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Correlation between Serum Chemerin, Blood Glucose and Lipid Profile in Type 2 Diabetes Patients with NAFLD

Alshaimaa Hatem Farhan[1], Ahmed I. Lotfy[2], Amr Ibrahim[2], Sherif Ali Mohamed Bahnasawy[2], Mohamed Elsayed Abdallah Ibrahim[3], Ibrahim Hagras Hasan[3], Moayad Abdel Wahab Jaalouk[4], Mohammd Raghdan Nader Albalkhi[4], Nora Mohamed Abdelreheem[5], Aly Hassan Muhammad Fayyadh[5], Enas Mohamed Ikram Sayed Badway[6], Eslam Elshafey[1*]

[1] Clinical Pathology Department, [2] GIT Department, [3] Internal Medicine Department, [5] Radiology Department, [6] Microbiology and Immunology Department, Al-Ahrar Teaching Hospital, General Organization for Teaching Hospitals and Institutes (GOTHI), Egypt

[4] Internal Medicine Department, Faculty of Medicine, Zagazig University, Egypt

***Corresponding author:** Eslam Elshafey, **Email:** eslamelshafeyelsaid245@gmail.com, **Mobile:** 00201281494169

ABSTRACT

Background: Patients with type 2 diabetes mellitus (T2DM) frequently have non-alcoholic fatty liver disease (NAFLD), which is linked to higher rates of morbidity and death. The pathophysiology of both NAFLD and type 2 diabetes has been linked to chemerin, an adipokine involved in metabolic control.

Aim: To evaluate the relationship between serum chemerin levels and metabolic parameters in T2DM patients with varying degrees of NAFLD severity.

Patients and methods: This cross-sectional study included 120 patients from Al-Ahrar Teaching Hospital, Egypt. The patients were divided into T2DM group (Group I, n=50) and a concurrent NAFLD group (Group II, n=70). NAFLD severity was categorized into mild (Group II a), moderate (Group II b), and severe (Group II c) based on ultrasonographic criteria. Glycemic, lipid, chemerin, and anthropometric values were measured. Independent predictors of the severity of NAFLD were found using a logistic regression model after correlations between chemerin and metabolic indicators were examined.

Results: There was a substantial difference between the studied groups in terms of Homeostatic Model Assessment for Insulin Resistance and chemerin, with group II c showing much higher levels than the other groups.

Conclusion: Serum chemerin could be a useful biomarker for NAFLD severity in T2DM patients, particularly when combined with standard metabolic measures. The strong associations with metabolic indicators suggest that chemerin may have a mechanistic role in the development of NAFLD in type 2 diabetes, while more research is needed to identify the exact mechanisms involved.

Keywords: NAFLD, Type 2 Diabetes Mellitus, Chemerin, Metabolic Parameters, Insulin Resistance.

INTRODUCTION

Globally, diabetes mellitus (DM) is now a major public health concern. By 2030, approximately 10.2% of all persons worldwide are predicted to develop diabetes mellitus. It is linked to a variety of metabolic disorders. The American Diabetes Association (ADA) states that the non-dyslipidaemic lipid levels for adults with type 2 DM are low density lipoprotein (LDL) < 100 mg/dL, high-density lipoprotein cholesterol (HDL-c) > 40 g/dL in men and > 50 mg/dL in women, triglycerides (TG) < 150 mg/dL, and total cholesterol <200 mg/dL [(1)].

Diabetic dyslipidemia is found in 72–85% of patients with type 2 diabetes and has been associated with an increased risk of cardiovascular diseases. Diabetic dyslipidemia is characterized by elevated TC, TG, and LDL levels and decreased HD levels. Reduced blood adiponectin (adipokinase) levels and increased insulin resistance have been associated with the etiopathology of dyslipidemia in diabetes mellitus [(2)].

Non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), and in more severe forms, cirrhosis, fibrosis, and hepatocellular cancer are hepatic symptoms of metabolic syndrome [(3)].

Fatty degeneration in liver histology is a clinical feature of non-alcoholic fatty liver disease (NAFLD). The metabolic disorders type 2 diabetes mellitus, insulin resistance, and obesity are intimately associated with NAFLD, with insulin resistance serving as the shared pathophysiological basis for all three conditions [(4)].

According to earlier research [(5)], NAFLD may raise a patient's risk of developing type 2 diabetes mellitus and its associated problems. According to additional research, those with type 2 diabetes mellitus also had noticeably greater rates of NAFLD prevalence and death.

Patients with T2DM and NAFLD have worse glycemic control than those with T2DM and NAFLD alone. They also have a higher chance of developing cirrhosis, NASH, or possibly hepatocellular carcinoma than those with NAFLD and T2DM alone. However, compared to patients without combined NAFLD, those with T2DM and NAFLD also had a much greater prevalence of complications of diabetes, including retinopathy, chronic kidney disease (CKD), and cardiovascular disease (CVD) [(6)].

