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Dyslipidemia is an Independent Predictor of Rapid Progressive Disease in Patientswith Chronic Liver Disease

Muhammad Yahya Memon [a], Gohar Ali [a], Syeda Iffat Bukhari [a], Nabiya Sandeelo [a], Haris Alvi [b], Abu Talib [b], Paras Imran [b], Imtiaz Baloch [b] and Syed Zulfiquar Ali Shah [c*]

[a] Department of Medicine, Dow University of Health Sciences / Dr. Ruth K. M. Pfau Civil Hospital Karachi, Pakistan.
[b] Department of Medicine, Dow University of Health Sciences and Civil Hospital Karachi, Pakistan.
[c] Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Introduction: In chronic liver disease (CLD), the lipid profile biomarkers are altered because of decreased lipoprotein biosynthetic capacity.
Objectives: To identify the association of dyslipidemia with various characteristics in chronic liver disease patients.
Patients and methods: This cross-sectional study was conducted at the Department of Medicine, Civil Hospital, Karachi. The study was conducted between 1st July to 31st December 2017. A total of 211 adults with chronic liver disease were included in the study.
Data regarding age, gender, body mass index (BMI), duration of CLD, family history of dyslipidemia, and severity of cirrhosis were obtained. A 5ml fasting (12-14 hours) venous blood was collected and sent to the laboratory forthe measurement of lipid profiles. Dyslipidemia was established based the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP III) guidelines and definition.

**Corresponding author: E-mail: zulfikar229@hotmail.com;*

Results: The mean age of the study patients was 43.16(8.63) years. The majority of the subjects were males (57.3%). The mean duration of CLD in years was 5.21(2.32). The prevalence of dyslipidemia was found to be 76.3%. Dyslipidemia was prevalent among patients of the age group > 45 years and male gender. Variables including age, gender, income, duration of CLD and family history of dyslipidemia showed significant association with dyslipidemia. In the multivariable stage analysis, the only retained significant variables are gender and family history of dyslipidemia.
Conclusion: The prevalence of dyslipidemia among chronic liver disease patients was high. Various characteristics of the CLD patients were found to be significantly associated with dyslipidemia and identified as potential risk factors for its development.

Keywords: Chronic liver disease; dyslipidemia; non-alcoholic fatty liver disease.

1. INTRODUCTION

Chronic liver disease (CLD) is a collective term used for the various hepatic disorders that lead to the replacement of normal liver parenchyma with fibrosis [1]. As the liver has many synthetic and metabolic functions, several metabolic derangements occur in CLD including clotting factors deficiencies, dyslipidemia, and even venous thromboembolism [2]. Dyslipidemia refers to an imbalance between lipids and lipoproteins [3]. The liver synthesizes both the lipoproteins for the transport of lipids and apolipoproteins for the metabolism of lipoproteins. Not only this but the liver is also involved in the metabolism, synthesis, and transport of cholesterol and fatty acids [4].

Derangements in the lipid profile markers become evident as CLD progresses to end-stage with cirrhosis and a reduction in cholesterol of low-density lipoprotein and high-density lipoprotein becoming evident [5]. As the metabolism of lipid gets disrupted, accumulation of lipid droplets within hepatocytes and decreased secretion of very low-density lipoprotein leads to hepatic steatosis and further liver injury [6].

Li et al. in their study implicated dyslipidemia as a risk factor for the incidence and severity of the drug-induced liver injury [7]. Whereas Méndez-Sánchez et al. reported dyslipidemia to be a risk factor for the progression of liver fibrosis.[8] With the implication of dyslipidemia in the incidence and severity of hepatic disorders, it is ever so important to assess the risk factors predisposing CLD patients to dyslipidemia. This is important because if screening for dyslipidemia is employed at early stages, better management plans can be designed for those at higher risk. In this regard, the present study aims to assess the association of various characteristics of CLD patients with dyslipidemia and their identification as potential risk factors.

2. PATIENTS AND METHODS

This cross-sectional study was conducted at the Medicine Department, Civil Hospital, Karachi. The study was conducted between1st July 2017 to 31st December 2017.

Participants from both genders were eligible for inclusion in the study provided that they belonged to the age range of 18 to 60 years and had CLD regardless of the etiology.

