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# A REVIEW STUDY ON CLINICAL PROFILE OF NON ALCOHOLIC FATTY LIVER (NAFLD)

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## ABSTRACT

**Introduction:** Non-alcoholic fatty liver disease is the condition in which hepatic accumulation is present these include liver disease caused by other factors, excessive alcohol consumption and other condition that may lead to hepatic steatosis. **Methodology**: Study 1 is a cross-sectional, prospective study that was conducted at Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India for a period of 5 months. The study included a total of 140 patients with Type 2 diabetes mellitus in the age group of 20-70 years, attending a medical outpatient clinic. study 2 is a prospective study, a total of 100 patients with Type-2 DM study population was included the age group of 20-70 years, attending a medical outpatient clinic. prospective study 3 was designed to enroll known T2DM patients (duration ≥3 years), in the age group of 25-65 years, attending an outpatient Medicine department of Dr. D. Y. Patil Medical College, Kolhapur, a tertiary care Centre. study 4 Study subjects were participants in the Valpolicella Heart Diabetes Study, a prospective observational study designed primarily to evaluate associations between type 2 diabetes and the incidence of chronic vascular complications. Study 5 participants in the Valpolicella Heart Diabetes Study. Briefly, we enrolled all of type 2 diabetic outpatients (n 2,103) who regularly attended our clinic in the period. **Discussion:** Hepatic steatosis and steatohepatitis can occur in association with a numerous disease affecting the liver including hepatitis A, hepatitis B, and C, autoimmune hepatitis, hypothyroidism, and hemochromatosis, however, much of the increase in the prevalence of NAFLD is driven by its pathophysiologic and epidemiologic connection to type 2 diabetes mellitus and obesity. **Conclusion:** Gender distribution of NAFLD in T2DM for study 1 having less incidence of fatty liver than study 2. Age distribution of NAFLD in Type-

2 DM patients of study 1 is better than study 2 and study 3 because the population with fatty liver is less in number. Study 4 is more significant than study 5 in its respective parameters.

**KEYWORDS**: NAFLD, DM, Hepaticsteatosis, Steatohepatitis.

## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is now the commonest cause of chronic liver disease in many developed countries. However, 10%–30% of subjects with NAFLD have non-alcoholic steatohepatitis (NASH) that can progress to cirrhosis, which puts patients at risk of liver-related complications. Due to the metabolic risk factors that are common to both NAFLD and cardiovascular disease, patients with NASH have an increased risk of cardiovascular death as well as liver-related mortality.[1]

Non-alcoholic fatty liver disease (NAFLD) is the condition in which hepatic fat accumulation is present after all other causes of hepatic steatosis are excluded; these include liver disease caused by other factors, excessive alcohol consumption, and other conditions that may lead to hepatic steatosis.

The clinical spectrum of NAFLD is wide-ranging and spans NAFLD to non-alcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). The incidence and prevalence of NAFLD are rising globally owing to increasing rates of obesity and diabetes. The development of liver cancer in patients with NAFLD, even without the presence of cirrhosis, was observed recently in a number of studies.[2]

## EPIDEMIOLOGY

Approximately 25% of adults in the US have a fatty liver in the absence of excessive alcohol consumption. In India, around 9-32% with NAFLD and females were 60% and in males 54.3% with Type-2 DM with the prevalence of NAFLD varying from 44.1% in western India to 72.4% in northern states. The highest prevalence recorded in 61-70 years group at 61.8% in India with the well established clinical association of NAFLD with elements of metabolic syndrome including dyslipidemia, hypertension, and obesity as T2DM population with these co-morbid conditions had 38%, 17%, and 14% higher risk respectively.[3]

A recent meta-analysis of 2019 including 8.5 million individuals from 22 countries showed that more than 80% of NASH patients were overweight, 72% had dyslipidemia and 44% had type 2 DM.[4]

