

PREVALENCE OF NAFLD AND IT'S ASSOCIATION WITH INSULIN RESISTANCE IN PATIENTS WITH DIABETES

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Abstract

Objectives: Non Alcoholic Fatty Liver Disease (NAFLD) is characterized by fatty infiltration of the liver, mostly in the form of triglycerides (TG), which exceeds 5% of the liver weight. NAFLD is strongly associated with Insulin Resistance (IR). Patients with NAFLD also having type 2 diabetes carry added risk of progressive forms of the disease particularly cirrhosis. They also have poor glycemic control owing to IR. So it is logical to identifying the patients with diabetes having NAFLD could estimate the future risk and help in prevention of chronic liver disease and delaying the progression to NASH and cirrhosis and various complications of Diabetes.

Methods: This was a cross sectional observational study conducted in department of medicine, N.S.C.B., MCH, Jabalpur in which 100 cases of diabetes were taken who satisfied inclusion and exclusion criteria. Abdominal USG was used for evidence of fatty liver and it's grading and fasting serum levels of insulin (FIL) and fasting blood sugar (FBS) were used to calculate HOMA IR value to find presence of IR.

Results: Our study showed prevalence of NAFLD was 56% (n=56), Among these, in 58.92% (n=33) cases NAFLD is associated with IR (chi square value-4.1, p value-0.041). Prevalence of NAFLD was slightly more in females-56.6% (n=30) as compare to males-55.32% (n=26). Strong association of NAFLD with IR is found among females as compare to males (p-0.022 and p-0.79 respectively). Waist circumference, Mean BMI, FBS, Triglycerides, FIL and HOMA IR levels in cases with NAFLD (95.11±12.46, 24.83±2.42, 176.13±66.79, 180.07±51.35, 13.59±15.42, 5.33±5.21) were higher as compare to non NAFLD (85.84±9.86, 22.41±2.16, 134.8±34.41, 139.09±39.27, 6.79±4.49, 2.37±1.94) respectively. The mean AST and ALT levels were higher in NAFLD group than Non NAFLD group (t= 2.23, 2.19) respectively with p value <0.05. Prevalence of NAFLD was 88.23% (n=15) in obese population.

Conclusion: Given the high prevalence of NAFLD in patients with diabetes, the possibility of NAFLD should be suspected in all of them. These patients with NAFLD have high propensity of IR than Non NAFLD patients, so are at higher risk of developing complications of diabetes, NASH and cirrhosis. Also obese diabetic patients have higher incidence of NAFLD and IR as compared to non-obese patients. It seems reasonable to expect that early diagnosis of NAFLD and early intervention with strict glycemic control and weight loss would prevent complications.

Introduction:

Type 2 diabetes mellitus (T2DM) has emerged as a pandemic and India, with >60 million people with diabetes, has the second largest diabetic kingdom in terms of population of the world. The projection shows that this number will increase to 100 million by 2030 (>90% T2DM).¹

Recent data increasingly support a complex interplay between diabetes mellitus and the pathologically defined nonalcoholic fatty liver disease (NAFLD). Although the association of diabetes and NAFLD is likely to be the result of a "common soil, through interrelated metabolic pathways currently only partly

understood, type 2 diabetes predicts the development of NAFLD and vice versa and each condition may serve as a progression factor for the other, in addition diabetes appears to accelerate the progression of NAFLD to nonalcoholic steatohepatitis (NASH), defined by the presence of necroinflammation, with varying degrees of liver fibrosis.

There is a strong relationship between hepatic TG content and IR. NAFLD is associated with IR^{2,3}.

Epidemiological studies suggest the prevalence of NAFLD to be around 9-32% in general Indian population, with a higher incidence amongst

overweight/obese and diabetic/ prediabetic patients.⁵

Prevalence of NAFLD in type 2 diabetes patients (India) varies from 12.5% to 87.5%.^{4,5} Although cardiovascular disease is the major cause of excess morbidity and mortality in type 2 diabetes, liver failure may also be a threat to patients with type 2 diabetes NAFLD. Therefore, it is important for physicians to be aware of the high likelihood that their patients with type 2 diabetes have NAFLD, as this is another potential complication that requires attention. Another important fact is diabetes is associated with metabolic syndrome and both of these have greater incidence of NAFLD, more over persons with NAFLD have Insulin resistance and patients of NAFLD with diabetes, due to insulin resistance supposed to have hyperglycemia relatively refractory to OHA leading to increased requirement of dose of OHA's and thus predisposes to greater risk of side effects.

