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Correlation of Insulin Resistance Indexes with Blood levels of Zonulin, clusterin in patients with Nonalcoholic Fatty Liver Disease

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ABSTRACT

Background: Nonalcoholic fatty liver disease (NAFLD) is a prevalent metabolic disorder affecting approximately **25% of the global population**. It is closely linked to **insulin resistance (IR), obesity, type 2 diabetes, and metabolic syndrome**.

Objectives: The of this study to analyze the correlation between insulin resistance indexes (HOMA-IR, TyG Index) and serum levels of zonulin and clusterin in patients with NAFLD.

Method and materials: A case-control study was conducted at Kirkuk Teaching Hospital in Iraq. The study took place from September 15, 2024, to January 18, 2025, and included 90 participants between 30 and 60 years of age─60 patients diagnosed with NAFLD (30 males and 30 females) and 30 healthy controls (15 males and 15 females). Serum measurements of fasting blood glucose (FBS) and triglycerides (TG) were performed using automated biochemical analyzers. Fasting insulin, zonulin, and clusterin were estimated by enzyme-linked immunosorbent assay (ELISA).

Results: NAFLD patients exhibited significantly higher fasting blood sugar (132.94 ± 21.34 mg/dL vs. 100.19 ± 10.61 mg/dL, $p<0.01$), triglycerides (191.19 ± 19.04 mg/dL vs. 144.53 ± 16.48 mg/dL, $p<0.01$), insulin (19.98 ± 4.54 mIU/mL vs. 8.97 ± 3.47 mIU/mL, $p<0.01$), HOMA-IR (6.73 ± 2.44 vs. 2.27 ± 1.03, $p<0.01$), and TyG Index (9.43 ± 0.23 vs. 8.88 ± 0.20, $p<0.01$) than controls. Zonulin (72.50 ± 8.24 ng/mL vs. 57.17 ± 8.26 ng/mL, $p<0.01$) and clusterin (186.82 ± 25.29 ng/mL vs. 132.79 ± 21.76 ng/mL, $p<0.01$) were also significantly elevated. Correlation analysis showed zonulin and clusterin were positively associated with insulin resistance markers (HOMA-IR, fasting insulin and TyG Index; $p<0.01$). ROC curve analysis revealed HOMA-IR (AUC = 0.975) as the most powerful diagnostic marker, followed by TyG Index (AUC = 0.966), clusterin (AUC = 0.945), and zonulin (AUC = 0.903).

Conclusions: Zonulin, and clusterin levels were significantly higher in patients with NAFLD, HOMA-IR remains the best predictor of NAFLD, while TyG Index, clusterin, and zonulin may serve as additional biomarkers.

Keywords: *Zonulin; hepatic steatosis; HOMA-IR; TyG Index*

1. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a multifaceted condition marked by the deposition of fat in the liver without any sign of excessive alcohol intake. This is a prevalent liver disease globally, impacting almost 25% of the world's population. It is strongly linked to obesity, type 2 diabetes, and metabolic syndrome[(1)]. NAFLD starts with the excessive accumulation of triglycerides in hepatocytes (simple steatosis) and progresses to hepatic steatosis accompanied by inflammation (non-alcoholic steatohepatitis, NASH), followed by fibrosis, cirrhosis, and finally hepatocellular carcinoma (HCC)[(1–4)].

The consumption of high-fat and high-calorie foods, coupled with a sedentary lifestyle, promotes the onset of obesity, insulin resistance, and type 2 diabetes mellitus, all of which lead to impaired metabolic regulation and the progression of fatty liver disease, now recognized as the most prevalent chronic liver disease globally [(5–7)].

Non-alcoholic fatty liver disease (NAFLD) represents a major hepatic disorder, needing large medical costs, causing economic harms, and lowering health-related quality of life [4] . The majority of patients are asymptomatic; However, they may report fatigue malaise, and a sense of fullness or discomfort in the right upper abdomen [8–9].

Timely identification and intervention of NAFL may stop progression to more severe NAFLD, including NASH, liver fibrosis, and cirrhosis. Liver biopsy is the gold standard for diagnosing hepatic steatosis and its progressive stages; however, other non-invasive techniques are available for clinical practice. Ultrasound is commonly used as a primary imaging modality in clinical practice due to its low cost, great availability, and absence of radiation exposure [6]. Lifestyle modifications, including significant weight reduction through low-calorie diets and increased physical activity, are seen as primary therapies for managing NAFLD, as weight loss is associated with a decrease in liver fat, potentially reversing disease development [10–11].