## METHODOLOGY

In study 1 cross-sectional, prospective study was conducted at Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India for a period of 5 months. The study included a total of 140 patients with Type 2 diabetes mellitus in the age group of 20-70 years, attending a medical outpatient clinic. The patients with history of alcohol consumption, chronic liver disease of any cause (hepatitis B or C, autoimmune hepatitis, hemochromatosis, Wilson's disease), type 1 diabetes mellitus, history of intake of hepatotoxic drugs, other hepatic diseases and refusal of the patient's to participate in the study were excluded from the present study,[5] Study 2 is a prospective study, a total of 100 patients with Type-2 DM study population was included the age group of 20-70 years, attending a medical outpatient clinic from November 2015 to November 2017.[6]

This prospective study 3 was designed to enroll known T2DM patients (duration ≥3 years), in the age group of 25-65 years, attending an outpatient Medicine department of Dr. D. Y. Patil Medical College, Kolhapur, a tertiary care Centre. This study was done in the department of Medicine in collaboration with the Department of Pathology in Dr. D. Y. Patil Medical College, Kolhapur.[7] In study 4 Study subjects were participants in the Valpolicella Heart Diabetes Study, a prospective observational study designed primarily to evaluate associations between type 2 diabetes and the incidence of chronic vascular complications. The study initially enrolled all of the outpatients with type 2 diabetes (n = 2,103, 66.3% of the entire sample of patients who attended our clinic) regularly attending our diabetes clinic in the period between 1 January 2000 and 31 December 2000 who were free of diagnosed CVD.[8]

In study 5 Study subjects were participants in the Valpolicella Heart Diabetes Study (1). Briefly, we enrolled all of type 2 diabetic outpatients (n  2,103) who regularly attended our clinic in the period January–December 2000 after excluding those who had manifest CVD and/or secondary causes of chronic liver disease (alcohol abuse, viral infection, or medications). During 6.5 years of follow-up (through December 2006; follow-up range: 5–84 months), 384 participants subsequently developed CVD events (myocardial infarction, ischemic stroke, coronary revascularization, or cardiovascular death), whereas 1,719 patients remained free of diagnosed CVD.[9]

## RESULTS

**Table 1: Gender Distribution Of Nafld In T2DM.**

| | Fatty Liver (%) | | | Nonfatty Liver (%) | | |
|---|---|---|---|---|---|---|
| | Male | Female | Total | Male | Female | Total |
| Study 1(N=140) | 17 (12.14%) | 27 (19.28%) | 44 (31.43%) | 38 (27.14%) | 58 (41.43%) | 96 (68.57%) |
| Study2(N=100) | 42 (65.62%) | 22 (34.38%) | 64 (100%) | 24 (66.66%) | 12 (33.33%) | 36 (100%) |

**Table 2: Age Distribution Of Nafld In T2DM Patients.**

| Study 1 (N=140) | | | Study 2 (N=100) | | | Study 3 (N=325). | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Age(Years) | Fatty Liver Group(%) | Non Fatty Liver Group(%) | Age(Years) | Fatty Liver Group (%) | Non Fatty Liver Group (%) | Age(Years) | Fatty Liver Group | | Non Fatty Liver Group (%) | |
| | | | | | | | Male | Female | Male | Female |
| <40 | 3 (2.14%) | 7 (5%) | 30- 39 | 08 (12.50%) | 03 (08.33%) | 25-40 | 26 | 32 | 22 | 43 |
| 41 – 50 | 12 (8.57%) | 23 (16.43%) | 40-49 | 16 (25.0 0%) | 13(36.11%) | 41-55 | 41 | 48 | 34 | 73 |
| 51 – 60 | 19 (13.57%) | 34 (24.29%) | 50-59 | 24 (37.50%) | 11(30.55%) | 56-70 | 6 | 12 | 8 | 20 |
| 61 – 70 | 10 (7.14%) | 32 (22.86%) | 60-69 | 14 (21.87%) | 9 (25.00%) | >71 | 2 | 11 | 6 | 11 |
| | | | ≥70 | 2 (03.12%) | 0 | | | | | |
| TOTAL (%) | 44 (31.43%) | 96 (68.57%) | TOTAL (%) | 64 | 36 | | 75 | 103 | 70 | 147 |

