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Assessment of Serum Interleukin-29 Level in Patients with Diabetic Retinopathy: Case-Control Study

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Abstract:

Background: Diabetic retinopathy (DR) is a frequent consequence of diabetes and the largest cause of blindness among people in general. Diabetic retinopathy is a diabetic complication that happens in type 2 diabetes individuals who do not control their serum glucose levels. This condition is accompanied with inflammation in the ocular tissues.

Interleukin-29 (IL-29), a member of the type 3 interferon family, is involved in host defenses against microorganisms; however, little is known regarding its function in metabolic diseases. IL-29 had a crucial role in the etiology of diabetes-induced inflammation and insulin resistance.

Aim of the study: This research aims to assess the serum Interleukin-29 levels in the sera of type 2 diabetic retinopathy compared to diabetic patients and healthy participants.

Materials and Methods: A case-control study was carried out on 96 volunteers within ages (33-70) years old who were split into three groups 27 healthy control (HC), 36 patients with T2DM, and 33 patients with type II diabetic retinopathy (DR) patients. Serum levels of IL-29 and fasting insulin (FI) were measured by Enzyme-Linked Immunosorbent Assay (ELISA).

Results: The T2DM and DR groups exhibited a non-significant age difference; however, a slight BMI difference was observed between the patient and healthy individual groups. There was no significant difference in FSG among patient groups ($P = 0.672$); however, the T2DM and DR groups exhibited a significant difference when compared to healthy controls ($P<0.001$). Analysis of IL-29 levels among T2DM, control, and DR groups demonstrated significant differences ($P<0.001$). This study investigated the correlation between IL-29 and clinical biomarkers. FSG and HOMA-IR exhibited positive correlations with IL29 ($r = 0.374$, $P<0.032$, $r = 0.356$, $P = 0.042$, respectively), While IL-29 showed no statistically significant negative correlation in the DR patients group. The IL-29 ROC curve demonstrated an AUC of 0.849, signifying enhanced accuracy and stability in the diagnosis and stratification of diabetic retinopathy, with a cut-off value of 28. 46 pg/ml ($P<0.001$). The sensitivity of these variables is 0.909, while the specificity is 0. 667.

Conclusion: The study demonstrated that patients with diabetic retinopathy exhibited elevated serum interleukin-29 levels in comparison to both diabetic and healthy control groups, suggesting its potential involvement in the progression and pathogenesis of diabetic retinopathy as a predictive risk factor for this complication.

Keywords: Interleukin-29, type II diabetes mellitus, and diabetic retinopathy.

1. Introduction:

Diabetes Mellitus, also referred to as diabetes, is a chronic metabolic condition characterized by

elevated serum glucose levels resulting from inadequate insulin synthesis, poor insulin utilization, or a combination of both. Insulin, a hormone produced by the pancreas, facilitates glucose absorption into cells, hence regulating serum glucose levels. Hyperglycemia transpires when the body either insufficiently produces insulin or develops resistance to its effects, resulting in the accumulation of glucose in the bloodstream ***(1, 2)***. Insulin resistance in type 2 diabetes mellitus, a heterogeneous condition, is characterized by varying degrees of insulin secretory abnormalities, subsequently leading to diminished pancreatic insulin production due to pancreatic beta-cell dysfunction. The correlation between pregnancy and gestational diabetes stems from a transient impediment to glucose use. Post-delivery, the irregular glucose metabolism frequently reverts to its usual condition. Pregnancy induces a rise in the production of insulin antagonists, resulting in heightened secretion and release of insulin. Gestational diabetes occurs when the pancreas is impaired and fails to produce adequate insulin to satisfy increased bodily requirements ***(3)***. Due to insufficient insulin secretion or activity, individuals with diabetes are unable to effectively metabolize glucose and synthesize fatty acids and triglycerides from carbohydrates or amino acids. In non-diabetic persons, the suppression of enzymes in the pentose phosphate, glycolytic, and lipogenic pathways results in heightened gluconeogenic, glycogenolytic, and lipolytic activity. This mechanism reverses the metabolic pathway as the cells are unable to recognize and absorb glucose in the bloodstream. Established associations exist between hereditary factors, raised glucose levels, hypertension, obesity, oxidative stress, dyslipidemia, and smoking, all contributing to an increased risk of morbidity and mortality from vascular complications in individuals with diabetes ***(4, 5)***.

