

# Study The Effect Of Chemerin Level In Type Ii Diabetic Patients With And Without Retinopathy

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## ABSTRACT

Diabetes Mellitus (DM) is metabolic disease having great effect on our health. the associated complications of diabetes that included cardiovascular disease, retinopathy, become raised at un regulating glucose. The development of Diabetic retinopathy (DR) has deeply attaching with oxidative damage, inflammation and various pro-angiogenic cytokines.

**Aim of study:** The presented study was designed to assess the effect of serum chemerin levels in type 2 diabetes patients with diabetic retinopathy and without diabetic retinopathy, and its relation to certain biochemical analysis.

**Patients and methods:** A total of 90 subjects participated in this research. They were divided into three groups, with 30 persons in the type 2 diabetic retinopathy group, 30 persons in the type 2 without diabetic retinopathy group, and another 30 healthy persons (aged between 33-55 years) in a control group, for comparison. Studies were carried out at the National Diabetic Center at Al-Mustansiriyah University. A significant increase in waist circumference, body mass index, fasting blood sugar, glycosylated haemoglobin, C-peptide, homeostasis model assessment-2 insulin resistance, B-cell % and Sensitivity % levels was found in both the type 2 diabetic retinopathy and type 2 without diabetic retinopathy groups, as compared with the control group.

**Results:** Serum chemerin and HS-CRP levels have a highly significant increase different ( $P < 0.001$ ) among type 2 diabetics with diabetic retinopathy and type 2 diabetics without diabetic retinopathy when compared with the control group. It was found that chemerin level is significantly higher in type 2 diabetic patients with diabetic retinopathy, as compared to type 2 diabetic patients without diabetic retinopathy and the control group.

**Conclusion:** The significant difference in chemerin (fasting blood sugar, insulin resistance, total cholesterol, triglyceride, low density lipoprotein and high sensitive c-reactive protein) between the type 2 diabetic group with diabetic retinopathy and type 2 diabetic group without diabetic retinopathy leads to the conclusion that the high levels of chemerin paved the pathogenesis diabetic retinopathy by enhancing inflammation, insulin resistance, oxidative stress and angiogenesis factor.

**Keywords:** Diabetic retinopathy (DR), chemerin level, Adipokines, HS-CRP

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## INTRODUCTION

Diabetic retinopathy (DR) is a microvascular complication of diabetes that affects the eyes [1,2]. Thus, if therapy cannot be found, DR will continue to be a leading cause of blindness [3]. Diabetic retinopathy (DR) is classified into two major types: non-proliferative and proliferative. The first visible signs of non-proliferative DR are microaneurysms which eventually rupture and lead to retinal hemorrhages, causing fluid to seep into the retina [4]. Although there are retinal surgeries that can reduce recrudescence, the key to preventing DR lies in glycaemic regulation and, controlling diabetes in its early stages [3]. Several studies have shown that the longer you have diabetes, hyperglycemia, and hypertension, the more likely you are to develop DR [5]. Even the state of hyperlipidemia alone is strong enough to create harm at the retina [6]. Peroxidation lipids processes that occur in the vascular wall led to creating different kinds of reactive carbonyl, as a result of these changes a big effect was found on both the structure and function of the vascular wall [7]. An actively contributing of hyperlipidaemia has caused to DR and macular edema (ME) by endothelial dysfunction and collapse of the blood retinal barrier leading to exudation of serum lipids and lipoproteins [8]. Oxidative damage, inflammation, and various pro-angiogenic cytokines are the initial core to the development of DR [9]. In the recent years, studies have found that chemerin which constitutes of 163 amino

acids is an immune agent that is normally created by adipose tissue and skin [10], it has a proactive role in the development of DR [11,12]. The N-terminal division into separate parts 20 aa signal peptide results in the release of dormant precursor (chemerin-S163) into extracellular niches or circulation system (Fig. 1A). The precursor requires further extracellular C-terminal cleavage at very different positions to produce active and deactivated chemerin. For example, the proteolytic cleavage at its C-terminus by plasmin, elastase and cathepsin G activates chemerin and yields various isoforms (chemerin-K158, -S157 and -F156) with different affinity to CMKLR1 (Fig. 1B and C) [13]. Patients bodies with type 2 diabetes mellitus (T2DM) have a wide range of metabolic influences caused by different types of hormones and cytokines called "adipokines", which are producing in adipose tissue. Facts have emerged recently that Chemerin, a newly discovered adipokine widely existent in the liver, kidney, and adipose tissue, contributes to glucose and lipid metabolic equilibrium by regulating differentiation and modifying the sites of adipocytes and their genes [14]. Adipokines have a large impact on glucose metabolism in different tissues and influence the overall energy balance at the systemic level. Adipokines are considered a necessity in the regulation of adipose tissue development and function [14,16,17]. Changes in adipokine levels adjunct to T2DM occur through insulin resistance induced by inflammation, and that is one of the

