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Original Research Article

Study on Clinical and Biochemical Changes in Non-Alcoholic Fatty Liver Disease in Type 2 Diabetes Mellitus

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Abstract:

Background: In affluent nations, non-alcoholic fatty liver disease (NAFLD) is the predominant cause of chronic liver disease. NAFLD has an even more aggressive course and can lead to early onset chronic liver disease in those with type 2 diabetic mellitus (T2DM). While hepatic ultrasonography is one of the numerous noninvasive techniques that can indicate the severity of NAFLD, biopsy is still the gold standard for diagnosing the condition. The purpose of this study was to use hepatic ultrasonography to assess the prevalence of NAFLD in patients with type 2 diabetes and to ascertain how it related to body mass index and other biochemical markers (glycated hemoglobin HbA1c, liver transaminases, and lipid profile).

Methods: This observational study was carried out at Darbhanga Medical College and Hospital December 2020 to May 2021. All the involved patients were known to have T2DM. After being consented, their body mass index (BMI) was determined, and patients were classified into mild, moderate, and severe fatty liver based on ultrasonographic criteria. Then, the biochemical blood measurements were performed by a standard laboratory procedure to determine their lipid profile, liver transaminases, and glycated hemoglobin levels.

Results: In this study a total of 109 patients (64 men and 45 women) with type 2 diabetes were included. The study group was divided into 2 subgroups: NAFLD - patients with USG evidence of fatty changes in the liver and Non-NAFLD – patients without any USG evidence of fatty changes in the liver. The prevalence of NAFLD was 65%, with men having a higher prevalence (56.3%) as compared to women (43.7%). Fatty liver showed a bimodal peak with a male predominance. More than half of the study population was obese and dyslipidemic, as identified by BMI and serum triglyceride levels. NAFLD subgroup had a higher prevalence of hypertension, smoking, obesity, central obesity, higher HbA1c and triglyceride levels and lower HDL level. Metabolic syndrome, as defined by IDF (2005) criteria, was present in 65% of the study group. CAD was more prevalent in the NAFLD subgroup (15%) compared to the non-NAFLD subgroup (13%). Using the Mann-Whitney test, it was found that BMI ($p=0.022$) correlated statistically to NAFLD, metabolic syndrome and CAD.

Conclusion: The overall prevalence of NAFLD among type 2 diabetes mellitus patients is significantly high. Elevated GPT, triglyceride and HbA1c levels may correlate with the development of NAFLD in diabetic patients.

Keywords: Diabetes mellitus type 2, Glycated hemoglobin, Lipid profile, Liver transaminases, Non-alcoholic fatty liver disease.

Introduction

Approximately one-third of persons in affluent nations may be afflicted with non-alcoholic fatty liver disease (NAFLD), an issue in public health that is becoming more widespread. The condition includes two non-alcoholic entities that differ in terms of clinical presentation and histology: fatty liver (NALF, steatosis hepatitis) and steatohepatitis (NASH, characterized by hepatocyte ballooning and lobular inflammation ± fibrosis). These conditions can eventually progress to end-stage liver disease and, in rare cases, hepatocellular cancer [1]. Most NAFLD patients are asymptomatic, and their condition is usually first identified during standard laboratory testing when abnormal liver functions are found. The liver enzymes aspartate aminotransferase and alanine aminotransferase are particularly high. However, as not all NAFLD patients have elevated levels of these enzymes, their levels do not always accurately indicate the severity of inflammation

and cirrhosis [2]. While imaging methods like MRI or liver ultrasonography can provide information about the degree of hepatic involvement in NAFLD, they are also unable to distinguish between NAFL and NASH3. Transient elastography is being studied as a noninvasive indicator of liver stiffness, levels of circulating cytokeratin-18 fragments, and measurements of a pool of fibrosis markers are among the other noninvasive indicators of liver inflammation and fibrosis [3,4]. The final diagnosis of non-alcoholic fatty liver disease (NAFLD) will still be made by histological examination of liver biopsy tissue, which can evaluate the extent of fibrosis and inflammation in the liver4.