Material and Methods

With the study design of observational cross sectional study conducted at the department of General Medicine, NSCB Medical College & Hospital, Jabalpur from March 2016 to April 2017 (Fourteen Months) on 100 patients with diabetes and who were willing to take part in the study and gave a written informed consent and who satisfied the inclusion and exclusion criteria. The study was initiated after obtaining an ethical clearance from the institutions ethics committee.

Inclusion Criteria for Cases:

- Adults (>21yrs) with type 2 diabetes who are previously diagnosed to have DM type2 and currently on dietary glycemic control or currently on oral hypoglycemic agents(OHA's) or newly diagnosed DM type 2 according to International Diabetes Federation Criteria⁶

Exclusion Criteria for Cases:

- Known cases of alcoholic liver disease or history of significant alcohol consumption (They should have a weekly alcohol intake of More than 21 drinks or >210gm alcohol for men and more than 14 drinks or >140gm alcohol for women.)
- Known or newly diagnosed cases of infective hepatitis and parasitic infections damaging liver cells.
- Cases with family history of liver dysfunction or liver cancers.

- Cases with history of consumption of hepatotoxic drugs or chemicals.
- All type 1 Diabetics.
- Patients with Multi Organ Dysfunction Syndrome.
- Patients on Injectable Insulin Preparation.

.In each patient selected, history, anthropometric measurements and clinical findings were recorded and relevant investigations were carried out.

Insulin resistance (HOMA IR) was calculated by estimating Fasting insulin levels (FIL) and Fasting blood sugar levels by simultaneously withdrawn blood sample after overnight fasting of at least 8 hours. Insulin resistance was calculated using HOMA – IR (Homeostatic Model Assessment Insulin Resistance). And its correlation with NAFLD was assessed

$$\text{HOMA-IR} = \frac{\{\text{Fasting plasma glucose in mg/dl}\} \{\text{Fasting plasma insulin in mIU/L}\}}{405}$$

The normal plasma fasting insulin levels taken as < 25 mIU/ L.⁷The cut off values of HOMA IR taken as 1.45(+1.34)⁸ in normal healthy individuals and other associated blood tests were performed. Modified NCEP:ATP III and IDF criteria for the diagnosis of metabolic syndrome is used for defining abnormal lipid profile(TG,HDL), waist circumference, blood pressure, fasting plasma glucose and obesity.

Abdominal Ultrasonography was done to detect fatty liver and simultaneous grading of fatty liver was done at the same time by same radiologist in each study subject and finally study subjects were divided in to 2 groups (NAFLD group and Non NAFLD group) and comparisons made between the 2 groups on various parameters.

Results

We studied total 100 cases of type 2 diabetes in the study period including 47 males and 53 females. The ratio of males to females in both groups (NAFLD and Non NAFLD) were not significant ($\chi^2=0.02$; $p>0.05$) hence comparable. Prevalence of NAFLD was 56% in our study with slight female preponderance (56.6%).

Age wise distribution of NAFLD cases

We included subjects of age groups ranging from >21 years to 70 years with mean age of 49.75 ± 11.681. Mean age of cases with NAFLD was 50.66±11.68 and mean age of cases without NAFLD was 48.59±11.45. ($\chi^2=1.9$; $p>0.05$). Highest prevalence

of NAFLD (70.6%) was found in age group 61-70 Years.(n=12 out of total 17 cases).

Age wise distribution of cases with insulin resistance

Total 49 cases (49%) found with *Insulin resistance*. Highest prevalence of IR was found in age group **61-70 Years (64.70%)**(n=11,out of 17 cases).