Individuals diagnosed with any of the following conditions concomitantly were excluded from this study; patients with diabetes mellitus, patients with a history of hyperlipidemia of any duration, patients with ischemic heart disease of any duration or those with end-stage renal diseaseof any duration, acute hepatitis of any duration, hypothyroidism confirmed by thyroid profile, patients taking lipid-lowering drugs for last 3 months confirmed from the medical record and any malignancies including HCC.

For sample size calculation the prevalence of dyslipidemia in chronic liver disease was considered as i.e. 83.6%9 with a margin of error of 5% and confidence interval of 95% the minimum calculated sample size was 211. Data were collected through a non-probability consecutive sampling technique.

The researcher obtained the data regarding age, duration of disease, and family history of dyslipidemia, BMI, income status, educational status, gender, and severity of cirrhosis and noted on pre-approved Performa. A 5ml fasting (12-14 hours) venous blood was collected and sent to the laboratory for lipid profile analysis. Dyslipidemia was labeled as abnormal concentrations of lipids and lipoproteins in the blood. The patient was labeled as suffering from dyslipidemias based on NECP ATP III guidelines if any one of the following were present: High-density lipoproteins (HDL) ≤ 40 mg/dL in males and ≤ 50 mg/dL in females, low-density

lipoproteins (LDL) ≥100 mg/dL, total cholesterol ≥ 200 mg/dL, triglycerides ≥ 150 mg/dL. The data were recorded in the Performa by the principal investigator.

Data entry and analysis were performed using SPSS version 20.0. Frequency (percentage) was computed for a categorical variable like gender, dyslipidemia, and family history of dyslipidemia. Mean (SD) were obtained for continuous variables such as age, duration of signs and symptoms suggestive of chronic liver disease, and BMI. Dyslipidemia was compared using $\chi 2$ test for demographic variables, a p-value less than 0.05 was considered as statistically significant. Furthermore, univariate, and multivariable logistic regression analyses were also performed.

3. RESULTS

3.1 Demographics

Data was obtained from 211 patients. The mean age of the study patients was 43.16±8 years and more than half of the patients were males (n=121;57.3%). Most of the participants (n=94; 44.5%) belonged to the >45 age group and income status of > Rs.30,000/ PKR- (n=93; 44%). The mean duration of CLD in years was 5.21±2.32. Nearly half of the patients (n=105; 49.8%) had mild cirrhosis whereas only 16.1% (n=34) had severe cirrhosis. In this study, the prevalence of dyslipidemia was found to be 76.3% (n=161) and 26.1% (n=55) of the patients that had a family history of dyslipidemia (Table 1).

3.2 Association of Dyslipidemia with Patient's Characteristics

Dyslipidemia was found to be more prevalent among patients that are above 45 years of age, male gender, and those with an income above 30,000 PKR. A significant association (p-value ≤ 0.05) was found between the incidence of dyslipidemia with age, gender, income, duration of CLD, and family history of dyslipidemia (Table 2).

Table 1. Demographic characteristics of CLD patients

Characteristics	n(%)
Age (Mean± SD) years	43.16(8.63)
29-35	48(22.7)
36-45	69(32.7)
>45	94(44.5)
Gender	
Female	90(42.7)
Male	121(57.3)
Income status, PKR	
<19,000	59(28.0)
19,000-30,000	59(28.0)
>30,000	93(44.0)
Education	
Non-formal education	37(17.5)
Primary	45(21.3)
Secondary	39(18.5)
Intermediate	43(20.4)
Graduate/ Masters	47(22.3)
BMI, Mean(SD), **Kg/m^2**	27.10(2.17)
23 – 25	35(16.6)
26 -28	114(54.0)
> 28	62(29.4)
Duration of CLD	
(Mean± SD) years	5.21(2.32)
1-3	45(21.3)
4-5	102(48.3)
> 5	64(30.3)
Severity of Cirrhosis	
Mild	105(49.8)
Moderate	72(34.1)
Severe	34(16.1)

Characteristics	n(%)
Family History of Dyslipidemia	
Absent	156(73.9)
Present	55(26.1)
Dyslipidemia	
Absent	50(23.7)
Present	161(76.3)