NAFLD prevalence is rising globally, with industrialized countries accounting for around 34%–46% of the obese population's cases. [5] It is commonly known that a number of risk factors, such as obesity, metabolic syndrome, insulin resistance, and type 2 diabetes, are highly correlated with the prevalence of non-alcoholic fatty liver disease. [6,7] The risk of diabetes and NAFLD are strongly correlated. The presence of NAFLD increases the risk of diabetes by about five times. [8,9]. This correlation may be explained by insulin resistance, dyslipidemia, hepatic TG buildup, and impaired B-cell function in type 2 diabetes mellitus and non-alcoholic fatty liver disease (NAFLD). [7] For certain people with type 2 diabetes, non-alcoholic fatty liver disease and its consequences are the cause of death. [10]

It suggests that type 2 DM risk is increased by NAFLD. Consequently, type 2 diabetes may hasten the development of NAFLD [11]. Patients with nonalcoholic fatty liver disease (NAFLD) who also have type 2 diabetes mellitus (DM) are likely to be more susceptible to the disease's progressive stages and to end-stage liver disease compared to those without diabetes [12,13].

Patients with type 2 diabetes and nonalcoholic fatty liver disease (NAFLD) may also be at risk for hepatic failure, even though cardiovascular disease is the primary source of excess morbidity and mortality in this population [13,14]. NAFLD is a potential consequence that needs to be addressed, thus it is crucial for doctors to be aware of the high possibility that their T2DM patients also have it.

The most popular method for routine NAFLD screening is ultrasonography because of its accessibility, affordability, noninvasive nature, and ease of use. Ultrasonography's sensitivity might be as high as 94% and as low as 60% [5,15].

When compared to the gold standard liver biopsy, liver ultrasonography performs less well in the diagnosis of non-alcoholic fatty liver disease (NAFLD), despite being far more accurate than measuring amino-transferase levels in plasma. [16] Even with the potential for improvement, the application of semi quantitative scoring based on several echographic indicators performs poorly when the hepatic triglyceride content reaches 12.5% [17]. The degree of fibrosis can be evaluated by magnetic resonance elastography or vibration controlled transient elastography (FibroScan). If accessible [18,19]. These two methods can potentially spare many patients from undergoing liver biopsies, as they exhibit a good connection with the histology results.

Material and Methods

This observational study was conducted at Department of Physiology, Darbhanga Medical College, Laheriasarai, Bihar. All type 2 diabetic patients admitted to the Department of Medicine, Darbhanga Medical College & Hospital, Laheriasarai, Bihar between December 2020 to May 2021 were screened historically, biochemically and ultrasonographically. In order to exclude alcoholic fatty liver, only teetotalers were included. All patients gave informed consent and the study protocol was approved by the ethics committee of the hospital. A detailed history of CAD risk factors like smoking, hypertension, physical activity and treatment taken was recorded. The presence of CAD was assessed from a history of angina (Modified Rose questionnaire), ECG changes (Minnesota codes), past history of CAD or treatment taken for CAD.

Detailed physical examination was carried out with emphasis on brachial blood pressure, height, weight, and waist-hip ratio. Laboratory investigations included fasting and 2-hour post-prandial blood glucose, HbA1c, blood urea, serum creatinine, lipid profile (total cholesterol, LDL, HDL, VLDL, and triglycerides) and liver function tests. All patients underwent ultrasound (USG) of the abdomen to detect fatty changes in the liver, performed by a single experienced radiologist, using a high resolution B-mode ultrasonography system having an electric linear transducer mid frequency of 3–5 MHz.

The scanning was done for an average of 20 minutes; images obtained were recorded and photographed. Fatty liver was defined as the presence of an ultrasonographic pattern consistent with ‘‘bright liver,’’ with evident ultrasonographic contrast between hepatic and renal parenchyma, vessel blurring.