Insulin resistance (IR) appears to play an essential role in the development of NAFLD. It really results in heightened hepatic lipogenesis and insufficient regulation of lipolysis in adipose tissue, so increasing the influx of fatty acids into the liver. Additionally, under insulin resistance conditions, the beta-oxidation of free fatty acids (FFAs) is reduced, hence promoting the hepatic buildup of lipids. Upon accumulation in the liver, FFAs can trigger modifications in insulin signaling pathways by activating serine kinases, hence promoting the systemic condition of IR[12,13]. The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) is a significant metric for evaluating insulin resistance and serves as the diagnostic criteria for NAFLD. The Triglyceride Glucose (TyG) Index is recognized as a reliable and direct surrogate marker of IR. It also possesses considerable importance in metabolic disorders, including NAFLD[14,15].

Zonulin is an acute-phase protein that regulates intestinal permeability by reducing the stability of tight junctions and is proposed as a biomarker for intestinal permeability, measurable in both blood and fecal samples.[16] .

Clusterin (CLU), or apolipoprotein J, is a secreted glycoprotein characterized by a highly conserved heterodimeric structure. It is expressed in various tissues and can be identified in all human bodily fluids [17].

2. MATERIALS AND METHODS

A case-control study was carried out on a total of 90 individuals (includes patients and healthy). This study was carried out with the approval of the Scientific Research Committee of College of Medicine, University of Tikrit, and the Regional Research Committee of Kirkuk Health Administration, and was conducted at Kirkuk Teaching Hospital, in Kirkuk City, Iraq.

The patients included in this study were recruited during the period from 15th September 2024 to 18th January 2025.

Study Groups

Patients diagnosed with NAFLD by upper abdomen ultra-sonogram were included in the study. This study investigated 60 patients (30 male and 30 female); they ranged in age from 30 to 60 years. Submitted to the primary accommodations from Kirkuk Teaching Hospital.

For standardization and comparison, a group of 30 apparently healthy individuals was selected (by upper abdomen ultra-sonogram). The individuals were matched for sex, age, and weight with the patient groups. The age range of the individuals was between 30 and 60 years, with 15 males and 15 females. This control group was confirmed to be free of any illness and not taking any medication.

After fasting for 8–12 hours, approximately 6 ml of venous blood was collected from each case. The blood was allowed to clot immediately and then centrifuged to separate the serum. Serum levels of zonulin, clusterin, and insulin levels were measured using sandwich enzyme-linked immunosorbent assay (ELISA) kits. Additionally, serum glucose and triglyceride were measured colorimetrically using commercially available kits on a fully automated analyzer in the Clinical Biochemistry Laboratory. The following equations were used to calculate HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) and TyG (Triglyceride-Glucose Index).

- Calculation of HOMA-IR[18]

$$HOMA - IR = \text{fasting serum insulin level(uIU/ml)} \times \text{fasting glucose level (mg/dL)}/405$$

- Calculation of triglyceride-glucose (TyG) index[19]

$$TyG\ index = \ln(\text{Fasting Triglycerides (mg/dL)} \times \text{Fasting Glucose (mg/dL)}/2)$$

All statistical analyses were performed using GraphPad Prism version 9.0 (GraphPad Software, San Diego, CA, USA) and IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). The ROC curve analysis was performed using MedCalc Statistical Software version 20.115 (MedCalc Software Ltd, Ostend, Belgium). Data normality was assessed using the Shapiro-Wilk test. Continuous variables are presented as mean ± standard deviation (SD). Between-group comparisons were conducted using the Mann-Whitney U test for non-normally distributed data and independent t-tests for normally distributed data. Correlations between variables were evaluated using Spearman's rank correlation coefficient. Statistical significance

was set at $p < 0.05$, with all tests being two-tailed.