CLD=Chronic Liver Disease,
BMI= Body Mass Index

Table 2. Association of dyslipidemia with Demographic characteristics among CLD patients

Characteristics	Dyslipidemia	Absent (n=50)	Present (n=161)	P value
Age, years, n(%)	29-35	18(37.5)	30(62.5)	0.033
	36-45	15(21.7)	54(78.3)	
	>45	17(18.1)	77(81.9)	
Gender, n(%)	Female	28(31.1)	62(68.9)	0.029
	Male	22(18.2)	99(81.8)	
Income status, PKR, n(%)	<19,000	29(49.2)	30(50.8)	<0.001
	19,000-30,000	11(18.6)	48(81.4)	
	>30,000	10(10.8)	83(89.2)	
Education, n(%)	Non-formal education	12(32.4)	25(67.6)	0.660
	Primary	10(22.2)	35(77.8)	
	Secondary	10(25.6)	29(74.4)	
	Intermediate	9(20.9)	34(79.1)	
	Graduate/ Masters	9(19.1)	38(80.9)	
BMI, Kg/m^2, n(%)	23 - 25	13(37.1)	22(62.9)	0.092
	26 -28	26(22.8)	88(77.2)	
	> 28	11(17.7)	51(82.3)	
Duration of CLD, years, **n(%)**	1-3	16(35.6)	29(64.4)	0.033
	4-5	25(24.5)	77(75.5)	
	> 5	9(14.1)	55(85.9)	
Severity of Cirrhosis, n(%)	Mild	29(27.6)	67(69.8)	0.089
	Moderate	15(20.8)	57(79.2)	
	Severe	6(17.6)	37(86.0)	
Family history of dyslipidemia, n(%)	Absent	45(28.8)	111(71.2)	0.003
	Present	5(9.1)	50(90.9)	

CLD= Chronic liver disease, BMI= Body Mass Index

3.3 Univariate and Multivariable Logistic Regression Model Results

Univariate and multivariable-adjusted logistic regression analyses were performed to evaluate the association of dyslipidemia among CLD patients. At the univariate level, the results indicate that variables such as age, gender, duration of CLD, and family history of dyslipidemia were significantly associated with dyslipidemia (p-values ≤ 0.05).

Several noteworthy results were obtained. Those above the age of 45 years had 2.718-time increased odds of developing dyslipidemia than the patients in the younger age bracket (p-value=0.013). Females had 2.032-time increased odds of having dyslipidemia as compared to their male counterparts (p-value= 0.03). Those with greater than a 5-year history of CLD had 3.372-time increased odds of having dyslipidemia compared to those with a shorter duration history (p-value= 0.011). Individuals who had a family history of dyslipidemia had 4.054-time increased odds of having dyslipidemia over those without a family history (p-value= 0.005). Variables with a p-value ≤ 0.10 at the univariate stage were continued for multivariable analysis. In the multivariable stage analysis, gender (p-value < 0.001) and family history of dyslipidemia (p-value= 0.004) were the only retained significant variables.

Table 3. Univariate and Multivariable-adjusted logistic regression analysis for the association of dyslipidemia among CLD patients

	Univariate Analysis			Multivariable Analysis		
Characteristics	**OR**	**95% CI**	**p-value**	**AOR**	**95% CI**	**p-value**
Age (Mean± SD) years			**0.037**			**0.610**
29-35	Ref			Ref		
36-45	2.160	0.953 –4.893	0.065	1.532	0.569 –4.127	0.399
>45	2.718	1.239 –5.962	0.013	1.644	0.573 –4.718	0.355
Gender						
Male	Ref			Ref		
Female	2.032	1.069 –3.863	**0.030**	4.614	1.990 –10.701	**<0.001**
Education			**0.666**	-	-	-
Non-formal education	Ref					
Primary	1.680	0.628 –4.493	0.301	-	-	-
Secondary	1.392	0.515 –3.766	0.515	-	-	-
Intermediate	1.813	0.663 –4.963	0.247	-	-	-
Graduate/ Masters	2.027	0.745 –5.514	0.167	-	-	-
BMI (Kg/m^2)			**0.100**			**0.509**
23 – 25	Ref			Ref		
26 -28	2.000	0.887 –4.511	0.095	1.594	0.606 –4.193	0.344
> 28	2.740	1.064 –7.055	0.037	0.957	0.310 –2.955	0.939
Duration of CLD (years)			**0.038**			**0.127**
1-3	Ref			Ref		
4-5	1.699	0.795 –3.630	0.171	2.560	0.998 –6.567	0.051
> 5	3.372	1.327 –8.565	0.011	3.154	0.685 –14.520	0.140
Severity of Cirrhosis			**0.096**			**0.394**
Mild	Ref			Ref		
Moderate	1.645	0.803 –3.367	0.173	1.778	0.742 –4.260	0.197
Severe	2.669	1.016 –7.016	0.046	0.927	0.207 –4.143	0.921
Family history of dyslipidemia						
Absent	Ref			Ref		
Present	4.054	1.518 –10.82	**0.005**	5.416	1.735 –16.905	**0.004**

