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Assessment of Lecithin-Cholesterol Acyltransferase Levels in Non-Alcoholic Fatty Liver Disease and it Correlation with Lipid Profile and Liver Enzymes

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Abstract

Hepatocyte fat accumulation is the hallmark of non-alcoholic fatty liver disease (NAFLD), a common metabolic liver condition. A liver-derived enzyme involved in lipid metabolism, lecithin-cholesterol acyltransferase (LCAT) may be a biomarker of hepatic metabolic function. In order to determine the impact of NAFLD on this enzyme, the current study compared the serum levels of LCAT in NAFLD patients with matched controls. It also examined the relationship between LCAT and total cholesterol (TC), low density lipoprotein-cholestrol (LDL-c), high density lipoprotein-cholesterol (HDL-c), aspartate transaminase (AST), fibrosis-4 INDEX (FIB-4), triglycerides (TG), and total cholesterol. Ninety people participated in a case-control study: forty-five NAFLD patients and forty-five age-, sex-, and BMI-matched controls. ELISA was used to determine the LCAT level. Clinical informations were measured, including liver enzymes and lipid profile. FIB-4 index was used for the evaluation of the fibrosis risk, and transabdominal ultrasonography was utilized to grade steatosis. LCAT levels were considerably lower in NAFLD patients compared to those in the control group ($p < 0.001$). LCAT had significant negative correlation with LDL-c, AST, ALT, and the FIB-4 index. On the other hand, LCAT and HDL-c had a positive correlation. However, there was non significant correlation between LCAT and TG, age, sex, or BMI.

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lipid metabolism, LCAT, fibrosis, steatosis, and NAFLD.

Introduction

Hepatic fat accumulation in people who drink little or no alcohol is the hallmark of a broad clinical syndrome known as non-alcoholic fatty liver disease(NAFLD). The spectrum of this illness range from benign hepatic steatosis to the more serious types, such as non alcoholic steatohepatitis (NASH), which is characterised by liver inflammation and may eventually proceed to cirrhosis, fibrosis, or hepatocellular carcinoma(HCC) (1,2). NAFLD is becoming more widespread worldwide in the midst of the ongoing obesity pandemic because it frequently coexists with metabolic comorbidities such type 2 diabetes mellitus ,obesity, and dyslipidaemia (3,4). oxidative stress (7), Insulin resistance (5,6), excessive calorie and fructose intake, disruption of the gut microbiota (8), and persistent low-grade inflammation are all part of the complex pathophysiology of NAFLD. Numerous genetic, behavioural, environmental, and dietary factors also have an impact on these processes (8–12).

Over the past thirty years, the prevalence of NAFLD has increased by more than 50%, from 25.3% between 1990 and 2006 to 38.0% between 2016 and 2019 (13). A combination of clinical and biochemical evaluation, imaging investigations, and occasionally a liver biopsy are used to diagnose NAFLD (14, 15). Excluding other causes of steatosis, such as viral hepatitis, autoimmune liver disease, hemochromatosis, and heavy alcohol consumption, which can result in identical symptoms and liver damage, is a crucial diagnostic criterion.

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The most popular noninvasive imaging test for evaluating liver fat is ultrasound. It may demonstrate the liver's increased echogenicity in comparison to the kidney. Additionally, liver fat content can be evaluated and more specific information regarding liver structure can be obtained using computed tomography (CT) and magnetic resonance imaging (MRI) (16). A variety of validated non-invasive techniques, including transient elastography, the fibrosis-4 (FIB-4) index, the Aspartate aminotransferase (AST) to Alanine aminotransferase ratio, the AST/platelet ratio index(APRI), and the NAFLD Fibrosis Score(NFS), are widely recommended and validated tests due to the low cost and non invasiveness, even though liver biopsy is still the gold standard for determining the severity of fibrosis (17,18).

Numerous metabolic problems, including changes in lipid metabolism, have been linked to NAFLD. Lecithin-cholesterol acyltransferase (LCAT), one of the major enzymes in lipid metabolism, is essential for the esterification of free cholesterol to cholesteryl esters, which facilitates the movement of cholesterol through the bloodstream (19,20). Additionally, NAFLD may raise ALT and AST levels.