3. RESULTS

This study shows that fasting blood sugar (FBS) levels were significantly higher in patients (132.94 ± 21.34 mg/dL) compared to controls (100.19 ± 10.61 mg/dL) ($p<0.01$). Similarly, triglyceride (TG) levels were elevated in patients (191.19 ± 19.04 mg/dL) compared to controls (144.53 ± 16.48 mg/dL) ($p<0.01$), indicating lipid abnormalities. Additionally, insulin levels were significantly increased in patients (19.98 ± 4.54 mIU/mL) compared to controls (8.97 ± 3.47 mIU/mL) ($p<0.01$). The HOMA-IR index was also markedly higher in patients (6.73 ± 2.44) than in the control group (2.27 ± 1.03) ($p<0.01$), reflecting greater insulin resistance. Lastly, the Triglyceride-Glucose Index (TyG) was significantly elevated in patients (9.43 ± 0.23) compared to controls (8.88 ± 0.20) ($p<0.01$), further supporting the presence of metabolic disturbances, as shown in Table 1.

Table 1: Comparison of Metabolic Parameters Levels Between Patients and Controls.

Parameter	Patients (n=60)	Controls (n=30)	p-value
FBS mg/dl	132.94 ± 21.34	100.19 ± 10.61	<0.01
TG mg/dl	191.19 ± 19.04	144.53 ± 16.48	<0.01
Insulin level mIU/mL	19.98 ± 4.54	8.97 ± 3.47	<0.01
HOMA-IR	6.73 ± 2.44	2.27 ± 1.03	<0.01
TyG	9.43 ± 0.23	8.88 ± 0.20	<0.01

The values are expressed as mean ± standard deviation, and the p-values are provided to assess the statistical significance of the differences between the groups.

This study demonstrates that both Clusterin and Zonulin levels were significantly elevated in patients compared to the control group. Clusterin levels were markedly higher in patients (186.82 ± 25.29 ng/mL) compared to controls (132.79 ± 21.76 ng/mL), with a statistically significant difference ($p<0.01$). Similarly, Zonulin levels were significantly increased in patients (72.50 ± 8.24 ng/mL) compared to the control group (57.17 ± 8.26 ng/mL) ($p<0.01$). As shown in Table 2.

Table 2: Comparison of Serum Clusterin and Zonulin Levels Between Patients and Controls.

Parameter	Patients (n=60)	Controls (n=30)	p-value
Clusterin ng/ml	186.82 ± 25.29	132.79 ± 21.76	<0.01
Zonulin ng/ml	72.50 ± 8.24	57.17 ± 8.26	<0.01

Values are presented as mean ± standard deviation. Both biomarkers showed significantly higher concentrations in patients compared to controls ($p < 0.01$). Clusterin demonstrated a more pronounced elevation (40.7% increase) compared to zonulin (26.8% increase) in the patient group. Statistical significance was determined using Mann-Whitney U test.

Table 3: Correlation analysis of various biomarkers and clinical parameters in patients group.

		clusterin ng/ml	Zonulin ng/ml	HOMA -IR	insulin level mIU/mL	TyG
clusterin ng/ml	r	1.00	0.463	0.393	0.479	0.329
	p		<0.001	0.002	<0.001	0.010
Zonulin ng/ml	r	0.463	1.00	0.416	0.422	0.537
	p	<0.001		<0.001	<0.001	<0.001
HOMA -IR	r	0.393	0.416	1.00	0.949	0.847
	p	0.002	<0.001		<0.001	<0.001
insulin level	r	0.479	0.422	0.949	1.00	0.726

mIU/mL	p	<0.001	<0.001	<0.001		<0.001
TyG	r	0.329	0.537	0.847	0.726	1.00
	p	0.010	<0.001	<0.001	<0.001	
FBS mg/dl	r	0.247	0.400	0.890	0.720	0.914
	p	0.057	0.002	<0.001	<0.001	<0.001
TG mg/dl	r	0.310	0.543	0.469	0.468	0.749
	p	0.016	<0.001	<0.001	<0.001	<0.001

The matrices display Pearson correlation coefficients (r) and their corresponding p-values (p), Patient group.

Table 4: Diagnostic Performance Metrics of Key Biomarkers and Clinical Parameters.