According to the National Health and Nutrition Examination Survey conducted in the United States, type

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2 diabetes mellitus and insulin resistance are both independent risk factors for NAFLD and increase the chance of NAFLD death [7].

The most reliable method for diagnosing NAFLD and NASH cirrhosis is liver biopsy. However, in clinical practice, liver biopsies are challenging to employ for extensive screening in the broader public because they are intrusive, low acceptance, and high expense. NAFLD is frequently screened for and diagnosed with conventional ultrasonography [8]. However, because there are so many people with type 2 diabetes, routine liver ultrasonography screening is necessary for all of these patients, which results in very high medical costs. Furthermore, many community hospitals and rural health facilities lack both certified ultra-sonographers and ultrasound equipment. As a result, a number of earlier studies have raised hopes for early NAFLD patient screening using different blood indicators [9].

Liver enzymes and blood lipids are well-known serum biochemical indicators of standard physical examinations. According to past studies, variations in liver enzyme levels do not necessarily correspond to the severity of hepatic steatosis, making them an unreliable indication of NAFLD. NAFLD is closely linked to dyslipidemia, which includes reductions in HDL- c and increases in triglycerides (TG), cholesterol (TC), and LDL-c [10].

The liver interacts with adipose tissue, an organ that stores energy and is also regarded as an endocrine organ that secretes polypeptides known as adipokines. A growing body of research indicates that adipokines are connected to a variety of physiological functions, including insulin resistance, inflammation, immunity, and NAFLD [11].

RARRES2 is the name given to chemerin. It is created as the inactive form, prochemerin, which is then triggered by inflammatory serine proteases and coagulation to undergo cterminal cleavage. By attaching itself to chemerin-like receptors 1 (CMKLR1), 23 (ChemR), and 2 (CCmotif) receptor-like, chemerin can trigger the immune inflammatory response. The primary sources of chemerin formation are hepatocytes and visceral adipose tissue. According to research, the chemerin/CMKLR1 signaling pathway is stimulated by obesity and insulin resistance, which causes the inflammatory response [12].

PATIENTS AND METHODS

This study was conducted at Al-Ahrar Teaching Hospital, Egypt on patients diagnosed with type 2 diabetes mellitus (T2DM) for at least one year.

Inclusion criteria:

1. Patients aged 30-70 years.
2. For at least a year, a diagnosis of T2DM has been made. The WHO's 1998 diagnostic criteria for diabetes mellitus [13] served as the basis for the diagnosis of type 2 diabetes mellitus. These requirements included blood glucose values of 7.0 mmol/l during fasting, blood glucose levels of 11.1 mmol/l during random testing for diabetes symptoms, or after two hours, the glucose tolerance test revealed blood glucose levels of 11.1 mmol/l.
3. Non-alcoholic fatty liver disease was confirmed by ultrasonography.

Exclusion criteria:

1. Individuals suffering from type 1 diabetes.
2. Past history of heavy drinking (>20 g/day for women and >30 g/day for men).
3. The existence of additional liver conditions (drug-induced liver damage, autoimmune hepatitis, and viral hepatitis).
4. Using drugs that are known to cause hepatic steatosis, such as tamoxifen, methotrexate, and corticosteroids.
5. Lactation or pregnancy.
6. Individuals suffering from mental illness, cancer, or liver or kidney problems.

Clinical assessment:

A thorough clinical evaluation was performed on each participant, which included:

1. Demographic data, such as height, weight, age, sex, and smoking status.
2. A thorough medical history that includes comorbidities, current medications, and the length of time the patient has had diabetes.
3. Physical assessment, which includes the following measurements:
   - Weight and height (for the purpose of calculating Body Mass Index; BMI).
   - The circumference of the waist.
   - Mercury manometers were used to monitor blood pressure (seated systolic/diastolic BP) in triplicate following a 10-minute rest.

Laboratory investigations

All participants were given blood samples following an 8-hour overnight fast. Measurements were made of the following parameters:

1. FBG, fasting blood glucose.
2. Two hours following a meal, the postprandial blood glucose (PPBG) is measured.
3. High-performance liquid chromatography (HLC-723G8, TOSOH CORPORATION, Japan) was used to measure glycated hemoglobin (HbA1c).
4. Lipid profile:
   - Total cholesterol (TC).
   - Triglycerides (TG).
   - High-density lipoprotein cholesterol (HDL-c).
   - Low-density lipoprotein cholesterol (LDL-c).
5. Liver function tests:

- Alanine aminotransferase (ALT).
- Aspartate aminotransferase (AST).

Liver function, FBG, and lipid profiles were measured using an automated biochemical analyzer (AU 5800, Beckman Coulter, USA).