Additionally, oxidative stress and chronic inflammation are linked to NAFLD and can have a detrimental effect on LCAT function (21). By altering the activity of lipid metabolism-related enzymes, inflammatory cytokines may disrupt normal lipid metabolism. Moreover, insulin resistance, which can reduce LCAT activity, is closely associated with NAFLD. LCAT activity is typically impacted by increased free fatty acid levels and altered hepatic lipid metabolism caused by insulin resistance (21). Therefore, controlling NAFLD is crucial for both liver health and the body's general metabolism.

Taking into account, the purpose of this study is to determine the relationship between LCAT and NAFLD by comparing the blood levels of LCAT in patients with NAFLD to those in matched controls. Additionally, the purpose of this study is to assess the association between blood LCAT and triglycerides (TG), low density lipoprotein-cholestrol (LDL-c), total cholesterol (TC), high density lipoprotein-cholesterol (HDL-c), alanine transaminase (ALT), aspartate transaminase (AST), and fibrosis-4 index (FIB-4).

Materials and Methods

This case-control study was carried out in the Gastroenterology and Hepatology Teaching Hospital in the Medical City/ Baghdad/ Iraq, between November 2024 and February 2025. Ninety participants were enrolled in our study: forty-five NAFLD patients who had been diagnosed by ultrasonography by a gastroenterologist (22) and forty-five subjects who matched the NAFLD patient in terms of age, sex, and BMI. The sonographer was blind to the laboratory data, and the ultrasound diagnosis is based on how echogenic the liver parenchyma is compared to the right kidney's cortex. In order to guarantee that the control group's distribution of age, sex, and BMI is similar to that of the case group, controls were chosen using frequency matching. Instead of matching individual pairs, this involves matching groups based on the overall qualities. Adults of both sexes, ages 18 to 64, made up the recruited subjects. Each participant gave their verbal agreement after being made aware of the study's objectives and anticipated advantages. Diabetes mellitus, dyslipidaemia that existed prior to NAFLD diagnosis, fish eye disease, use of certain medications that affect LCAT level (e.g., statins) within the last three months, alcohol consumption, the existence of chronic inflammatory diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis), pregnancy or lactation, and any other significant comorbidity that could affect the study outcomes (e.g., severe cardiovascular disease). Additionally, illnesses like viral hepatitis, some drugs (such as steroids,methotrexate, tamoxifen, and amiodarone), and inherited or acquired diseases such as Wilson's disease were excluded since they could interfere with the diagnosis of NAFLD. Structured interviews and medical records were used to gather information about participants' medical histories, including the existence of diabetes or the aforementioned diseases, as well as any medications that might have an impact on our outcome, in order to control potential confounding factors.

The study was performed in accordance to the Helsinki Declaration principles and was approved by the Research Ethics Committee in the College of Pharmacy/University of Baghdad. A verbal consent was taken from all participants after been informed about the objectives of this study and the expected benefits.

Each fasting participant had six millilitres of blood drawn from them. To count platelets using a haematology autoanalyzer (Sysmex XP-300; Japan), one millilitre was put in an ethylenediaminetetraacetic acid (EDTA) tube. To extract serum, the leftover blood sample was put in gel tube, left to coagulate for fifteen minutes, and then been centrifuged for fifteen minutes at 4000 rpm. A portion of the serum was utilised to directly assess the lipid profile, AST, and ALT levels using the COBAS 311 automated analyser (Roche Diagnostics, Switzerland). To prevent repeated freeze-thaw cycles, the remaining serum was aliquoted, and samples were maintained frozen at -20 °C until analysis. In accordance with the manufacturer's instructions, the serum LCAT level was determined using the enzyme-linked immunosorbent assay (ELISA) (Huma Reader HS, Human; Germany) with the matching human ELISA kits (ELK Biotechnology; USA).

