RESEARCH ARTICLE

Role of Lipid Profile in the Assessment of Nonalcoholic Steatohepatitis in Prediabetic and Diabetic Patients with Nonalcoholic Fatty Liver Disease

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is a chronic condition ranging from simple steatosis and fatty liver to more severe manifestations like nonalcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma. Excess fat deposition is common in NAFLD and it is strongly correlated with insulin resistance and associated conditions, such as obesity, metabolic syndrome, type II diabetes mellitus, or hyperglycemic conditions. Most people with NAFLD remain asymptomatic until development of irreversible damage of liver tissue. The present study was planned to study the role of lipid profile in assessment of NASH in prediabetic and diabetic patients with NAFLD. Prediabetic (n = 100) and diabetic (n = 100) patients with NAFLD were enrolled for the study. Of the total 200 patients, 16% confirmed for NASH. Serum cholesterol > 200 mg/dL, triglycerides > 150 mg/dL, and high-density lipoprotein (HDL) < 60 mg/dL exhibited a strong association with occurrence of NASH. The study demonstrated that increased cholesterol (p = 0.000) and triglyceride (p = 0.009) and low HDL (p = 0.006) were significant markers in NASH patients. The study therefore recommends that prediabetic and diabetic patients with NAFLD should be regularly screened for lipid levels and patients with dyslipidemia should be considered to be at risk of developing NASH. Early identification of the disease can be helpful in providing timely treatment.

Keywords: Dyslipidemia, Insulin resistance, Lipid profile, Nonalcoholic fatty liver disease, Nonalcoholic steatohepatitis.

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INTRODUCTION

Nonalcoholic fatty liver disease refers to a group of disorders including asymptomatic conditions like fatty liver to more severe condition like NASH, which present with progressive apoptosis and fibrosis. Nonalcoholic steatohepatitis was first defined by Ludwig et al[1] as a condition presenting with inflammatory changes in liver function tests. Nonalcoholic fatty liver disease is commonly associated with insulin resistance and hence with other comorbid conditions like obesity, type II diabetes mellitus, and dyslipidemia.[2]

Prevalence of NAFLD is increasing rapidly as prevalence of diabetes and obesity is increasing worldwide.[3] The worst side of this disease is that awareness of NAFLD is not enough in general population as well as in clinical practice. Early diagnosis of NAFLD is usually missed due to underestimation of disease.

Liver biopsy has been identified as the gold standard for diagnosis as well as evaluation of the degree of necrotic inflammation of liver tissue in NASH.[4] Though liver biopsy provides a confirmation of the disease, it involves invasive procedure and hence researchers have been exploring reliable biomarkers that can be helpful in early detection of the disease.

The present study was planned to assess the role of estimation of components of lipid profile in diagnosis and treatment of NASH in prediabetic and diabetic patients with NAFLD.

MATERIALS AND METHODS

This was a single-center observational study conducted on patients visiting the Gastroenterology Outpatient Department of Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan, India. Approval from the Institutional Ethics Committee and informed consent were obtained prior to enrolling the patients. Complete history and ultrasonography findings were recorded for confirmation of NAFLD. The enrolled patients were categorized as prediabetic (n = 100) and diabetic (n = 100) based on

the criteria defined by the American Diabetes Association. Patients more than 60 years of age, alcoholics, suffering from chronic liver disease induced by drugs, viral infections, or of autoimmune origin or on medication for fatty liver disease were excluded from the study. Fasting blood samples were collected using standard aseptic techniques and analyzed for serum lipid profile, which included serum cholesterol, triglycerides, and HDL-cholesterol. Low-density lipoprotein (LDL) and very low density lipoprotein (VLDL) were calculated using Friedewald's formula. Occurrence of NASH was confirmed by fibroscan.

RESULTS

Results obtained were subjected to statistical analysis using Statistical Package for the Social Sciences software. In the prediabetic group the male/female ratio was 74:26, while it was 65:35 in the diabetic group (Table 1 and Graph 1). Among the diabetic subjects (n = 100), 28% patients presented with NASH, while among the prediabetic subjects (n = 100), the prevalence of NASH was only 10%.