6. Serum chemerin levels.

Serum chemerin measurement:

A commercial ELISA kit from Wkea Med Supplies Corp., (USA) was used to quantify serum chemerin levels in accordance with the manufacturer's instructions. Every sample was examined twice, and the mean value was used for statistical analysis.

Diagnosis of NAFLD:

An abdominal ultrasound was used to diagnose NAFLD. The ultrasound scans were carried out by a qualified radiologist who was blind to the clinical and biochemical information about the patients. Characteristics like blurring of the hepatic arteries, deep attenuation of the ultrasound signal, and increased liver echogenicity relative to the kidney were used to demonstrate hepatic steatosis's existence. Standard ultrasonographic criteria were used to assess the three NAFLD severity levels: mild, moderate, and severe.

Ethical considerations:

Informed written consent was obtained from all patients.The study was approved by Research Ethical Committee, General Organization for Teaching Hospitals and Institutes (GOTHI).

Statistical analysis

The data was imported and examined using the Statistical Package for the Social Sciences (SPSS) software, version 20.0. A one-way ANOVA, post hoc least significant difference (LSD) test, Pearson's correlation coefficient, and receiver operating characteristic (ROC) curve analysis were used. p-value < 0.05 was considered statistically significant.

RESULTS

Table (1): Demographic data among the studied groups

		Group I: (n=50)	Group II a: (n=25)	Group II b: (n=21)	Group II c: (n=24)	P value	P value
Age (years)	**Mean ± SD**	40.9±6.5	41.1±9.2	40.5±7.2	40.4±5.9	0.982	
	Range	30-55	30-58	31-55	30-52		
Sex	**Male**	30 (60%)	16 (64%)	14 (66.70%)	13 (54.20%)	0.839	
	Female	20 (40%)	9 (36%)	7 (33.30%)	11 (45.80%)		
BMI	**Mean ± SD**	24.1±0.9	25±1.1	27.7±1	29.9±0.9	**0.001**	P1=0.001 P2=0.001 P3=0.001 P4=0.001 P5=0.001 P6=0.001
	Range	22.1-25.8	22.5-26.9	25.8-29.4	28.4-31.5		

BMI: Body mass index, **P1:** I and II a, **P2:** I and II b, **P3:** I and II c, **P4:** II a and II b, **P5:** II a and II c, **P6:** II b and II c

The studied groups did not differ significantly in terms of age or sex; however, group II c's BMI was significantly greater than that of the other groups (Table 1).

Table (2): Comparison of blood pressure among the studied groups

		Group I: (n=50)	Group II a: (n=25)	Group II b: (n=21)	Group II c: (n=24)	P value
Systolic pressure (mm/Hg)	**Mean ± SD**	128.5±10.1	127.2±9.9	128.3±8.9	127.3±9.9	0.932
	Range	110-145	110-145	110-145	110-145	
Diastolic pressure (mm/Hg)	**Mean ± SD**	83.1±6.2	80±8.7	82.4±5.1	81.6±7.6	0.338
	Range	70-95	60-95	70-90	65-95	

There were no significant differences in systolic and diastolic blood pressure across the studied groups (Table 2).

Table (3): Comparison of blood glucose among the studied groups

		Group I: (n=50)	Group II a: (n=25)	Group II b: (n=21)	Group II c: (n=24)	P value	P value
FPG (mg/dl)	**Mean ± SD**	118.9±7.2	125.3±9.3	141±34.2	169.9±5.8	**0.001***	P1=0.352 P2=0.003* P3=0.001* P4=0.059 P5=0.001* P6=0.001*
2hPG (mg/dl)	**Mean ± SD**	206.2±14.3	217.1±18.6	242.9±53.1	301.3±9.2	**0.001***	P1=0.368 P2=0.005* P3=0.001* P4=0.081 P5=0.001* P6=0.001*
HbA1c	**Mean ± SD**	7.5±0.5	8.6±0.5	9.4±0.7	10.4±0.7	**0.001***	P1=0.001* P2=0.001* P3=0.001* P4=0.001* P5=0.001* P6=0.001*

FPG: Fasting plasma glucose, **2Hpg:** 2-hour plasma glucose, **HbA1c:** glycated hemoglobin, **P1:** I and II a, **P2:** I and II b, **P3:** I and II c, **P4:** II a and II b, **P5:** II a and II c, **P6:** II b and II c, *: significant.

There was a substantial difference between the studied groups in terms of blood glucose, FPG, 2hPG, and HbA1c, with group II c having significantly higher levels than the other groups (Table 3).