Microvascular problems include Diabetic Retinopathy, a condition characterized by visual impairment and blindness due to damage to the retinal blood vessels. It is the principal cause of blindness in individuals of working age ***(6)***. Diabetic neuropathy presents with nerve degeneration characterized by pain, tingling, numbness, and reduced sensory awareness, especially in the limbs. Autonomic neuropathy can result in physiological impairments in the gastrointestinal, genitourinary, cardiovascular, and other body systems ***(7-9)***. Macrovascular problems encompass cardiovascular disease, a diabetes condition that markedly elevates the risk of peripheral arterial disease, myocardial infarction, coronary artery disease, and stroke. Individuals with diabetes possess a two to fourfold increased risk of acquiring cardiovascular disease relative to individuals without the ailment ***(10, 11)***. Peripheral vascular disease is characterized by atherosclerosis, resulting in insufficient blood supply to the extremities, hence increasing the risk of lower limb amputations, peripheral neuropathy, and compromised wound healing ***(12)***.

Interleukin-29 (IL-29) is a recently identified type III interferon. Binding to its receptor complex amplifies signal transmission, activates subsequent signaling pathways, and thus triggers the creation of inflammatory markers. Recent findings indicate that inflammatory autoimmune illnesses, including rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis, Sjögren's syndrome, psoriasis, and systemic sclerosis, exhibit dysregulated expression of IL-29 ***(13, 14)***. Moreover, functional studies indicate that IL-29 may have a role in the progression of inflammatory autoimmune diseases. This analysis will methodically assess the current understanding of IL-29 ***(15, 16)***. The obtained findings demonstrated the regulatory function of IL-29 and its significant influence on the medication's efficacy. IL-29 has attracted much interest. Recent discoveries indicated that certain tissues produced IL-29 autonomously and exhibited unique reactions to IL-29 ***(17)***. Tumor cells, intestinal epithelial cells, T lymphocytes, and dendritic cells exhibit the interleukin-29 receptor. Significant discourse has emerged on the essential function of IL-29 in lung cancer and its prospective application in therapeutic strategies ***(18)*****.** IL-29 is essential for host defense against pathogens and is elevated in cells infected by viruses. IL-29 exhibits antitumor efficacy in several malignancies, including lung cancer, esophageal carcinomas, and colorectal cancer ***(19)***.

2. Materials and Methods:

Study design: A case-control study design and all the samples of subjects were collected with in between August and November of 2023.

Ethical Approval

This study was approved by the regional ethical committee of the University of Kufa, Faculty of Science Institutional Ethics board (1422 on 9/4/2023) informed consent was obtained from participants.

Subjects

***Patients*:** This investigation involved two patient groups of patients with ages (33-70) years which included 69 Patients; the first group consisted of 36 (14 Males: 22 Females) patients with type 2 diabetes mellitus without complications were collected from Al-Manathera Hospital at AL-Najaf, Iraq. Thirty-three (12 Males: 21 Females) individuals with type II diabetic retinopathy, all DR samples were collected within the period from August-November of 2023 at Al-Sader Medical City-Eye surgery room in AL-Najaf Governorate Each patient was diagnosed according to WHO criteria by the eye surgeon. Patients were assessed according to their medical histories to determine the presence of any systemic illnesses that could affect the examined parameters. Individuals with liver, heart, thyroid disorders, or uncontrolled hypertension were excluded from the study. The regional ethics committee of the Faculty of Science at the University of Kufa accepted the study.

Controls: Twenty-seven apparently healthy person volunteers (13 male: 14 female) were included in this study as a healthy control. Their ages and sex were approximately the same as those of patients.

Blood samples

Five milliliters of venous blood were extracted from each patient or control group utilizing disposable syringes equipped with single-use needles. The gel tube contained the blood samples. Blood samples were permitted to clot for fifteen minutes at ambient temperature before to centrifugation for ten minutes at 4000 rpm. The serum was subsequently separated and divided into four Eppendorf tubes (the hemolysis samples were discarded) and stored at -20 °C until analysis was finalized.