Inclusion Criteria

- 35 years of age or above
- Known case of type 2 diabetes mellitus

Exclusion Criteria

- Known liver disease, HBsAg or HCV positivity

- Ingestion of hepatotoxic drug(s)
- Known alcoholics

Resting 12-lead ECG were Minnesota coded

1. **Probable CHD was defined as Minnesota coding**

- 1.1–1.2 (large Q and QS waves) and

2. **Possible CHD as Minnesota coding**

- 1.3 (small Q and QS),
- 4.1–4.4 (ST-T depression),
- 5.1–5.3 (flattened or inverted T waves)
- 7.1.1(complete left bundle branch block)
- Possible CHD (ST/T changes)
- Probable CHD (Q/QS changes)

Ultrasonography: Fatty liver was defined as the presence of a pattern consistent with 'bright liver,' with evident contrast between hepatic and renal parenchyma, intrahepatic vessel blurring, and narrowing of the lumen of the hepatic veins in the absence of findings suggestive of chronic liver disease. Posterior attenuation is closely related to steatosis. Fatty liver is associated with an impaired hepatic blood flow characterized by increased intrahepatic resistances.

The statistical calculations were performed by Statistical Package for Social Sciences version 24 (SPSS 24; IBM Corp; USA).

Results

Table 1: Comparison of various parameters between the groups

Parameter	Group	Mean	Std. Dev.	SE of Mean	Mean Difference	Z	P -Value
Age(yrs)	Normal	53.97	10.65	1.73			
	NAFLD	55.14	12.43	1.48	-1.167	-0.302	0.762
Duration of Diabetes(yrs)	Normal	5.78	4.53	0.74			
	NAFLD	5.74	4.61	0.55	0.043	-0.138	0.891
BMI(kg/m2)	Normal	24.84	3.34	0.54			
	NAFLD	26.32	3.23	0.38	-1.482	-2.283	0.022
Waist to Hip Ratio	Normal	0.95	0.11	0.02			
	NAFLD	0.97	0.15	0.02	-0.024	-0.66	0.505
SBP(mm/Hg)	Normal	137.6	15.67	2.54			
	NAFLD	140.1	17.61	2.09	-2.509	-1.050	0.294
	Normal	84.21	13.08	2.12			
DBP(mm/Hg)	NAFLD	86.34	9.14	1.08	-2.128	-0.861	0.389
	Normal	188.2	76.78	12.45			
FBS(mg/dL)	NAFLD	206.0	68.31	8.11	-17.751	-1.676	0.094
PPBS(mg/dL)	Normal	244.3	73.99	12.00			
	NAFLD	268.1	84.38	10.01	-23.825	-1.479	0.139
HbA1c	Normal	8.88	2.17	0.35			
	NAFLD	8.75	1.82	0.22	0.121	-0.057	0.954
Total cholesterol(mg%)	Normal	171.5	35.78	5.80			
	NAFLD	186.4	43.24	5.13	-14.965	-1.976	0.050
LDL Cholesterol (mg%)	Normal	106.3	30.28	4.91			
	NAFLD	111.1	30.91	3.67	-4.825	-0.674	0.500
HDL Cholesterol(mg%)	Normal	35.21	9.07	1.47			
	NAFLD	35.17	8.51	1.01	0.042	-0.188	0.851
Triglycerides (mg%)	Normal	191.7	5.52	8.36			
	NAFLD	187.5	42.85	5.09	4.202	-0.102	0.918
AST(IU/L)	Normal	45.66	65.89	10.69			
	NAFLD	85.77	165.8	19.69	-40.117	-1.420	0.156
ALT(IU/L)	Normal	39.11	49.53	8.03			
	NAFLD	55.20	79.39	9.42	-16.092	-0.462	0.644

*denotes significant difference. Statistically significant difference was observed between Normal & NAFLD group with respect to mean BMI ($P<0.05$). Higher mean BMI was recorded in NAFLD group compared to Normal group. No significant difference was observed between the two groups for any of the other parameters ($P\geq0.05$).