Table (4): Comparison of lipid profile among the studied groups

		Group I: (n=50)	Group II a: (n=25)	Group II b: (n=21)	Group II c: (n=24)	P value	P value
TG (mg/dl)	**Mean ± SD**	132.7±13.2	143.5±16.7	149.6±20.2	163.2±27.5	**0.001***	P1=0.021* P2=0.001* P3=0.001* P4=0.271 P5=0.001* P6=0.018*
	Range	107-162	120-170	107-186	120-215		
TC (mg/dl)	**Mean ± SD**	171 ±13.1	188±23.4	197.5±28.7	215.8±49.9	**0.001***	P1=0.017* P2=0.001* P3=0.001* P4=0.267 P5=0.001* P6=0.034*
LDL-c (mg/dl)	**Mean ± SD**	85.9±14.1	109.4±19.1	122.4±26.2	146.2±6.4	**0.001***	P1=0.001* P2=0.001* P3=0.001* P4=0.102 P5=0.001* P6=0.003*
HDL-c (mg/dl)	**Mean ± SD**	58.5±5.2	49.9±7.8	45.2±5	36.9±4.3	**0.001**	P1=0.001* P2=0.001* P3=0.001* P4=0.006* P5=0.001* P6=0.001*

TC: total cholesterol, **TG:** triglyceride, **HDL-c:** High-density lipoprotein cholesterol, **LDL-c:** low-density lipoprotein cholesterol, **P1:** I and II a, **P2:** I and II b, **P3:** I and II c, **P4:** II a and II b, **P5:** II a and II c, **P6:** II b and II c, *: significant.

Table (5): Comparison of liver enzyme among the studied groups

		Group I: (n=50)	Group II a: (n=25)	Group II b: (n=21)	Group II c: (n=24)	P value
ALT (U/L)	**Mean ± SD**	30.4±5.7	29.4±5.9	31±6.5	30.2±5.1	0.813
	Range	15-40	18-38	15-40	20-38	
AST (U/L)	**Mean ± SD**	29.2±5.1	27.6±6.6	29.8±4.3	28.5±5.7	0.503
	Range	20-39	14-39	21-38	20-39	

ALT: Alanine transaminase, **AST:** Aspartate aminotransferase

There was no significant difference in ALT and AST levels across the study groups (Table 5).

Table (6): Comparison of HOMA-IR and Chemerin among the studied groups

		Group I: (n=50)	Group II a: (n=25)	Group II b: (n=21)	Group II c: (n=24)	P value	P value
HOMA-IR	**Mean ± SD**	5.4±0.7	6.7±0.6	8.4±0.6	10.6±0.8	**0.001***	P1=0.001* P2=0.001* P3=0.001* P4=0.001* P5=0.001* P6=0.001*
	Range	3.2-6.4	5.5-7.6	7.2-9.6	9.5-13.3		
Chemerin	**Mean ± SD**	62.1±6.4	67.5±5.6	75.2±7.5	87.3±7.9	**0.001***	P1=0.001* P2=0.001* P3=0.001* P4=0.001* P5=0.001* P6=0.001*
	Range	45-74	55-77	58-86	68-99		

HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, **P1:** I and II a, **P2:** I and II b, **P3:** I and II c, **P4:** II a and II b, **P5:** II a and II c, **P6:** II b and II c, *: significant.

Table 6 shows that group II c had significantly higher levels of Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and chemerin compared to the other groups (P<0.01).

Table (7): Correlation between Chemerin and different parameters among the studied groups

Correlations	Chemerin	
	r	P value
Age	**0.043**	0.645
BMI	**0.786**	**0.001***
Systolic pressure	**0.022**	0.814
Diastolic pressure	**0.013**	0.884
FPG	**0.576**	**0.001***
2hPG	**0.584**	**0.001***
HbA1c	**0.679**	**0.001***
TG	**0.500**	**0.001***
TC	**0.463**	**0.001***
LDL-c	**0.561**	**0.001***
HDL-c	**-0.647**	**0.001***
ALT	**0.044**	0.631
AST	**-0.007**	0.941
HOMA-IR	**0.777**	**0.001***

r: regression, **BMI:** Body mass index, **FPG:** Fasting plasma glucose, **2Hpg:** 2-hour plasma glucose, **HbA1c:** glycated hemoglobin, **TC:** total cholesterol, **TG:** triglyceride, **HDL-c:** High-density lipoprotein cholesterol, **LDL-c:** low-density lipoprotein cholesterol, **ALT:** Alanine transaminase, **AST:** Aspartate aminotransferase, HOMA-IR: homeostatic model assessment for insulin resistance, *: significant.

Chemerin showed a substantial positive correlation with BMI, FPG, 2hPG, HbA1c, TG, TC, LDL-c, and HOMA-IR, but a negative correlation with HDL-c (Table 7).