Biochemical Investigations

Human IL-29 ELISA reagent kits were purchased from Melsin Medical Co., human insulin ELISA kits were purchased from Nanjing Pars Biochem CO., and fasting serum glucose (Glucose-LQ). Cholesterol-LQ (CHOD-POD.) HDL Cholesterol P was purchased from SPINREACT, and the last one was Triglycerides – Liquizyme GPO-PAP was purchased from an Egyptian Company for Biotechnology (S.A.E).

Low-density lipoprotein – cholesterol (LDL–C) was calculated using the Friedewald equation while VLDL-C was calculated by dividing T.G. by five ***(20)*** .

$$\text{LDL-C} = \text{TC} - (\text{HDL-C} + \text{VLDL-C})$$

$$\text{VLDL-C} = \text{TG}/5$$

Assessment of HOMA-IR and HOMA-β were done by used the following equations ***(21)***:

$$\text{HOMA IR} = [\text{glucose (in mg/dl)} * \text{insulin (µIU/mL)}] / 405$$

$$\text{HOMA } \beta = 20\times \text{ insulin}/ (\text{Glucose} - 63)$$

Anthropometric values:

Obesity was defined by body mass index (BMI), which was computed using the following formula: BMI (kg/m^2) = Weight (kg) / $(\text{Height})^2$ (m^2). The WHO categorization of BMI for underweight individuals (BMI<18.5 kg/m^2), normal adults (BMI=18.5-24.9 kg/m^2), overweight adults (BMI=25.0-30.0 kg/m^2), and obese adults (BMI>30.0 kg/m^2) ***(22)***.

Biostatistical Analysis:

The Kolmogorov-Smirnov test was employed to examine the distribution types of the results group. An analysis of variance (ANOVA) test was used to evaluate the differences in scale variables between the diagnostic groups. For regularly distributed data, the findings were expressed as (mean ± standard deviation). Correlation analysis is evaluating the link between a parametric variable and another variable by examining scale variables, employing Pearson's correlation coefficients (r). Statistical significance was determined for all two-tailed hypothesis tests with p-values under 0.05. Receiver operating characteristic (ROC) curves were employed to identify the diagnostic indicators for T2DM. The area under the curve (AUC) signifies that the concentration cut-off values attain optimum sensitivity and specificity. The data were gathered and examined using IBM's Statistical Package for Social Sciences, version 26 (SPSS, Chicago, Illinois, USA) ***(23)***.

3. Results and Discussion:

This evaluation focuses on individuals diagnosed with type 2 diabetes mellitus and diabetic retinopathy. A total of 96 samples were collected, comprising 27 healthy volunteers, 36 patients with type 2 diabetes mellitus without complications, and 33 patients with diabetic retinopathy. A comparison estimation between the groups was performed. Table 1 indicates that there is no statistically significant difference in age among the groups. A statistically significant difference in BMI was observed between the patient groups and healthy individuals. Additionally, there was no statistically significant difference shown between the T2DM and DR groups. Although there was no statistically significant difference in fasting serum glucose (FSG) between the patient groups (P = 0.672), there was a statistically significant difference in FSG between (T2DM) and diabetic retinopathy (DR) groups compared to the healthy controls (P<0.001). Comparisons of IL-29 levels across the T2DM, control, and DR groups revealed significant differences (P<0.001).

Table (1): Biochemical characteristics of Diabetic retinopathy and type 2 diabetes mellitus patients and healthy as the control group.

Parameters	**HC Group**		**T2DM Group**		**DR Group**		**P-value**
	Mean	**±SD**	**Mean**	**±SD**	**Mean**	**±SD**	
No.	**27**		**36**		**33**		
Age (years)	51.96	12.18	52.44	10.38	55.91	8.08	a= 0.852 b= 0.136 c= 0.158
BMI kg/m^2	24.04	3.41	27.24	2.18	28.94	4.67	a= 0.002 b= 0.001 c= 0.086
FSG mg/dL	91.80	11.60	177.45	75.40	170.63	73.65	a= 0.001 b= 0.001 c= 0.672
FI (µIU\mL)	12.24	3.47	8.05	2.16	4.95	2.00	a= 0.001 b= 0.001 c= 0.001
HOMA-β	8.24	1.97	2.08	1.18	1.46	1.32	a= 0.001 b= 0.001 c= 0.034
HOMA-IR	2.84	1.13	3.36	1.34	2.07	1.20	a= 0.128 b= 0.026 c= 0.001
TG mg/dL	154	31.13	211.76	69.89	156.31	76.18	a= 0.002 b= 0.925 c= 0.001
TC mg/dL	182.86	62.23	173.39	43.41	175.34	59.52	a= 0.492 b= 0.592 c= 0.881
HDL-C mg/dL	34.37	14.28	25.58	10.15	38.09	12.08	a= 0.002 b= 0.191 c= 0.001