**Table 3: Baseline Characteristic 0f The Study Population.**

| STUDY 4(N= 744) | | | | STUDY 5 | | | |
|---|---|---|---|---|---|---|---|
| **Variables** | **Control Subjects** | **Case Subjects** | **P** | **Variables** | **Control Subjects** | **Case Subjects** | **P** |
| N | 496 | 248 | - | N | 1719 | 384 | |
| Sex (% men) | 62 | 62 | NS | Sex (% men) | 62% | 63% | 0.80 |
| Age (years) | 65± 3 | 66± 4 | NS | Age (years) | 59± 3 | 61±4 | 0.001 |
| BMI (kg/m2 ) | 26± 3 | 29 ±4 | <0.001 | BMI (kg/m2 ) | 26±3 | 28±4 | 0.001 |
| Waist circumference (cm) | 93± 13 | 101 ±14 | <0.001 | Waist circumference (cm) | 93 ±11 | 99± 13 | 0.001 |
| Duration of diabetes (years) | 13 ±14 | 14 ±3 | NS | Duration of diabetes (years) | 14± 3 | 16 ±3 | 0.60 |
| Oral hypoglycemic agents (%) | 61.9 | 63.3 | NS | Oral hypoglycemic agents (%) | 62 | 65 | 0.30 |
| Current smokers (%) | 12 | 14 | NS | Current smokers (%) | 22 | 23 | 0.70 |
| Systolic blood pressure (mmHg) | 124.1±13 | 131±15 | <0.001 | Systolic blood pressure (mmHg) | 127± 12 | 131± 16 | 0.001 |
| Diastolic blood pressure (mmHg) | 79±12 | 83±10 | <0.001 | Diastolic blood pressure (mmHg) | 80 ±12 | 83 ±14 | 0.001 |
| A1C (%) | 6.9±0.8 | 7.2±0.9 | <0.001 | A1C (%) | 6.9±0.8 | 7.3±1.0 | 0.001 |
| Triglycerides (mmol/l) | 1.24±0.6 | 1.62±0.9 | <0.001 | Triglycerides (mmol/l) | 1.32±0.6 | 1.62±1.0 | 0.001 |
| HDL cholesterol (mmol/l) | 1.39±0.3 | 1.25±0.4 | <0.001 | HDL cholesterol (mmol/l) | 1.40±0.3 | 1.32±0.4 | 0.001 |
| LDL cholesterol (mmol/l) | 3.29±0.4 | 3.27±0.5 | NS | LDL cholesterol (mmol/l) | 3.35±0.4 | 3.32±0.5 | 0.80 |
| AST (units/l) | 20±10 | 26±12 | <0.01 | AST (units/l) | 20±6 | 26±12 | 0.001 |
| ALT (units/l) | 23±12 | 33±14 | <0.001 | ALT (units/l) | 24±6 | 32±13 | 0.001 |
| GGT (units/l) | 27±14 | 38±16 | <0.001 | GGT (units/l) | 23±10 | 34±14 | 0,001 |
| Microalbuminuria (%) | 20 | 23 | NS | Microalbuminuria (%) | - | - | - |
| ATP III–defined metabolic syndrome (%) | 52 | 73 | <0.001 | ATP III–defined metabolic syndrome (%) | 59 | 75 | 0.001 |
| NAFLD (%) | 56 | 94 | <0.001 | NAFLD (%) | 61 | 96 | 0.001 |
| | | | | Antihypertensives users | 60 | 75 | 0.001 |
| | | | | Asprin users | 49 | 48 | 0.80 |
| | | | | Lipid-lowering users | 34 | 36 | 0.60 |

