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ORIGINAL RESEARCH

INTELECTIN-1 AS A DIAGNOSTIC BIOMARKER FOR NONALCOHOLIC FATTY LIVER DISEASE

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ABSTRACT

In this study, non-alcoholic fatty liver disease (NAFLD) is characterized by the accumulation of fats in the liver cells of individuals who abstain from alcohol consumption. Here, the objective was to assess the levels of intelectin-1, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), insulin, random blood sugar (RBS), total protein, albumin, globulin, triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) in the serum of NAFLD patients. Also, the study investigated the changes in intelectin-1 and other biochemical parameters' ratios in patients and compared them to healthy subjects. It was also determined if alterations in intelectin-1 levels can serve as a diagnostic predictor of NAFLD. 90 volunteers were involved in this study, among them 60 who were patients diagnosed with NAFLD at Baquba Teaching Hospital, Diyala Province, Iraq, between January 10, 2022, and December 30, 2022. The other 30 were healthy individuals who were recruited as a control group. It was found that levels of intelectin-1 in serum were significantly higher in NAFLD patients compared to healthy individuals ($p < 0.05$). Significant elevations ($p < 0.05$) were observed in the mean values of ALT and AST in patients compared to controls. Levels of insulin, ALP, total protein, Albumin, RBS, and Globulin showed non-significant elevations in patients compared to controls ($p > 0.05$). Serum levels of TC, TG, LDL, and VLDL demonstrated substantial and significant elevations ($p < 0.05$) in patients compared to controls, while HDL levels were reduced, albeit non-significantly. We found that intelectin-1 levels exhibited the highest sensitivity and area under the curve (AUC) in the receiver operating characteristic curve compared to other biochemical factors. Thus, an increase in intelectin-1 levels that are accompanied by the elevation of TG, TC, LDL, VLDL, and liver function parameters can serve as a predictor in diagnosing NAFLD patients.

Keywords: NAFLD; intelectin-1; insulin; lipids; RBS; total protein

INTRODUCTION

Globally, Nonalcoholic fatty liver disease (NAFLD) is one of the largest public liver diseases¹. NAFLD is characterized by the accumulation of triglycerides in hepatic cells in individuals who abstain from alcohol consumption. This condition initially exhibits no indications of liver cell inflammation or damage². If not identified or addressed in its initial phases, NAFLD can progress to liver cirrhosis, a grave condition

that may lead to mortality. The disease is frequently associated with other health conditions, including type 2 diabetes, hypertension, obesity, metabolic syndrome, and cardiovascular complications³.

Hepatic insulin resistance in patients with NAFLD impairs the ability of insulin to suppress glucose production, causing mild hyperglycemia. This stimulation could increase insulin secretion and result in hyperinsulinemia. The metabolic disruptions are intricately connected to the buildup of fat in the liver,

even when the body mass index (BMI) is not elevated⁴. Here, pro-inflammatory cytokines play a pivotal role in the progression of fatty liver disease⁵.

Adipokines are a group of regulatory proteins derived from adipose tissue that play diverse roles across the central, local, and peripheral systems⁶. These molecules are notably important in the context of fatty liver disease, as their concentrations vary between individuals with the condition and those without it⁷. Intelectin-1, also referred to as Omentin-1, is a type of adipokine. It is a polypeptide hormone that is produced and released primarily by visceral fat tissue. It can be found surrounding the internal organs, such as the liver, intestines, and kidneys⁸. Alteration of intelectin-1 expression is associated with several chronic inflammatory illnesses⁹. Intelectin-1 increases insulin sensitivity and glucose uptake¹⁰ and alters the metabolism of fat¹¹. Hence, the levels of insulin and glucose affect the intelectin-1 level¹². Recent research has identified associations between the high and low concentrations of intelectin-1 and a broad spectrum of chronic inflammatory disorders¹³.

In our work, we compared the concentrations of intelectin-1 and other biomarkers measured in patients with NAFLD to those of the healthy control. In addition to this, we aimed to find whether or not changes in intelectin-1 levels could be used as a marker for identifying patients with NAFLD.