A commercially available ELISA kit (Catalogue Number: ELK3186) designed specifically for the quantitative assessment of human LCAT was utilised in the current study to measure LCAT. The sensitivity limit of detection (LOD) was [0.19 ng/mL], and the detection range was [0.47 to 30 ng/mL]. Each sample was analyzed in duplicate to confirm accuracy. It was found that the intra-assay and inter-assay coefficients of variation (CVs) were 8>% and 10>%, respectively.

A human LCAT-specific monoclonal antibody was pre-coated in each well of a microtiter plate as part of the procedure. A biotin-conjugated secondary antibody specific for LCAT was given to bind to the immobilised enzyme after standards or diluted samples were added to the wells. The biotin-labeled antibody is then specifically bound by avidin linked to horseradish peroxidase (HRP). After 50 minutes of incubation, a tetramethylbenzidine (TMB) substrate solution was added to start a colorimetric reaction that was catalysed by horseradish peroxidase (HRP). This resulted in the production of a blue colour in wells that contained the entire LCAT-antibody-avidin-HRP complex. The addition of a sulphuric acid stop solution stopped the enzymatic reaction, changing the hue from blue to yellow.

A microplate reader was used to measure absorbance at 450 nm, and each sample's optical density (OD) was compared to a standard curve made from known amounts of LCAT to ascertain the test samples' enzyme concentration. All of the readings, which were expressed in ng/mL, were within the assay's validation range.

Triglycerides in serum or plasma were measured using an enzymatic colorimetric method based on a sequence of linked reactions. Lipoprotein lipase (LPL) initially hydrolyses triglycerides into glycerol and free fatty acids (FFAs). Glycerol kinase (GK) then phosphorylates glycerol in the presence of ATP, producing glycerol-3-phosphate and adenosine diphosphate (ADP).

In the subsequent stage, glycerol-3-phosphate oxidase (GPO) oxidises glycerol-3-phosphate to produce hydrogen peroxide ($H2O_2$) and dihydroxyacetone phosphate. In a peroxidase (POD)-catalyzed process, the produced $H2O_2$ then interacts with 4-aminoantipyrine (4-AAP) and a phenolic molecule, N-ethyl-N-(3-sulfopropyl)-m-anisidine (ESPA); a summary of the reaction is given below:

$$\text{Triglycerides} \xrightarrow{LPL} \text{Glycerol} + \text{Free Fatty Acids}$$

$$\text{Glycerol} + \text{ATP} \xrightarrow{GK} \text{Glycerol-3-Phosphate} + \text{ADP}$$

$$\text{Glycerol-3-Phosphate} + O_2 \xrightarrow{GPO} \text{Dihydroxyacetone Phosphate} + H_2O_2$$

$$2H_2O_2 + \text{4-AAP} + \text{ESPA} \xrightarrow{POD} \text{Quinoneimine Dye} + H_2O$$

The absorbance of the resulted red-colored quinoneimine dye was measured at a specific wavelength (510nm), and the triglyceride concentration is calculated basing on the intensity of the color formed.

An enzymatic colorimetric method involving a sequence of reactions catalysed by cholesterol esterase (CE), cholesterol oxidase (CO), and peroxidase (POD) was used to determine the serum total cholesterol

concentration (24). Cholesterol esterase first hydrolyses cholesterol esters, the main kind of circulating cholesterol, producing free cholesterol and fatty acids. Cholesterol oxidase then oxidises the liberated cholesterol, producing cholestenone and $H2O_2$ as byproducts. The final stage involves hydrogen peroxide reacting with 4-AAP and phenol in a peroxidase-catalyzed coupling process to generate a quinoneimine colour. The reaction is summarised as follows:

$$\text{Cholesteryl Esters} \xrightarrow{CE} \text{Cholesterol} + \text{Fatty Acids}$$

$$\text{Cholesterol} + O_2 \xrightarrow{CO} \text{Cholestenone} + H_2O_2$$

$$H_2O_2 + \text{4-AAP} + \text{Phenol} \xrightarrow{POD} \text{Quinoneimine Dye} + H_2O$$

The absorbance of the resulted quinoneimine dye was read at specific wavelength (510 nm), and the total cholesterol concentration was calculated based on the intensity of the color produced.