In study 1 Out of 140 patients who participated in the study, 44 (31.43%) were found to have Non-alcoholic fatty liver disease (NAFLD). In the present study, a total of 140 Type 2 diabetes mellitus patients were enrolled, 55 (39. 29%) were males and 85 (60.71%) were

females The highest prevalence of NAFLD was recorded in the age group of 51-60 years and it was more prevalent among females than males. Out of 140 Type 2 diabetes mellitus patients, 10 were aged < 40 years, 35 patients were aged between 41-50 years, 53 were aged between 51-60 years and 42 were in the age group of 61-70 years.[5] In study 2 A total of 100 subjects were recruited of which 106 subjects with Type-2DM were included in data analysis. 6 subjects were excluded due to incomplete laboratory evaluation. The present study observed a higher frequency of NAFLD in the diabetic female population (22/100) compared with the male population (42/100) (Table 1) with a Female to Male ratio of 1:1.8. Statistically, there is no significant difference between male and female subjects. The mean age of the patients with Type-2DM was 51.81±9.87 years. The frequency of patients with NAFLD was more in the age group of 50-59years.[6] In study 3 A total of 325 patients, with more number of female patients 180 (55.38%) than male patients 145 (44.61%) were recruited with the suspicion of Nonalcoholic Fatty Liver Disease (NAFLD) Out of 325 patients enrolled in the study, n=178 (54.76%) Type-2DM patients (n=103 female and n=75 male), was identified as having NAFLD, based upon NHANES III criteria The prevalence of NAFLD was found to be more in females n=103 than males. The majority of the patients were found in 41-55 years of age group followed by 25-40 years and least in more than 71 years of age group.[7] In study 4 During 5 years of follow-up, we documented 248 incident CVD events: 142 were nonfatal CHD (101 myocardial infarction and 41 coronary artery bypass grafting/percutaneous transluminal coronary angioplasty), 29 nonfatal ischemic stroke, and 77 deaths from cardiovascular events.[8] In study 5 During follow-up, we documented 384 CVD events: 219 cases of nonfatal coronary heart disease (151 myocardial infarction and 68 revascularization procedures), 44 cases of nonfatal ischemic stroke, and 121 cardiovascular deaths. subjects who developed CVD events during follow-up were older, had higher liver enzymes and A1C, and had a greater prevalence of metabolic syndrome than those who did not develop CVD events. Sex, smoking, LDL cholesterol, diabetes duration, and treatment did not differ between the groups. The frequency of NAFLD was markedly higher in those who developed CVD events than in those who did not, without significant sex differences.[9]

## DISCUSSION

Non-alcoholic fatty liver disease (NAFLD) is a common disorder that was less diagnosed earlier due to the low index of suspicion, but now its prevalence has been increasing globally. Hepatic steatosis and steatohepatitis can occur in association with a numerous disease

affecting the liver including hepatitis A, hepatitis B, and C, autoimmune hepatitis, hypothyroidism and hemochromatosis. However, much of the increase in the prevalence of NAFLD is driven by its pathophysiologic and epidemiologic connection to type 2 diabetes mellitus and obesity.[5] Non-alcoholic fatty liver disease (NAFLD) characterizes a variety of diseases, characterized histologically by the extreme growth of hepatic fat in the absence of significant alcohol consumption; with or without swelling, varying degree of fibrosis, and cirrhosis. A number of studies have found a positive relationship between hyperinsulinemia, abnormal glucose tolerance, and NAFLD. Mishra et al, found the prevalence of metabolic syndrome and NAFLD to be 24% and 14.8%, respectively, in nonalcoholic North Indian men. Gupte et al observed that NAFLD such as mild, moderate, and severe was existing in 65.5%, 12.5%, and 9.35% of otherwise asymptomatic type 2 diabetics, respectively.

Multiple components of the metabolic syndrome which increased in type 2 diabetics with a high prevalence of NAFLD and NASH found by Prashanth et al. On histologically, Banerjee et al found that only fatty change was contemporary in 43%, NASH in 40% and more advanced disease in 23%.[6] There are no pan-India population-based studies on the prevalence of NAFLD in the Type-2DM population. This is the first cross-sectional, multi-center study to report on the prevalence of NAFLD in the Indian Type-2DM population. The majority of epidemiological studies on NAFLD in general or in the Type-2DM population, in particular, are based on histological evidence of steatosis or fatty infiltration proven by imaging. This study makes the effort to record the prevalence of NAFLD and NASH in Type-2DM patients on the basis of elevated aminotransferase levels and liver biopsy for the confirmation of NASH.[7]