Table 2: Comparison of historical parameters across the groups (Chi-squared test)

Parameter		Normal		NAFLD		X2	p-value
		n	%	n	%		
Alcoholism	Present	0	0%	0	0%		
	Absent	38	100%	71	100%		
	Total	38	100%	71	100%	-----	-----
Hepatotoxic drug ingestion	Present	0	0	0	0%		
	Absent	38	100%	71	100%		
	Total	38	100%	71	100%	----	-----
HBAsg	Present	0	0%	0	0		
	Absent	38	100%	71	100%		
	Total	38	100%	71	100%	-----	-----
Chest pain on exertion/at rest	Present	2	5%	6	8%		
	Absent	36	95%	65	92%	0.370	0.543
	Total	38	100%	71	100%		
Dyspnea on exertion	Present	2	5%	1	1%		
	Absent	36	95%	70	99%		
	Total	38	100%	71	100%	1.374	.241
Past h/o IHD	Present	1	3%	2	3%		
	Absent	37	97%	69	97%		
	Total	38	100%	71	100%	0.003	0.955
HTN	Present	12	32%	31	44%		
	Absent	26	68%	40	56%		
	Total	38	100%	71	100%	1.513	0.219
Smoking	Present	16	42%	33	46%		
	Absent	22	48%	38	54%		
	Total	38	100%	71	100%	0.191	0.662

No significant association is observed between the groups and any of the parameters (P≥0.05).

Table 3: comparison of three parameter (Metabolic syndrome, HbA1c and CAD) across the group

Parameter		Normal		NAFLD		χ^2	p - value	Odds ratio for Groups =NAFLD	95% CI for OR	
		n	%	n	%				Lower bound	Upper bound
Metabolic syndrome	Present	20	53%	46	65%			1.199	0.271	1.346
	Absent	18	47%	25	35%					
	Total	38	100%	71	100%	1.532	0.216			
HbA1c >7	Yes	34	89%	60	85%			0.870	0.619	1.224
	No	4	11%	11	15%					
	Total	38	100%	71%	100%	0.514	0.473			
CAD	Present	5	13%	11	15%			1.066	0.741	1.53
	Absent	33	87%	60	85%					
	Total	38	100%	71	100%	0.108	0.743			

No significant association is observed between metabolic syndrome and the groups (P>0.05).

No significant association is observed between HbA1c >7 and the groups (P>0.05).

No significant association is observed between CAD and the groups (P>0.05).

Discussion

A total of 109 patients (64 men and 45 women) with type 2 diabetes were included. The prevalence of NAFLD was 65%, with men having a higher prevalence (56.3%) as compared to women (43.7%). Fatty liver showed a bimodal peak with a male predominance. More than half of the study population was obese and dyslipidemic, as almost 53.5% and 57.9% had BMI >25 kg/m^2 and serum triglycerides >150 mg/dl, respectively. The prevalence of obesity (BMI >25 kg/m^2) in patients with NAFLD was 53.5%, as compared to 46.5% in non-NAFLD patients. CAD was more prevalent in the NAFLD subgroup (15%) as compared to the non-NAFLD subgroup (13%).

On analysing the risk factors for CAD, the NAFLD subgroup had a higher prevalence of hypertension, smoking, obesity (measured by BMI), central obesity (measured by waist circumference and WHR), higher HbA1c and triglyceride levels and lower HDL level.

The NCEP, ATP III definition of the metabolic syndrome is based on simple clinical and

biochemical parameters, while other available definitions of the metabolic syndrome include measures which are expensive and difficult to measure in developing countries. There is increasing belief that NCEP, ATP III definition of the metabolic syndrome is not optimal for the identification of risks for T2DM or CHD, and does not identify the metabolic syndrome correctly in South Asians. Most important limitation is that the internationally accepted cut-off points of waist circumference (men >102 cm, and women, >88 cm) for diagnosis of abdominal obesity are not applicable for South Asians. This is supported by our recent data that show that waist circumference levels of >90 cm and >80 cm for men and women, respectively, were associated with high odds ratios for the presence of cardiovascular risk factor(s).

Recently, International Diabetes Federation (IDF) recommended a new definition of the metabolic syndrome. This definition included three major modifications as compared to NCEP, ATP III definition;

1. central obesity has been made a mandatory variable,
2. the cut-offs of waist circumference have been lowered (male, 94cm; female, 80 cm), and for south Asians: (male, 90 cm; female, 80cm),
3. Cut-off level for fasting plasma glucose has been lowered to 100mg/dl.