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mechanisms attributed to this dysregulation of adipokines [18]. For example, a high level of pro-inflammatory cytokines promotes obesity and the development of a chronic inflammatory condition that resulted in dysfunctional adipose tissue function [19,20]. Chemerin characteristics as (RARRES2) called retinoic acid receptor responder 2 [13,21]. There are presumptions that show some outcomes about chemerin and its possible linker with obesity and the development of T2DM [22]. This study was designed to study the effect of chemerin levels in Iraqi type 2 diabetes patients with and without Diabetic retinopathy. document.

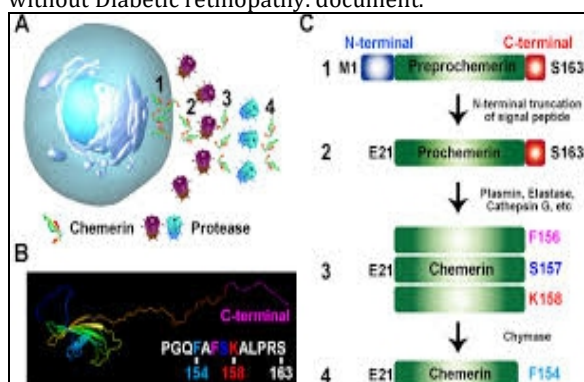


Figure 1: Structure of Chemerin

### MATERIALS AND METHODS

Sixty patients with type 2 diabetes mellitus were divided into two groups of 30 persons each. One group consists of patients with diabetic retinopathy (DR), and the other without DR. They were compared with a control group that comprises of 30 healthy individuals aged between 33-55 years. The research was carried out at the National Diabetes Center (NDC) AL- Mustansiriyah University, in Baghdad, Iraq, from January 2020 until the end of September 2020. Data such as age, sex, duration of disease, weight, height, Body Mass Index (BMI), waist circumference, Waist-Hip Ratio (WHR) and other biochemical parameters were collected from all participants.

#### Ethical approval

All participants were duly briefed and provided with adequate information concerning the study. Each and every participant has given their informed consent to voluntarily take part in the research, which includes having their information collected and recorded by the Scientific Committee of the National Centre for Diabetic Treatment and Research, and collaborating with the specialist doctors and laboratory workforce who are helping to carry out this research.

#### Exclusion Criteria

All information on medical history was obtained directly from participants through private interview sessions. People who took any medications or people with kidney disease, liver disease, malignant disorders, and pituitary or thyroid disease were not approved for this investigation.

#### Measurement

##### Sample collection

Blood sample from vein was collected from fasting individuals between 8.00am-10.00am. The blood sample is divided into two aliquots; the first aliquot is dispensed in tube containing EDTA for HbA<sub>1c</sub> determination, while the second aliquot is put in the serum separator tube

centrifuged at (3000 rpm) for 15 minutes, and after allowing the blood clot to remain at room temperature for about 30-60 minutes, the serum was then kept at -20°C in sterile condition until it is used.

#### Anthropometric Measurements

##### Determination of Body Mass Index (BMI)

The following equation provides a simplified calculation method for determining BMI (Eq. 1) [23]

$$\text{BMI} = \text{weight (kg)} / \text{length (m}^2\text{)} \quad (1)$$

##### Determination of Waist to Hip Ratio (WHR)

Waist-Hip ratio was used as an indicator to assess central obesity. W/H ratio is calculated by dividing waist circumference (in cm) by hip circumference (in cm) [24].

##### Determination of Insulin Resistance

Insulin resistance parameters from Homeostasis Model Assessment 2- insulin Resistance (HOMA2-IR), HOMA insulin sensitivity (HOMA2-S%), and HOMA beta cell function (HOMA2-B%) were all calculated using HOMA2-Calculator software downloaded free of charge from (<http://www.dtu.ox.ac.uk/homacalculator/download.php>). The subject will be considered as insulin resistant if HOMA2-IR > 3 [25].