MATERIALS AND METHODS

2-1 Collection of samples

Blood samples of a total number of 90 were collected between October 1st, 2022, and December 30th, 2022, at Baquba Teaching Hospital in Diyala Governorate/Iraq. Among these samples, 60 were obtained from NAFLD patients diagnosed via ultrasound examination conducted by a specialist physician. These patients were 31 males and 29 females, aged from 30 to 70 years. The other samples (30) were taken from “apparently” healthy individuals who participated as the control group and aged between 30 and 70 years. This group was divided equally based on gender classification, 15 males and 15 females. Each participant provided 5 ml of venous blood utilizing polymeric sterile medical syringes. The drawn blood samples were then set in plain tubes and allowed to clot for 10-30 minutes. The serum was separated by centrifugation for 5 minutes at 3000 rpm. Each serum sample was

divided into three parts: the first part was used for the estimation of cholesterol, triglycerides (TG), aspartate aminotransferase (AST), high-density lipoprotein (HDL), alkaline phosphatase (ALP), alanine aminotransferase (ALT), albumin (ALB), random blood sugar (RBS), globulin, and total protein. The second sample was allocated for insulin analysis, while the third was preserved at -20 °C in a deep freezer until required for the ELISA-based quantification of Intelectin-1. Anthropometric measurements were obtained, encompassing age, height, weight, and waist circumference. The body mass index (BMI) was calculated using the formula: weight (kg) divided by height (m) squared.

2-2 Analysis of clinical parameters

To determine the concentration of Intelectin-1 in serum samples, an ELISA kit manufactured by Human Company (Germany) was utilized. Serum insulin levels were assessed using the HS-INSULIN-CHECK-1 rapid quantitative assay. Commercial kits from Human Company (Germany) were also used to measure AST, ALT, ALP, albumin, globulin, and total protein. Additionally, serum levels of random blood sugar (RBS), triglycerides (TG), total cholesterol (TC), and high-density lipoprotein (HDL) were analyzed with the aid of a German-made COBS 411 automated chemical analyzer. The low-density lipoprotein (LDL)-Cholesterol and very low-density lipoprotein (VLDL)-Cholesterol were derived using the Friedewald equation, as follows: LDL-Cholesterol = [Total Cholesterol] - [HDL-Cholesterol] - ([Triglycerides]/5), VLDL-Cholesterol = [Triglycerides]/5.

2-3 Statistical analysis

The statistical analysis was performed using SPSS software version 25, The results were presented as mean values accompanied by standard deviations. To assess the significance of differences between variable factors, an independent chi-square test and t-test were employed. Here, a significance level of $p < 0.05$ was considered statistically significant. Pearson correlations were established using the t-test to determine the significance of correlations between two quantitative variables.

3.RESULTS

The study results revealed significant differences ($p < 0.05$) in age, body mass index (BMI), and waist circumference between the two studied groups. The mean values for age, BMI, and waist circumference were higher in patients (46.78 ± 12.30 years, 31.79 ± 5.72 kg/m², and 108.33 ± 16.48 cm, respectively) compared to healthy individuals (40.07 ± 10.05 years, 26.22 ± 5.57 kg/m², and 92.21 ± 11.41 cm, respectively), as presented in Table 1.

Table 1. Comparison of Age, BMI, and Waist Circumference between Nonalcoholic Fatty Liver Disease Patients and Healthy Individuals

Groups		N	Mean ± Std. Deviation	P value
Age (years)	Patients	60	46.78 ± 12.30	p<0.05*
	Healthy	30	40.07 ± 10.05	
BMI (Kg/m ²)	Patients	60	31.79 ± 5.72	P<0.05*
	Healthy	30	26.22 ± 5.57	
Waist (cm)	Patients	60	108.33 ± 16.48	p<0.05*
	Healthy	30	92.21 ± 11.41	

*= significant, **= high significant, ***= very high significant

3-2 Anthropometries of Fatty Liver patients and the healthy group

As previously stated, the age range of the nonalcoholic fatty liver disease patients was 30-70 with an average of 46.78 ± 12.30. The results indicate that nonalcoholic fatty liver disease incidence rises along with age for both genders, but this enhancement is not statistically significant (P > 0.05). Nevertheless, males comprise the majority of affected NAFLD patients, accounting for 53.3% compared to 46.7% of females. Regarding gender and age groups, the current findings suggest no remarkable differences (P > 0.05) between age and gender groups within the studied groups. However, based on BMI levels, high differences (P ≤ 0.05) were observed between the patients and healthy groups. The majority of patients (90.0%) fell within the obese weight BMI category, whereas the majority of healthy individuals (70.0%) fell within the normal weight BMI category. Table 2 illustrates these findings.