Serum lipid levels estimated were presented as mean ± standard deviation (SD) for the prediabetic and diabetic groups. On applying Student's t-test, it was observed that among the diabetic group, mean serum triglyceride was significantly higher (p = 0.000), followed by serum cholesterol (p = 0.024) and VLDL (p = 0.020). However, HDL and LDL did not exhibit any significant variation (Table 2 and Graph 2).

Table 1: Distribution of NAFLD patients on the basis of sex

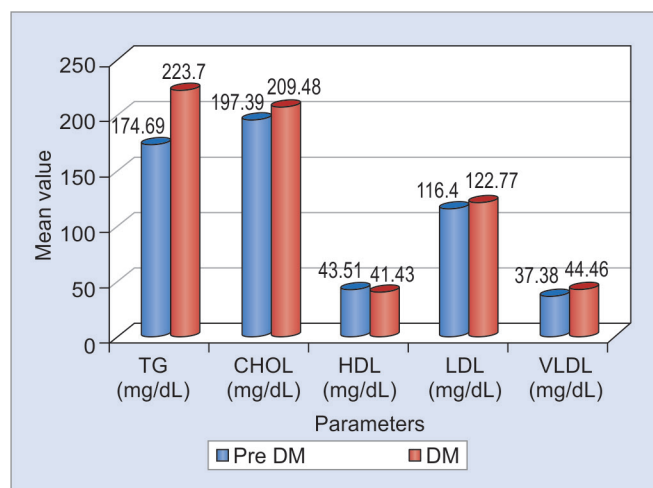| Sex	Prediabetic	Diabetic
Female	26	35
Male	74	65
Total	100	100
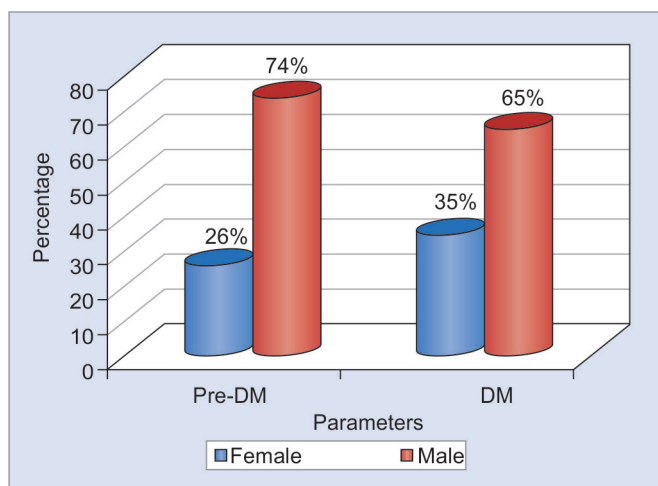
Graph 1: Male/female distribution of prediabetic and diabetic patients with NAFLD

Table 2: Lipid profile in prediabetic and diabetic patients with NAFLD

| Parameters	Mean ± SD		t-value	p-value
	Pre-DM	DM		
Triglyceride (mg/dL)	174.69 ± 82.59	223.70 ± 102.17	−3.730	0
Cholesterol (CHOL) (mg/dL)	197.39 ± 39.27	209.48 ± 36.08	−2.267	0.024
HDL (mg/dL)	43.51 ± 12.46	41.43 ± 14.07	1.107	NS
LDL (mg/dL)	116.40 ± 33.98	122.77 ± 33.49	−1.335	NS
VLDL (mg/dL)	37.38 ± 21.76	44.46 ± 21.03	−2.430	0.020

DM: Diabetes mellitus; NS: Nonsignificant

Graph 2: Comparison of serum lipid profile in prediabetic and diabetic patients of NAFLD

Of the total 200 NAFLD patients enrolled for the present study, 38 (16%) confirmed for NASH. The prevalence of NASH in association with the lipid levels was evaluated by applying chi-square test. The present study demonstrated that dyslipidemia is clearly associated with the development of NASH. Serum cholesterol level >200 mg/dL, serum triglycerides >150 mg/dL, and HDL-cholesterol <60 mg/dL tend to have a positive influence in prevalence of NASH. The presence of cholesterol >200 mg/dL was highly significant factor in the NASH cases (χ^2 = 14.61, p = 0.000) followed by serum triglycerides >150 mg/dL (χ^2 = 6.92, p = 0.009) and serum HDL <60 mg/dL (χ^2 = 7.446, p = 0.006) (Tables 3 to 5 and Graphs 3 to 5).

