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Elevated RBP4 Levels in Iraqi Diabetic Patients with Type 2 Diabetes Mellitus and Associated with Diabetic Retinopathy

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Abstract: Diabetes is high blood sugar levels are a defining feature of the chronic medical condition diabetes. There are three main types of diabetes: T1DM, an autoimmune condition in which the immune system attacks and kills the cells in the pancreas responsible for producing insulin, T2DM, the most common complication in diabetics is Diabetic Retinopathy (DR) which is damage that affects the eye retina and results from increased blood Sugar in the blood and is considered to be the primary factor the leading causing blindness in diabetics and is among the most frequent microvascular complications associated with diabetes disease. Non-proliferative DR (NPDR), the early stage of the disease that can cause vision issues, and proliferative DR (PDR) are the two main forms (This level of diabetic retinopathy is further advanced). The purpose of the study was to assess how RBP4 and a few biochemical tests affected the progression of DR in T2DM patients from Iraq. The study was conducted in Diyala and Bagdad governorates. 150 participants, 100 patients with T2DM and 50 healthy control age range (40-80) years, the disease duration ranged from (1-30) years, and they were classified into two main groups patient group (DR and DWR), and the control group the study started from November 2022 to January 2023. The mean level of RBP4 increased in group DR compared with the control group and DWR groups. The statistical significance of these differences was substantial (P>0.01). The DR patients had an (HS) increase (P<0.01) in the Urea and FBG. additionally, the patients' group compared with the control had a highly significant increase in creatinine and there was a highly significant decline in the GFR (P<0.01), While, there were (NS) differences in age, gender, and uric acid (p>0.05) within the study groups.

Key points: Diabetes Mellitus, Diabetic Retinopathy, Retinol binding protein 4.

1. Introduction

Diabetes is a widespread disease that contributes significantly to both mortality and morbidity rates.[1] Cardiovascular complications lead to Death that affects T2DM patients by 50%. [2] One of the biggest health problems of our time is T2DM, and by 2045, its prevalence is predicted to have increased by more than 50%.[3]. Diabetic Retinopathy (DR) is the damage that affected the eye retina that results from increased blood sugar in the blood and is considered to be the primary factor the leading causing blindness in diabetics.[4] The retinal vasculature is impacted by DR. The retinal

capillary capillaries experience an increase in white blood cell aggregation, which is followed by cell deterioration. A shortage of oxygen due to blood vessel narrowing (hypoxia) encourages the generation of vascular endothelial growth factor (VEGF), which in turn leads to neovascularization and the destruction of the delicate neuroretinal balance. Following that, visual acuity declines.[5] The illness advances gradually. The damaged blood vessels leak fluid and blood into the retina during the early stages of non-proliferative diabetic retinopathy (NPDR), which results in swelling and blurred vision. New blood vessels develop in the retina during more severe phases of proliferative diabetic retinopathy (PDR), which can result in bleeding, scarring, and finally vision loss. Additionally, floaters, difficulty seeing at night, and blurred or distorted vision may be signs of diabetic retinopathy. However, there might not be any obvious symptoms in the early stages.[6] RBP4 is a retinol transporter protein (vitamin A alcohol), It is mostly produced in the liver and moves through the blood as a retinol-bound hepatokine in a complex with transthyretin.[7]. In addition to its role in insulin signaling, RBP4 has also been linked to the emergence of diabetes complications such as nephropathy and diabetic retinopathy. RBP4 can activate inflammatory pathways and encourage oxidative stress, which can cause tissue damage and the emergence of diabetic problems, according to studies. Overall, the exact mechanisms underlying the association between RBP4 and DM are still being studied, but it is clear that high levels of RBP4 are a risk factor for insulin resistance and the development of DM and its complications.[8] RBP4 is a therapeutic target in ophthalmology research since it is important for vision. that the RPB4 could be used as a possible therapeutic target to cure diabetic retinopathy. RPB4 may have a significant role in the onset of diabetic retinopathy by controlling angiogenesis in the retina, although the two conditions are not directly related.[9] The role of RBP4 in DM is related to its control of insulin sensitivity in adipose tissue and the liver. RBP4 binds to its receptor, STRA6, and facilitates retinol uptake into cells in healthy persons, helping to control insulin sensitivity. High amounts of RBP4 can, however, interfere with this procedure and impede insulin signaling in those with DM and insulin resistance.[10]

2. Methods and instruments

2.1 sample

2.1 A-Sample collect

Blood samples (8 ml) were taken from each participant in the study groups. (Control group and patients with T2DM). Each sample was divided into two portions (6 ml was placed into a gel tube inside a centrifuge for biochemical tests, ELISA techniques), and 2 ml was placed into an EDTA tube for HbA1C testing. The HBA1C test was performed using the ichroma™ II device, which is characterized by speed, high accuracy, and sensitivity in reading the results. While the biochemical tests were performed using an Automated Chemistry Analyzer (BS-230) and ELISA (HS) techniques.