Table 2. Comparative Anthropometric Merits of Participants Using the Chi-Square Test

			Groups		Total	P value
			Patients	Healthy		
Gender	Male	N	32	15	47	p>0.05
		%	53.3%	50.0%	52.2%	
	Female	N	28	15	43	
		%	46.7%	50.0%	47.8%	
Age group (years)	30-39	N	15	18	39	p>0.05
		%	25.0%	60.0%	43.3%	
	40-49	N	13	6	19	
		%	21.7%	20.0%	21.1%	
	50-59	N	21	5	20	
		%	35.0%	16.7%	22.2%	
	60-70	N	11	1	12	
		%	18.3%	3.3%	13.3%	
BMI	Normal	N	6	21	15	P<0.05*
		%	10.0%	70.0%	16.7%	
	Obese	N	54	9	75	
		%	90.0%	30.0%	83.3%	

*= significant, **= high significant, ***= very high significant

3-3 Comparison of liver function factors in the investigated groups

The results indicate significant differences (p < 0.05) between the ALT and AST biomarkers among the studied groups. The mean values for ALT and AST were higher in patients (28.51 ± 12.78 and 32.23 ± 10.36, respectively) compared to the healthy group. However, no significant differences (p > 0.05) were observed for ALP and albumin levels between the studied groups. Our findings in this regard are summarized in Table 3.

Table 3. Comparative Liver Function Factors Between Studied Groups Using T-Test

Groups	N	Mean± Std. Deviation	P value
ALT (U/L)	Patients	60	28.51±12.78
	Healthy	30	18.05±5.72
AST (U/L)	Patients	60	32.23±10.36
	Healthy	30	23.05±6.80
ALP (U/L)	Patients	60	186.68±53.82
	Healthy	30	182.16±47.20
Albumin (g/dl)	Patients	60	3.31±0.65
	Healthy	30	3.67±0.35

*= significant, **= high significant, ***= very high significant

3-4 Comparison of RBS and lipid profile between the investigated groups

The study results revealed significant differences ($p < 0.05$) in cholesterol, TG, VLDL, and LDL levels when comparing between the studied groups. The mean values of cholesterol, TG, VLDL, and LDL were significantly higher in patients (237.70 ± 50.93 , 337.62 ± 152.09 , 67.52 ± 30.42 , and 132.31 ± 53.93 , respectively) than in healthy controls (194.10 ± 29.80 , 197.00 ± 42.07 , 49.83 ± 25.41 , and 104.44 ± 33.26 , respectively). HDL and RBS levels were decreased in patients compared to healthy controls, but the decreases were without significant differences ($p > 0.05$) between the studied groups as depicted in Table 4.

Table 4. Comparative RBS and Lipid Profile Parameters Between Studied Groups Using T-Test

Groups	N	Mean± Std. Deviation	P value
RBS(mg/dl)	Patients	60	150.86 ± 78.54
	Healthy	30	155.27 ± 72.13
Cholesterol (mg/dl)	Patients	60	237.70±50.93
	Healthy	30	194.10±29.80
TG (mg/dl)	Patients	60	337.62±152.09
	Healthy	30	197.00±42.07
VLDL (mg/dl)	Patients	60	67.52±30.42
	Healthy	30	49.83±25.41
HDL (mg/dl)	Patients	60	36.98±5.03
	Healthy	30	40.77±5.92
LDL (mg/dl)	Patients	60	132.31±53.93
	Healthy	30	104.44±33.26

*= significant, **= high significant, ***= very high significant

3-5 Comparison of proteins, globulin, insulin, and Intelectin-1 in studied groups

The results did not reveal significant differences ($p > 0.05$) in the values of RBS, total protein, globulin, and insulin between the two studied groups. Although these parameters showed increases in patients compared to controls, these increases were not statistically significant ($p > 0.05$). However, the mean value of intelectin-1 was significantly higher in patients (1.00 ± 0.29) compared to healthy controls, with a p-value less than 0.05, indicating a statistically significant difference. These outcomes are summarized in Table 5 below.

Table 5. A comparison of the Protein, Globulin, Insulin, and Intelectin-1 Levels Between Studied Groups Using the T-Test

Groups	N	Mean± Std. Deviation	P value
Protein (g/dl)	Patients	60	7.93±0.17
	Healthy	30	7.86±0.22
Globulin (g/dl)	Patients	60	4.62±0.69
	Healthy	30	4.19±0.44
Insulin (IU/ml)	Patients	60	18.06±5.95
	Healthy	30	16.59±4.39
Intelectin-1 (ng/mL)	Patients	60	1.10±0.30
	Healthy	30	0.41±0.25

*= significant, **= high significant, ***= very high significant

3-6. Receiver Operating Characteristic (ROC) Curve, Sensitivity, and Specificity of Variables

The plotting of the receiver operating characteristic (ROC) curve provides a measure of the investigative power of serological tests, expressed as the AUC. The AUC simplifies the comparison of various tests into a single number. Hence, Table 6 illustrates that intelectin-1 exhibits the highest AUC and sensitivity of 0.921 and 91%, respectively. In contrast, ALT, AST, cholesterol, TG, VLDL, and globulin parameters displayed sensitivities of 73%, 75%, 74%, 83%, 70%, and 73%, respectively, in screening patients. These sensitivities were significantly higher ($p < 0.05$) compared to ALP, RBS, and HDL (28%, 44%, and 36%, respectively).

