

**Study of non-alcoholic fatty liver disease in patients of type 2 diabetes mellitus.**

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**Abstract**

India is becoming the world’s diabetic capital and NAFLD a major concern. In India prevalence of NAFLD is around 9% to 32% of general population. As per studies conducted in Indian population the prevalence of NAFLD is 59.67% in T2DM. Type 2 Diabetes Mellitus has been found as an important risk factor affecting NAFLD.

The present study is conducted to assess the prevalence of Non-Alcoholic Fatty Liver Disease in patients of Type 2 Diabetes Mellitus. The study concluded that the NAFLD had a prevalence of 40% in the patients of type 2 diabetes mellitus. Further assessment for risk factors showed that the higher BMI, dyslipidemia, and type 2 diabetes mellitus were associated with development of NAFLD.

**Keywords:** Fatty Liver Disease and Type 2 Diabetes Mellitus.

**Introduction**

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide, with a

global prevalence of 25.2%.<sup>1</sup> Non-alcoholic fatty liver disease is characterized by: (i) the presence of hepatic steatosis, as determined by imaging or histological diagnosis; (ii) no history of excessive alcohol drinking or the consumption of <140 g/week ethanol intake for men (<70 g/week for women) in the past 12 months; and (iii) no competing etiologies for hepatic steatosis and no coexisting causes for chronic liver disease.<sup>2,3</sup>

Clinically, NAFLD patients tend to have components of metabolic syndrome such as obesity, type 2 diabetes mellitus (T2DM), hyperlipidemia (HL) and hypertension (HT).<sup>4,5</sup>

Among these comorbidities, T2DM seems to be the most important risk factor for having NAFLD and non-alcoholic steatohepatitis (NASH) and the most important clinical predictor of adverse clinical outcomes such as advanced hepatic fibrosis and mortality.<sup>6,7,8</sup>

A recent meta-analysis reported the global prevalence of T2DM as 22.51% among radiologically defined NAFLD patients. On the other hand, the same study suggested

that the prevalence of T2DM among histologically proven NASH patients is 43.63%.<sup>1</sup>

Other studies suggested the prevalence of NAFLD by magnetic resonance spectroscopy and the prevalence of histologically-proven NASH in patients with T2DM and normal liver enzymes are 50% and 56%; respectively.<sup>9</sup> These data support the bidirectional relationship between T2DM and NAFLD/NASH, which share a common pathogenic mechanism.<sup>10,11</sup>

India is becoming the world's diabetic capital and NAFLD a major concern. In India prevalence of NAFLD is around 9% to 32% of general population.<sup>12</sup> As per studies conducted in Indian population the prevalence of NAFLD is 59.67% in T2DM. The prevalence of NAFLD increases to 57.5% to 74% in obese persons and 90% in morbidly obese persons.<sup>13,14,15,16</sup>

Due the growing epidemic of NAFLD and lack of treatment options, there has been everlasting search into the risk factors and pathophysiologic mechanisms leading to NAFLD and its progression. One such risk factor significantly affecting NAFLD is Type 2 Diabetes Mellitus.

The present study is conducted to assess the prevalence of Non-Alcoholic Fatty Liver Disease in patients of Type 2 Diabetes Mellitus.

### Objective

1. To find out the prevalence of Non Alcoholic Fatty Liver Disease in the patients of Type 2 Diabetes Mellitus.

### Methods

The study is carried out at MGM Medical College & Hospital, Kamothe, Navi-Mumbai. Total 100 patients of Type 2 Diabetes Mellitus attending the Medicine OPD are selected for the study. Careful examination of patients is done and based on the inclusion and exclusion criteria 100 patients are selected.

### Inclusion criteria

1. Patients who were known cases of Type 2 Diabetes Mellitus.
2. Patients who were newly diagnosed Type 2 Diabetes Mellitus.
3. Patients of either gender within the age group of 30 to 75 years.