2.1 B-Procedure

The preparation process for the tests was carried out by drawing fresh blood from both groups (patients and control group), and the drawn blood was placed in EDTA anticoagulation tubes and a Gel tube.

For HBA1C testing, fresh blood (5 µl) of EDTA was taken using micropipettes and placed in a test buffer tube, then placed in a test strip and waited for the required period (12 minutes) and then the result was read on the display of the ichroma™ II device. In addition, blood serum (500 µL) was taken from the gel tube using micropipettes and placed in an automated chemistry analyzer and waited for about half an hour as well as ELISA techniques. After that, the test results were read separately on the display screen of the device.

2.2 Study design

During this study, one hundred blood samples were collected from individuals (patient group) for the period from November 2022 to January 2023 who visited the Specialized Eye Surgery Center /

Diyala and Ibn Al-Haytham Teaching Eye Hospital / Baghdad. Those who suffer from type 2 diabetes and diabetic retinopathy. In addition, 50 samples were collected from healthy people (the control group) within the age group 40-80 years, for both sexes, patients and healthy subjects. Descriptive information was taken for each individual (name, age, sex, height, weight, and historical duration of diabetes and other diseases)

2.3 Ethical approval

The consent of all patients to take blood samples for the study was obtained from them orally. also. received approval for this study on 30/11/2022, from the Scientific Committee for Research.

2.4 Statistical analysis

Frequency, percentage, mean, and standard deviation methods for analyzing descriptive data were applied. ROC, Monte Carol test (MCP), and T-tests on independent samples were all used. In the test, The SPSS 26.0 application was used to examine current data.

1-For data presentation, use:

A - data presented in a tabular (Complex frequency distribution table).

B - Presentation of mathematics (Mean and standard deviation).

2- For analysis of data using:

A- t-test independent samples.

B- Monte Carol test (MCP).

The comparison of significance (p-value) for each test was taken into account:

A-P-values (P>0.05) were non-significant (NS).

B-P-value (P≤0.05) indicated significance (S).

C-P-values (P≤0.01) were highly significant (HS).

3- Results and Discussion

3.1 Age features of patients and control by Gender :

According to the table (1) :The findings show the majority of diabetic patients without retinopathy (DWR) and diabetic retinopathy patients are between the ages of (50-59) years with a percentage of 36-38 % out of 100 patients. The present study shows No-significant differences (P.value<0.05) for two variables Age and Gender between the patient group and control group.

Table 1: Distribution of Studied groups according to Age (Year) groups by Gender

Agerange (Years)	DWR(n=50)			DR(n=50)			Control (n=50)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
(40-49)	10(20%)	8(16%)	18(36%)	6(12%)	1(2%)	7 (14%)	6(12%)	1(2%)	7(14%)
(50-59)	12(24%)	7(14%)	19(38%)	10(20%)	8(16%)	18(36%)	10(20%)	8(16%)	18(36%)
(60-69)	6(12%)	2(4%)	8(16%)	9(18%)	8(16%)	17(34%)	9(18%)	8(16%)	17(34%)
(70-80)	2(4%)	3(6%)	5(10%)	5(10%)	3(6%)	8(16%)	5(10%)	3(6%)	8(16%)
Total	30(60%)	20(40%)	50(100%)	**30**(60%)	**20**(40%)	50(100%)	**30**(60%)	**20**(40%)	50(100%)
P-Value (MCP)*	**MCP=.347 P>0.05 (NS)**			**MCP=.727 P>0.05 (NS)**			**MCP=.547 P>0.05 (NS)**		

The study's findings are consistent with the results of Yaseen, et al., studies which found that T2DM was most prevalent in the age group (41-65) years old, which is the majority among both genders.[11] Further, The conclusions of the study are in line with the Annani-Akollor et al., whose age range that discovered (51-70) years had an increase in all diabetic illnesses, including diabetic retinopathy.[12] The conclusion was the same as that of Karatas et al., who investigated that Age and gender did not have statistical significance (NS) for diabetes individuals.[13] Furthermore, those between the ages of 45 and 64 are the ones most prone to get diabetes. Age has an impact on

the pathophysiology of glucose intolerance in the elderly because it reduces insulin sensitivity and modifies or impairs the beta cell's ability to compensate for increased insulin resistance.[14]

3.2 Comparison between Study groups according to RBP4, GFR, UREA, Creatinine, Uric acid, FBG, and HBA1C.

According to the data in Table (2), The patients levels increased in the mean ± SD of Urea, Creatinine, FBG, HBA1C, and RBP4 (29.41±8.149, 0.730±0.189, 184.19±72.848, 7.103±2.308 and 30.580±10.677) respectively, compared to the healthy control.