Gender wise distribution of NAFLD

The prevalence of *NAFLD* among *males* was **55.30%** and among *females* was **56.60%**.The chi square value

was 0.02 with p value>0.05 and there was no significant difference in NAFLD between the genders in both the groups.

Gender wise distribution of insulin resistance

Prevalence of IR among *males* was **42.55%** and **54.71%** among *females*. The chi square value was 1.46 with p value>0.05 and there was no significant difference in IR between the genders

Table 1: Gender wise distribution of NAFLD with IR

Gender	NAFLD with IR Present (n=33)	NAFLD with IR Absent (n=23)	Total
Male	12 (40.8%)	14 (53%)	26
Female	21 (59.2%)	09 (47%)	30
Total	33(100%)	23(100%)	56

- The Odds of NAFLD among males with IR is 1.39 higher as compare to males without IR ,however this is not found statistically significant(p=0.79)
- However Odds of NAFLD among females with IR is 4.37 higher as compare to females without IR with (p=0.022) which is found **statistically significant**.(Table no.1)

Table 2: Comparison of insulin resistance between NAFLD and non nafld group.

Insulin Resistance	Cases with NAFLD (n=56)	Cases without NAFLD(n=44)	Total
Present	33 (58.9%)	16 (36.4%)	49
Absent	23 (41.1 %)	28 (63.6 %)	51
Total	56 (100%)	44 (100%)	100

$\chi^2=4.15;p<0.05$

- Among the 56 cases of NAFLD, insulin resistance was present in **33(58.9%)** cases as compared to cases without NAFLD where insulin resistance was present in **16(36.4%)** cases .The Odds ratio-2.51,chi square value was 4.15 with a p value of <0.05 that was **significant**.(Table no.2)

Table 3: Comparison of mean bmi, waist circumference, tg, fbs, fasting insulin level & homa IR between NAFLD and non NAFLD group

Variables	Cases with NAFLD (n=56)	Cases without NAFLD (n=44)	Significance
BMI(Kg/mtr2)	24.83±2.42	22.41±2.16	t=4.08 p<0.001
WC(Cm)	95.11±12.46	85.84±9.86	T=4.04 P<0.001
TG(mg/dl)	180.07±51.35	139.09±39.27	t=4.38 p,0.001
FBS(mg/dl)	176.13±66.79	134.8±34.41	t = 3.73 p<0.001
Fasting Insulin Levels (mIU/L)	13.59±15.42	6.79±4.49	t = 2.83 p<0.001
HOMA IR	5.33±5.21	2.37±1.94	t = 3.58 p<0.001

- The mean BMI,WC,TG,FBS, Fasting insulin level and HOMA IR values were higher in NAFLD group than Non NAFLD group (t= 4.08,4.04,4.38,3.73,2.83,3.58) respectively with p value <0.001 that was **highly significant**.(Table no.3)

Table 4: Comparison of mean ast and alt levels between NAFLD and non NAFLD group.

Variables	Cases with NAFLD (n=56)	Cases without NAFLD(n=44)	Significance
AST(IU/L)	51.35±35.21	37.64±23.02	t=2.23 p<0.05
ALT(IU/L)	53.6±30.35	41.67±22.14	t=2.19 P<0.05

- The mean AST and ALT levels were higher in NAFLD group than Non NAFLD group with (t= 2.23,2.19) respectively with p value <0.05 that was **statistically significant**. (Table no.4)

Table 5: Observations based on grading of NAFLD

GRADE	NAFLD CASES	PERCENTAGE
1	36	64.28%
2	16	28.57%
3	4	7.1%

- Majority of cases with NAFLD were grade 1(64.28%) followed by grade 2(28.57%) and 7.1% cases were grade 3 fatty liver.(Table no.5)

Table 6: Comparison of complications of diabetes between NAFLD and non NAFLD group

