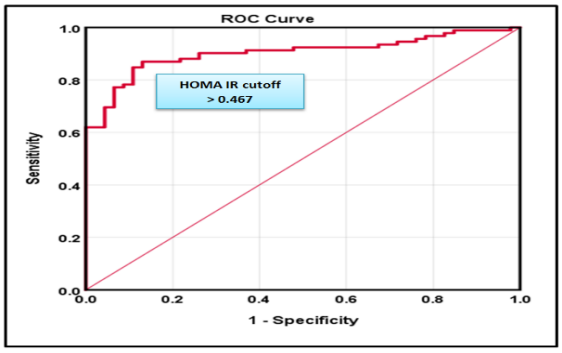

Figure 3. ROC curve of HOMA-IR.

The current study showed the results of the age factor distribution showed a highly significant difference ($p< 0.001$) between the studied groups. Both groups of patients showed a significant increase compared to the control groups. Because T2DM progresses slowly and is frequently not occurred in the early stages for the patient to detect the symptoms of typical diabetes, it is well known that T2DM frequently goes on for many years without being diagnosed. On the basis that the risk of type 2

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Baghdad Science Journal

diabetes increases with age, obesity, and inactivity[16]. Body mass index results presented in this study showed a highly significant difference ($p< 0.001$) between the studied groups. Both groups of patients showed a significant increase compared to control groups, whereas there was no discernible difference found between the DM and pre-DM groups themselves. The intergenerational progression of diabetes mellitus and obesity gained strong attention in many studies[17]. In high-income nations, more than 90 percent of all DM cases include T2DM, which is closely linked to overweight[18]. According to Joshi et al., who discovered that diabetic patients' BMI was significantly higher than that of non-diabetic patients[19]. This is consistent with the current study.

The waist-to-hip ratio results revealed that there are significant differences in Waist to Hip ratio (WHR) between the patient and healthy groups ($P\leq0.01$). The current results are consistent with Awasthi et al[20] they showed that anthropometric measurements in healthy people are lower than in patients with diabetes. Furthermore, many studies reported a strong relationship between hypertension and metabolic syndrome with waist-to-hip ratio and waist-to-height ratio. Despite the accuracy of WHR as a measurement of obesity and its association with morbidity, various studies found that WHR is the most effective screening tool than BMI. This is for individuals at cardiovascular risk. In addition, some researchers found that BMI, WHR, and were more sensitive indicators of diabetes[21] .

The mean values of (FBG) and (HbA1c) for all the studied groups in the current study were recorded. The mean values in this revealed significant differences in FBG and HbA1c between the two DM and pre-DM groups and the control healthy group ($P\leq0.01$), so, the current study agrees with Elimam et al[22], and Misra et al[23] .

The current study findings demonstrate that type 2 diabetes patients have much greater levels of insulin hormone than the control group, as indicated in Table 2 and also the level of HOMA-IR in patients with type 2 diabetes showed a highly significant increase ($p<0.001$) compared with the control group, while no significant difference was found between Pre-DM and control group and this result is in agreement with the study of Sati et al [24] and Elias et al [25] who revealed that DM patients have elevated IR and insulin levels compared to the control group. This result can be explained by the fact that insulin resistance is most likely the initial metabolic aberration in DM type 2. Raised serum glucose levels brought on by insulin resistance led to the pancreas's overproduction of insulin. When hyperglycemia is continuous and chronic, the pancreatic -cells are damaged and cease To function.[26]

Current results of Lipid Profile levels showed highly significant differences in cholesterol, and triglycerides, while serum HDL-C level was low in T2DM than the control group, but no significant difference in the two groups of DM and pre-DM, compared to the control groups. This result agrees with Yassin et al [27]and Ali et al[28].

