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linkage between the duration of diabetes mellitus type-2 with the biochemical measurements and the extent of chronic complications

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Abstract

Background: Retinopathy in Type 2 Diabetes Mellitus (T2DM) is characterized by damage to the blood vessels in the retina, as a result of diabetes-related effects diabetic retinopathy (DR) is a noteworthy complication of diabetes. **Objective:** Studying the effect of the duration of type 2 diabetes on some biochemical parameters in the blood and their relationship to the extent of chronic complications such as retinopathy. **Methods**: 131 Individuals of both sexes, aged between 41 and 78 years, diagnosed with type 2 diabetes mellitus. The number of T2DM with retinopathy was (68) including (36) females and (32) males, while T2DM without retinopathy was (63) including (28) females and (35) males. Certain biomarkers were evaluated such as HbA1C, Creatinine, fasting serum glucose (FSG), Cholesterol, triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL). Statistical analysis was conducted using a t-test to compare two parameters in the same group or between the studied groups. **Results**: The findings indicate significant correlations among different biomarkers in the studied groups DR and DM, also (P value) and Pearson correlation (r) values show a relationship between biomarkers and retinopathy complications. **Conclusions**: There are notable correlations between creatinine levels and the duration of the disease in both the studied groups DR and DM, also there are highly significant correlations observed between HbA1C levels, creatinine, and the duration of diabetes mellitus (DM) without retinopathy, and this may be considered as a risk factor for the occurrence of retinopathy complication in a long duration of diabetes mellitus disease.

Keywords: T2DM duration, creatinine, retinopathy.

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1. INTRODUCTION

Type 2 Diabetes, or (T2DM), is a disorder in a metabolic condition that is usually marked by insulin resistance and diminished insulin secretion by which the body's cells exhibit reduced responsiveness to insulin, resulting in higher levels of glucose in the bloodstream (1,2). Below are the essential aspects of T2DM (3-7).

❖ **Insulin Resistance:** In type 2 diabetes, cells develop insulin resistance, (the essential and main hormone for blood sugar regulation), this resistance imposes a challenge for cells to effectively absorb glucose from the bloodstream.

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❖ **Impaired Insulin Secretion:** As time progresses, the pancreas (the gland that is responsible for insulin production), might need great effort to release a sufficient quantity of insulin to counteract the resistance, this exacerbates the increases in blood glucose levels.

❖ **Beta-Cell Dysfunction**: In the early stages, there's a compensatory boost in insulin production to uphold regular glucose levels. Nevertheless, with the advancement of the disease, beta cells undergo changes, causing a shortfall in insulin secretion and resulting in hyperglycemia.

❖ **Obesity and Lifestyle Factors**: The majority of individuals with type 2 diabetes are overweight or exhibit a higher body fat percentage, especially around the abdominal area. The worldwide surge in obesity, sedentary habits, and the consumption of high-calorie diets has played a significant role in the escalating occurrence and prevalence of type 2 diabetes.

❖ **Risk Factors**: The development of type 2 diabetes is influenced by various factors, encompassing obesity, genetics, one's ethnic background, and advancing in age.

T2DM is a chronic condition disease that typically lasts for a lifetime, however, the progression of T2DM can vary from person to person.

A study was carried out by Greenhill 2017 to find the correlation between T2DM and sleep in children, he did his study on 4525 children, and he suggested that increasing the duration of sleep could lead to lowering body fat levels and diminishing the risk of Type 2 diabetes from an early age (7).

Schlienger 2013 mentioned that individuals diagnosed with type 2 diabetes face an elevated risk of numerous complications, primarily stemming from intricate and interlinked mechanisms like hyperglycemia, insulin resistance, low-grade inflammation, and accelerated atherogenesis. Conditions such as cardiocerebrovascular disease are commonly linked to type 2 diabetes and can pose life-threatening risks, especially coronary artery disease, heart failure, and stroke (9, 10).