### Exclusion criteria

1. Patients with other types of diabetes like Type 1 DM, gestational diabetes, Maturity Onset Diabetes of Young, LADA, steroid induced diabetes, etc.
2. Patients with history of alcohol consumption or any other addictions.
3. Pregnant patients.
4. Patients who were positive for HbsAg, HCV, or had any history of any other chronic liver diseases, jaundice, hepatitis.
5. Patients who were on Methotrexate, Estrogen, Cortisol, CCBs, Amiodarone, Valproic acid, antiviral medications, etc.
6. Patients who do not consent to participate in the study.

### Investigations

#### Blood examination

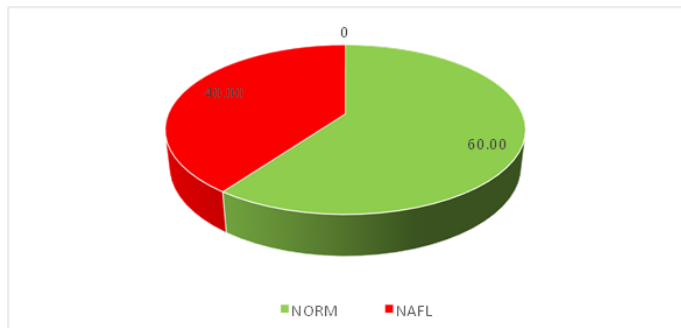
- |                   |                             |
|-------------------|-----------------------------|
| • HbA1c           | Plasma Sugar                |
| • LFT and RFT     | Total Cholesterol           |
| • Triglycerides   | HDL Cholesterol             |
| • LDL Cholesterol | Serum electrolytes          |
| • Urine sugars    | HBsAg and Anti HCV antibody |

All the patients underwent USG abdomen to assess the liver.

### Statistical Analysis

The data was analysed using statistical software (IBM SPSS, IBM Corporation, Armonk, NY, USA).

Graph 1: Distribution of the study population according to the presence of NAFLD.

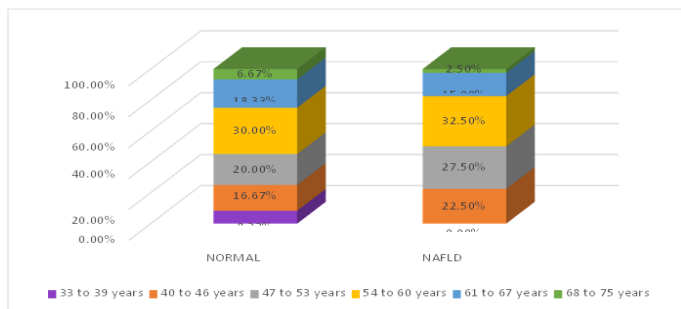


**Inference:** Out of total 100 patients of Type 2 Diabetes Mellitus, 40% patients showed presence of NAFLD.

Table 1: Age-wise distribution of the study population

Age groups	Normal		Nafld Grade 1		Nafld Grade 2		Nafld Grade 3		Total	
	N	%	N	%	N	%	N	%	N	%
33 TO 39	5	5%	0	0%	0	0%	0	0%	5	5%
40 TO 46	10	10%	9	9%	0	0%	0	0%	19	19%
47 TO 53	12	12%	11	11%	0	0%	0	0%	23	23%
54 TO 60	18	18%	13	13%	0	0%	0	0%	31	31%
61 TO 67	11	11%	6	6%	0	0%	0	0%	17	17%
68 TO 75	4	4%	1	1%	0	0%	0	0%	5	5%
TOTAL	60	60%	40	40%	0	0%	0	0%	100	100%
Mean ± SD	53.70 ± 9.71		53.30 ± 7.50		0 ± 0		0 ± 0		53.54 ± 8.85	
Range	33 to 75 years									
P value	0.826									
Statistical Significance	Not Statistically Significant									

Graph 2: Age-wise distribution of the study population in the two groups.

