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Patterns of Dyslipidemia among Patients with Non-Alcoholic Fatty Liver Disease

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) affects a significant proportion and is frequently associated with dyslipidemia and metabolic disorders. **Objective:** To explore the patterns of dyslipidemia among patients with NAFLD and their association with disease severity. **Methods:** A cross-sectional study was conducted at the Department of Cardiology, Liaquat National Hospital, Karachi. All participants diagnosed with NAFLD were included, and NAFLD severity was assessed using Fibro Scan, categorizing patients into no significant fibrosis, mild fibrosis, significant fibrosis, and advanced fibrosis. Dyslipidemia patterns were evaluated based on lipid profiles. **Results:** The cohort (n=300) had a mean age of 51.44 years, with a majority being female (60.3%) and over 45 years old (71.3%). NAFLD severity was distributed as follows: 33% mild fibrosis, 32% no significant fibrosis, 29.3% significant fibrosis, and 5.7% advanced fibrosis. As NAFLD severity increased, waist circumference, liver enzyme levels (AST and ALT), and lipid markers (TC, LDL-C, TG) increased, while HDL-C decreased. Advanced cases showed higher hemoglobin A1c levels and increased hepatic steatosis and CAP values. Dyslipidemia associated with metabolic syndrome (24%), low HDL-C (61.3%), and hypertriglyceridemia (2%) were observed, with combined and general hyperlipidemia affecting 3.7% and 1.3% of participants, respectively. The patterns of dyslipidemia varied with severity; normolipidemia was common in cases with no significant fibrosis, combined hyperlipidemia was seen in significant fibrosis, and hyperlipidemia was exclusive to advanced NAFLD. **Conclusion:** It was concluded that the study found significant associations between NAFLD severity and dyslipidemia patterns.

INTRODUCTION

NAFLD has become a major focus of basic science investigation and clinical practice as it is an increasingly prevalent and potentially hazardous condition. NAFLD prevalence is estimated at 5-20% of the general population, increasing to 75% among patients with obesity and diabetes [1, 2]. Even though NAFLD is common in global practice, its pathophysiology, particularly in its progression, is not completely understood [3]. NAFLD, currently described as the hepatic expression of MetS, is now globally recognized as the most common liver disease [4]. The diseases can be as simple as steatosis, defined with at least 5% fat deposition in hepatocytes and may advance as fibrosis and necrotizing inflammation. While this progression can lead to the development of Non-alcoholic steatohepatitis (NASH), in the most severe stages of this condition, such complications as cirrhosis or hepatocellular carcinoma may occur [5]. More significantly, these histological alterations develop without alcohol or other hepatotoxic agents in the subjects' system [6, 7]. Fat accumulated in the liver as lipids affects hepatocytes physiology; lipids are deposited as lipid droplets, which are surrounded by proteins that could affect the liver disease progression [7, 8]. Disruptions in lipid metabolism profile were NAFLD characterized by low plasma triglyceride output, low fatty acid uptake in the liver, changes in lipolysis and enhanced very-low-density lipoprotein (VLDL) and fatty acid-free profile [9]. These derangements result in the synthesis of qualitatively altered adipokines, including leptin, adiponectin, and retinol-binding protein 4, that in turn influence signalling

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networks and induce inflammation and oxidative stress [10, 11]. In addition, these lipid disorders are made worse by obesity and insulin resistance. Hepatic steatosis has been implicated in reduced hepatic glucose uptake, increased gluconeogenesis and decreased insulin signalling [12, 13]. NAFLD is also associated with other cardiovascular risk factors (hypertension, smoking, obesity, dyslipidemia and hyperglycemia) [14]. Recent studies demonstrate that NAFLD is correlated with low-grade atherosclerosis and a higher rate of cardiovascular disease (CVD) [15, 16]. Hypertriglyceridemia and high low-density lipoprotein cholesterol (LDL-C) are established as common CVD risk factors in NAFLD [17]. Such longitudinal findings also confirm that NAFLD patients are at higher risk for liver and cardiovascular disease and mortality [18, 19]. It is hypothesized that specific dyslipidemia patterns, including elevated total cholesterol (TC), LDL-C, and triglycerides, along with reduced HDL-C, are significantly associated with the severity of NAFLD. Identifying these associations will provide insights into the role of lipid abnormalities in disease progression.

This study aims to identify the patterns of dyslipidemia among patients with NAFLD and their association with disease severity.