OR= Odds Ratio; AOR- Adjusted Odds Ratio; CI = Confidence Interval; Ref = Reference Category

4. DISCUSSION

A deranged lipid profile is anticipated in hepatic disorders as liver is involved in both the endogenous and exogenous cycles of lipid metabolism and peripheral distribution of lipids [9].

Majority of our study participants were above 45 years of age which is in concordance with a previous study conducted in the local population in which CLD was found to be more prevalent in populations in the same age range. [10,11].In contrast, several other studies have reported CLD to be a disease of middle age. [1, 12, 13] Our study revealed gender predilection with the males affected more than the females. However, further analysis revealed females to be at a significantly greater risk of developing dyslipidemia. This can be explained by the analogy that women throughout the course of their lives undergo hormonal changes including at puberty, menarche, pregnancy, and menopause, each of these hormonal changes has the potential to disrupt serum lipoprotein levels and hence poses a greater risk for the women to develop dyslipidemia [14].

It was observed that patients beyond the overweight range (BMI >28) were significantly at an increased risk of developing dyslipidemia partly because obese people tend to lead an unhealthy lifestyle for example, consumption of fatty foods, and inadequate physical activity [15]. It was also noted that, dyslipidemia that is associated with obesity has increased lipid profile markers whereas the lipid profile markers in dyslipidemia associated with CLD tend to decrease with the increasing severity of the disease [1,16].

Higher-income status showed a significant association with dyslipidemia and this finding is consistent with the findings of Huang et al who explained a higher socioeconomic status to be associated with the predisposition of the developmentof dyslipidemia [17].

In our study, the education status of the study participants wasn't identified as an independent factor associated with the development of dyslipidemia. This finding is in contrast to the studies conducted by Santo et al. in the Brazilian population and Polychronopoulou et al. in the Greek population which demonstrated a significant association of educational status with altered lipid profile [18,19]. The difference in the findings can be attributed to the differences in the ethnic background and also the context in which the relationship was assessed.

Family history of dyslipidemia was found in our study to be the single most important factor that was significantly associated with dyslipidemia. This finding is in concordance with various studies that also demonstrated a positive relationship between the two [20,21].

We observed that both the duration and the severity of CLD in the univariate analysis to be associated with an increased risk of developing dyslipidemia. Our findings are consistent with Farooque et al. and Ghadir et al. who also reported increased derangement of lipid profile markers with increasing severity of the disease. [10,22] This finding highlights the decreasing biosynthetic activity of the liver with the increasing severity of the disease. In addition, a positive correlation has been reported between the severity of liver disease and known markers of atherogenic risk [23]. This combined with the findings in our study warrants the need to assess the lipid profile of the patients presenting with CLD and risk stratification to provide better management to those with a higher risk of developing dyslipidemia.

5. CONCLUSION

In summary, our study revealed various characteristics of CLD patients to be associated with abnormal lipid parameters and assessed these characteristics as potential risk factors for dyslipidemia and highlighted the role that assessment of dyslipidemia could play in the risk stratification and better management of CLD patients. Further investigations are required to investigate dyslipidemia as an independent factor to assess the severity of liver disease and the degree of liver damage.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

The research synopsis was approved by Research Evaluation Unit (REU) committee with REU No. 31611, College of Physicians & Surgeons Pakistan (CPSP). Informed consent was taken after describing the aim and procedure of the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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