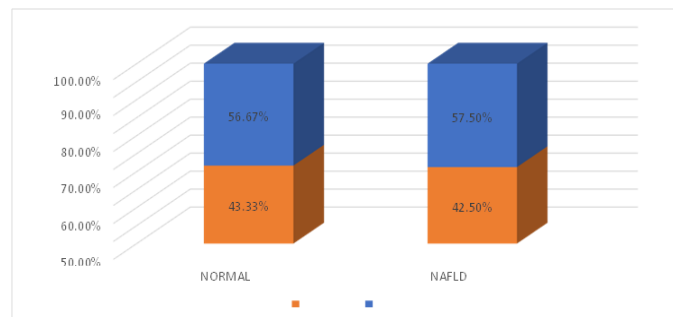


**Inference:** Among the patients of Type 2 Diabetes Mellitus with NAFLD, 32.5% patients belonged to the age group of 54-60 years followed by 27.5% patients in age group of 47-53 years and 22.5% patients in age group of 40-46 years.

Table 2: Gender wise distribution of the study population

Gender	Normal		Nafld		Total	
	N	%	N	%	N	%
Females	26	26%	17	17%	43	43%
Males	34	34%	23	23%	57	57%
Total	60	60%	40	40%	100	100%
P value	0.934					
Statistical Significance	Not Statistically Significant					

Graph 3: Gender wise distribution of the study population in the two groups.

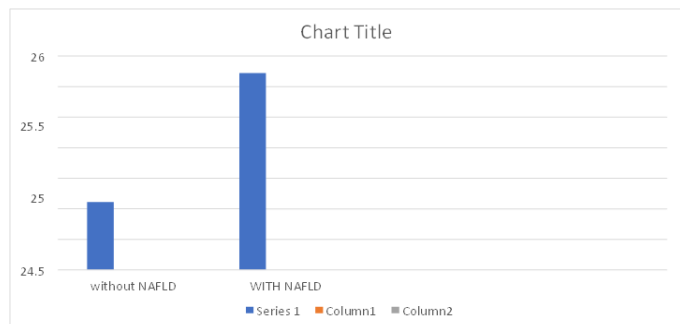


**Inference:** Among patients of Type 2 diabetes mellitus with NAFLD, males (57.5%) were more when compared to females (42.5%).

Table 3: Distribution of the study population according to the BMI.

Parameter	Normal	Nafld	P Value
BMI (kg/m <sup>2</sup> )	23.61 ± 1.90	25.72 ± 2.03	<0.001*

Graph 4: Distribution of the study population according to the BMI.



**Inference:** BMI was significantly higher ( $25.72 \pm 2.03\text{kg/m}^2$ ) in patients of Type 2 diabetes mellitus with NAFLD, as compared to patients without NAFLD ( $23.61 \pm 1.90\text{kg/m}^2$ ).

Table 4: Distribution of the study population according to the presence of hypertension

Hypertension	Normal		Nafld		Total	
	N	%	N	%	N	%
Absent	40	40%	20	20%	60	60%
Present	20	20%	20	20%	40	40%

Table 5: Distribution of the study population according to the liver function tests.

Parameter	Normal	NAFLD	P Value
Bilirubin (T) (mg/dL)	$0.74 \pm 0.31$	$0.78 \pm 0.33$	0.485
Bilirubin (D) (mg/dL)	$0.19 \pm 0.13$	$0.21 \pm 0.17$	0.329
Bilirubin (ID) (mg/dL)	$0.55 \pm 0.23$	$0.57 \pm 0.24$	0.758
SGOT (U/L) (AST)	$31.25 \pm 22.61$	$24.88 \pm 9.19$	0.094
SGPT (U/L) (ALT)	$30.35 \pm 29.68$	$24.52 \pm 10.25$	0.236
ALK. PHOSP. (IU/L)	$127.25 \pm 38.22$	$120.60 \pm 29.26$	0.353
Protein (T) (g/dL)	$7.00 \pm 0.67$	$7.01 \pm 0.63$	0.981
Albumin (mg/dL)	$3.72 \pm 0.55$	$3.58 \pm 0.46$	0.180

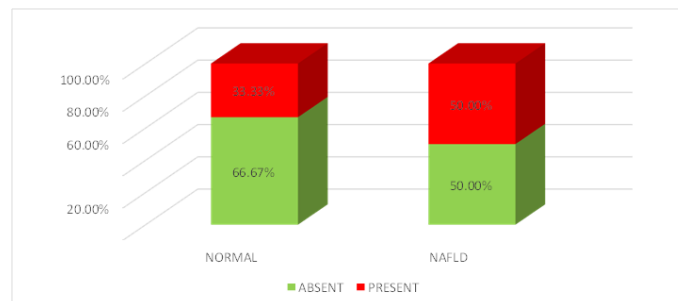
**Inferenc:** Liver enzymes SGOT (AST) and SGPT (ALT) were found to be normal both in patients of Type 2 diabetes mellitus with NAFLD and without NAFLD.