METHODS

A cross-sectional study was conducted in the Department of Cardiology at Liaquat National Hospital, Karachi, Pakistan, from September to December 2024. To protect the privacy and well-being of each participant, the study was conducted in compliance with ethical guidelines. Written informed consent was taken from all patients prior to their inclusion in the study. Ethical approval was granted by the Institutional Review Board and Medical Ethics Committee of Liaquat National Hospital (LNH) [Ref: App #1091-2024-LNH-ERC]. The sample size was calculated by the Sample Size Calculator by Wan nor Arifin, based on a 15% prevalence rate of fatty liver disease [20] and a 5% margin of error.The estimated sample size was 196 participants.To account for potential attrition, a total of 300 participants were enrolled.Eligible individuals included patients diagnosed with fatty liver disease, 20 years of age or older, and both males and females. Pregnant patients or those who had positive serologic markers for hepatitis B or C, characteristic of liver cirrhosis or advanced fibrosis on CT or ultrasound, history of splenectomy, and for whom serum lipid concentrations were unknown, were excluded from the study.Data collection involved several procedures.Participants' height and weight were measured to calculate BMI, with measurements taken while participants were casually dressed and barefoot.Information regarding co-morbidities, including diabetes, hypertension, and ischemic heart disease (IHD), was obtained from patient medical records and confirmed through clinical history and physician diagnoses. Following an overnight fast, blood samples were collected for biochemical analysis. TC, TG, HDL-C, and LDL-C levels were measured using enzymatic colourimetric methods on a Roche Cobas 8000 modular analyzer. Liver function parameters, including Aspartate Transaminase (AST) and alanine transaminase (ALT), were assessed using standard automated biochemical analyzers. Glycemic control was evaluated by measuring HbA1c and random blood sugar (RBS) levels, with HbA1c determined through a high-performance liquid chromatography (HPLC)-based system. RBS levels were measured using a standard glucometer (e.g., Accu-Chek Active, Roche Diagnostics) through capillary blood samples obtained via finger prick. Abdominal ultrasound was used to diagnose and evaluate NAFLD, with a steatotic liver appearing brighter and a cirrhotic liver showing irregularities. Fatty liver severity was categorized based on liver attenuation index (LAI) values from unenhanced hepatic CT images. The severity of NAFLD was assessed using transient elastography with Fibro-Scan®, which was categorized into four outcomes, i.e. no significant fibrosis, mild fibrosis, significant fibrosis, and advanced fibrosis. Controlled Attenuation Parameter (CAP) values were measured to evaluate liver health. Fibro-Scan assessed hepatic steatosis by emitting acoustic waves through the liver and measuring their attenuation, with higher CAP values indicating greater fat accumulation. This provided a comprehensive assessment of liver fat content and stiffness, aiding in the classification of hepatic steatosis and fibrosis severity. Further assessment of the dyslipidemia included patterns according to lipid profiles, where ischemic outcomes were characterized by the following: TG ≥200 mg/dL, LDL-C ≥160 mg/dL, and HDL-C ≤40 mg/dL. The statistical analysis was performed by SPSS version 22.0. Descriptive statistics were utilized to summarize both continuous and categorical variables. For continuous variables, comparisons were made using the one-way ANOVA. Categorical data were examined with the Chi-square/Fisher Exact test, where a significance level was set at ≤0.05.

RESULTS

The cohort included 39.7% males, with an average age of 51.44 years, and 71.3% were over 45 years old. Common co-morbidities included diabetes (35.7%), hypertension (30.7%), and ischemic heart disease (33.7%). The average BMI was 30.54 kg/m^2, indicating a high prevalence of obesity (98.7%).Liver function tests showed average AST and ALT levels of 38.47 IU/L and 52.39 IU/L, respectively. Lipid profiles included an average TC of 198.69 mg/dL, LDL-C of 125.13 mg/dL, HDL-C of 36.60 mg/dL, and triglycerides of 135.55 mg/dL.Glycemic control metrics revealed an average random blood sugar of 166.89 mg/dL and HbA1c of 6.65% (Table 1).

