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Study of prevalence of non-alcoholic fatty liver disease among pre-diabetic and diabetic patients

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Abstract: Background: Non-alcoholic fatty liver disease (NAFLD) is a common condition characterized by excess fat in the liver, which ranges from simple steatosis to steatohepatitis, cirrhosis, and hepatocellular carcinoma (HCC) in the absence of excessive alcohol intake. This study aimed to determine the prevalence of NAFLD among pre-diabetic and diabetic patients at a tertiary hospital.

Methods: This single-center, prospective, comparative, parallel-group, observational study included male and female patients between 30 and 70 years old who were either diabetic or pre-diabetic. A total of 600 patients with NAFLD were studied.

Results: Of the 200 diabetes cases studied, the prevalence of NAFLD was 52% (104 cases), while the prevalence of NAFLD among pre-diabetic cases was 45.5% (91 cases), and the prevalence of NAFLD among normal cases was 30.5% (61 cases). The prevalence of NAFLD was significant among females in all patient groups. Diabetic patients with NAFLD had a higher BMI and waist circumference than pre-diabetic and non-diabetic patients, and this difference was statistically significant. Diabetic patients with NAFLD also had higher Glycohemoglobin (%) and fasting glucose (mmol/L) than pre-diabetic and non-diabetic patients, and this difference was statistically significant. Liver function tests and other parameters such as total bilirubin, AST, ALT, GGT, LDL, HDL, total cholesterol, triglycerides, and platelet count were comparable in diabetic, pre-diabetic, and non-diabetic patients, and the difference was not statistically significant.

Conclusion: The prevalence of NAFLD among diabetic patients was 52%, while the prevalence of NAFLD among pre-diabetic cases was 45.5%. These findings highlight the importance of early screening and prevention strategies for patients with diabetes and pre-diabetes to reduce the burden of NAFLD.

Keywords: NAFLD; Diabetic patients; Pre-diabetes; Metabolic syndrome.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a prevalent condition characterized by excess fat accumulation in the liver, which ranges from simple steatosis to steatohepatitis, cirrhosis, and hepatocellular carcinoma (HCC) in the absence of excessive alcohol consumption [1]. The diagnosis of NAFLD is established by histology or imaging with macrovesicular steatosis in >5% of hepatocytes, proton density fat fraction >5.6% as assessed by proton magnetic resonance spectroscopy (MRS) or quantitative fat/water selective magnetic resonance imaging (MRI), with no secondary cause for steatosis [2].

Individuals with type 2 diabetes are at an increased risk of developing NAFLD and have a higher risk of developing fibrosis and cirrhosis compared to non-diabetic individuals. Poorly controlled diabetes promotes hepatic steatosis, and there is a vicious cycle between the two conditions. Thus, hepatic steatosis, diabetes, and metabolic syndrome are part of the same disease process that ultimately leads to increased morbidity and mortality [3,4].

Since NAFLD is closely linked to metabolic syndrome, it is considered the hepatic manifestation of the syndrome [5]. Therefore, evaluating the risk for NAFLD is recommended in all patients with any component of metabolic syndrome as all components of the metabolic syndrome correlate with the degree of liver fat content, and vice versa [2]. This study aimed to determine the prevalence of non-alcoholic fatty liver disease among pre-diabetic and diabetic patients at a tertiary hospital.

2. Materials and Methods

This single-center, prospective, comparative, parallel-group, observational study was conducted in the Department of Medicine at PCMC's PGI & YCMH Medical College & Hospital, Pimpri, Pune, India. The study was conducted over a period of two years, from January 2021 to December 2022, and was approved by the institutional ethical committee.

2.1. Inclusion Criteria

The inclusion criteria for this study were male and female patients between the ages of 30 and 70 years, who were either diabetic or pre-diabetic and willing to participate in the study. Diabetes was defined as glycohemoglobin (HbA1c) level of 6.5%, fasting plasma glucose level of 7 mmol/L, self-reported diabetes, or the use of anti-diabetic medications. Pre-diabetes was defined as HbA1c level between 5.7-6.5% or fasting plasma glucose level between 5.6-7 mmol/L.