Table 6: Distribution of the study population according to the renal function tests.

Parameter	Normal	Nafld	P value
UREA (mg/dL)	$32.70 \pm 14.72$	$35.25 \pm 14.43$	0.394
CREATININE (mg/dL)	$0.78 \pm 0.31$	$0.85 \pm 0.35$	0.338

Total	60	60%	40	40%	100	100%
P value	0.096					
Statistical Significance	Not Statistically Significant					

Graph 5: Distribution of the study population according to the presence of hypertension in the two groups.



**Inference:** Hypertension was seen in about 50% of patients of Type 2 diabetes mellitus with NAFLD.

BUN (mg/dL)	15.39 ± 8.01	16.79 ± 6.91	0.369
URIC ACID (mg/dL)	5.03 ± 1.53	6.02 ± 2.33	0.021*

**Inference:** Uric acid levels were found to be higher among patients of Type 2 diabetes mellitus with NAFLD, as compared to patients without NAFLD.

Table 7: Distribution of the study population according to the electrolytes

Parameter	Normal	NAFLD	P Value
Sodium (meq/L)	135.67 ± 3.58	135.18 ± 3.80	0.513
Potassium (mmol/L)	4.34 ± 0.45	4.22 ± 0.42	0.174

**Inference:** Level of electrolytes were similar in patients of Type 2 diabetes mellitus with NAFLD and without NAFLD.

Table 8: Distribution of the study population according to the blood sugar levels

Parameter	Normal	NAFLD	P Value
HbA1C (%)	9.01 ± 2.13	11.83 ± 3.09	<0.001*
FBS (mg/dL)	167.29 ± 68.04	231.14 ± 81.27	<0.001*
PLBS (mg/dL)	264.34 ± 83.56	369.83 ± 105.44	<0.001*

**Inference:** FBS, PLBS and HbA1c were significantly higher in the cases of Type 2 diabetes mellitus with NAFLD as compared to patients without NAFLD; P value: less than 0.05.

Table 9: Distribution of the study population according to the lipid profile

Parameter	Normal	NAFLD	P Value
T-C (mg/dL)	140.78 ± 33.81	188.05 ± 52.26	<0.001*
HDL-C (mg/dL)	39.73 ± 9.76	43.50 ± 12.55	0.095
LDL-C (mg/dL)	67.50 ± 26.79	84.00 ± 30.31	0.005*
VLDL-C (mg/dL)	33.78 ± 12.95	61.55 ± 35.39	<0.001*
Triglycerides (mg/dL)	167.02 ± 65.51	288.40 ± 150.23	<0.001*

**Discussion**

One of the major causes of chronic liver diseases is Non Alcoholic Fatty Liver Disease which has now become a global epidemic affecting 1 in 4 adults, with an estimated prevalence between 25% and 30%, and appears to be associated with the steadily increasing rates of metabolic syndrome (Mets) and its components (obesity, Type 2 Diabetes Mellitus, and dyslipidemia).<sup>17</sup> The mandatory feature of NAFLD is the presence of liver steatosis (LS) in the absence of other causes of chronic liver disease.<sup>18</sup> Type 2 Diabetes Mellitus with NAFLD is considered as a multifactorial disease with genetic and environmental

factors. Insulin Resistance is considered as a key risk factor for the occurrence and development of T2DM with NAFLD. IR in the peripheral tissue and liver is one of the main causes of this condition, leading to the increase in circulating glucose levels and lipid substrates for lipid accumulation in the liver.<sup>19</sup> The high incidence and rapid progression of NAFLD in cases with T2DM indicates a unifying underlying pathophysiologic mechanism. Not much studies have been conducted in this regard. Therefore, the present study was conducted to study the prevalence of NAFLD in cases of T2DM.