The assessment of serum HDL-cholesterol was performed using a selective enzymatic colorimetric method (25). This assay specifically precipitates or masks chylomicrons, very-low-density lipoproteins, and LDL through a polyanionic reagent that promotes the formation of insoluble complexes. As a result, these lipoproteins become inactive in the subsequent enzymatic reactions. In contrast, HDL particles remain soluble due to the presence of a surfactant, enabling the precise assessment of their cholesterol concentration. The free cholesterol in HDL is first hydrolysed by cholesterol esterase (CE) to produce free cholesterol, which is then oxidised by cholesterol oxidase (CO) to yield cholestenone and hydrogen peroxide (H_2O_2). In the final stage, hydrogen peroxide reacts with 4-AAP and phenol in the presence of peroxidase to yield a red quinoneimine colour. The absorbance of this coloured product is evaluated spectrophotometrically at 550 nm, and the HDL-cholesterol concentration is determined from the optical density (OD) result.

LDL-cholesterol was determined using the Friedewald equation, a recognised indirect approach for estimating LDL-cholesterol in standard lipid profile. This method employs previously determined values of total cholesterol, HDL-cholesterol, and triglycerides, predicated on the assumption that very-low-density lipoprotein-cholesterol is roughly one-fifth of the triglyceride level (when expressed in mg/dl). The equation is articulated as:

LDL-cholesterol = Total cholesterol − HDL-cholesterol − (Triglyceride/5)

Serum ALT activity was evaluated using a kinetic spectrophotometric method that monitors the enzyme reaction rate throughout time (27). In this assay, ALT catalyses the reversible transamination of L-alanine and α-ketoglutarate, producing pyruvate and L-glutamate. Pyruvate is converted into lactate by the enzyme lactate dehydrogenase (LDH), concurrently oxidising nicotinamide adenine dinucleotide hydride (NADH) to NAD^+ ; the summary of this reaction is outlined below:

$$\text{L-Alanine} + \alpha\text{-Ketoglutarate} \xleftrightarrow{\text{ALT}} \text{Pyruvate} + \text{L-Glutamate}$$

$$\text{Pyruvate} + \text{NADH} + H^+ \xrightarrow{LDH} \text{Lactate} + NAD^+$$

The decrease in absorbance at 340 nm, due to the consumption of NADH, is measured at designated intervals.

The rate of absorbance decrease is exactly proportional to the ALT enzymatic activity in the sample, as the amount of NADH consumed reflects the concentration of pyruvate, and hence, ALT, present.

The serum activity of AST was assessed using a kinetic spectrophotometric method (28). AST catalyses the transamination reaction between L-aspartate and α-ketoglutarate, producing oxaloacetate and L-glutamate. Oxaloacetate is subsequently reduced to malate by the enzyme malate dehydrogenase (MDH) in the presence of NADH, which is simultaneously oxidised to NAD^+ ; the reaction summary is outlined below:

$$\text{L-Aspartate} + \alpha\text{-Ketoglutarate} \quad \underset{ALT}{\leftrightarrow} \text{Oxaloacetate} + \text{L-Glutamate}$$

$$\text{Oxaloacetate} + \text{NADH} + \text{H}^+ \quad \underset{MDH}{\rightarrow} \text{Malate} + \text{NAD}^+$$

The process is monitored by measuring the reduction in absorbance at 340 nm, which corresponds to the consumption of NADH. The decline in absorbance rate is directly correlated with the AST activity in the sample.

Body mass index was calculated for participants using the following formula[29] :

BMI= Weight(kg.)/Hight^2(in meteres)

The Fibrosis-4 index was computed to evaluate the risk of liver fibrosis in patients with NAFLD using the following formula(30):

FIB-4 = [Age (years) × AST (U/L)] / [Platelet count (10^9/L) × √ALT (U/L)]. [30]

According to the European Association for the Study of the Liver (EASL) criteria: scores < 1.30 indicate low risk of fibrosis, scores 1.30–2.67 indicate intermediate risk, and scores > 2.67 represent high risk (with higher rule-out thresholds such as <2.0 in patients >65 years) (31).