Focusing on the specificity, ALB and HDL demonstrated the highest values (76% and 60%, respectively) compared to globulin, insulin, AST, cholesterol, and VLDL, where they were 30%, 43%, 36%, 43%, and 43%, respectively, with significant differences observed ($p < 0.05$).

Table 6. The ROC Curve with Sensitivity and Specificity of All Variables

Test Result Variable(s)	Area	Std. Error	P value	Sensitivity %	Specificity %
ALT	0.728	0.054	$p < 0.001^{***}$	73	46
AST	0.749	0.055	$p < 0.001^{***}$	75	36
ALP	0.523	0.063	$p > 0.05$	53	45
ALB	0.288	0.056	$p < 0.001^{***}$	28	76
RBS	0.430	0.061	$p > 0.05$	44	56
Cholesterol	0.762	0.050	$p < 0.001^{***}$	74	43
TG	0.829	0.042	$p < 0.001^{***}$	83	50
VLDL	0.703	0.060	$p < 0.01^{**}$	70	43
HDL	0.381	0.066	$p > 0.05$	36	60
LDL	0.654	0.057	$P < 0.05^*$	66	46
Protein	0.613	0.067	$p > 0.05$	58	53
Globulin	0.724	0.055	$p < 0.001^{***}$	73	30
Insulin	0.559	0.066	$p > 0.05$	56	43
Intelectin-1	0.921	0.032	$p < 0.001^{***}$	91	26

*= significant, **= high significant, ***= very high significant

DISCUSSION

The study results indicate a correlation between NAFLD and increasing age, with males being the most affected group. These findings are consistent with previous studies, including those by Toshihide¹⁴, James¹⁵, and Amedeo¹⁶, which have demonstrated a close association between age and the development of NAFLD. Additionally, the study aligns with research by Ylse¹⁷, which suggests that NAFLD prevalence is higher in postmenopausal women and those with polycystic ovary syndrome (PCOS) compared to premenopausal women. Moreover, it was observed that men under 55 years of age are more likely to develop NAFLD than women of the same age, with incidence rates increasing in women after menopause. This increase in incidence among postmenopausal women may be

attributed to hormonal changes, particularly a decrease in estrogen levels after menopause. The dietary changes and elevated cholesterol levels, including high levels of low-density lipoprotein (LDL) in the blood, could rule as well¹⁸. Furthermore, women in menopause often experience weight gain with a redistribution of fat to visceral areas^{18,19}.

Based on BMI levels, the results showed significant differences ($P \leq 0.05$) between patients and healthy individuals, with patients exhibiting the highest ratio within the obese weight BMI category (90.0%). Whereas, healthy subjects predominantly fell within the normal weight BMI category and represented 70.0%. Both male and female patients had higher BMI

levels compared to healthy individuals, with statistically significant differences ($P < 0.001$). These findings are consistent with Fabbrini's work [20], in which a strong relationship between BMI and NAFLD was demonstrated. Obesity increases the risk of developing NAFLD due to an imbalance between fatty acid synthesis, oxidation, and excretion. High BMI levels can lead to metabolic disturbances, cardiovascular disease, and increased risk of mortality²¹.

According to our results, the mean waist circumference was higher for patients compared to controls, with significant differences ($P < 0.05$). These findings are consistent with those of Zheng²² and Cerbere²³, which demonstrated a close association between waist circumference and NAFLD. Additionally, the results are in good agreement with those of Bruno et al.²⁴, who found that postmenopausal females tend to have higher waist circumferences compared to males in the same age group. However, our findings are in contrast with Pinidiyapathirage's ones²⁵, who reported that men with NAFLD had higher waist circumferences compared to women.

Furthermore, our results revealed a high increase in cholesterol levels ($P < 0.05$) in patients compared to healthy controls. This elevation could be attributed to LDL-cholesterol breakdown, facilitated by the activity of the cholesterol acyl transferase enzyme. In fact, this enzyme is stimulated by the absence of insulin, and resulting in an increase absorption of cholesterol in the intestines. Additionally, the consumption of meals rich in saturated fats can contribute to elevated cholesterol levels in the body²⁶.