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Table 1: Demographic and Clinical Characteristics of the Study Population(n=300)

Variables		n (%)
Gender	Male	119 (39.7%)
	Female	181 (60.3%)
Age (Years); Mean ± SD		51.44 ± 8.48
Age Group	≤45 Years	86 (28.7%)
	>45 Years	214 (71.3%%)
Co-Morbid	Diabetes	107 (35.7%)
	Hypertension	92 (30.7%)
	IHD	101 (33.7%)
BMI (kg/m^2); Mean ± SD		30.54 ± 3.50
Obesity	Yes	296 (98.7%)
	No	4 (1.3%)
Waist Circumference (cm); Mean ± SD		103.79 ± 8.57
Liver Function Test Mean ± SD	AST (IU/L)	38.47 ± 13.15
	ALT (IU/L)	52.39 ± 18.50
Lipid Profile Mean ± SD	TC (mg/dL)	198.69 ± 56.52
	LDL-C (mg/dL)	125.13 ± 18.49
	HDL-C (mg/dL)	36.60 ± 7.90
	TG (mg/dL)	135.55 ± 29.67
Glycemic Control Mean ± SD	RBS (mg/dL)	166.89 ± 60.07
	HbA1c (%)	6.65 ± 1.38

The distribution of dyslipidemia patterns among the patients shows that 24% had dyslipidemia associated with metabolic syndrome (MetS). A notable 61.30% of patients exhibited low HDL-C levels, while hypertriglyceridemia was relatively uncommon, affecting just 2% of patients. Normolipidemia was observed in 7.70% of the cohort. Combined hyperlipidemia and general hyperlipidemia were seen in 3.70% and 1.30% of participants, respectively (Figure 1).

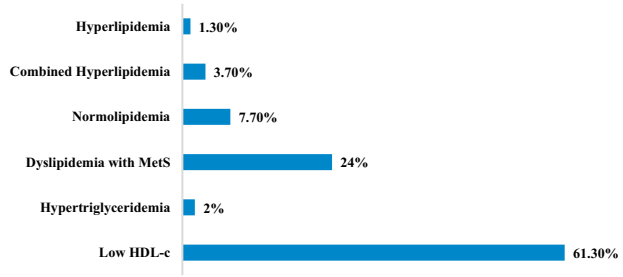

Figure 1: Patterns of Dyslipidemia among study participants

Mild NAFLD was observed in 33% of cases, while 32% had no significant fibrosis. Significant NAFLD was present in 29.30% of cases, and advanced NAFLD was found in the least proportion, at 5.70% (Figure 2).

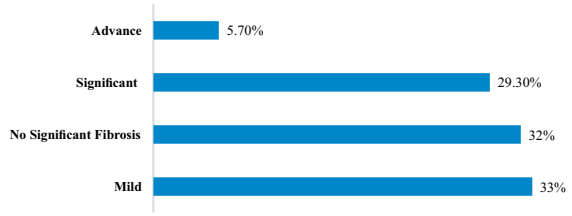

Figure 2: NAFLD Severity by Fibro Scan among the Enrolled Patients

Results illustrate the relationship between NAFLD severity and various patient characteristics, revealing significant associations across several parameters. Gender did not influence the NAFLD severity (p=0.298). As NAFLD severity increases, so does the waist circumference, and levels of liver enzymes (AST and ALT), as well as lipid profile markers like TC, LDL-C, and TG, while HDL-C decreases. Obesity prevalence remains high and consistent across severity levels, and although random blood sugar levels do not vary significantly, hemoglobin A1c levels are higher in advanced NAFLD cases. The hepatic steatosis score and CAP values also increase significantly with severity, indicating a progression in liver fat accumulation (Table 2).

Table 2: Stratification of NAFLD Severity by Fibro Scan with Respect to Patient Characteristics

Age Group		NAFLD Severity by Fibro Scan				p-Value
		No significant fibrosis	Mild	Significant	Advanced	
Gender	Male	40 (41.7%)	40 (40.4%)	36 (40.9%)	3 (17.6%)	0.298
	Female	56 (58.3%)	59 (59.6%)	52 (59.1%)	14 (82.4%)	
Age (Years); Mean ± SD		48.6 ± 8.02	50.58 ± 8.25	53.56 ± 8.01	61.52 ± 3.5	<0.01*
Age Group	≤45 years	33 (34.4%)	35 (35.4)	18 (20.5%)	-	<0.01*
	>45 years	63 (65.6%)	64 (64.6%)	70 (79.5%)	17 (100%)	
BMI (kg/m^2); Mean ± SD		30.6 ± 3.57	30.53 ± 3.62	30.47 ± 3.33	30.7 ± 3.65	0.992
Obesity	Yes	96 (100%)	96 (97%)	87 (98.9%)	17 (100%)	0.339
	No	-	3(3)	1(1.1)	-	