The statistical significance of these differences was substantial (P>0.01). But the Uric Acid value of patients was (29.41±8.149, and 4.35±1.27) respectively, indicating that these differences were (NS)(P>0.05). additionally, the patients compared with the controls had an (HS) decrease in the mean ± SD of eGFR (99.59±16.777). Moreover, when comparing the DR with the DWR groups, the results showed an increase in the mean ± SD level in Urea, FBG, and RBP4, respectively (32.32±8.085, 198.58±67.573, and 39.486±6.689). These differences were (HS)significant (P<0.01). While, the results of eGFR, Creatinine, Uric acid, and HBA1C have (NS) (P<0.05) between them.

Table (2): Comparison between the patient group and control group of the biochemical parameters.

Parameters	Patients group compared with the control Mean ± SD		P. value	DR compared with DWR Mean ± SD		P. value
	Patient group No. 100	Control No. 50		DWR No. 50	DR No. 50	
eGFR	99.59±16.777	108.96±12.898	0.001	102.56±16.372	96.62±16.812	0.077
Urea	29.41±8.149	25.96±7.521	0.013	26.50±7.178	32.32±8.085	0.0001
Creatinine	0.730±0.189	0.633±0.133	0.0001	0.7240±0.178	0.7374±0.200	0.724
Uric acid	4.35±1.27	4.014±0.860	0.058	4.35±1.27	4.250±1.253	0.057
F.B.G	184.19±72.848	92.90±10.027	0.0001	169.80±75.717	198.58±67.573	0.048
HbA1c	7.103±2.308	4.809±0.567	0.0001	8.3568±1.474	8.1432±2.372	0.59
RPB4	30.580±10.677	12.761±2.754	0.0001	21.675±4.874	39.486±6.689	0.0001

Diabetic retinopathy patients were positively associated with FBG (P.value 0.04) and had a stronger relationship with Urea and RBP4 (P > 0.01) and this was confirmed by Takele et al., in their study. Whereas, there was no association of diabetic retinopathy with eGFR, creatinine, and uric acid, which was agreed with by Sullivan et al. In addition, HBA1C (p < 0.05) compared with diabetic without retinopathy was not statistically significant.[15] These outcomes are consistent with the research conducted by Sullivan et al., Who explained that the results of the (GFR) were low for patients with diabetes in comparison to the control group and this difference was of high statistical significance (HS) (P>0.01) [16]. Increased blood sugar levels can affect how hemodynamics and metabolic variables interact. Atypical glucose metabolism results in the activation of intracellular cytokines, the (PKC) protein kinase C enzyme, and cytokines, which raise intrarenal pressure, an elevation in vascular permeability, and lower eGFR.[17] While, The results were compatible with the conclusions of Babaliche et al., who proved that the increase in the percentage of (GFR) when comparing diabetic retinopathy patients (DR) with patients without retinopathy (DWR) was not statistically significant (NS). [18]. The findings agreed with those of Zhuang et al., who discovered a statistical (HS) between the urea levels in patients and the control group.[19] The findings was are similar of showed Omar et al., who that urea levels in DR were higher than in control (HS). Although the possibility that elevated urea levels are a risk factor for the condition, diabetic retinopathy is also significantly influenced by other variables, including blood sugar control and cholesterol levels. [20]. While when comparing between the control and the patient groups, the difference in creatinine was (HS) and this is consistent with the finding of what Kocak et al..[21] When blood glucose levels are uncontrolled in people with diabetes, This could result in kidney blood vessel damage. causing a condition called diabetic nephropathy. Diabetic nephropathy can impair the kidneys' ability to filter out waste products like urea and creatinine, resulting in an increase in the blood. Therefore, an increase in urea and creatinine levels in people with diabetes