Statistical analysis

The statistical analysis was conducted utilising SPSS, version 27. The normality of data distribution was evaluated via the Shapiro-Wilk and Kolmogorov-Smirnov tests. Categorical variables were expressed as frequencies and percentages, and their differences were assessed using the Chi-square test. Numerical variables were presented as medians accompanied by interquartile ranges (IQR). The Mann-Whitney U test was utilised to compare the differences between the two study groups. Spearman's correlation was utilised to assess the relationship between the examined variables.

Results

The age range of NAFLD patients was 36.22 years (11.32) with a median and interquartile range, spanning from 18 to 60 years; conversely, the control group had an age range of 33 years (10) with a median and interquartile range, ranging from 20 to 64 years. The sex distribution was essentially same across the groups, with males constituting 48.8% of the NAFLD group and 51.2% of the control group, while females represented 51.2% and 48.8%, respectively (p= 0.833). BMI of NAFLD patients was 33.02 (9.75) kg/m² (median, IQR), while that of the control group was 32.04 (4.76) kg/m² (median, IQR); this difference was not statistically significant (p= 0.990).
No significant variations in age, sex, or BMI were seen between the two study groups, demonstrating effective matching and reducing any confounding effects from these variables.

Serum level of LCAT enzyme for patients with non alcoholic fatty liver disease was significantly lower, averaged 1.73 (0.28) ng/ml, comparing to 3.00 (0.9) ng/ml for the control group subjects (p< 0.001); as shown in Table (1). These findings suggest an association of LCAT with the altered lipid metabolism that is accompanied the disease.

Table 1. Lecithin-cholestrol acyl transferase levels

The variable	Non-alcoholic fatty liver disease (n=45)	Control group (n=45)	P- value
Lecithin-cholestrol acyl transferase (ng/ml)	1.73 (0.28)	3.00 (0.9)	<0.001

n : number of participants

Correlation analysis demonstrated many significant associations between LCAT and other factors, as illustrated in Table 2. Serum LCAT levels exhibited a significant negative association with AST (ρ = –0.611, p<0.001),ALT (ρ = –0.541, p<0.001), FIB-4 index (ρ= –0.608, p<0.001), and LDL-c (ρ = –0.352, p>0.001). In contrast, Lecithin-cholesterol acyl transferase enzyme had a positive connection with platelet count (ρ= 0.455, p<0.001) and HDL-c (ρ=0.518, p <0.001). Conversely, LCAT had no significant association with age, sex, BMI, or TG (p> 0.05 for all).

Table 2. Correlation of Lecithin-cholestrol acyl transferase with other variables of the participants

The variable	Ps	p-value
Total cholesterol	-0.118	0.266
Triglycerides	-0.18	0.089
Low-density lipoprotein-cholesterol	-0.352	<0.001
High-density lipoprotein-cholesterol	0.518	<0.001
Aspartate aminotransferase	-0.611	<0.001
Alanine aminotransferase	-0.541	<0.001
Platelets count	0.455	<0.001
FIB-4 Index	-0.608	<0.001

ρs: Spearman correlation coefficient.

To minimize the influence of between-group differences, correlation analyses between LCAT and clinical variables (such as AST, ALT, FIB-4, and lipid profile) were performed separately within the NAFLD cohort (n=45) to identify true prognostic associations.

Discussion

The current investigation revealed that serum LCAT levels were markedly reduced in NAFLD patients relative to matched controls. Lipid metabolism dysregulation is a hallmark of NAFLD, correlating with reduced LCAT levels, as LCAT plays a pivotal role in HDL particle maturation and the esterification of free cholesterol, both crucial for reverse cholesterol transport and lipid homeostasis. Reduced LCAT levels in NAFLD patients may indicate lipid buildup in hepatocytes, hence contributing to hepatic steatosis and the advancement of liver damage (33). The diminished LCAT levels in NAFLD patients observed in this study align with other research that associates decreased LCAT activity with several metabolic disorders and hepatic dysfunction (34).