In 2015, another study was carried out by Nentwich and Ulbig, they mentioned that in developed countries, diabetic retinopathy stands as the prevailing microvascular complication of diabetes mellitus and represents the primary cause of blindness among individuals of working age. They found that the primary causes of vision loss in individuals with diabetes mellitus are diabetic macular edema and proliferative diabetic retinopathy. Adequate control of blood glucose and blood pressure levels can significantly reduce the incidence or progression of these potentially blinding complications. Regular ophthalmic exams are essential for early detection of ocular issues, allowing for timely initiation of treatments such as laser photocoagulation in cases of clinically significant diabetic macular edema or early proliferative diabetic retinopathy. This approach substantially reduces the risk of blindness. In advanced stages of diabetic retinopathy, pars-plana vitrectomy is performed to address vitreous hemorrhage and tractional retinal detachment (11).

Bui et al., 2019 studied the effect of prolonged exposure to high blood sugar and how this can lead to damage in small blood vessels, individuals with an extended history of type 2 diabetes mellitus (T2DM) are at a higher risk of experiencing harmful microvascular complications. These complications include retinopathy, neuropathy, and nephropathy, posing significant threats to human health. The researcher did their study from November 2015 to January 2016, a cohort of 4,490 patients from both sexes (male and female) diagnosed with type 2 diabetes mellitus (T2DM), those patients were chosen from 8 hospitals in Tianjin, China. The outcomes of the multivariate logistic regression revealed that the duration of diabetes, insulin utilization, and the existence of hypertension and dyslipidemia emerged as the primary risk factors

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associated with the onset of microvascular complications in individuals with type 2 diabetes mellitus (T2DM) (12).

High blood sugar levels in people with type 2 diabetes can harm the tiny blood vessels in the retina, the light-responsive tissue at the rear of the eye. Such damage can give rise to diabetic retinopathy, a situation that might cause vision issues and, if not addressed, eventual blindness. Hafeez et al., 2022 by which 200 individuals diagnosed with type 2 diabetes for over 5 years, 28% exhibited diabetic retinopathy, while 59% showed signs of peripheral neuropathy. Interestingly, peripheral neuropathy was twice as prevalent as retinopathy. Among those with uncontrolled diabetes, 33.1% had retinopathy, and 65.46% had peripheral neuropathy (13).

The current study aimed to find the effect of the duration of T2DM on some biochemical parameters in the blood and their relationship to the extent of chronic complications, particularly retinopathy complications.

1. Patients and Methods

2.1. Study Population Patients

This study includes 131 patients of diabetes mellitus type 2, who were divided into two groups according to the presence or absence of retinopathy complications associated with diabetes mellitus. The number of T2DM with retinopathy was (68) including (36) females and (32) males, while T2DM without retinopathy was (63) including (28) females and (35) males.

Patients were selected from the Specialized Center for Endocrinology and Diabetes in Al Kindi Hospital in Baghdad, for the period from January to November 2023. All patients were diagnosed by history taking and clinical examination by specialist doctors. Retinopathy was diagnosed by an Ophthalmologist.

2.2 Sample selection

Patients with diabetes mellitus type 2, of age range (41-78) years old, of both sexes.

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Patients of diabetes mellitus who met the exclusion criteria of ages less than 40 years old, pregnant women, had other types of eye diseases or intraocular therapies and surgeries; patients with CVD, malignancies, kidney diseases, thyroid diseases, and chronic inflammation.

2.3 Data collection and outcome measurements

5 ml of venous blood samples were taken from all patients after an overnight fast; 3 ml was placed in a gel tube for analysis of FSG, creatinine, and lipids; left for 10 minutes to clot at room temperature then centrifuged at 3000 rpm for 10 minutes to obtain serum. The remaining 2 ml of blood was placed in an EDTA tube for HbA1C assay. The main supplier for analyzing kits was Roche/ Germany and Biolabo/ France origins; using Cobas C111 and Bio-Rad D-10/ HPLC for HbA1C analysis, whereas Cobas C311 system and autoanalyzer used for glucose, creatinine, and lipid profile determination. The principles of analysis were enzymatic-colorimetric in general.

Ethical permission was granted by the Department of Scientific Affairs' Ethical Permission Committee.

Statistical analysis

Use IBM SPSS statistics version 20.0 to compute the measured parameters and estimate the effect of certain factors and their correlations to the study hypothesis, anticipating independent samples t-test, Pearson correlation, ROC-analysis, and the probability for evaluation of significance at p-value ≤ 0.01 and ≤ 0.05.