In the present study, 54% of the cases belonged to the age group of 47 to 60 years. The range was age group of 30 to 75 years with mean age of  $53.54 \pm 8.85$  years. The age distribution was similar in the cases having NAFLD and the normal cases; P value: 0.826. There was a slight male preponderance (57%). The gender distribution was similar in the normal cases and cases with hepatomegaly. When assessed with the presence of fibrosis, the NAFLD cases having fibrosis were younger ( $44.25 \pm 10.19$  years) than the cases without fibrosis ( $54.83 \pm 6.72$  years); P value: 0.004. The gender distribution was similar on both the cases; P value: 0.234. In the study by Bhatt K. et al,<sup>20</sup> they included a total of 100 patients of T2DM. The mean age of the study population was  $55.07 \pm 13.47$  years; range: 19 to 88 years. They observed that the mean age of the cases having NAFLD was  $56.93 \pm 12.97$  years while of the non-NAFLD cases was  $53.54 \pm 13.8$  years; P value: 0.2. This was similar to the present study. In the study by Kalra S. et al,<sup>21</sup> they observed that the mean age of the study population was  $52.16 \pm 10.76$  years. They also observed a slight male preponderance. These findings were almost similar to the present study.

In the study by Targher G. et al,<sup>22</sup> they included a total of 248 cases and 496 controls from the Valpolicella Heart Diabetes Study, a prospective observational study designed primarily to evaluate associations between Type2DM and incidence of chronic vascular complications. During the average 5 years of follow-up in the study, a total of 248 cases developed nonfatal coronary heart disease, ischemic stroke, or cardiovascular death. These cases were included as cases. They observed that when the study population was grouped according to the presence of NAFLD, the gender distribution was similar in the cases with NAFLD and in

the cases without NAFLD. This was similar to the present study.

Thus, it was seen in the present study that the mean age of the cases having Type 2DM was  $53.54 \pm 8.85$  years with a slight male preponderance. There was no age and gender predilection for the development of NAFLD.

In the present study, prevalence of NAFLD was present in 40% of the cases. In the study by Bhatt K. et al<sup>20</sup>, they observed that the prevalence of NAFLD was 45% in the study population with T2DM. This was similar to the present study. In the study by Kalra S. et al<sup>21</sup>, they found that the overall prevalence of NAFLD in India was 56.5%. Region wise prevalence ranged from 44.1% to 72.4%. This was almost similar to the present study. In the meta-analysis by Atan N. et al,<sup>23</sup> they included 17 studies with a total of 10897 participants. They found that the pooled prevalence of NAFLD in T2DM patients is 54% (95% CI: 45% to 64%). This was almost similar to the present study. Thus, it was seen in the present study that the prevalence of NAFLD in T2DM cases is around 40%.

In the present study, hypertension was present in 40% of the total cases. Hypertension was present in 50 percent of patients with NAFLD. In the study by Kalra S. et al<sup>21</sup>, they found that hypertension was prevalent in 60.3% of the total study population. This was higher than seen in the present study. However, in their study the prevalence of hypertension was significantly more in the cases with NAFLD than in the cases without NAFLD; P value: 0.002 which was similar to present study.

In the present study, it was observed that the BMI in the cases with normal liver scan was lower ( $23.61 \pm 1.90$  kg/m<sup>2</sup>) than the cases with NAFLD ( $25.72 \pm 2.03$  kg/m<sup>2</sup>); P value: less than 0.001. In the study by Bhatt K. et al<sup>20</sup>, they observed that the mean BMI of the cases having NAFLD was  $28.27 \pm 3.77$  kg/m<sup>2</sup> while of the

non-NAFLD cases was  $26.19 \pm 4.02$  kg/m<sup>2</sup>. The BMI was significantly higher in the NAFLD cases than in the non-NAFLD cases; P value: 0.009. This was similar to the present study.