Prevalence of the metabolic syndrome was significantly higher in the NAFLD subgroup, as compared to those who did not have NAFLD (61.9% vs. 13.2%). Mean values of liver enzymes (AST and ALT) were higher in the NAFLD subgroup.

Patients with higher degree of liver steatosis disease had poorer glycaemic control and greater derangements in lipid profile. However, the metabolic syndrome was equally present in both subgroups. Liver enzymes were elevated in higher degrees of NAFLD (p=0.156). In the study done by A.K Agarwal et al, it was found that hypertension (p= 0.013), LDL cholesterol (p = 0.049), microalbuminuria (p =0.034) and NAFLD (p =0.016) were independent predictors of CAD.

A number of studies have found a positive relationship between hyperinsulinaemia, abnormal glucose tolerance, and NAFLD. Mishra et al found the prevalence of metabolic syndrome and NAFLD to be 24% and 14.8%, respectively, in non-alcoholic North Indian men. In a study by Mohan et al the prevalence of NAFLD (54.5%) was significantly higher in patients with diabetes compared to those with pre-diabetes (IGT or IFG) (33%), isolated IGT (32.4%), isolated IFG (27.3%) and normal glucose tolerance (NGT) (22.5%). Also in this study, it was found the prevalence of most cardio-metabolic risk factors was significantly higher in NAFLD patients. Gupta et al found that mild, moderate, and severe NAFLD was present in65.5%, 12.5%, and 9.35% of otherwise asymptomatic type 2 diabetics, respectively.

Prashanth et al found a high prevalence of NAFLD and NASH in type 2 diabetics which increased with multiple components of the metabolic syndrome. Banerjee et al observed that, on histology, only fatty change was present in 43%, NASH in 40% and more advanced disease in 23%.

In our study, the prevalence of NAFLD, as detected by ultrasound, was 65% which is comparable with the prevalence found in other studies (Gupta et al, Prashanth et al, Banerjee et al). As seen in other studies, mean total cholesterol and LDL levels did not correlate with NAFLD; however there was a significant correlation with high triglyceride and low HDL levels. Kessler et al showed that the prevalence of NAFLD, as diagnosed by ultrasound, was significantly higher in patients with acute myocardial infarction compared with that found in the general population; moreover, NAFLD was associated with greater severity of coronary artery disease independent of age, sex and body mass index.

A limitation of our study is that the diagnosis of NAFLD was based on ultrasonography and was not confirmed by liver biopsy. Ultrasonography is by far the commonest method of diagnosing NAFLD in clinical practice and has very good sensitivity and specificity. The sensitivity and specificity of ultrasound for detecting hepatic steatosis varies from 60 to 94% and 88 to 95%, respectively.

Studies suggest that liver biopsy is seldom necessary to diagnose NAFLD.

Conclusion

Clinicians should look for NAFLD in diabetics, especially in the presence of the metabolic syndrome. Once found, aggressive management of risk factors for CAD should be the primary goal, given the greater odds of developing CAD and the high prevalence of CAD in diabetics with NAFLD.

NAFLD is considered the hepatic manifestation of metabolic syndrome and clinicians should consider it as part of the management of the other components of this syndrome. The clinical spectrum of NAFLD warrants continued research to determine its pathogenesis and to improve diagnostic modalities. It is hoped that improved imaging techniques and the discovery of serum biomarkers, as well as the development of clinical algorithms, will enable a more accurate diagnosis of NASH without the need for a liver biopsy.

Since no proven, effective treatment is currently available for NASH, well designed clinical trials are needed to provide evidence-based

recommendations for the treatment of these patients. So far, preliminary data suggest that weight loss can be beneficial and should be encouraged in overweight patients with NAFLD.

As insulin resistance has a key role in the development of NAFLD, treating insulin resistance in the NAFLD population is a promising strategy. Although there is no current treatment for NASH, patients with NASH who have cirrhosis should be screened for esophageal varices and HCC. A multimodal treatment plan that targets obesity, insulin resistance, hyperlipidemia and hypertension might be the best option.

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