Table (8): Receiver observing characteristic analysis of chemerin for prediction of severity of NAFLD

	Cut-off	AUC	Sensitivity	Specificity	PPV	NPV	P value
Chemerin	77.5	0.96	71%	97.80%	91.70%	90.60%	0.001*

AUC: Area under the curve, **PPV:** positive predictive value, **NPV:** negative predictive value, *: significant

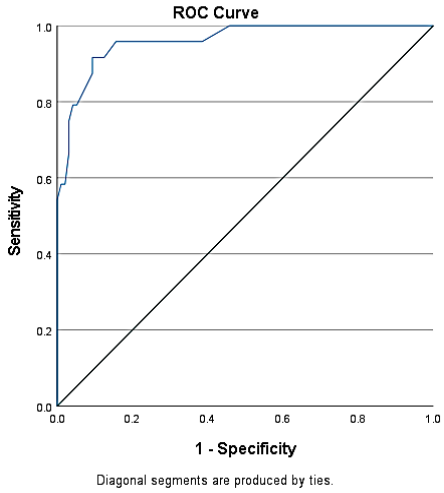

Figure (1): Receiver observing characteristic analysis of chemerin for prediction of severity of NAFLD

Chemerin, at a cut off of 77.5, can predict the severity of NAFLD with 71% sensitivity, 97.8% specificity, and the area under curve (AUC) of 0.96 (Table 8, figure 1).

The findings showed that BMI, HBa1c, TG, TC, HDL-c, and chemerin were all separate risk variables for NAFLD-exacerbated type 2 diabetes mellitus (Table 9).

Table (9): Logistic regression analysis for prediction of NAFLD

	Exp(B)	95% CI*		P value
		Lower	upper	
Sex	0.709	0.287	1.749	0.456
Age	0.99	0.929	1.055	0.753
BMI	19.352	3.027	123.7	**0.002***
Systolic pressure	0.943	0.832	1.069	0.362
Diastolic pressure	1.147	0.928	1.419	0.205
FPG	1.008	0.956	1.063	0.763
2hPG	1.013	0.979	1.049	0.465
HbA1c	17.032	3.979	72.908	**0.001***
TG	1.053	1.028	1.079	**0.001***
TC	1.03	1.014	1.046	**0.001***
LDL-c	1.014	0.993	1.036	0.186
HDL-c	0.72	0.605	0.857	**0.001***
ALT	1	0.925	1.081	0.993
AST	0.985	0.907	1.07	0.719
HOMA-IR**	102992.473	0.038	2.7	0.127
Chemerin	1.347	1.189	1.526	**0.001***

*: confidence interval, **: homeostatic model assessment for insulin resistance, **BMI:** Body mass index, **FPG:** Fasting plasma glucose, **2Hpg:** 2-hour plasma glucose, **HbA1c:** glycated hemoglobin, **TC:** total cholesterol, **TG:** triglyceride, **HDL-c:** High-density lipoprotein cholesterol, **LDL-c:** low-density lipoprotein cholesterol, **ALT:** Alanine transaminase, **AST:** Aspartate aminotransferase, HOMA-IR: homeostatic model assessment for insulin resistance, *: significant

DISCUSSION

The relationship between serum chemerin levels and metabolic indicators in patients with T2DM and NAFLD was examined in the current study. The severity of NAFLD was classified as mild, moderate, or severe using established ultrasonographic criteria. Our data revealed a number of important connections and patterns that require further investigation.

Our investigation found no significant differences in age and sex distribution among the tested groups, indicating equivalent baseline characteristics. However, BMI increased significantly across groups, with the highest levels seen in severe NAFLD patients (Group II c).

This finding is consistent with that of **Zhang *et al.*** [7], who discovered a substantial link between elevated BMI and NAFLD severity in T2DM patients. This association highlights the importance of obesity in the etiology of both illnesses. In line with, **Mohamed *et al.*** [14] sought to compare serum chemerin's diagnostic potential as a noninvasive marker for NAFLD diagnosis and grading in relation to the NAFLD fibrosis score. They found that there was a substantial difference in BMI between NAFLD cases and control groups. The link between obesity and NAFLD has previously been established [15].

Our investigation found no significant variations in blood pressure parameters across the groups, implying that hypertension may not be a distinguishing feature in the evolution of NAFLD in T2DM patients. This is in contrast to prior research, such as **Song *et al.*** [16], which reported a positive association between blood pressure and NAFLD severity. This disparity could be related to differences in patient populations or varying levels of blood pressure control in the analyzed cohorts.

In our investigation, the glycemic indices (FPG, 2hPG, and HbA1c) showed a substantial progressive increase with NAFLD severity, especially in Group II c. The mean HbA1c level rose from 7.5% in the T2DM-only group to 10.4% in severe NAFLD patients. These findings are congruent with those of **Xin *et al.*** [17], who found similar patterns of glycemic worsening with increasing NAFLD severity. This shows that NAFLD may contribute to poor glycemic control in T2DM patients, presumably by increasing insulin resistance and hepatic glucose production.