In the study by Targher G. et al<sup>22</sup>, they observed that when the study population was grouped according to the presence of NAFLD, they observed that all the individual components of metabolic syndrome were more frequent in cases having NAFLD than in the cases without NAFLD; P value: less than 0.001. In the study by Kalra S. et al<sup>21</sup>, they observed that obesity was significantly more prevalent in the cases with NAFLD (53.6%) compared to the cases without NAFLD (47%); P value: 0.027. In the meta-analysis by Atan N. et al,<sup>23</sup> they observed that high BMI in T2DM patients was associated with NAFLD. This is in agreement with the present study. Thus, it is seen in the present study that high BMI are significantly associated with NAFLD in T2DM patients.

In the present study, it was observed that uric acid was higher in the cases having NAFLD ( $6.02 \pm 2.33$  mg/dL) as compared to the normal cases ( $5.03 \pm 1.53$  mg/dL); P value: 0.021. Among the studies on relationship between NAFLD and uric acid most displays strong association between hyperuricemia and NAFLD. Thus, as a risk factor, uric acid might develop as one prediction marker for the occurrence and severity of NAFLD incidences, which implies that uric acid may be a potential therapeutic target for NAFLD, especially in patients with hyperuricemia. In the study conducted by Zhang C. et al,<sup>24</sup> there was a strong association between hyperuricemia and NAFLD. These findings were similar to our present study.

When assessed according to the diabetic profile, the mean levels of HbA1c, FBS and PLBS were significantly higher in the cases having NAFLD than the normal cases;

P value: less than 0.001. When assessed according to the lipid profile, the mean levels of total cholesterol, LDL cholesterol, VLDL cholesterol and triglycerides were significantly higher in the cases having NAFLD than the normal cases; P value: less than 0.05. HDL cholesterol was similar in both the groups; P value: more than 0.05. Rest all parameters, viz., LFT, RFT and serum electrolytes were similar in both the groups; P value: more than 0.05.

In the study by Bhatt K. et al<sup>20</sup>, the mean serum triglycerides levels were more in the NAFLD group ( $200.9 \pm 63.4$  mg/dL) than in the non-NAFLD group ( $168.5 \pm 42.62$  mg/dL); P value: 0.003. The transaminases were similar in both the groups; P value more than 0.05. These findings were similar to the present study. In the study by Targher G. et al<sup>22</sup>, they observed that when the study population was grouped according to the presence of NAFLD, they observed that metabolic syndrome and all its individual components were more frequent in cases having NAFLD than in the cases without NAFLD; P value: less than 0.001. In the study by Kalra S. et al<sup>21</sup>, they found that the prevalence of dys lipidemia was 59.6% in the NAFLD group and 43.3% in the Non-NAFLD group. The prevalence was significantly more in the cases with NAFLD; P value: less than 0.001.

In the meta-analysis by Atan N. et al<sup>23</sup>, they observed that transaminases (SGPT and SGOT) levels in NAFLD group in T2DM patients were not statistically high in subgroup analysis versus the pooled prevalence of NAFLD. Similar were the findings in the study by Reid A.<sup>[177]</sup> who found that there was no correlation between transaminases levels and the prevalence of NAFLD in T2DM patients. Thus, it is seen the present study that in T2DM patients, increased HbA1c, FBS, PLBS, Uric acid, lipid profile are associated with NAFLD. Hepatic

transaminases (SGOT and SGPT) and other liver and renal function tests may be normal.

### **Conclusion**

It was found from the present study that NAFLD had a prevalence of 40% in the patients of type 2 diabetes mellitus. The prevalence of hypertension is 40% in cases of T2DM. However, hypertension was not significantly associated with NAFLD. Increased BMI, and increased HbA1c, FBS, PLBS, uric acid, lipid profile were associated with NAFLD in patients of Type 2 Diabetes Mellitus. So the overall prevalence of NAFLD in type 2 diabetes mellitus patients was 40% in this study.

On further assessment for risk factors it is found that, higher BMI, dys lipidemia, and type 2 diabetes mellitus were associated with development of NAFLD. These findings were more or less similar in the majority of studies done on this subject from time to time from various countries.

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