The deposition of increased cholesterol in blood vessels can lead to elevated blood pressure. Furthermore, cholesterol deposits with fatty substances may result in the formation of blood clots and arteriosclerosis due to the constriction of blood vessels and obstruction of blood flow²⁷. These factors increase the risk of severe heart disease²⁸. It is important to note that NAFLD is often associated with the increased mortality rate linked to heart and cardiovascular diseases²⁹. Therefore, the observed elevation in cholesterol levels in NAFLD patients underscores the importance of managing cholesterol levels as part of the comprehensive

care for individuals with NAFLD. This mitigates the risk of cardiovascular complications and improves overall health outcomes. However, this result is consistent with the findings of Altparmak's study, in which patients with liver disease exhibit higher cholesterol levels compared to healthy individuals³⁰. Additionally, the results of Ho et al. revealed a direct relationship between increased cholesterol levels, portal phlebitis, and cirrhosis in NAFLD³¹. Furthermore, Enjoji et al. suggested treating patients with fatty liver disease by controlling dietary cholesterol intake [32]. Higher levels of triglycerides in patients were observed compared to healthy individuals, which lined with the results of the Leylabadlo and Kwon studies^{33, 34}. Finally, Khamseh showed a high association between triglycerides and NAFLD³⁵. Here, all mentioned studies had similar findings to ours.

To investigate LDL, our results indicate a significant increase in the LDL level when the patient group is compared to healthy ones. These findings are consistent with those of Siddiqui and Tang studies, which demonstrated a significant elevation in LDL in patients compared to the control group^{36,37}. Furthermore, the results revealed a significant increase in VLDL levels in patients compared to controls. These findings align with those of Adiels et al.'s study, which showed a strong association between VLDL and NAFLD³⁸.

Regarding HDL levels, the mean values were non-significantly lower for patients compared to healthy individuals ($p > 0.05$). These results are in agreement with those found by Mirhafez studies, which demonstrated decreased HDL levels in individuals with fatty liver metabolism compared to healthy controls [39]. HDL plays a crucial role in transporting cholesterol from the body's cells to the liver, where it is purified and eliminated as waste. This process is beneficial for the body's overall health.

However, in contrast, our present research showed that the ALT and AST levels were significantly higher in the patient group compared to the healthy one, suggesting a direct correlation between NAFLD and these variables ($p < 0.05$). Our results corroborate those of Francque and Younossi, who found that NAFLD patients had higher ALT levels [40,41]. Prashanth et al. also discovered that steatohepatitis patients had higher ALT levels⁴², and

other research has shown that NAFLD patients have elevated AST levels^{43,44}.

Similarly, the ALP levels in patients of this investigation were relatively higher compared to healthy subjects with a small difference ($p > 0.05$). Thereby, these results are consistent with those of Bazick study, which showed an increase in ALP levels in patients with fatty liver and cirrhosis⁴⁵. Furthermore, a current study demonstrated that ALP was used as an independent biomarker for cirrhosis of the liver and NAFLD in obese individuals [46], which was also indicated in patients with steatohepatitis⁴².

The results of our study revealed a remarkable difference ($p < 0.05$) in levels of intelectin-1 between patients (1.10 ± 0.30 ng/mL) and the healthy group (0.41 ± 0.25 ng/mL). This could be an indicator of a relationship between

NAFLD and the increase in intelectin-1 levels. Yimaz et al. demonstrated similar findings suggesting that intelectin-1 serves as an independent indicator of hepatocyte hypertrophy [47]. Another supporting evidence is the results of Eisinger et al.'s study, which showed high levels of intelectin-1 in cirrhotic liver patients [48]. Hence, intelectin-1 levels may serve as a biomarker for NAFLD and could play a role in the pathophysiology of liver diseases.

CONCLUSION

Our findings demonstrate an increase in serum levels of intelectin-1 in patients with NAFLD. Intelectin-1 levels were significantly higher in NAFLD patients and exhibited the AUC and highest sensitivity in the ROC curve analysis. Furthermore, intelectin-1 showed a positive correlation with lipid profile and liver function parameters. Therefore, the elevation in plasma intelectin-1 levels, along with increased serum levels of total cholesterol, TG, LDL, VLDL, and liver function parameters, may serve as a potential indicator of liver insufficiency in NAFLD patients. Thereby, those can be utilized as predictors in the diagnosis of NAFLD.

DECLARATIONS

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None.

Conflict of Interest

The authors declare no known conflict for this work.

Ethical Approval

The study received ethical clearance from the Ethics Committee at the National Centre for Training and Human Development/Baquba Teaching Hospital of the Iraqi Health, as well as from the Ethical Committee at the University of Diyala. All participants provided written informed consent before taking part.

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