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WC (cm); Mean ± SD		94.16 ± 4.26	106.58 ± 7.32	110.09 ± 3.57	109.29 ± 3.8	<0.01*
LFT; Mean ± SD	AST (IU/L)	37.07 ± 10.35	41.68 ± 16.09	36.77 ± 12.74	36.41 ± 5.53	0.030*
	ALT (IU/L)	46.95 ± 16.99	56.29 ± 16.81	53.27 ± 20.34	55.88 ± 20.26	<0.01*
Lipid Profile Mean ± SD	TC (mg/dL)	184.73 ± 42.31	181.24 ± 47.52	218.03 ± 60.61	278.94 ± 57.53	<0.01*
	LDL-C (mg/dL)	119.3 ± 10.98	119.36 ± 14.33	131.65 ± 21.01	157.94 ± 15.18	<0.01*
	HDL-C (mg/dL)	38.28 ± 8.8	37.98 ± 6.46	34.37 ± 7.65	31.58 ± 7	<0.01*
	TG (mg/dL)	123.67 ± 11.86	130.32 ± 23.3	150.76 ± 38.14	154.35 ± 41.47	<0.01*
Glycemic Control Mean ± SD	RBS (mg/dL)	161.73 ± 53.03	161.22 ± 55.08	178.76 ± 73.51	167.64 ± 40.51	<0.01*
	HbA1c (%)	6.44 ± 1.37	6.64 ± 1.4	6.67 ± 1.24	7.86 ± 1.4	<0.01*
Co-Morbid	Diabetes	35 (36.5%)	32 (32.3%)	33 (37.5%)	7 (41.2%)	0.170
	Hypertension	33 (34.4%)	29 (29.3%)	25 (28.4%)	5 (29.4%)	<0.01*
	IHD	28 (29.2%)	38 (38.4%)	30 (34.1%)	5 (29.4%)	0.865
Hepatic Steatosis Score		0.36 ± 0.6	2.53 ± 0.87	2.95 ± 0.2	2.88 ± 0.33	<0.01*
Steatosis	Yes	42 (43.8%)	69 (69.7%)	69 (78.4%)	13 (76.5%)	<0.01*
	No	54 (56.3%)	30 (30.3%)	19 (21.6%)	4 (23.5%)	
CAP; Mean ± SD		247.59 ± 61.68	282.26 ± 60.94	304.93 ± 61.94	307.23 ± 70.12	<0.01*
CAP Group	Nil Significance (<248 dB/m)	56 (58.3%)	36 (36.4%)	22 (25%)	5 (29.4%)	<0.01*
	Mild (248-280 dB/m)	16 (16.7%)	12 (12.1%)	7 (8%)	-	
	Moderate (281-319 dB/m)	2 (2.1%)	5 (5.1%)	2 (2.3%)	-	
	Severe (>319 dB/m)	22(22.9%)	46 (46.5%)	57 (64.8%)	12 (70.6%)	

WC: Waist Circumference; LFT: Liver Function Test; RBS: Random Blood Sugar; HDL-C: High-Density Lipoprotein Cholesterol; HbA1c: Hemoglobin A1c Values are given as n (%) or Mean ± SD. Chi-square/Fisher's exact test was applied. One-way ANOVA was applied, where a *p<0.05 was considered statistically significant.

The study illustrated dyslipidemia patterns about NAFLD severity as assessed by Fibro Scan. It revealed that normolipidemia was most common among individuals with no significant fibrosis, while combined hyperlipidemia was predominantly observed in those with significant fibrosis. Hyperlipidemia was exclusively found in the advanced stage of NAFLD. Dyslipidemia associated with metabolic syndrome (MetS) was notably prevalent in patients with significant fibrosis, whereas low HDL-C and hypertriglyceridemia were more frequent in the higher stages of NAFLD (Table 3).

Table 3: Patterns of Dyslipidemia Across NAFLD Severity Levels

Patterns of Dyslipidemia	NAFLD Severity by Fibro Scan				p-Value
	No significant fibrosis	Mild	Significant	Advanced	
Normolipidemia	10 (43.5%)	9 (39.1%)	2 (8.7%)	2 (8.7%)	<0.01*
Combined Hyperlipidemia	-	-	9 (81.8%)	2 (18.2%)	
Hyperlipidemia	-	-	-	4 (100%)	
Dyslipidemia with MetS	12 (16.7%)	22 (30.6%)	36 (50%)	2 (2.8%)	
Low HDL-C	74 (40.2%)	67 (36.4%)	39 (21.2%)	4 (2.2%)	
Hypertriglyceridemia	-	1 (16.7%)	2 (33.3%)	3 (50%)	

Values are given as n (%). Chi-square/Fisher's exact test was applied. *p<0.05 is considered statistically significant.