#### Biochemical Assessment

All biochemical assessment was estimated enzymatically using the colorimetric following the protocol of the available kits supplied by BIOLABO/France.

##### Determination of Fasting Blood Sugar (FBS)

Serum FBS is measured according to Trinder method [26].

##### Determination of Serum Total Cholesterol (TC)

The method for the measurement of total cholesterol in serum involves was based upon an enzymatic colorimetric method according to sources [27,28]

##### Determination of Serum Triacylglycerol (TG)

This method is based on the enzymatic hydrolysis of serum triglyceride to glycerol and free fatty acids (FFA) by lipoprotein lipase (LPL) [29].

##### Determination of Serum High Density Lipoprotein-Cholesterol (HDL-C)

Serum HDL is directly measured using the enzymatic colorimetric method on [30].

##### Determination of Serum Low Density Lipoprotein-Cholesterol (LDL-C)

Friedewald's equation [31] an indirect simplified mathematical method for calculating low-density lipoproteins. It only applies at TG levels below 400 mg / dL.

$$\text{LDL-C} = \text{TC} - [\text{HDL-C} + \text{TAG}/5].$$

##### Determination of Serum Non-High-Density Lipoprotein Cholesterol (Non-HDL-C)

It was calculated directly as follows:

$$\text{Serum non-HDL-C} = (\text{S.TC} - \text{S.HDL-C}) [32].$$

##### Determination of Glycated Haemoglobin (HbA<sub>1c</sub>)

The Bio-Rad VARIANT Haemoglobin A<sub>1c</sub> programme utilizes principles of ion-exchange high-performance liquid chromatography (HPLC) for automatic and accurate separation of HbA<sub>1c</sub> [33].

#### Parameters Assessment

##### Determination of C-peptide hormone

C-peptide is determined using a sandwich chemiluminescence immunoassay technique supplied by Liaison/DiaSorin/ Italy Kit.

##### Determination of Chemerin

Human chemerin level is determined using ELISA kit (Ray Biotech, Parkway land, Catalogue ELH-Chemerin).

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## **Determination of Serum high sensitivity C-reactive protein (hs-CRP) concentrations**

This assay employs the quantitative sandwich enzyme immune assay technique. It was measured by ELISA kit (Biosource/USA.Catalog MBS703598).

## **Statistical analysis**

The data obtained during the current study were analysed statistically using SPSS to determine the significance of the different parameters by one-way ANOVA, data represent mean  $\pm$  SE;  $P < 0.05$  was regarded as significant.

## **RESULTS AND DISCUSSION**

The data of our study combined from (60) patients who were divided into two groups (T2DM with DR, T2DM without DR) (30) patients for each group, in addition (30) persons as healthy group. Anthropometric characteristics of the three groups were enrolled in Table 1., no statistically significant differences in age, weight, height, hip, and WHR were observed between the comparison groups. Body mass index (BMI) levels of T2DM with DR group gave rise to significant different ( $P < 0.05$ ) higher than control group and no significant differences when compared with T2DM without DR. No significant differences were recorded between T2DM patients with DR and T2DM without DR as respect to waist, % HbA1C, C-peptide, HOMA2-IR, % B-cell and % Sensitivity; whereas there was a significant increase ( $P < 0.05$ ) between the groups (T2DM with DR and T2DM without DR) compared to control group for the same above values. While the FBS levels has no significant differences between T2DM with and without DR groups but the FBS levels shows a high significant increase different ( $P < 0.001$ ) as compared to patients in control group, serum chemerin and HS-CRP levels have a high significant increase different ( $P < 0.001$ ) among T2DM with DR and without DR when compared with control group. The findings achieved in this study fully conformed with the results of a previous study [6,34]. A group of researchers have proven the link between chemerin and metabolic syndrome, obesity and insulin resistance [35,36] also, other studies affirmed the relation between Chemerin levels and components of metabolic syndrome, including body mass index, hypertension and plasma triglycerides [37,38,39,40]. In this study our data showed a positive correlation in chemerin levels with BMI, serum triglycerides and total-cholesterol. BMI expresses the degree of systemic body fat and obesity [41]. That correlation discerns the connection between serum chemerin and BMI and it is linked with obesity. According to the results obtained from Table 2, there are significant increase different ( $P < 0.05$ ), high significant increase different ( $P < 0.01$ ) in (TC, TG and LDL) levels among each group of study (T2DM with, without DR and control), respectively. Further, a significant decrease ( $P < 0.05$ ) was shown in HDL levels among each group of (T2DM with DR, T2DM without DR and control). Moreover, there is no significant different at non-HDL levels between (T2DM with DR and T2DM without DR) group, while high significant decrease different ( $P < 0.05$ ) were detected in non-HDL levels when compared with patients in groups other than control group, these results were in agreement with the study [42].