3. RESULTS AND DISCUSSION

The demography of the study is represented in Table 1 showing all the parameters measured in T2DM individuals with and without retinopathy according to gender. Table 1 represents the demography of the study, by comparing diabetes mellitus with retinopathy (DR) and diabetes mellitus without retinopathy (DM); the statistics outline a significant difference in the age between males and females in

the DR group with a p-value of 0.013; the mean values were 56.53±8.64 for males while it was 62.056±9.13 in females indicating the age of males with DR is lower than DR females, and also there is a significant difference between DR and DM women in their ages showing values 62.056±9.13 and 55.18±8.28 respectively which indicate that the age of DR women is higher than DM women. The table also shows that the number of females with DR is higher than males (36 and 32 with a duration of 14.16 and 10.169 respectively), this finding was confirmed by Li et al., 2020 who mentioned that, in individuals with T2DM, the occurrence of DR was more common among females than males; particularly in those of mean ages over 60 with duration over 10 years, may include the role of estrogen in shielding RGC-5 cells from injury caused by excessive glucose through the mitochondrial route. Furthermore, estrogen was discovered to perform a safeguarding role by lowering vascular resistance in major ocular veins and to be an essential controller of circulation in the retina (14).

Table 1 also declares that the values of FSG and HbA1C in DR females are 215.4 and 9.68 respectively, while in DR males the values are 200.88 and 9.57 respectively with highly significant (P-value 0.001) differences in the level of HbA1C between the two sexes in DM group, these findings are similar with the results obtained by Stimson et al., 2020 who find that males exhibited a notably lower HbA1c level compared to females (15).

The level of Creatinine in DR males and females shows the mean values 0.965±0.34 and 0.802±0.22 indicating a reduced level in women than men with a significant value 0.021. T2DM group is associated clinically with a lower-than-normal level of creatinine in both males and females, however, the significance in DR is much higher in males than females, this result matches with the findings of Song and his colleague that low blood creatinine levels brought on by weakened skeletal muscle may be linked to an increased risk of T2DM (16).

Cholesterol in DR males and females is higher in DR patients (178.4 and 175.56 respectively) than in DM patients (150.97 and 151.08 respectively) this indicates that controlling the level of cholesterol must keep it at a low level to prevent the risk of retinopathy, this result match with a study conducted by Popescu and Moța, 2009 who mentioned that there is a significant correlation between retinopathy and dyslipidemia, indicating that the implementation of systemic lipid-lowering therapy in individuals with T2DM is advantageous for those with retinal changes, aiming to prevent visual impairment (17).

This study also found a significant difference in TG between DR and DM patients with values 186.26 vs. 106.79 in males, and 167.05 vs. 102.45 in females respectively, while the HDL shows a significant difference (P value ≤ 0.01) in males and doesn't show it in women. As for VLDL and LDL, the current study indicates significant differences between DR and DM in both males and females (P-value ≤ 0.01) for VLDL and (P-value ≤ 0.05) in LDL, these findings are similar to other studies (18-21).

Table 2 presents the data comparison between the studied groups and within each group depending on the duration of diabetes mellitus disease (cutoff value ten years). Table 2 display comparison of measured parameters between the studied groups depending on the illness durations (≤ 10 or >10 years); indicating no significance (P-value > 0.05) in the ages of patients, except highly significant (P-value ≤ 0.01) difference within the DR group; while the duration has a significant effect particularly when it is over 10 years (mean values were 16.22±4.25 for DR and 13.50±2.37 for DM) with (P-value = 0.012), this result is match with the finding of Voigt et al. 2018 who mentioned in their results that the duration of the diseases increase the possibility of the occurrence of retinopathy which is

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usually based on the duration of diabetes, stood at 1.1% during diagnosis, 6.6% within less than 5 years, this percent increased to 12% for T2DM between 5 to 10 years, and reached to 24% spanning 10 to 15 years, and came up to 39.9% after 15 to 20 years, 52.7% following for patients after 20 to 25 years, and reached to 58.7% after 25 to 30 years, and peaked at 63% after 30 years or more (22). In addition, it appears that the duration of the disease has an obvious effect as the results reflect significant differences in the mean of the duration of illness between the sub-groups of the studied groups.

The fasting serum glucose (FSG) shows significant differences (P-value < 0.01) between the studied groups of illness's duration ≤ 10 years, with a mean value of 208.59 for DR patients and 140.94 for DM, this finding matches with a study carried out by Ranganathan et al., 2022 who found that elevated fasting blood sugar levels were linked to the presence of diabetic retinopathy (23).