DISCUSSION

This study provides a cross-sectional analysis of dyslipidemia patterns in patients with NAFLD, evaluated using Fibro Scan, which measures liver stiffness and fat content.Our results indicate that 65.5% of patients were classified as having insignificant or mild NAFLD, 29.3% as having significant NAFLD, and 5.7% as having advanced NAFLD.This distribution is consistent with Sen *et al.*, who observed a predominance of mild cases, although severe cases were less common [21]. In contrast, Bhusal *et al.*, reported a higher proportion of mild cases and none with severe NAFLD [22], which could reflect differences in patient demographics or diagnostic criteria. NAFLD has also been associated with different MetS, such as impaired glucose tolerance, insulin resistance and lipid abnormalities [23-25].Hypercholesterolemia and hypertriglyceridemia, included in the range of dyslipidemia ,are diagnosed in 20-80 % of NAFLD patients.In the current study, 24% of patients had dyslipidemia, which is prevalent in MetS patients in their database. In particular, 61.3% of patients had a low concentration of HDL-C, which is an index of dyslipidemia and is normally related to cardiovascular diseases.However, hypertriglyceridemia

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was less frequent, with only 2% of the patients presenting with this condition. Only 7.7% of the entire cohort were normolipidemic.Patients with both combined hyperlipidemia and general hyperlipidemia were identified in 3.7% and 1.3% of participants, respectively. Approximately one-half of the NAFLD patients had abnormally elevated cholesterol and/or triglyceride levels as compared to the unaffected population [21]. Research indicates significant sex differences in NAFLD prevalence and severity. Although the gender effect did not play a role in determination of the degree of NAFLD in the present population. In contrast some studies do report a link between the two, it is found that men generally have higher NAFLD rates during reproductive years, while postmenopausal women show increased prevalence, suggesting a protective role of estrogen [26]. Metabolomic profiling reveals distinct sex-related patterns in NAFLD progression, with specific metabolites associated with disease severity in males and females [27]. The liver-adipose tissue crosstalk, influenced by sex hormones, plays a crucial role in regulating lipid and glucose metabolism, contributing to the observed sexual dimorphism in NAFLD [28]. These sex differences extend to risk factors, fibrosis, and clinical outcomes, highlighting the need for sex-specific considerations in clinical trials and treatment approaches [26]. Understanding these gender-based differences may lead to the development of novel, sex-specific therapeutic strategies for NAFLD management [28]. We also established that subjects with more severe NAFLD levels have a higher mean BMI, WC, levels of both hepatic transaminases (AST and ALT), and lipid profile parameters including TC, LDL-C, and TG; and lower levels of HDL-C. These findings indicate that the progression of NAFLD worsens metabolic imbalance as the disease advances. RBS was reasonably well controlled, although a higher ratio of Hba1c suggested that the patients with more severe NAFLD may have a worse glucose metabolism. Similarly, the hepatic steatosis score and CAP increased with worsening in the severity of NAFLD due to fat deposition in the liver. Indeed, the results of this study support previous findings, which have shown links between NAFLD, on one hand, and obesity as well as disturbances in metabolic parameters on the other. Abnormal levels of ALT, an enzyme that indicates liver inflammation, are present in patients with NAFLD, which supports the findings shown by Khurram and Ashraf regarding the presence of a variety of factors like high BMI, diabetes, and dyslipidemia in NAFLD patients [29]. In a broad sense, our finding serves to establish a relationship between NAFLD and dyslipidemia, with significant changes in lipid profiles according to the advancement of NAFLD. These findings highlight the need for clinician awareness of lipid levels and the inclusion of lipid profile testing in managing NAFLD and its related metabolic comorbidities. Managing lipid abnormalities in NAFLD patients may help prevent the worsening of liver disease and, thus, enhance patient prognosis.

CONCLUSIONS

It was concluded that the dyslipidemia patterns are significantly associated with the severity of NAFLD. Thus, we conclude that higher levels of TC, LDL-C and triglycerides and lower levels of HDL-C significantly correlate with advanced stages of NAFLD. The findings indicate the importance of monitoring the lipid levels in NAFLD patients, suggesting that dyslipidemia may play an important role in worsening liver disease.

Authors Contribution

Conceptualization: KUS, NB
Methodology: KUS, SK, AS, MWA, NB, SAB
Formal analysis: KUS, SK, AS, MWA
Writing review and editing: SK, NB, SAB
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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