The findings of the statistical analysis revealed that there was a very significant difference between the three groups tested, and the current study demonstrated that the levels of Retinol-binding protin 4 were substantially higher in diabetes patient groups as compared to the control group. The current study agrees with Murata et al[29], Takebayashi et al[30] and Ail et al[31]. Another study also showed that one of the earliest human studies implicating RBP4 with insulin resistance and diabetes was reported in 1999. Despite the lack of stated effect sizes, this investigation discovered that RBP4 levels were higher in T2DM patients than in healthy controls[32].

Conclusion

According to the findings of this study, Retinol-binding protin4 is an excellent marker for diagnosing the analyzed case. This conclusion was backed by ROC data analysis, which revealed an AUC value of (0.991).

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Author's Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- Authors sign on ethical consideration's approval.
- Ethical Clearance: The project was approved by the local ethical committee at University of Baghdad.
- No animal studies are present in the manuscript.
- No potentially identified images or data are present in the manuscript.

Authors' Contribution Statement

H.M.H. and K.G.K. contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

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تقييم مستوى البروتين المرتبط بالريتينول 4 لمرضى عراقيين بالسكري النوع الثاني وحالة ما قبل السكري كعامل تنبؤي

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الخلاصة

تضاعف انتشار مرض السكري من النوع 2 في السنوات الأخيرة نتيجة الخلل في إنتاج الأنسولين ، والذي يمكن أن يتطور ليشكل مضاعفات مرض السكري التي تؤثر على الكلى والأعصاب والعينين. ونتيجة لذلك ، فإن التشخيص المبكر والتصنيف لمرض السكري من النوع الثاني ضروريان لمساعدة الطبيب على التقييم. وفقًا لذلك ، هدفت الدراسة الحالية إلى تحديد مستويات بروتين ارتباط الريتينول 4 (RBP4) في المرضى الذين يعانون من السكري النوع الثاني وما قبل السكري كمنبئ مبكر لحالة المرض. وكنتيجة لذلك ، هدفت الدراسة الحالية الى تحديد مستوى البروتين المرتبط بالريتينول 4 لمرضى السكري النوع الثاني وحالة ما قبل السكري كمؤشر مبكر لحالة المرض. شملت الدراسة الحالية على 138 شخصا، مقسمة الى ثلاث مجاميع على اساس معايير مستوى السكر الصيامي والهيموكلوبين المسكر تمثل مجموعة السكري(46 مريضا) ومجموعة ماقبل السكري (46 شخصا) ومجموعة الاصحاء (46 شخصا) عند مراجعتهم للمركز الوطني للسكري- الجامعة المستنصرية. تم استخدام مقايسة الممتز المناعي المرتبط بالانزيم للكشف عن مسنوى البروتين المرتبط بالريتينول 4 والانسولين وتقنيات القياس الطيفي لتحديد مستويات السكر الصيامي والدهون. اظهرت نتائج البروتين المرتبط بالريتينول 4 فروق معنوية($P\leq0.0001$) بين المجموعات المدروسة. كما أظهرت نتائج الأنسولين اختلافات معنوية ($P\leq0.0001$) بين مجموعة مرضى السكر ومجموعة السيطرة. واظهرت نتائج مقاومة الانسولين فروق معنويه($P\leq0.0001$ كما اظهرت نتائج ملف الدهون تأثير معنوي ($P\leq 0.050$), ($P\leq0.0001$), ($P\leq0.002$) ماعدا HDL التي اظهرت عدم وجود فرق معنوي($P\leq.0.148$). يمكن الاستنتاج ان البروتين المرتبط بالريتينول 4 يمكن ان يكون مؤشر مبكر لمرض السكري وعززت ذلك نتائج تحليل ال ROC والتي اكدت الى ان البروتين المرتبط بالريتينول 4 هو مؤشر ممتاز لتشخيص الحالة المدروسة.

الكلمات المفتاحية: مرض السكري النوع الثاني، مقاومة الانسولين، الانسولين، ماقبل السكري، البروتين المرتبط بالريتينول 4.