Also, this is in line with **El-Karaksy *et al.*** [18], who found that the mean HbA1c value for T1D patients with liver affection was 8.1 ± 1.2, whereas it was 7.6 ± 1.7 for patients with a normal liver. According to **Abdallah *et al.*** [19], the mean HbA1c percentage levels of the NAFLD patients who were enrolled in their study were $11.2\% \pm 1.9$, whereas the mean HbA1c levels of the patients with normal ultrasonography results were $9.9\% \pm 1.8$. The two groups differed significantly from one another ($P = 0.003$). In the NAFLD group, patients with poor glycemic control defined as HbA1c % > 10 were also substantially more common.

The lipid profile analysis in our study showed notable changes in each group, with NAFLD patients seeing a progressive worsening. In individuals with severe NAFLD, HDL-c significantly decreased while triglycerides, total cholesterol, and LDL-c significantly increased. Notably, HDL-c and NAFLD severity have an inverse association, which may indicate that HDL-c protects against the advancement of NAFLD. This is also in line with the findings of **Abdallah *et al.*** [19], who found that people with NAFLD had considerably reduced HDL ($p = 0.001$) and significantly higher serum lipid levels ($p = 0.001$, 0.019, and 0.001) for LDL, triglycerides, and cholesterol; respectively. Also, the results of **Barros *et al.*** [20] supported our findings, demonstrating that individuals with changed hepatic US findings had significantly higher triglyceride readings and lower HDL than patients with normal livers ($p = 0.028$ and 0.034, respectively). However, their research showed that there was no appreciable variation in the levels of LDL and total cholesterol across the normal liver group and cases with aberrant hepatic US findings. This runs counter to our findings.

It's interesting to note that, despite liver illness, there were no discernible changes in the groups' levels of the liver enzymes ALT and AST. Nonetheless, **Chen *et al.*** [21] observed that this conclusion is in line with current research that suggests normal liver enzymes do not rule out NAFLD. This highlights how crucial it is to test for NAFLD in T2DM patients using more than just liver enzymes. On the other hand, **Abdallah *et al.*** [19] found that patients with NAFLD had statistically significant higher levels of AST and ALT ($P = 0.019$ and 0.015, respectively).

Chemerin levels in our study significantly increased as the severity of NAFLD increased. In individuals with severe non-alcoholic fatty liver disease (NAFLD), the mean chemerin levels rose from 62.1 ng/ml to 87.3 ng/ml. The work of **Rodriguez *et al.*** [22], who also discovered increased chemerin levels in NAFLD patients, supports this substantial connection. Our findings are supported by **Zhuang *et al.*** [23], who discovered that NAFLD cases had higher serum chemerin levels than controls. These levels sharply declined after receiving metformin, indicating a strong correlation between NAFLD and both insulin resistance and serum chemerin levels. Additionally, this is consistent with the findings of **Mohamed *et al.*** [24], who found that serum chemerin levels were considerably greater in NAFLD cases compared to controls. Additionally, there was a favorable correlation between these levels and the NAFLD grade.

This observation is consistent with previous findings showing NAFLD patients have higher levels of chemerin [7, 25]. According to **Lehrke *et al.* [26],** adipocytes have higher levels of chemerin, which might decrease tyrosine phosphorylation, stimulate serine/threonine kinases, prevent glucose 4 from translocating, and result in insulin resistance in adipocytes.

Serum metabolin levels were shown to be considerably higher in populations with metabolic syndrome risk factors in another investigation conducted on a Caucasian population. According to this study, individuals suffering from type 2 diabetes complicated by NAFLD had a significantly higher serum chemerin level than individuals suffering from basic type 2 diabetes. Additionally, the more severe the NAFLD, the higher the serum chemerin level [27].

Additionally, **Kłusek-Oksiuta *et al.* [28]** sought to assess the levels of the blood of obese children with non-alcoholic fatty liver disease contains vaspin, chemerin, and omentin. Comparing to the control group they found that children with NAFLD had noticeably greater levels of chemerin. Compared to non-hepatopathic individuals, children with advanced liver steatosis had a significantly greater concentration of chemerin ($p = 0.02$). However, other studies found no discernible change in the levels of chemerin between the control and NAFLD groups [29, 30].

According to our research, HOMA-IR significantly increased as the severity of NAFLD increased. This is in line with **Zhang *et al.* [7],** who found that whereas pancreatic β-cell function was dramatically reduced, HOMA-IR was significantly elevated in individuals having NAFLD-complicated type 2 diabetes mellitus as opposed to those with simple type 2 diabetes mellitus. The severity of NAFLD increased with greater levels of HOMA-IR and decreased pancreatic β-cell activity.