Complications	Cases with NAFLD (n=56)	Cases without NAFLD(n=44)	Total	SIGNIFICANCE
Diabetic Retinopathy	14 (77.7%)	4 (22.2%)	18	$\chi^2=3.2;p>0.05$
Diabetic Nephropathy	18 (75%)	6 (25%)	24	$\chi^2=3.6;p>0.05$
Diabetic Neuropathy	22 (68.75%)	10 (31.25%)	32	$\chi^2=2.39;p>0.05$
Diabetic Gastroparesis	19 (52.77%)	17 (47.22%)	36	$\chi^2=0.07;p>0.05$
Cardiovascular complications	27 (69.2%)	12 (30.8%)	39	$\chi^2=3.12;p>0.05$
Cerebrovascular accidents	4 (66.6%)	2 (33.3%)	06	$\chi^2=0.014;p>0.05$
Hypertension	32 (65.3%)	17 (34.7%)	49	$\chi^2=2.67;p>0.05$

- Above table shows that incidence of various complications of Diabetes Mellitus were relatively more in NAFLD group as compare to Non NAFLD group. However these correlations were not found statistically significant between the two groups.(Table No.6)

DISCUSSION

Non-alcoholic fatty liver disease (NAFLD) is a global hepatic pandemic of modern age which was practically unheard of even 30 years ago, is now considered one of the most common liver disorders in the western world. It is one of the most common liver disorders in US.¹⁰

The prevalence of NAFLD has increased in parallel with the epidemics of obesity and type 2 diabetes, which are risk factors for NAFLD.

Whereas the association of type 2 diabetes with micro-vascular complications and macro-vascular disease is well established, the association of type 2 diabetes with NAFLD is more recently recognized and probably less well known to physicians. Furthermore, because patients are usually asymptomatic and routine blood tests are often normal, it may be a diagnosis that is overlooked in patients with type 2 diabetes.

There is evidence that patients with NAFLD who have type 2 diabetes are particularly at risk of progressive forms of the disease and that they are at higher risk

of developing cirrhosis compared with those who do not have diabetes.

Hence we conducted an observational cross sectional study at the department of General Medicine, NSCB Medical College & Hospital, Jabalpur from March 2016 to Aug. 2017 on 100 patients with diabetes and who were willing to take part in the study and gave a written informed consent and who satisfied the inclusion and exclusion criteria, to study prevalence of NAFLD among patients with diabetes and if insulin resistance had any role in patients with NAFLD. In our study we evaluated the various parameters and the following observations were made in relation to other studies.

Prevalence of NAFLD in type 2 diabetes patients (India) varies widely from 12.5% to 87.5%.^{4,5}

In our study the overall prevalence of NAFLD in patients with Diabetes mellitus was 56% which is found consistent with previous studies.^{11,12,19}

While in some studies⁹ it was prevalent in 41% cases and in others¹⁸ it was found in 88% cases.

Prashanth and colleagues⁵ studied 204 type 2 diabetic patients in Mumbai, India in 2009 and reported that 87% of them had NAFLD on histologic findings.

Considering similar sample size taken in our studies, results of many previous studies produced similar results.^{12,13}

In our study the mean age of study subjects was observed at 49.75 ±11.68 years, while mean age of cases with NAFLD was 50.66 ±1.89 and mean age of cases with-out NAFLD was 48.59 ±11.45. The age group which had majority of NAFLD cases was between 51-60 years with 17 cases (n=33) having NAFLD prevalence of 51.5%. The age group having maximum prevalence of NAFLD cases was 61-70 years with 12 cases (n=17) having NAFLD (70.6%). One of the study done on Indian population previously also reported shifting trend of occurrence of NAFLD in later ages.^{12,20}

In present study 47% cases (n=47) were males and 53% (n=53) were females. The ratio of males to females in both groups were not significant ($\chi^2=0.02$; $p>0.05$) hence were comparable.

In our study 55.32% males and 56.60 % females are found out to have NAFLD suggesting slight female predominance in of NAFLD in diabetics. In some

previous studies, NAFLD was considered to be more common among women.¹² while in others it was found more prevalent in males.²⁰

In our study among males 20 (42.55%) had insulin resistance as compared to females among whom 29 (54.71%) had insulin resistance. Differences in hormonal profile and fat distribution between males and females possibly could be explanation for this observation.