Variable	AUC	95% CI	Cutoffs	Sens.	Spec.	+LR	-LR	+PV	-PV
Zonulin ng/ml	0.903	0.823 to 0.956	>66.13	81.67	86.67	6.13	0.21	92.5	70.3
Clusterin ng/ml	0.945	0.876 to 0.982	>162.88	83.33	93.33	12.50	0.18	96.2	73.7
TyG	0.966	0.904 to 0.993	>9.056	93.33	80.00	4.67	0.083	90.3	85.7
HOMA IR	0.975	0.918 to 0.996	>3.420	96.67	86.67	7.25	0.038	93.5	92.9

Area Under the Curve (AUC) - CI 95% Confidence Interval - Sensitivity (Sens.) -

Specificity (Spec.) - Positive Likelihood Ratio (+LR) - Negative Likelihood Ratio (-LR) - Positive Predictive Value (+PV) Negative Predictive Value (-PV).

4. DISCUSSION

FBS levels were significantly elevated in patients (132.94 ± 21.34 mg/dl) compared to controls (100.19 ± 10.61 mg/dl) ($p < 0.01$). The 32.7% increase indicates impaired glucose regulation in patients. The notably larger standard deviation in patients suggests more variable glycemic control compared to controls.

The present investigation indicated that FBS was considerably higher in the NAFLD group compared to the control group. This aligned with another research in which FBS was similarly the NAFLD group exhibited greater values in comparison to the control group [20].

A strong link has been found between dysglycemia and fatty liver disease. Specifically, it was discovered that higher FBF levels were associated with an increased likelihood of FLD [21].

Fasting insulin concentrations were significantly higher in patients (19.98 ± 4.54 mIU/mL) compared to controls (8.97 ± 3.47 mIU/mL) ($p < 0.01$). This 122.7% elevation indicates marked hyperinsulinemia in the patient group.

This study found that the NAFLD group had much higher fasting insulin levels than the control group. This was in agreement with another study that found that fasting insulin levels were much higher in the NAFLD group compared to the control group[22] .This has been explained by the fact that NAFLD patients have lower insulin sensitivity [23].

Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) values were markedly elevated in patients (6.73 ± 2.44) compared to controls (2.27 ± 1.03) ($p < 0.01$). This increase indicates substantial insulin resistance in the patient group. The higher standard deviation in the patient group suggests greater variability in insulin resistance among patients compared to controls.

This study found that the NAFLD group had much higher HOMA-IR than the control group. This was in agreement with

other studies that found that HOMA-IR was much higher in the NAFLD group compared to the control group[24,25].

The Triglyceride-Glucose (TyG) index showed significant elevation in patients (9.43 ± 0.23) versus controls (8.88 ± 0.20) ($p < 0.01$). While the absolute difference appears modest, the narrow standard deviations in both groups indicate this is a consistent and reliable finding, suggesting altered glucose-lipid homeostasis in patient.

In this study, the Triglyceride-Glucose (TyG) index was significantly higher in the patient group compared with the control group. These observations agree with those of Simental-Mendia et al [25] and Peng, et al[26] both of whom reported elevated TyG levels in NAFLD patients compared to controls. Zhang et al demonstrated TyG efficacy in detecting insulin resistance in NAFLD patients, showing high sensitivity and specificity[27].

Analysis of serum clusterin levels revealed significantly elevated concentrations in patients (186.82 ± 25.29 ng/ml) compared to control subjects (132.79 ± 21.76 ng/ml) ($p < 0.01$). This marked elevation, representing an approximately 40.7% increase, suggests substantial alterations in clusterin expression in the patient group. The relatively narrow standard deviations in both groups indicate consistent clusterin elevation across the patient population, strengthening the reliability of this finding. The results of our study agree with Wang et al, who found that the participants with NAFLD had significantly higher serum clusterin levels than those without NAFLD [28].

Although clusterin is a glycoprotein that is found in many organs, it is thought to come mostly from the liver because hepatocytes have higher amounts of clusterin mRNA expression than other cells [29]. This protein is crucial for controlling inflammation and immune reactions because it works with complement factors, immunoglobulins, and different pathways that cause inflammation [30] .Remarkably, an increase in clusterin levels has been linked to insulin resistance, suggesting that it may play a role in metabolic control [31]. Despite a decrease in the amount of clusterin bound to lipoproteins, hyperlipidemia causes an increase in serum clusterin (apo J) levels[32].

In the framework of NAFLD, which is characterized by inflammation, metabolic dysregulation, and insulin resistance, our results indicate that clusterin is raised and might potentially play a role in the development of the illness.