The positive connection we found between chemerin and a number of metabolic markers (lipid profile, BMI, and glycemic indices) points to chemerin's possible use as a biomarker for the severity of NAFLD in individuals with type 2 diabetes. This was consistent with the findings of **Mohamed *et al.* [24],** who found a positive relationship between serum chemerin and BMI, serum triglycerides, serum cholesterol, and random blood sugar. According to earlier studies, **Ismail *et al.* [25]** and **Karczewska-Kupczewska *et al.* [31]**, there was a favorable connection between the lipid profile and serum chemerin and glycemic indices.

Karczewska-Kupczewska *et al.* [31] who aimed to examine young ------, serum chemerin levels and SAT chemerin expression in healthy persons in relation to obesity and insulin sensitivity. They found that compared to other groups, those who were obese had higher levels of serum chemerin.

According to the ROC analysis, chemerin demonstrated remarkable diagnostic performance (sensitivity 71%, specificity 97.8%, AUC 0.96) for predicting the severity of NAFLD at a cut-off value of 77.5 ng/ml. Although the moderate sensitivity means it may miss some cases, the high specificity implies that chemerin could be a useful tool for diagnosing severe NAFLD cases in T2DM patients. However, in a different investigation, serum chemerin showed 87.72% specificity ($P<0.001$) and 56.44% sensitivity at a cut-off level of 186.7 ng/mL [14]. These differences could result from different kits, different procedures, and different dilutions that the manufacturers recommend.

BMI, HbA1c, TG, TC, HDL-c, and chemerin were found to be independent risk variables for T2DM exacerbated by NAFLD by the logistic regression analysis. Chemerin's potential as a biomarker is further supported by this multivariate study, which also indicates that a combination of these indicators may have a higher predictive value for NAFLD in T2DM patients than any one of them alone. A detailed identification of the involvement of adipokines, particularly chemerin, in NAFLD is necessary due to the contradicting data regarding the pathophysiologic pathways tying them to the disease. As a result, it might be employed as a noninvasive biomarker for NAFLD diagnosis, and treatments that try to alter their levels might make it a new target for NAFLD treatment [32].

CONCLUSION

Our data collectively revealed that serum chemerin levels, as well as BMI, glycemic indices, and lipid profiles, were found to have a substantial correlation with NAFLD severity in type 2 diabetes patients. These data imply that chemerin could be a useful biomarker for diagnosing and monitoring NAFLD severity in T2DM patients. Further research is required to investigate the molecular mechanisms linking chemerin to NAFLD development and its potential as a therapeutic target.

REFERENCES

1. **Saeedi P, Petersohn I, Salpea P *et al.* (2019):** Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. Diabetes Res Clin Pract., 157:107843.
2. **Athyros G, Doumas M, Imprialos P *et al.* (2018):** Diabetes and lipid metabolism. Hormones, 17: 61-67.
3. **Radu F, Potcovaru G, Salmen T *et al.* (2023):** The link between NAFLD and metabolic syndrome. Diagnostics, 13(4): 614-620.
4. **Kosmalski M, Ziółkowska S, Czarny P *et al.* (2022):** The coexistence of nonalcoholic fatty liver disease and type 2 diabetes mellitus. J Clin Med., 11(5): 1375-1382.
5. **Mavrogiannaki N, Migdalis N (2013):** Nonalcoholic fatty

liver disease, diabetes mellitus and cardiovascular disease: Newer data. Int J Endocrino., 450639.