Table 3: NASH prevalence in NAFLD patients on the basis of serum triglyceride levels

Groups	Subgroups		Chi-square	p-value
	TG < 150 No. (%) mg/dL	TG > 150 No. (%) mg/dL		
NASH	06 (16)	32 (84)	6.920	0.009
No NASH	53 (33)	109 (67)		
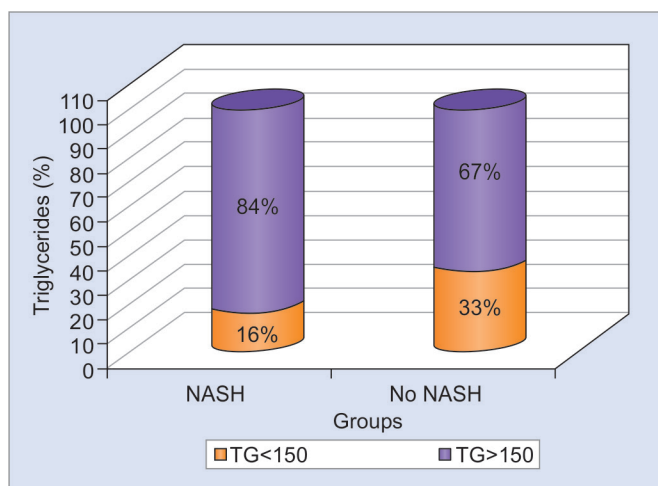
Graph 3: Comparison of NASH occurrence among NAFLD patients on the basis of serum triglyceride levels

DISCUSSION

Nonalcoholic fatty liver disease is a disease involving fat accumulation in absence of alcohol consumption. It is a spectrum of liver diseases from simple steatosis to less related cirrhosis or further hepatic carcinomas. The etiology of NAFLD may include varied causative factors and comorbid conditions. Diabetes and insulin resistance have been identified as factors that increase the risk of NAFLD.

In addition, NAFLD or NASH management needs collaborate work of multiple specialists like gastroenterologist, hepatologist, endocrinologist, cardiologist, and well-designed and managed screening for biomarkers.

In a review by Okanoue et al,[5] prevalence of NAFLD and NASH in Japan was studied. It was reported that the prevalence of NASH in diabetic patients may be as high as 30 to 40%. Previous studies have also observed that diabetes is a risk factor for development of NAFLD and further its progression to advanced liver disease including NASH.

In an epidemiological study by El-Serag et al,[6] two to three times increased risk of future end-stage liver disease and hepatocellular carcinoma was reported in diabetic patients. Recent studies by Portillo et al,[7] Cusi,[8] and Wong et al[9] have established that increased plasma glucose level may lead to toxicity, thereby activating the apoptosis pathway and hence worsened NASH.

In another study by Souza et al,[10] conditions of hypercholesterolemia, hypertriglyceridemia, or both were reported in as high as 80% of the NAFLD patients. Accumulation of triglycerides in hepatic tissue is a common observation in NAFLD patients. This occurs as a result of upregulation of fatty acid oxidation along with VLDL secretions.[11-13] The conditions are observed to be worsened due to postprandial hyperlipidemia.[14] Excess of chylomicrons and triglycerides enhance the process of atherosclerosis and results in endothelial dysfunction.
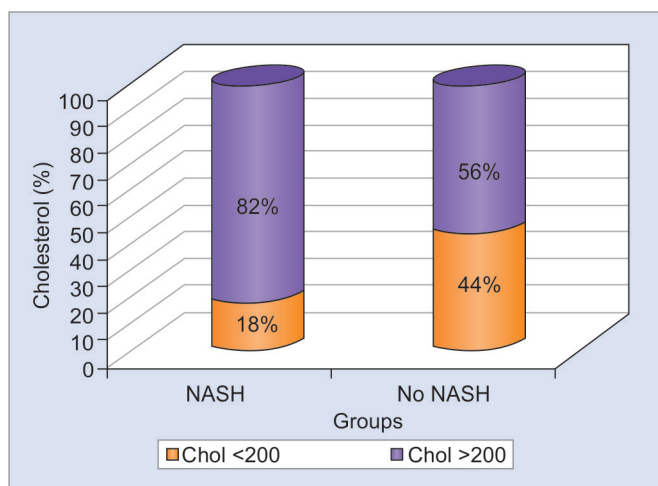
On the one hand, hyperlipidemia contributes to plaque formation in the endothelial lining of blood vessels and on the other hand, production of lipolytic products