In study 1 the prevalence rate of NAFLD was highest in the 51-60 years age group, subsequently followed by 41-50 years, age group. The present study also discloses that the prevalence of the non-alcoholic fatty liver disease is higher in female patients (19.28%) with T2DM compared with the male population (12.14%). NAFLD and type 2 diabetes mellitus when they exist together to have a poorer prognosis in terms of higher frequency of cirrhosis, morbidity, and mortality.[5] In Study2 The prevalence rate of NAFLD was highest in the 50 to 59 years age group (24/100), subsequently followed by 40-49 years (16/100), 60-69 years (14/100) and less than 40 years age groups (8/100). The study also revealed a higher prevalence of NAFLD in male patients (42/100) with Type-2DM compared with the female community (22/100).

The larger number of male subjects included in the study population may account for the male fondnessseen in this study. Controversially trend was reported by S Kalra et al, in which the frequency of the disease was more in female patients.[6] In study3 the overall prevalence of NAFLD in the Type-2DM Indian population was found to be n=178 (54.76%), which is in line with a prevalence of 54.5% described by Mohan et al, but higher than the prevalence rate of 12.5% and 20% described in other studies. However, the study by Prashanth et al showed a higher prevalence rate of 87% Type-2DM patients had NAFLD on histology.[7] In study 4 the prospective nested case-control study, we have shown, for the first time, that NAFLD is associated with an increased risk of future CVD events among type 2 diabetic individuals. Importantly, this association is independent of classical risk factors, liver enzymes, and the metabolic syndrome, a highly atherogenic condition that is strongly correlated to NAFLD. These results are supported by previous prospective studies reporting strong associations of elevated liver enzymes (particularly serum GGT levels) as surrogate markers of NAFLD, with the occurrence of CVD events in both nondiabetic subjects and type 2 diabetic patients. In a study of 14,874 middle-aged Finnish men and women, mildly elevated GGT levels were independently associated with an increased risk of ischemic stroke in both sexes. Among 7,613 middle-aged British men followed for 11.5 years, elevated GGT levels were independently associated with a significant increase in mortality from all causes and from CHD.

Our results are also supported by a prospective study of 132 patients with biopsy-proven NAFLD followed for 18 years, demonstrating that CVD deaths were the second most common cause of death in NAFLD patients, with rates equaling those of liver-related deaths and trailing only cancer-related deaths. Finally, our results extend recent cross-sectional observations documenting a marked increase in carotid artery wall thickness and elevated prevalence of atherosclerotic carotid plaques among diabetic and nondiabetic individuals with NAFLD. The biological mechanisms by which NAFLD could contribute to accelerated atherosclerosis are still poorly known. Our data suggest that in people with type 2 diabetes, the relationship between NAFLD and increased CVD risk most likely reflects the overall atherogenic impact of the metabolic syndrome phenotype, principally hypertension, and dyslipidemia, as supported by our multivariate analyses. However, because in this study NAFLD correlated to CVD events, independent of metabolic syndrome and classic risk factors, it is conceivable that other atherogenic mechanisms could be involved.[8]

Unfortunately, we did not directly measure insulin resistance in our population. Recent evidence has raised concern that the current ATP III definition of the metabolic syndrome has low sensitivity for identifying insulin resistance in subjects. Conversely, several studies have consistently documented that insulin resistance predicts incident CVD events and plays a pivotal role in the development of poor clinical outcomes in NAFLD patients. Thus, NAFLD in its more advanced forms might act as a stimulus for further increased whole-body insulin resistance and dyslipidemia, leading to accelerated atherosclerosis.[9] This hypothesis is also partly validated by recent prospective studies demonstrating that raised liver enzymes independently predict the development of type 2 diabetes and other metabolic syndrome features.[10]

## CONCLUSION

Gender distribution of NAFLD in T2DM for study 1 having less incidence of fatty liver than study 2. Age distribution of NAFLD in Type-2DM patients of study 1 is better than study 2 and study 3 because the population with fatty liver is less in number. Study 4 is more significant than study 5 in its respective parameters.

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## CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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