6. **Khneizer G, Rizvi S, Gawrieh S (2021):** Non-alcoholic fatty liver disease and diabetes mellitus. Diabetes Res Clin Pract., 4: 417-440.
7. **Zhang Z, Wang J, Wang H (2018):** Correlation of blood glucose, serum chemerin and insulin resistance with NAFLD in patients with type 2 diabetes mellitus. Exp Ther Med., 15 (3): 2936-2940.
8. **Castera L, Friedrich-Rust M, Loomba R (2019):** Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. Gastroenterology, 156:1264–81.e4.
9. **Zhu W, Liang A, Shi P *et al.* (2022):** Higher serum uric acid to HDL-cholesterol ratio is associated with onset of non-alcoholic fatty liver disease in a non-obese Chinese population with normal blood lipid levels. BMC Gastroenterol., 22:196.
10. **Zou Y, Zhong L, Hu C *et al.* (2021):** LDL/HDL cholesterol ratio is associated with new-onset NAFLD in Chinese non-obese people with normal lipids: A 5-year longitudinal cohort study. Lipids Health Dis., 20:28.
11. **Boutari C, Perakakis N, Mantzoros C (2018):** Association of Adipokines with Development and Progression of Nonalcoholic Fatty Liver Disease. Endocrinol Metab., 33: 33-43.
12. **Mirmajidi S, Izadi A, Saghafi-Asl M *et al.* (2019):** Inflammatory Potential of Diet: Association With Chemerin, Omentin, Lipopolysaccharide-Binding Protein, and Insulin Resistance in the Apparently Healthy Obese. J Am Coll Nutr., 38 (4): 302-310.
13. **Alberti G, Zimmet Z (1998):** Definition, diagnosis and classification of diabetes mellitus and its complications. Part. diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med., 15: 539–553.
14. **Mohamed A, Sabry S, Abdallah A *et al.* (2017):** Circulating adipokines in children with nonalcoholic fatty liver disease: possible noninvasive diagnostic markers. Ann Gastroenterol., 30 (4): 457-463.
15. **Polyzos A, Bugianesi E, Kountouras J *et al.* (2017):** Nonalcoholic fatty liver disease: updates on associations with the metabolic syndrome and lipid profile and effects of treatment with PPAR-γ agonists. Metabolism, 66: 64-8.
16. **Song R, Liu L, Ling H *et al.* (2022):** Severity of Nonalcoholic Fatty Liver Disease is Associated with Cardiovascular Outcomes in Patients With Prehypertension or Hypertension: A Community-Based Cohort Study. Front Endocrinol., 13:942647.
17. **Xin Z, Huang J, Cao Q *et al.* (2022):** Nonalcoholic fatty liver disease in relation to the remission and progression along the glycemic continuum. J Diabetes., 14(9):606-619.
18. **El-Karaksy M, Anwar G, Esmat G *et al.* (2010):** Prevalence of hepatic abnormalities in a cohort of Egyptian children with type 1 diabetes mellitus. Pediatr Diabetes., 11:467.
19. **Abdallah R, Youness R, Bedeir M *et al.* (2023):** Clinical and diagnostic characteristics of non-alcoholic fatty liver disease among Egyptian children and adolescents with type1 diabetes. Diabetol Metab Syndr., 15(1):52.
20. **Barros V, Monteiro C, Terra C *et al.* (2021):** Prevalence of non-alcoholic fatty liver disease and its associated factors in individuals with type 1 diabetes: a cross-sectional study in a tertiary care center in Brazil. Diabetol Metab Syndr., 13(1):33.
21. **Chen J, Yue J, Fu J *et al.* (2023):** A prediction model of liver fat fraction and presence of non-alcoholic fatty liver disease (NAFLD) among patients with overweight or obesity. Endocrine J., 70(10): 977-985.
22. **Rodríguez M, González-Diéguez L, Varela M *et al.* (2021):** Impact of alcohol abstinence on the risk of hepatocellular carcinoma in patients with alcohol-related liver cirrhosis. Official J Am Coll Gastroenterol., 116(12): 2390-2398.
23. **Zhuang X, Sun F, Li L *et al.* (2015):** Therapeutic Effect of Metformin on Chemerin in Non-Obese Patients with Non-Alcoholic Fatty Liver Disease (NAFLD). Clin Lab., 61 (10): 1409-1414.
24. **Mohamed G, Salama M, Byoumy E *et al.* (2021):** Chemerin as a non-invasive serum marker for non-alcoholic fatty liver disease. Egypt J Hosp Med., 84(1):1786-90.
25. **Ismail S, Elgendy N, El Sayed Z *et al.* (2019):** Chemerin and Vaspin as Noninvasive Biomarkers in the Pathogenesis and Diagnosis of Non- Alcoholic Fatty Liver Disease. Am J Med Med Sci., 9 (1): 7-13.
26. **Lehrke M, Becker A, Greif M *et al.* (2009):** Chemerin is associated with markers of inflammation and components of the metabolic syndrome but does not predict coronary atherosclerosis. Eur J Endocrinol.,161:339–344.
27. **Stejskal D, Karpisek M, Hanulova Z *et al.* (2008):** Chemerin is an independent marker of the metabolic syndrome in a Caucasian population - a pilot study. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.,152:217–221.
28. **Kłusek-Oksiuta M, Bialokoz-Kalinowska I, Tarasów E *et al.* (2014):** Chemerin as a novel non-invasive serum marker of intrahepatic lipid content in obese children. Ital J Pediatr., 40, 84.
29. **Ye Z, Wang S, Yang Z *et al.* (2014):** Serum lipocalin-2, cathepsin S and chemerin levels and nonalcoholic fatty liver disease. Mol Biol Rep., 41 (3): 1317-1323.
30. **Pohl R, Haberl E, Rein-Fischboeck L *et al.* (2017):** Hepatic chemerin mRNA expression is reduced in human nonalcoholic steatohepatitis. Eur J Clin Invest., 47 (1): 7-18.
31. **Karczewska-Kupczewska M, Nikołajuk A, Stefanowicz M *et al.* (2020):** Serum and adipose tissue chemerin is differentially related to insulin sensitivity. Endocr Connect., 9(5):360-369.
32. **Suliga E, Wawszczak M, Gluszek S (2018):** The roles of vaspin, chemerin, and omentin in the determination of metabolic Syndrome. Medical Studies/Studia Medyczne, 34 (2): 160–177.