In the current study, the HbAIC shows a significant difference for duration less and more than 10 years with p-values (0.001 & 0.037 respectively), due to its importance as the main factor that causes retinopathy which was also approved by other researchers (24,25).

Whereas, creatinine does not show significant differences between the studied groups depending on the duration of the illness, unless in the DM (P value = 0.009), and it's near to significance (P value = 0.059) in DR, however a study conducted by Mujeeb et al. 2021, that was aimed to examine the ratio of urine protein (UP) and urine creatinine (UC) in diabetes mellitus and its impact as a risk factor for both the occurrence and severity of diabetic retinopathy (DR) find that the urine protein-to-creatinine ratio (PCR) can serve as an indicator for the risk and advancement of diabetic retinopathy (26).

Significant differences in cholesterol levels between DR and DM (P-values 0.001 and 0.029 accordingly for less and over 10 years duration of the disease), this result of the current study matches with the finding of Hammer et al. 2023, they found that the accumulation of cholesterol and the formation of cholesterol crystals (CC) constitute a unified pathogenic mechanism in the progression of diabetic retinopathy due to inflammation and microglia activation that lead to cell death (27).

The triglyceride TG analysis shows a highly significant difference between DR and DM patients (P-values 0.001 and 0.008 respectively for less and over 10 years duration), this was also depicted by Srinivasan et al. 2020, who found that elevated TG/Glucose index levels are correlate with the existence of retinopathy and nephropathy in people with diabetes, suggesting its potential utility for monitoring metabolic status in clinical settings, thought that TG may be connected to endothelial dysfunction and lipid peroxidation, which are related to retinal difficulties in diabetes and microvascular issues (28).

While the HDL doesn't show any significant differences between the study groups in correlation to the duration of the disease. In the current study no matter how long the duration (less or more than 10 years), which is opposite to the finding of a study carried out by Kostapanos and Elisaf in 2014, they found that individuals with T2DM not only display reduced levels of HDL-C but also experience dysfunctional HDL. Moreover, a diminished concentration of HDL may elevate the susceptibility to developing T2DM by impairing β cell survival and secretory function (29).

Regarding VLDL, the present study reveals highly significant differences between the study groups with P-values ≤ 0.01 for less and more than 10 years duration, while the LDL shows a significant difference only in patients with less than 10 years duration which matches with the finding of a study carried out by Bonilha et al. 2021 who find that in individuals with T2DM, atherosclerotic disease

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progresses earlier, influenced by changes in LDL metabolism (30).

Another study finds that substantially low LDL-C levels without statin intervention were notably linked to an elevated risk of T2DM, the connection between very low LDL-C levels unrelated to lipid-lowering therapy and the likelihood of developing T2DM will be crucial [31].

Table 3 represents the correlation between the parameters in DR and DM groups. Table 3 shows the relationships between the observed variables within the examined groups, all the variables indicate a significant correlation between the biomarkers and the retinopathy; all p-values are below 0.05, as for Pearson Correlation (r), all the values are below the range ± 1 indicating the significant correlations between the biomarkers and the DR as well as with DM. There is a significant correlation between age and duration with a p-value (of 0.017), and (r) value (of 0.638), this finding is similar to the finding of Jenchitr et al., 2004 (32) who mentioned that the severity of retinopathy was not only associated with an extended duration of diabetes but also correlated with elevated glycosylated hemoglobin levels, increased systolic blood pressure, and the presence of proteinuria. These findings also match with the findings of the current study regarding HbAIC with p-value (0.001) and r-value (-0.429). This conclusion was also applied in DM patients with p-values (of 0.04, and 0.001), while the r-value shows 0.356, and 0.611 for the duration with age and HbAIC respectively.

The correlation among Creatinine with Age, duration, and HDL was also detected in current research showing a significant correlation with p-values (0.023, 0.032, and 0.042), r-values were (0.275, 0.261, and -0.248) respectively for DR; while for DM, the p-values for Creatinine with duration, and HbA1C were (0.002 and 0.005), and r-values (0.381 and 0.348) respectively, which is the same findings of Zhang et al., 2018 (33) who concludes in their study that variability in serum creatinine and estimated glomerular filtration rate is linked to the presence and severity of diabetic retinopathy, irrespective of intra-individual means.