The association between LCAT activity and hepatic disorders has been highlighted by a previous investigation in cattle. According to Nakagawa et al., dairy cows with spontaneous fatty liver disease had significantly lower LCAT activity. This was linked to lower serum levels of apolipoprotein A-I, an essential physiological activator of LCAT. According to Nakagawa et al., reduced LCAT activity could result from either decreased plasma activation of LCAT due to decreased apolipoprotein A-I levels or from degraded hepatic production and secretion(33).

In a different study, He et al. looked at LCAT expression in HCC tissues and found that it was significantly downregulated. This decrease in LCAT expression correlated negatively with the prognosis of HCC, suggesting that LCAT may serve as both a metabolic enzyme and a prognostic factor in liver cancers.

In contrast to our results, a previous study by Nass et al. found that plasma LCAT activity was elevated

in people at elevated risk for NAFLD, as defined by a fatty liver index (FLI) ≥ 60, and remained significantly associated with NAFLD even after adjusting for important metabolic variables like insulin resistance, obesity, and type 2 diabetes (36). The divergence between the current study and the research conducted by Nass et al. may be ascribed to various methodological and demographic variations. The current work quantitatively assessed serum LCAT concentrations via an ELISA approach, while the cited study tested LCAT activity using an exogenous substrate assay, which may not accurately represent circulating LCAT levels. Additionally, participants in this study were sourced from a well-defined cohort, with NAFLD diagnosis conducted via abdominal ultrasonography by expert gastroenterologists following EASL criteria, whereas the other study employed a surrogate index, specifically the FLI. Moreover, the current study implemented a stringent exclusion of people with comorbidities that could obscure LCAT expression. Furthermore, variations in genetic background, environmental exposures, dietary habits, and ethnicity between the Middle Eastern group in this study and the European cohort examined by Nass et al. may affect LCAT regulation. In light of these conflicting results, additional research is necessary to investigate the function of LCAT in biopsy-validated NAFLD, especially across persons with diverse genetic origins and employing standardised measuring methodologies.

Numerous noteworthy correlations between LCAT serum levels and the factors under inquiry were found in the current study. LCAT showed a positive correlation with HDL cholesterol and platelet count, but a negative correlation with liver enzymes (AST, ALT), the FIB-4 index, and atherogenic lipids, such as triglycerides and LDL cholesterol. These results highlight LCAT's possible hepatoprotective and anti-inflammatory effects in NAFLD, suggesting that lower LCAT levels could indicate more serious hepatic impairment or systemic metabolic stress. Human studies have shown that people with NAFLD, particularly those with more liver fat or more severe fibrosis, had lower LCAT activity or concentration. In one cohort, patients with moderate to severe steatosis had lower LCAT activity, as measured indirectly by cholesterol ester/free cholesterol ratios; in another, fibrosis-positive NAFLD patients had lower HDL-bound LCAT levels, even after controlling for HDL particle count (37–39). These results support our findings and suggest that decreased LCAT may reflect impaired lipid control or increased hepatic dysfunction in NAFLD.

There are many noteworthy advantages to this study. This work adds to the growing field of metabolic and hepatic research by being one of the few case-control studies looking at the connection between LCAT and NAFLD. In order to improve the validity and reliability of group comparisons, the study carefully controlled for confounding variables by matching participants based on age, sex, and BMI. In the end, the impact of other factors known to affect lipid metabolism was lessened by the application of strict exclusion criteria.

Despite the positive outcomes, this study had a number of drawbacks. The ability to establish causal correlations between LCAT and NAFLD is limited by the observational design. The absence of liver biopsy, the gold standard for assessing hepatic steatosis and fibrosis, is another disadvantage. The use of non-invasive tools in the investigation, such as ultrasound and the FIB-4 score, may have led to classification bias.

Conclusion

In summary, this study demonstrates that patients with non-alcoholic fatty liver disease (NAFLD) show significantly lower serum levels of lecithin-cholesterol acyltransferase (LCAT) when compared to matched control group. Moreover, this study revealed significant negative correlation between LCAT and AST, ALT, FIB-4 index, and LDL-c. Conversely, LCAT showed positive correlation with HDL-c. On the other hand LCAT showed no significant correlation with each of age, sex, BMI, and TG.

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