2.2. Exclusion Criteria

The exclusion criteria for this study were patients with alcohol consumption of more than 20 grams per day, known liver diseases (hepatitis viruses A to E, autoimmune disease, Wilson's disease, alpha 1 anti-trypsin deficiency, and hemochromatosis) or any chronic liver disease. Patients on medications known to induce fatty liver or insulin sensitization such as estrogens, amiodarone, methotrexate, tamoxifen, glitazones, and metformin, patients with drug-induced hepatitis, malignancies, and congenital liver diseases were also excluded. Patients and controls who consumed alcohol > 20 g/day were also excluded.

The study was explained to the patients in the local language, and written consent was obtained for participation in the study. After obtaining informed consent, a complete history taking and physical examination were performed. The collected data included age, gender, BMI, waist-hip ratio, screening for HCV and HBsAg. Biochemical parameters such as fasting HbA1c, fasting plasma glucose, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), SGOT:SGPT ratio, total bilirubin, indirect bilirubin, direct bilirubin, serum creatinine, blood urea, and alkaline phosphatases were estimated in all patients.

The diagnosis of NAFLD was made based on ultrasonography and histological confirmation whenever possible. An increase in hepatic echogenicity, taking renal echogenicity as a reference, the presence of enhancement and lack of differentiation in periportal intensity, and the vascular wall due to great hyperechogenicity of the parenchyma were considered as NAFLD.

A qualified radiologist performed hepatic ultrasonography tests and categorized the levels of fatty liver into four grades based on the following criteria:

1. Grade-0: "absence of steatosis with normal echogenicity of the liver"
2. Grade-1: "mild steatosis, with echogenicity of the liver greater than that of the right renal cortex, but the echogenic wall of the main portal vein still greater than that of the right renal cortex"
3. Grade-2: "moderate steatosis, with impaired echogenicity of the main portal vein wall"
4. Grade-3: "severe steatosis, with impaired echogenicity of the main portal vein wall and impaired visualization of the posterior hepatic parenchyma or the diaphragm"

Data were collected and compiled using Microsoft Excel and analyzed using SPSS 23.0 version. Continuous variables were presented as means and standard deviations (SD), while categorical variables were presented as ratios and proportions. Differences in proportions between categorical variables were tested using chi-square or Fisher's exact tests, as applicable. A p-value less than 0.05 was considered statistically significant.

3. Results

3.1. Prevalence of NAFLD

A total of 600 patients with NAFLD were included in the study. The prevalence of NAFLD was found to be 52% (104 cases) among diabetic patients, 45.5% (91 cases) among pre-diabetic patients, and 30.5% (61

cases) among non-diabetic patients (Table 1). The prevalence of NAFLD was significantly higher in females, regardless of their diabetic status.

Table 1. General characteristics

Characteristics	Diabetes (n=104)	Pre-diabetes (n=91)	No diabetes (n=61)	P-value
Age (years)	55.42 ± 9.67	55.23 ± 10.35	49.45 ± 12.03	0.052
Gender (male/female)				
Male	46 (46.02%)	40 (45.2%)	28 (46.27%)	0.001
Female	58 (53.98%)	51 (54.8%)	33 (53.73%)	
Weight (kg)	89.3 ± 7.46	86.5 ± 8.56	85.5 ± 9.67	0.035
Waist circumference (cm)	110.9 ± 6.46	109.2 ± 8.45	108.2 ± 7.34	0.021
Body Mass index (kg/m2)	28.88 ± 4.53	27.4 ± 5.46	27.32 ± 4.91	0.001
Normal	54 (41.48%)	32 (57.28%)	35 (42.79%)	
Overweight	31 (34.66%)	20 (25.39%)	18 (33.83%)	
Obese	19 (23.86%)	9 (17.34%)	8 (23.38%)	

3.2. Clinical Characteristics

Diabetic patients with NAFLD had significantly higher BMI and waist circumference compared to pre-diabetic and non-diabetic patients (Table 1).

3.3. Biochemical Parameters

Table 2 shows that diabetic patients with NAFLD had significantly higher levels of glycohemoglobin (%) and fasting glucose (mmol/L) compared to pre-diabetic and non-diabetic patients.

Liver function tests and other parameters such as total bilirubin, AST (aspartate aminotransferase), ALT (alanine aminotransferase), GGT (gamma glutamyl transferase), LDL (low-density lipoprotein), HDL (high-density lipoprotein), total cholesterol, triglycerides, and platelet count were comparable in diabetic, pre-diabetic, and non-diabetic patients (Table 3). The differences were not statistically significant.

Overall, the results suggest a higher prevalence of NAFLD in diabetic and pre-diabetic patients, with significant differences observed in clinical and biochemical parameters among the different groups.