**Table 4:** NASH prevalence in NAFLD patients on the basis of serum cholesterol levels

| | Subgroups | | | |
| | CHOL < 200 | CHOL > 200 | | |
Groups	No. (%) mg/dL	No. (%) mg/dL	Chi-square	p-value
NASH	07 (18)	31 (82)	14.61	0
No NASH	71 (44)	91 (56)		

Table 5: NASH prevalence in NAFLD patients on the basis of serum HDL levels

| | Subgroups | | | |
| | HDL < 60 No. | HDL > 60 No. | | |
Groups	(%) mg/dL	(%) mg/dL	Chi-square	p-value
NASH	38 (100)	00	7.446	0.006
No NASH	148 (91)	14 (09)		

Graph 4: Comparison of NASH occurrence among NAFLD patients on the basis of serum cholesterol levels
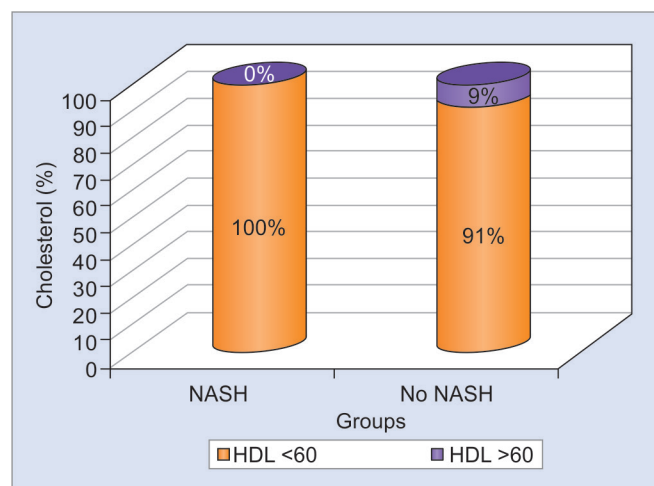
Graph 5: Comparison of NASH occurrence among NAFLD patients on the basis of serum HDL levels

activates the proinflammatory signaling pathways of endothelial cells.[15,16]

Previous studies by Kantartzis et al[17] and Adiels et al[13] have highlighted the association of NAFLD with low HDL levels and high VLDL levels. Gastaldelli[18] and Vanni et al[19] have proposed direct relationship between NAFLD and metabolic syndrome. The above studies have recommended that NAFLD can be considered as the hepatic manifestations of metabolic syndrome.

CONCLUSION

The present study shows that diabetes patients are at high risk to develop NAFLD or other associated complications including cirrhosis and hepatic carcinomas. Diabetes with dyslipidemia (high cholesterol, high triglyceride) further increases the risk of developing NAFLD which may have poor prognosis. Liver biopsy is the test of choice in case of NAFLD to differentiate hepatic ballooning due to NAFLD or any other hepatic pathology like infections or overuse of drugs. Liver biopsy involves a costly and invasive procedure and may have performer bias. Moreover, it may not be available at all centers. Screening for risk markers like lipid profile may serve as a useful tool in diagnosis and identification of patients at risk. Early diagnosis of NAFLD can help patients improve their condition by adopting healthy lifestyle changes and hence improving the prognosis. The study recommends further research on the role of other diabetic markers including glycemic control and insulin levels in risk assessment of prediabetic and diabetic patients with NAFLD.

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