may indicate reduced kidney function, which is a common complication of uncontrolled diabetes. These markers are often used to monitor the progression of diabetic nephropathy and the overall health of the kidneys.[22]. It is important to note that an increase in urea and creatinine levels can also be caused by factors other than diabetic nephropathy, such as dehydration, certain medications, or liver disease. Therefore, healthcare providers may use additional tests, such as (eGFR) and urine albumin-to-creatinine ratio, to assess kidney function and to determine the underlying cause of the elevated levels. Managing B.glucose levels, blood pressure, and maintaining a healthy lifestyle can help prevent or slow down the progression of diabetic nephropathy and reduce the risk of Renal failure. Therefore, working with their healthcare professional to manage their illness and routinely check their kidney function is crucial for people with diabetes.[23] But when comparing the results of patients (DR) with (DWR), the results were of non-statistical significance, and this is reached by Tomita et al., in the previous study to the creatinine levels showed (NS) differences between the two groups. [24] The current study agrees with the study done by Hameed et al., who don't detect statistically significant (NS) variations between patients' uric acid levels When comparing the DR with DWR and the control group. [25] These findings concur and corroborate those of Omar et al., who demonstrated that fasting blood sugar in diabetic patients was greater than in controls, this increase was statistically highly significant (HS). [26] This was confirmed by Huang et al., in their study, in which they concluded that the level of fasting blood glucose in DR patients was larger than the diabetic without retinopathy, this increase was statistically highly significant (HS). [27]. A significant relationship exists between FBG levels, DR, and High blood sugar levels can harm the tiny blood vessels in the retina, which results in diabetic retinopathy. In uncontrolled diabetes with persistent hyperglycemia, the generation of advanced glycation end products (AGE) is enhanced. which contributes to the development of DR. [28] These conclusions are in line with those of Jabbar J. et al., who discovered that the HBA1c in diabetic patients was greater than in the control. The amount of glycated hemoglobin rises together with the FBG level. HbA1c is a dependable indicator of glucose control across red blood cell life, which is typically 120 days.[29] Furthermore, the study by Reid et al. agrees with this study and shows that The HbA1c at follow-up did (NS) impact the progression of diabetic retinopathy when Comparison with the DWR.[30] In the current study, diabetes patients had considerably higher circulating RBP4 than the control group, and this finding was consistent with Jia Ying Chen et al,. [31]. The liver is the main producer of retinol-binding protein 4, which is responsible for moving retinol (vitamin A) through the blood. A rise in RBP4 levels has occasionally been noted in people with (DR), an eye-related consequence of diabetes. There is a relationship between increased levels of RBP4 and DM. Patients had higher levels of RBP4 in their blood than non-diabetics. High levels of RBP4 have been associated with insulin resistance, a common feature of type 2 diabetes. Also, high levels of RBP4 can interfere with insulin signaling pathways, leading to decreased insulin sensitivity. [32]. In addition, RBP4 has also been linked to the development of diabetes complications such as diabetic retinopathy, which is damage to blood vessels in the retina that can lead to vision loss. therefore, monitoring RBP4 levels in diabetic patients may provide insight into the risk of developing insulin resistance and diabetes complications. However, more research is needed to fully understand the role of RBP4 in diabetes and its complications. Resistance of insulin can contribute to the development of DR, so RBP4 may play important role in this process during increased inflammation and oxidative stress, both of which have been implicated in the development of DR. This is found Takebayashi et al,.that increased RBP4 is strongly associated with DR, and this is we confirmed in our current study.[33]

3.6 RBP4's Receiver Operational Characteristic (ROC) curve contrasting the patient group with the control group.

In Fig.(1) and table (3) the cutoff value for RBP4 was >29.15 with 94% sensitivity and 100% specificity, according to the (ROC) curve of the level between the patient group and the Control group. having an Area Under the Curve (AUC) of 0.978 and highly significant (P>0.01HS).

Table (3): (ROC) of RBP4 ng/ml.

Variables	Cut-off value	Accuracy	AUC	Sensitivity %	Specificity %
RBP4	**>29.15**	**0.9400**	**0.978**	**94.00**	**100.00**

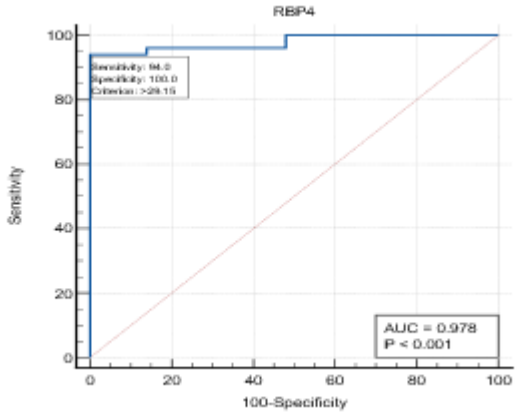

Fig (1): ROC curve of RBP4 among the Control group with the patient group

4. Conclusions

Elevated levels of RBP4 and FBG have been consistently associated with the severity of DR, while the relationship between urea and retinopathy is less clear. These biomarkers might help assess the risk of DR and track the condition's development. However, further study is needed to fully understand their role in the progression of this complication.

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