Lipids profile had been proposed as a main participant in retinal exudate formation in DR. It's had been proven that when lipids profile levels are elevated a big damage to

endothelial occurred as well as the reduction in the bioavailability of nitric oxide which play a role in retinal exudates formation in DR [43]. Numerous studies have demonstrated the effect of lipid profile on retinopathy or maculopathy [44,45,6]. A study by [34] proposed that chemerin had a chief role to regulate fat metabolism and expedition the adipolysis. Other authors had confirmed chemerin role at damping the creation of cyclic adenosine monophosphate, activate hormone-sensitive lipase and reinforce metabolism of fat cells and release of glycerol and free fatty acids (FFA) [46]. An Aggravate of obesity process and exacerbate hyperlipidaemia would be promoted when glycerol and FFA synthesized triglycerides and very-low density lipoprotein in the liver, then be stored in white adipose tissue [46]. Earlier, the reaction between serum lipid and DR was clear up and discussed [47]. retinal hard exudates in DR could be slowed by controlling serum lipid levels at normal values. [44, 48]. Ultimately, chemerin could share in the development of DR by supporting hyperlipoproteinemia. The baseline measurements by correlation coefficients analysis in Table 3, became clear that BMI, weight, waist, HbA1C %, and HOMA2-IR had remained positive significant ( $P < 0.05$ ) associated with serum chemerin as listed in T2DM with and without DR. The positive correlation of serum chemerin with BMI indicated that chemerin is related to obesity. Moreover, chemerin levels showed a positive significant correlation with C-peptide concentration in T2DM with DR, while no correlation was observed between chemerin level and C-peptide concentration in T2DM without DR. A positive highly significant correlation ( $P < 0.001$ ) between serum chemerin level with (FBS, TC, TG, LDL, hs-CRP) in T2DM with and without DR, is in agreement with the study [49]. The new traded classification of chemerin consider it as an innovative adipokine. It regulates adipogenesis and adipocyte metabolism as evidenced by experimental data showing that loss of chemerin abrogates adipocyte differentiation and modifies the expression of genes critical in glucose and lipid metabolism [22]. These consequentially Information that supported by studies have provided experimental evidence for additional roles of chemerin in diverse biological processes including: cell proliferation, differentiation, angiogenesis, renal function and energy metabolism [50]. An evidence on the effect of chemerin on glycometabolism is available, but the role and importance of chemerin is unfathomable due to the conflicting results obtained from different in vitro or in vivo studies [51]. An activity of chemerin has been reported to prevent the response of skeletal muscle cells and the digestive system to insulin sensitivity and inhibit glucose uptake during an experiment [51] which proved the role of chemerin on both inhibitory and stimulatory glucose uptake. An inflammatory substance ,oxidative stress and angiogenesis are morphogenetic materials were supported by chemerin; therefore, they have the most prominent effect in the pathogenesis of diabetic retinopathy [52]. A negative significant Correlation ( $P < 0.05$ ) was found between chemerin level and HDL in patients with T2DM with and without DR. Age, hip, height, WHR, %B -cell, % Sensitivity and non-HDL in patients with T2DM with and without DR shows no correlation with chemerin level. The results that manifest from Figure 2 shows that externally, the chemerin level in the sera of T2DM with RD was higher in values compared with T2DM without RD patients and the control subjects. The

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cause of blindness in most diabetic patients is diabetic retinopathy, and many studies have linked the role of chemerin with the development of DR [11]. Oxidative stress damage, inflammation and manifold proangiogenic cytokines have perfect correlation on development of DR [9]. Many studies have found no difference on the chemerin level in T2DM patients in the group with DR and in the control group [37, 53], which supported our results. Also, the patients who are having overweight or obese and T2DM with DR problems shown higher serum chemerin levels compared to the other groups [54], this is also in agreement with the present study.