Table 2. Glucose parameters

	Diabetes (n=176)	Pre-diabetes (n=223)	No diabetes (n=201)	P-value
Glycohemoglobin (%)	8.1 ± 2.3	6.18 ± 1.4	5.8 ± 1.3	0.001
Fasting glucose (mmol/L)	7.88 ± 2.81	5.88 ± 1.46	5.22 ± 1.02	0.001

Table 3. Liver function tests

	Diabetes (n=176)	Pre-diabetes (n=223)	No diabetes (n=201)	P-value
Total bilirubin (umol/L)	4.65 ± 1.45	5.01 ± 1.72	4.81 ± 1.82	0.13
AST (IU/L) (aspartate aminotransferase)	25.5 ± 9.67	24.3 ± 7.46	26.5 ± 8.56	0.35
ALT (IU/L) (alanine aminotransferase)	28.2 ± 7.34	25.9 ± 6.46	29.2 ± 8.45	0.36
GGT (IU/L) (gamma glutamyl transferase)	27.32 ± 4.91	25.88 ± 4.53	27.4 ± 5.46	0.63
LDL (mg/dL) (low-density lipoprotein)	119.35 ± 8.34	115.38 ± 11.53	118.09 ± 11.23	0.72
HDL (mg/dL) (high-density lipoprotein)	45.93 ± 5.35	45.30 ± 4.53	50.34 ± 6.35	0.51
Total cholesterol (mg/dL)	191.92 ± 16.56	194.57 ± 15.81	189.24 ± 21.24	0.39
Triglycerides (mg/dL)	161.33 ± 19.24	162.34 ± 14.51	151.34 ± 19.32	0.62
Platelet (1,000 cells/μL)	240.42 ± 14.56	251.30 ± 11.93	250.56 ± 15.12	0.54

4. Discussion

Recently, awareness regarding NAFLD is increasing in India due to the rising prevalence of obesity and diabetes [6]. NAFLD has been identified as a cause of unexplained elevation in transaminases, and is an important cause of cryptogenic cirrhosis and hepatocellular carcinoma in India [7]. NAFLD occurs as a component of metabolic disorders associated with insulin resistance as the pathophysiological hallmark, and is clinically manifested as hepatic, pancreatic, and cardiac endothelial cell dysfunction and disease. In

NAFLD, the most common cause of death is cardiovascular disease, and nonhepatic cancers are also frequently observed apart from liver disease [8,9].

According to Shalimar *et al.* [10], the estimated pooled prevalence of NAFLD among adults was 38.6% (95% CI 32-45.5). The estimated prevalence of NAFLD in average risk and high-risk subgroups was 28.1% (95% CI 20.8-36) and 52.8% (95% CI 46.5-59.1), respectively. Hospital-based data showed a higher estimated NAFLD prevalence (40.8% [95% CI 32.6-49.3%]) than community-based data (28.2% [95% CI 16.9-41%]). Among children, the estimated pooled prevalence was 35.4% (95% CI 18.2-54.7). The prevalence among non-obese and obese children was 12.4 (95% CI 4.4-23.5) and 63.4 (95% CI 59.4-67.3), respectively.

In study by Singh S *et al.*, [11] 124 out of the 515 (24.08%) NAFLD patients were diabetics, 118 out of 515 (22.9%) were pre-diabetics, while only 3 out of 100 controls had impaired glucose tolerance. Diabetic patients were older. NAFLD patients with diabetes had significantly higher waist circumference [98.02 $\pm$ 12.01 vs 93.89 $\pm$ 8.8, p = 0.000] as compared to the NAFLD patients without diabetes. Fasting blood sugar [124 $\pm$ 46.3 vs 90.8 $\pm$ 10.2, p = 0.000], triglyceride level [218.4 $\pm$ 17.6 vs 192 $\pm$ 9, p = 0.03] and HOMA-IR [2.6 $\pm$ 0.36 vs 1.84 $\pm$ 0.2, p < 0.001] were significantly higher in NAFLD-diabetes group. Hypertension [35% vs 11.7%, p = 0.000] was commoner in diabetic NAFLD patients. Histopathology in the diabetic patients revealed steatosis alone in 34.2% cases, borderline NASH in 31.4% and definite NASH in 34.2%. Fatty change alone was noted in 16.5% cases, borderline NASH in 34.1%, while 49% had definite NASH on liver biopsy of NAFLD patients without diabetes. The prevalence of diabetes and prediabetes is six times more in NAFLD patients than in healthy controls. NAFLD patients with diabetes have higher metabolic risk factors such as large waistline, hypertension, high triglyceride levels and increased insulin resistance.