LDL-C mg/dL	117.52	57.77	105.46	37.67	105.99	57.40	a= 0.323 b= 0.354 c= 0.963
VLDL-C mg/dL	30.92	6.22	42.35	13.97	31.26	15.23	a= 0.002 b= 0.925 c= 0.001
IL-29 pg/mL	20.89	2.02	25.30	3.79	33.07	8.56	a= 0.002 b= 0.001 c= 0.001

*Note: Significant= (p-value< 0.05), a= HC *Vs.* T2DM, b= HC *Vs.* DR and c= T2DM *Vs.* DR.

An analysis was conducted to examine the correlations between IL-29 and clinical biomarkers. in the T2DM group, IL-29 has a significant positive correlation with FSG and HOMA-IR levels in the T2DM patients group. At the same time, it had a negative significant correlation with HOMA-β. However, the other factors had a non-significant correlation with IL-29 in the T2DM individuals as shown in Table (2). In diabetic retinopathy patients, IL-29 showed a statistically significant positive connection with FSG and HOMA-IR (r = 0.374, P<0.032, r = 0.356, P = 0.042, respectively). While IL-29 showed no statistically significant negative correlation in the DR patients group, as seen in Table 3.

Table (2): Correlation of Serum IL-29 Levels with Biomarkers in Individuals with T2DM

Parameter	r	P-value
Age/year	-0.195	0.255
BMI kg/m^2	0.017	0.920
FSG (mg/dl)	0.715**	0.001
Fasting Insulin	-0.299	0.077
HOMA-β	-0.349*	0.037
HOMA-IR	0.458**	0.005
TG mg/dL	-0.068	0.694
TC mg/dL	0.225	0.187
HDL-C mg/dL	-0.064	0.713
LDL-C mg/dL	0.302	0.074
VLDL-C mg/dL	-0.068	0.694

r= Pearson's correlation factor.

Table (3): Correlation between serum level of Interleukin-29 with clinical biomarkers in patients with diabetic retinopathy.

Parameter	r	P-value
Age/year	-0.088	0.626
BMI kg/m2	0.005	0.980
FSG (mg/dl)	0.374*	0.032
Fasting Insulin	0.061	0.738
HOMA-β	-0.197	0.272
HOMA-IR	0.356*	0.042
TG mg/dL	-0.081	0.654

TC mg/dL	0.081	0.655
HDL-C mg/dL	-0.109	0.545
LDL-C mg/dL	0.128	0.477
VLDL-C mg/dL	-0.081	0.654

r= Pearson's correlation factor.

The receiver operating characteristic curve (ROC) for IL-29 has been analyzed, revealing an area under the curve (AUC) of 0.849, as seen in Table 4 and Figure 1. IL-29 demonstrated excellent performance (accuracy and stability) in the diagnosis and classification of diabetic retinopathy, with a cut-off value of 28.46 pg/ml (P<0.001). The sensitivity and specificity for these factors are 0.909 and 0.667, respectively.

Table (4): Receiver-operating characteristic (ROC) curves of serum Interleukin-29, cut-off, sensitivity, specificity, AUC.