There is a strong relationship between hepatic TG content and IR. NAFLD is associated with IR.² Many studies have shown that insulin resistance has a critical role in the pathogenesis of NAFLD.

In our study 58.92% cases NAFLD is associated with insulin resistance and that is found statistically significant (odds ratio-2.51 with c/i-1.11-5.66) (p value-0.041).

Bhatt et al¹² also observed that patients in the NAFLD group had a higher prevalence of Insulin resistance as measured by S. fasting insulin, HOMA-IR, and QUICKI; as compared to non-NAFLD group ($P = 0.03$ and 0.04 , respectively).

Previous studies also found similar results with higher values of HOMA-IR in NAFLD group.¹⁴

In our study the mean AST was 51.35+35.21 in NAFLD group and 37.64 +23.02 in cases (p value<0.05), also the mean ALT was 53.6+30.35 in NAFLD group and 41.67 +22.14 in cases without NAFLD, p-value-0.031(<0.05). Similar results observed in previous studies.¹¹

A mild to moderate (1.5 to 4-fold) elevation of the serum AST or ALT level, or both, is common, The serum ALT level is usually greater than the AST level in NAFLD, in contrast to the pattern of alcoholic hepatitis.

In the study by **Vera S. G. Ferreira et al¹⁴** found significantly higher levels of ALT, AST and γ -GT in patients with NAFLD, which could be a consequence of hepatic aggression resulting from the infiltration of fatty acids, bringing about inflammatory stimulus.

Elevation of levels of ALT and AST or both to mild and moderate levels is a very common finding in NAFLD. Similarly in T2DM patients, chronic mild elevations of liver enzymes are frequently encountered, Emphasizing the already known fact that T2DM has a strong association with NAFLD, including its severe form NASH.

ALT appears to have a role in gluconeogenesis and seems to be more related to liver fat accumulation than AST.

The mean HOMA-IR value of our study was 4.02 ± 4.3 . The mean HOMA-IR value in cases with NAFLD and without NAFLD were 5.33 ± 5.21 and 2.37 ± 1.94 respectively with t test value -3.58 (p value < 0.0001) which is found statistically very highly significant. Similar results were observed in previous studies.¹² In present study, mean FIL was 10.4 ± 12.34 . Among cases with NAFLD mean FIL was 13.59 ± 15.42 and 6.79 ± 4.49 in Non NAFLD group (t test -2.83 , p value < 0.006) which is statistically highly significant.

In a study reported similar results with FIL was strongly correlated presence of NAFLD.¹² In our study 36 cases (64.28%) were having grade 1 fatty liver, 16 cases (28.57%) having grade 2 and 4 cases (7.14%) were having grade 3 fatty liver.

In our study majority of the cases were over-weight (42%) $n=27$. Among over weight patients, prevalence of NAFLD was 64.30% and Out of total 18 obese patients 16 patients have NAFLD (84.6%) and 100% ($n=5$) morbidly obese cases have NAFLD. The mean BMI was 24.83 ± 3.42 in cases with NAFLD while mean BMI was 22.41 ± 2.16 among Non NAFLD group (t test $=4.08$, p value $=0.001$) which is found statistically very highly significant. Studies supporting this observation also showed high likelihood of NAFLD in obese diabetics.^{9,12}

In present study, mean waist circumference was 91.03 ± 12.24 . Among cases with NAFLD mean WC was 95.11 ± 12.46 and 85.84 ± 9.86 in Non NAFLD group (t test -4.04 , p value < 0.001) which is statistically highly significant. Studies based on waist circumference and occurrence of NAFLD showed positive association of increased waist circumference and presence of NAFLD.^{9,12}

In our study High TG was linked with increased prevalence of NAFLD (mean TG in NAFLD group was 180.07 ± 51.39 Vs 139.09 ± 39.27 in Non NAFLD group, t test $=4.38$, P value < 0.03) similar correlation is reported in our study with serum total cholesterol (mean Tch $=198.48 \pm 41.96$ and 177.57 ± 22.96 in NAFLD Vs Non NAFLD group respectively with t test $=2.97$, p value < 0.04)