Table 4 shows the ROC analysis by which positive actual is stated in the DR group. Our study demonstrates in Table 4 the top three markers as discriminators between DR and T2DM, those are the duration of the disease, HbA1C, and creatinine. At AUC (0.767), the duration of the disease highlights two cutoff points (9.50 and 10.50) at which any value higher than either of the two points is encouraging for retinopathy, 73-84% of patients without retinopathy, conversely 60-70% are accurately DR. In turn at (0.865) AUC, HbA1C was confidently distinguished between DR as positive instances and T2DM patients without retinopathy as negative events were 93% of patients truly diagnosed with retinopathy, and 63 % of patients were precisely categorized as DM without retinopathy. On the other hand, at AUC (0.66), the third biomarker creatinine plays an important differentiator factor between the studied groups at which 62% of patients DM without retinopathy and 71% are DR with lower cutoff value than normal (0.71).

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Table (1): Biochemical parameters assessed in Males and Females of the study groups

Measured Parameters	DR group			DM Group			
	Sex	**N**	**Mean ± Std. D**	**Sex**	**N**	**Mean ± Std. D**	**Significance [b]**
Creatinine	Male Female **Significance[a]**	**32** **36**	0.965±0.34 0.802±0.22 **0.021***	Male Female **Significance[a]**	**35** **28**	**0.797±0.26** **0.73±0.23** **0.25**	**0.025*** 0.179
HbA1C	Male Female **Significance[a]**	**32** **36**	9.57±2.16 9.68±2.10 **0.84**	Male Female **Significance[a]**	**35** **28**	6.42±1.24 7.26±1.63 **0.03***	**0.001**** **0.001****
Age	Male Female **Significance[a]**	**32** **36**	56.53±8.64 62.056±9.13 **0.013***	Male Female **Significance[a]**	**35** **28**	53.08±6.79 55.18±8.28 **0.275**	0.07 **0.003****
Duration	Male Female **Significance[a]**	**32** **36**	10.169±6.15 14.16±5.96 **0.009****	Male Female **Significance[a]**	**35** **28**	6.00±3.79 7.25±4.76 **0.25**	**0.001**** **0.001****
FSG	Male Female **Significance[a]**	**32** **36**	200.88±83.67 215.4±80.04 **0.47**	Male Female **Significance[a]**	**35** **28**	138.23±53.24 160.47±56.13 **0.22**	**0.001**** **0.002****
HDL	Male Female **Significance[a]**	**32** **36**	38.92±8.14 44.49±12.06 **0.028***	Male Female **Significance[a]**	**35** **28**	47.79±8.57 46.28±8.88 **0.50**	**0.001**** 0.513
TG	Male Female **Significance[a]**	**32** **36**	186.26±92.70 167.05±93.79 **0.40**	Male Female **Significance[a]**	**35** **28**	106.79±56.72 102.45±31.69 **0.72**	**0.001**** **0.001****
Cholesterol	Male Female **Significance[a]**	**32** **36**	178.4±44.28 175.56±49.13 **0.80**	Male Female **Significance[a]**	**35** **28**	150.97±30.29 151.08±25.84 **0.988**	**0.004**** **0.013***
VLDL	Male Female **Significance[a]**	**32** **36**	37.25±18.54 33.41±18.76 **0.40**	Male Female **Significance[a]**	**35** **28**	22.24±11.74 21.85±8.10 **0.881**	**0.001**** **0.002****
LDL	Male Female **Significance[a]**	**32** **36**	104.31±41.21 99.39±36.93 **0.605**	Male Female **Significance[a]**	**35** **28**	82.05±29.93 84.12±22.18 **0.76**	0.013* 0.045*

a: Significance between sexes in each of the studied groups b: Significance in sexes between the studied groups. *: significant differences at p-value ≤ 0.05; **: highly significant differences at p-value ≤ 0.01.