Serum zonulin concentrations demonstrated a significant elevation in the patient group (72.50 ± 8.24 ng/ml) compared to controls (57.17 ± 8.26 ng/ml) ($p < 0.01$). This 26.8% increase in zonulin levels suggests potential alterations in intestinal permeability among patients. The comparable standard deviations between groups indicates consistent zonulin elevation across the patient population. The results of our study agree with Wang et al, who demonstrated that serum zonulin concentration is increased in children and adolescents with NAFLD than those without NAFLD[28].

Nonalcoholic Fatty Liver Disease is characterized by excessive fat deposition in the liver and is associated with low-grade chronic inflammation, involves an elevated production of interleukin-6 (IL-6), which in turn induces zonulin expression via Signal Transducer and Activator of Transcription 3(STAT3) activation and miR-18a [33–35]. Zonulin acts as a pivotal regulator of intestinal permeability, and its increased levels lead to the so-called “leaky gut,” allowing bacterial translocation and the influx of bacterial products into the bloodstream. This process increases hepatic inflammation, thereby advancing the disease from simple steatosis to the more severe non-alcoholic steatohepatitis (NASH) [36].

Hendy et al, demonstrated elevated zonulin and IL-6 levels in NAFLD patients compared with healthy controls[37]. Our study aligns with these findings about elevated zonulin in NAFLD patients.

Our study revealed significant positive correlations between serum clusterin levels and multiple metabolic. Zonulin ($r = 0.463$, $p < 0.001$) showed a strong association with clusterin, suggesting a potential link between gut permeability and metabolic dysfunction. In terms of insulin resistance, clusterin correlated positively with HOMA-IR ($r = 0.393$, $p = 0.002$), fasting insulin levels ($r = 0.479$, $p < 0.001$), TyG index ($r = 0.329$, $p = 0.010$), and fasting blood sugar (FBS) ($r = 0.247$, $p = 0.057$), indicating its involvement in glucose metabolism and insulin sensitivity.

Furthermore, clusterin exhibited positive correlations with triglycerides (TG) ($r = 0.310$, $p = 0.016$). These findings collectively highlight clusterin as a key biomarker in NAFLD, influencing insulin resistance, lipid metabolism.

Our study revealed significant positive correlations between zonulin levels and multiple metabolic. Zonulin showed a positive correlation with insulin resistance markers, including HOMA-IR ($r = 0.416$, $p < 0.001$), fasting insulin levels ($r = 0.422$, $p < 0.001$), TyG index ($r = 0.537$, $p < 0.001$) and fasting blood sugar (FBS) ($r = 0.400$, $p < 0.001$), suggesting its role in glucose metabolism impairment and insulin resistance. Additionally, zonulin was significantly correlated with triglycerides (TG) ($r = 0.543$, $p < 0.001$). These findings highlight zonulin’s potential role in metabolic dysfunction, linking it to insulin resistance, and lipid dysregulation, which are key contributors to NAFLD pathophysiology.

As shown in table (4) our study demonstrated that HOMA-IR is the most powerful marker (AUC = 0.975), with high sensitivity (96.67%) and specificity (86.67%). Its low -LR (0.038) makes it the best for ruling out disease, while its high sensitivity ensures minimal missed cases.

TyG ranks second (AUC = 0.966), with strong sensitivity (93.33%) but lower specificity (80.00%). It is highly effective for ruling out disease but slightly weaker for confirming diagnoses compared to HOMA-IR and Clusterin.

Clusterin is a strong marker (AUC = 0.945), with high specificity (93.33%) and a superior +LR (12.50), making it the best for confirming disease. However, its lower sensitivity (83.33%) makes it less effective for ruling out cases.

Zonulin is the weakest among the four (AUC = 0.903), with moderate sensitivity (81.67%) and specificity (86.67%). It has the lowest +LR (6.13) and highest -LR (0.21), making it the least reliable but still useful when combined with stronger markers.

5. CONCLUSION

NAFLD patients exhibit significant metabolic dysregulation, including insulin resistance, increased zonulin, and elevated clusterin levels. These findings suggest a potential role of zonulin and clusterin in NAFLD pathophysiology, particularly in metabolic dysfunction and gut permeability alterations. HOMA-IR remains the best predictor of NAFLD, while TyG Index, clusterin, and zonulin may serve as additional biomarkers.

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