Said T *et al.*, [12] studied 426 patients aged 48.52 $\pm$ 10.13 years (226 women (53.6%)), including 213 with fatty liver disease, were enrolled. The mean fasting blood glucose in NAFLD patients was significantly higher (0.97 $\pm$ 0.13 213 Vs 0.92 $\pm$ 0.11, p < 0.001). The prevalence of pre-diabetes was higher in the NAFLDs than in the control population (14.6% vs 8.9%, p < 0.001), women were more affected than men (20.4% vs 8%, P < 0.01). We noted a positive correlation between pre-diabetes and insulin resistance (n = 426, r = 0.124 P = 0.013). In multivariate analysis, the factors independently associated with pre-diabetes were metabolic syndrome, plasma cholesterol = 2g/l, and insulin resistance.

In a study by Basaveshwar M *et al.* [13], 122 patients were studied, of which 58 (47.5%) had NAFLD. The most common sonographic grade of NAFLD was mild fatty liver (62%), followed by moderate (36%), then severe fatty liver (2%). The mean SGOT, SGPT, and ALP levels were 31$\pm$14.4 IU/L, 25$\pm$14.2 IU/L, and 104$\pm$47.6, respectively. Patients with NAFLD had a significantly higher level of ALP than patients without NAFLD. 58.6% of patients with NAFLD had a BMI above normal, compared to 36.2% of patients without NAFLD who had an elevated BMI. This difference was statistically significant (p=0.0001).

In a study by Ng CH *et al.* [14], out of 32,234 patients, 28.92% were identified to have NAFLD. Of these patients, 36.04%, 38.32%, and 25.63% were non-diabetic, prediabetic, and diabetic, respectively. Diabetic NAFLD significantly increased the risk of cardiovascular disease (CVD), stroke, chronic kidney disease, all-cause, and CVD mortality compared to non-diabetic NAFLD. However, prediabetic NAFLD only significantly increased the risk of CVD and did not result in a higher risk of mortality.

Newton KP *et al.* [15] studied 675 children with NAFLD, with a mean age of 12.6 years and a mean BMI of 32.5. The estimated prevalence of prediabetes was 23.4% (95% CI, 20.2%-26.6%), and the estimated prevalence of type 2 diabetes was 6.5% (95% CI, 4.6%-8.4%). Girls with NAFLD had 1.6 (95% CI, 1.04-2.40) times greater odds of having prediabetes and 5.0 (95% CI, 2.49-9.98) times greater odds of having type 2 diabetes than boys with NAFLD. The prevalence of NASH was higher in those with type 2 diabetes (43.2%) compared with prediabetes (34.2%) or normal glucose (22%) (P < .001). The odds of having NASH were significantly higher in those with prediabetes (OR, 1.9; 95% CI, 1.21-2.9) or type 2 diabetes (OR, 3.1; 95% CI, 1.5-6.2) compared with those with normal glucose.

Nonalcoholic fatty liver disease also has serious health consequences outside of the liver and is associated with metabolic impairment and an increasing risk for cardiovascular disease, insulin resistance, and subsequent type 2 diabetes [16]. While awareness of the link between diabetes and NAFLD is well established, prediabetes is a lesser-known entity in NAFLD. Prediabetes, a state of dysfunction albeit to a lesser degree of insulin sensitivity and impairment of β-cell function, has been found to be associated with NAFLD and its accompanying metabolic complications [12,17].

5. Conclusion

The present study highlights a high prevalence of NAFLD among diabetic patients (52%) and pre-diabetic cases (45.5%). Given the significant burden of diabetes and NAFLD in the population, individuals with pre-diabetic and diabetic NAFLD should be referred early for further risk assessment and appropriate management. It is crucial to implement effective strategies for the prevention and management of these conditions, including lifestyle modifications and pharmacological interventions, to reduce the risk of disease progression and associated complications. Further research is needed to better understand the pathogenesis and natural history of NAFLD in diabetic and pre-diabetic patients, which could provide insights into potential novel therapeutic targets for this growing health problem.

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Conflicts of Interest: "Authors declare that they do not have any conflict of interests."

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