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Table (2): Comparison of illness duration between the study groups

	DR group			DM Group			
	Duration	**N**	**Mean ± Std. D**	**Duration**	**N**	**Mean ± Std. D**	**Significance [a]**
Creatinine	≤ 10 >10 **Significance**	27 41	0.81±0.16 0.93±0.35 **0.059**	≤ 10 >10 **Significance**	53 10	0.73±0.18 0.95±0.42 **0.009****	0.062 0.873
HbA1C	≤ 10 >10 **Significance**	27 41	9.71±2.11 9.58±2.14 **0.811**	≤ 10 >10 **Significance**	10 53	6.56±1.36 8.04±1.48 **0.013***	**0.001**** **0.037***
Age	≤ 10 >10 **Significance**	27 41	53.18±6.64 63.58±8.43 **0.001****	≤ 10 >10 **Significance**	53 10	53.07±6.63 59.00±10.02 **0.101**	0.945 0.206
Duration	≤ 10 >10 **Significance**	27 41	6.29±3.71 16.22±4.25 **0.001****	≤ 10 >10 **Significance**	53 10	5.25±3.10 13.50±2.37 **0.001****	0.213 **0.012***
FSG	≤ 10 >10 **Significance**	27 41	208.59±89.95 208.57±76.56 **0.999**	≤ 10 >10 **Significance**	53 10	140.94±52.24 186.13±57.78 **0.04***	**0.001**** 0.328
HDL	≤ 10 >10 **Significance**	27 41	43.66±12.54 40.69±9.28 **0.267**	≤ 10 >10 **Significance**	53 10	47.24±7.89 46.49±12.56 **0.806**	0.184 0.105
TG	≤ 10 >10 **Significance**	27 41	168.31±76.62 181.21±103.10 **0.557**	≤ 10 >10 **Significance**	53 10	107.63±50.38 90.21±15.93 **0.048***	**0.001**** **0.008****
Cholesterol	≤ 10 >10 **Significance**	27 41	178.85±40.13 175.64±50.84 **0.783**	≤ 10 >10 **Significance**	53 10	152.52±26.70 143.07±35.62 **0.442**	**0.001**** **0.029****
VLDL	≤ 10 >10 **Significance**	27 41	33.66±15.32 36.24±20.62 **0.557**	≤ 10 >10 **Significance**	53 10	22.72±10.93 18.62±3.47 **0.032***	**0.002**** **0.01****
LDL	≤ 10 >10 **Significance**	27 41	101.45±38.03 101.87±39.74 **0.965**	≤ 10 >10 **Significance**	53 10	81.99±27.28 88.16±23.13 **0.466**	**0.01**** 0.166

a: Significance between subgroups of the main study groups; *(P<0.05): Significant
****(P< 0.01): Highly significant**

Table (3): Correlations among measured parameters within the studied groups

Correlations within DR			Correlations within DM		
Parameters	**Significance (P value)**	**Pearson Correlation (r)**	**Parameters**	**Significance (P value)**	**Pearson Correlation (r)**
Duration * Age	0. 017	0.638**	Duration * Age	0.04	0.356**
Creatinine * Duration	0.032	0.261*	Creatinine * Duration	0.002	0.381**
Creatinine * Age	0.023	0.275*	HbA1C Duration	0.001	0.611**
HbA1C * Age	0.001	-0.429-**	Creatinine * HbA1C	0.005	0.348**
Creatinine * HDL	0.042	-0.248-*	TG * HbA1C	0.011	0.320*
			VLDL * Duration	0.028	0.278*
** Correlation is significant at the 0.01 level (2-tailed) * Correlation is significant at the 0.05 level (2-tailed)					

Table (4): The ROC analysis

Parameters	Cutoff point	Sensitivity	Asymptotic Significance [b]	specificity	AUC
Duration	9.50	0.706	0.001	0.730	0.767
	10.50	0.603		0.841	
HbA1C	6.65	0.93	0.001	0.635	0.865
Creatinine	0.71	0.71	0.002	0.62	0.660
The positive actual state is DR. AUC: Area Under the Curve; b. Null hypothesis: true area = 0.5					

4. CONCLUSION

There is a significant correlation between creatinine and the duration of the disease in DM with and without retinopathy. Highly significant correlations between HbA1C with creatinine and the duration of the DM disease without retinopathy may be considered as risk factors for the occurrence of retinopathy complications on long duration of DM disease. In addition to the presence of discrepancies in the creatinine levels in DM and DR groups.

RECOMMENDATION

This study highlights the necessity of measuring the creatinine level as a routine analysis in diabetic patients, especially when its level is 0.71 mg/dl, with a duration of the disease exceeding 9.5-10.50 years and an HbA1C level of more than 6.65%.

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