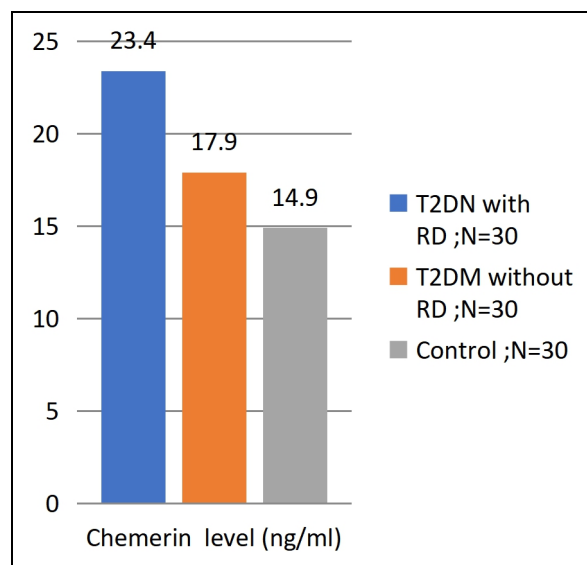


Figure 2: Chemerin level in the sera of type 2 diabetic with RD, type 2 diabetic without RD patient and control subjects.

As for the results taken from Figure 3, the hs-CRP level in the sera of T2DM with RD was of higher value than the hs-CRP level of T2DM in patients without RD and the control subjects. This concurs with the obtained information that this inflammatory factor may play an essential role in the pathogenesis of microangiopathy, the mechanism of which, in the diabetic microangiopathy, the insulin resisters induction compliments the stimulation leading to damage in endothelia cell and the release of nitric oxide synthase [49]. The inflammatory

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marker C-reactive protein (CRP) has been shown to predict vascular death and major cardiovascular events in a 10- year frame. A high level of CRP in the blood is a sign that there may be an inflammatory process occurring in the body. It is the moderate and chronic increase in CRP levels measured by high sensitivity C - reactive protein (HS-CRP) that represents a risk factor for cardiovascular disease [55].

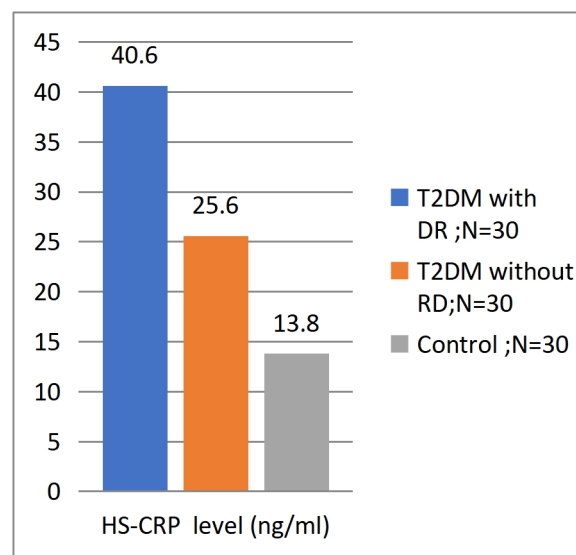


Figure 3: HS- CRP level in the sera of type 2 diabetic with RD, type 2 diabetic without RD patient and control subjects.

### CONCLUSION

Depended on our results which found that chemerin level has significantly higher in type 2 diabetic patients with diabetic retinopathy, as compared to type 2 diabetic patients without diabetic retinopathy and the control group. The significant difference in chemerin (fasting blood sugar, insulin resistance, total cholesterol, triglyceride, low density lipoprotein and high sensitive c-reactive protein) between the type 2 diabetic group with diabetic retinopathy and type 2 diabetic group without diabetic retinopathy leads to clarify the conclusion that the main cause of pathogenesis diabetic retinopathy was the higher chemerin levels which have an important role in promoting inflammatory, insulin resistance, oxidative stress, and angiogenesis factor.