Test Result Variable(s)	Cut-off Value	Sensitivity	Specificity	AUC	Confidence Interval at 95%		P-value
					Lower	Upper	
IL-29 Pg/ml	28.46	0.909	0.667	0.849	0.760	0.938	0.001

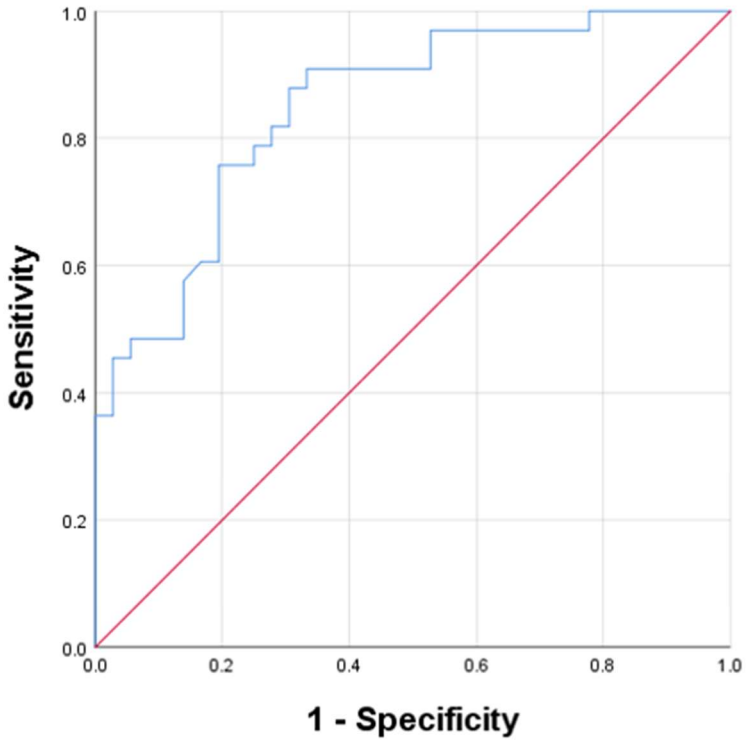

Figure (1): Receiver-operating characteristic (ROC) curves of serum IL-29 reveal valuable discrimination of patients with diabetic retinopathy.

This study exposed a significant elevation in serum level of IL-29 in T2DM and DR patient groups may be associated to the functions of IL-29 in moderate inflammation and the immune system. Suggestion proposes that IL-29 may contribute to the progression of diabetic retinopathy, a common result of diabetes that leads to

retinal damage. Experimental studies have shown a correlation between elevated IL-29 levels and tissue damage and inflammation in many diseases, such as diabetic retinopathy. Patients with diabetic retinopathy revealed raised levels of IL-29 expression in comparison to control and type 2 diabetes mellitus patients. This suggests that these patients have a more noticeable inflammatory response and that IL-29 contributes to the progression of eyes tissue damage. These findings are consistent with previous ***(24), (25)***.

Past studies showed that INF-γ expression was significantly elevated in patients with diabetic retinopathy (DR), while IL-6 levels remained unchanged in the DR group. The increase in INF-γ was particularly noted in patients with proliferative DR ***(26)***.

Previous research investigations have shown that monocytes have a positive response to IL-29, leading to the production of several cytokines and an increase in their levels, including IL-6 ***(27)***. A researcher explained that the development of diabetic retinopathy, pro-inflammatory INF-γ is recognized for its role in enhancing endothelial permeability following the induction of vascular dysfunction and the activation of caspase-3 ***(28).*** other researchers showed that Interleukin-6 (IL-6) concentrations in the vitreous exhibit a significant correlation with the severity and progression of diabetic retinopathy (DR) ***(29)***. another paper presented that Interleukin-6 (IL-6), a proinflammatory cytokine, may play a role in proliferative diabetic retinopathy (PDR). The elevated intravitreal levels observed can be attributed to intraocular production of IL-6 ***(30)***.

This study builds on prior research, revealing potential correlations between IL-29 levels and metabolic indicators such as fasting insulin and blood glucose. An association has been identified between elevated fasting blood glucose levels and increased IL-29 levels in diabetic retinopathy, suggesting a potential role of IL-29 in insulin resistance and glucose metabolism. Moreover, in the context of diabetic retinopathy, multiple studies indicate an inverse correlation between fasting insulin levels and IL-29 levels. The identified negative correlation indicates that higher levels of IL-29 in individuals with diabetic retinopathy may correlate with reduced insulin sensitivity and diminished insulin synthesis ***(25, 31-39)***.

Conclusion:

This study examined the elevated levels of IL-29 in patients with diabetes and diabetic retinopathy, suggesting its potential role as a predictive marker for complications associated with diabetic progression.

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Declaration of interests:

The authors declare no found conflict of interest.

Founding: None.

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