Krishnakant Bhatt et al¹² found serum TG was highly significantly correlated with NAFLD (p value $=0.003$) while **Kuldeepchandel et al**¹⁹ found positive

correlation with serum TG (p value < 0.0001) and Tch (p value < 0.02). We have found mean FBS and PPBS significantly raised between NAFLD group as compare to non NAFLD group. In our study we found mean FBS $=176.13 \pm 66.79$ in cases with NAFLD Vs 134.8 ± 34.41 in Non NAFLD group, t test $=3.73$, p value < 0.001 which is statistically highly significant. While we found mean PPBS $=205.61 \pm 68.4$ in NAFLD group as compare to mean PPBS $=166 \pm 40.43$ in Non NAFLD group, t test $=3.4$, p value < 0.001

Results of our study are consistent with study by **T.K.V. Sharavanan et al**¹⁵ they reported mean FBS (mg/dl) 161.92 ± 55.43 in NAFLD cases and 133.18 ± 43.54 in Non NAFLD cases, t test $=4.39$, p value < 0.001 . and Mean PPBS (mg/dl) 280.21 ± 86.32 in NAFLD cases while 236.68 ± 69.59 in Non NAFLD cases, t test $=4.21$, p value < 0.001 .

Among various macrovascular and Microvascular complications of Diabetes (CVS and CNS involvement, diabetic retinopathy, diabetic nephropathy, diabetic gastroparesis and diabetic neuropathy) we have not found any statistically significant positive correlation with NAFLD which is also consistent with previous study done by **Nathalie C. Leite et al**¹⁶ However they found positive correlation with NAFLD and diabetic nephropathy. Most common complication of Diabetes was found in the form of cardiovascular involvement (39% cases) in our study.

We have reported 49% prevalence of Hypertension in our study cases. However presence of hypertension in between NAFLD and Non NAFLD group it was not found statistically significant ($\chi^2=2.67$; p > 0.05). In previous studies also hypertension was found to be prevalent in 50% cases.¹⁷

Conclusion

Prevalence of NAFLD in cases with DM was 56% which is higher than general population also Prevalence tends to increase with increasing age and Slight Female preponderance of NAFLD. Female subjects who are insulin resistant has significant association with prevalence of NAFLD. Also NAFLD is strongly associated with Insulin Resistance. Levels of AST and ALT were significantly raised in cases with NAFLD than in cases without NAFLD. Mean FBS, TG, FIL, HOMA IR, BMI, Waist Circumference also were Significantly raised in subjects with NAFLD. Majority of cases with NAFLD have grade 1 fatty liver. Obese patients have more prevalence of NAFLD as

compare to non-obese. Obesity has positive correlation with occurrence of NAFLD.

Cardiovascular involvement (39% cases) was found in the form of most common complication of diabetes.

As reported from various studies the high prevalence of NAFLD in patients with diabetes, the possibility of NAFLD should be considered in all of them. Virtually the entire spectrum of liver disease is seen in patients with type 2 diabetes. This includes abnormal liver enzymes, NAFLD, NASH, cirrhosis, hepatocellular carcinoma, and acute liver failure. So NAFLD is the benign counterpart of NASH and Cirrhosis. These patients with NAFLD have high propensity of IR than patients without NAFLD, due to which they are at higher risk of developing complications of diabetes, NASH and cirrhosis.

NAFLD is linked to metabolic syndrome, reflected by higher incidence of NAFLD and IR in obese individuals as compared to non-obese persons. Persons with NAFLD have IR and patients of NAFLD in conjunction with diabetes, due to IR supposed to have hyperglycemia relatively refractory to OHA leading to increased requirement of dose of OHA's which predisposes to greater risk of side effects of OHA's and also poor glycemic control due to IR predisposes to early onset micro as well as macrovascular complications of diabetes. It seems reasonable to predict that early diagnosis of NAFLD and early intervention with strict glycemic control and weight loss would prevent further complications.

Individual Contributors:

- Entire concept of the study, Study design ,Intellectual inputs and supervision work by **Dr. Ritu Gupta**
- Entire field work, DATA collection and Compilation work by **Dr.Shivesh Thakur**

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