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## Study The Effect Of Chemerin Level In Type Ii Diabetic Patients With And Without Retinopathy

Table 1: Biochemical Parameters in the study groups

Parameters	T2DM with DR Mean±SD n (30)	T2DM without DR Mean±SD n (30)	Control Mean±SD n (30)	P1	P2	P3
Male Female	14(47%) 16(53%)	14(47%) 16(53%)	16(53%) 14(47%)	NS NS	NS NS	NS NS
Age (year)	49.1±7.10	51.56±5.35	38.76±38.76	NS	NS	NS
Weight(kg)	88.53±19.27	80.26±12.96	73.96±10.78	NS	NS	NS
High (cm)	167.03±10.6	165.46±8.17	169±5.50	NS	NS	NS
BMI	31.61±5.64	29.23±3.703	25.89±3.53	NS	0.05*	NS
Waist(cm)	107.26±11.85	102.16±8.74	87.83±7.43	NS	0.05*	0.05*
Hip (cm)	106.7±10.62	104.43±8.43	102.73±9.67	NS	NS	NS
WHR	1.00± 0.06	0.98±0.06	0.857±0.05	NS	NS	NS
FBS (mg/dl)	203.267±58.56	193.6±39.36	99.8±5.76	NS	0.001**	0.001**
HbA1C %	8.593±1.46	8.43±1.36	4.83±0.31	NS	0.05*	0.05*
C-peptide(ng/ml)	4.46±0.79	3.8±1.37	1.823±0.33	NS	0.05*	0.05*
HOMA2-IR	4.26± 0.84	3.79±1.24	1.41±0.25	NS	0.05*	0.05*
%B-cell	56.76±25.28	54.83±17.06	90.27±23.23	NS	0.05*	0.05*
% Sensitivity	30.747±10.15	48.89±66.94	76.97±15.07	NS	0.05*	0.05*
HS-CRP (ng/dl)	40.667±5.26	25.6±7.00	13.8±4.71	0.001**	0.001**	0.001**
S. Chemerin (ng/dl)	23.421±6.97	17.965±5.31	14.9±3.20	0.001**	0.001**	0.01**

n=number; Data are given as mean±SD; NS is no significant; P\* is significantly P<0.05, and high significant P<0.01 and p<0.001., P1; T2DM with DR vs T2DM without

DR, P2: T2DM with DR vs Control, P3: T2DM without DR vs Control.

without (DR) and Control

Table 2: levels of Lipids Profile in T2DM with (DR), T2DM

Parameters	T2DM with DR Mean±SD n (30)	T2DM without DR Mean±SD n (30)	Control Mean±SD n (30)	P1	P2	P3
TC (mg/dl)	232.1±23.44	204.967 ± 20.43	158.967±28.87	0.05*	0.05*	0.05*
TG (mg/dl)	269.5±30.96	196.63±36.60	91.567±42.89	0.05*	0.01**	0.01**
HDL (mg/dl)	34.7±1.36	43.733±2.95	53.066±5.34	0.05	0.05*	0.05*
non-HDL (mg/dl)	197.4±53.14	171.23±44.77	105.9±28.52	NS	0.01**	0.01**
LDL (mg/dl)	163.5±25.95	122.307±29.47	87.3±29.55	0.05*	0.05*	0.01**

## Study The Effect Of Chemerin Level In Type Ii Diabetic Patients With And Without Retinopathy

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n=number; Data are given as mean±SD; NS is no significant; P\* is significantly P<0.05, and high significant P<0.01., P1; T2DM with DR vs T2DM without DR, P2: T2DM with DR vs Control, P3: T2DM without DR vs Control.

Table 3: Correlation Coefficient of serum chemerin level between T2DM with and without (DR) and all Parameters study

Parameters	Chemerin Level (ng/dl)	
	T2DM with (DR)	T2DM without (DR)
	r	r
Age (year)	0.194	0.135
Weight(kg)	0.213*	0.306*
High (cm)	0.181	0.168
BMI	0.365*	0.353*
Waist(cm)	0.348*	0.339*
Hip (cm)	0.151	0.112
WHR	0.081	0.047
FBS (mg/dl)	0.525**	0.356*
HbA1C %	0.386*	0.239*
C-peptide(ng/ml)	0.271*	0.08
HOMA2-IR	0.212*	0.336*
%B-cell	0.178	0.183
% Sensitivity	0.143	-0.201
TC (mg/dl)	0.574**	0.495*
TG (mg/dl)	0.633**	0.333*
HDL (mg/dl)	-0.349*	-0.348*
non-HDL (mg/dl)	0.122	0.228
LDL(mg/dl)	0.554**	0.475**
hs-CRP (ng/dl)	0.324**	0.323**

\*Correlation is significant at the 0.05 level.

\*\*Correlation is significant at the 0.01 level.