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Does Insulin Resistance And Dyslipidemia Affect Severity Of Steatosis And Fibrosis In Patients Of Type 2 Diabetes Mellitus- A Cross Sectional Study

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Abstract
Background- *It is widely known patients with type 2 diabetes frequently exhibit symptoms of NAFLD which is a multisystem illness that affects several organs, including the cardiovascular, hepatic, and cerebrovascular systems. Numerous risk factors have been linked to the advancement of NASH but not many have studied to determine the risk factors for the severity of steatosis and liver fibrosis. So, the purpose of this study was to assess the effects of dyslipidemia and insulin resistance in individuals who had severe liver fibrosis and steatosis.*
Methodology- *A cross-sectional study was conducted in the department of internal medicine on diabetic for more than 5 years with features of fatty liver on ultrasonography. Fibroscan was conducted for these patients and classified as steatosis group or fibrosis group. Demographic Anthopometric and biochemical data was collected. Linear regression analysis was done to establish association between independent and dependent variables.*
Results*- 335 patients were divided into fibrosis and steatosis group with 129 and 206 patients respectively. Age, BMI, fasting insulin, blood glucose, HOMA-IR and liver enzymes were all significantly higher in patients with fibrosis. 27.7% (57/206) of steatosis patients had severe grade steatosis and 18.6% (24/129) of fibrosis patients had severe grade fibrosis. 4 patients had cirrhosis of liver. With every increase of BMI by 0.09 units, fasting blood glucose by 2.51 units, HbA1c by 1.78 and fasting insulin by 0.32 units, fibrosis worsened.*
Conclusion- *BMI, fasting insulin, HbA1c, blood glucose, HOMA-IR, dyslipidemia and liver enzymes were all significantly higher in patients with fibrosis. Indian patients with T2DM and obesity, with duration of diabetes above 5 years & with HOMA-IR>=3 and dyslipidaemia should be further evaluated for hepatic fibrosis.*

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I. INTRODUCTION

The clinical spectrum of nonalcoholic fatty liver disease (NAFLD) includes lobular inflammation, balloon degeneration, hepatic fibrosis, and cirrhosis, as well as localized fatty infiltration of the liver (simple hepatic steatosis). With an estimated 25% global prevalence, nonalcoholic fatty liver disease (NAFLD) has emerged as the most prevalent cause of chronic liver disease in the industrialized world as a result of epidemiological shifts brought about by modernization and changes in lifestyles. [1-3]

At present, nonalcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease globally. It has a significant correlation with other metabolic conditions such as obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome (MetS) [2,4,5]. NAFLD is the second most common reason for liver transplantation. (6) Estimates place the incidence at 24% worldwide, with the highest rates found in South America and the Middle East and Asia, and the lowest rates found in Africa. (7)

Advanced fibrosis, non-alcoholic steatohepatitis (NASH), and NAFLD have been recognized to be associated with type 2 diabetes. The pooled prevalence of people with type 2 diabetes with NAFLD and NASH patients was 23% and 44%, respectively, in a large meta-analysis spanning 22 nations; these numbers are higher than those of the general population. [8] Advanced hepatic fibrosis can be independently predicted by T2DM [9, 10].

Numerous risk factors, including nutrition, MetS, T2DM, obesity, Hispanic ethnicity, and polymorphisms in the patatin-like phospholipase domain-containing 3 (PNPLA3) gene, have been linked to the advancement of NASH. [11–13] Still poorly known, nonetheless, are the pathogenic pathways by which certain NAFLD patients advance to NASH. [15–14] However, there hasn't been much research done to determine the risk factors for the severity of steatosis and liver fibrosis. Therefore, the purpose of this study was to assess the effects of dyslipidemia and insulin resistance in individuals who had severe liver fibrosis and steatosis.

II. METHODOLOGY

Study Design and Setting

A cross-sectional study was conducted on patients diagnosed with Type 2 Diabetes Mellitus for more than 5 years and were found to have fatty liver on ultrasonography for a period of 1 year in the department of internal medicine at a tertiary care center of Northern India.

Study Participants

Study participants included in the study had history of Type 2 diabetes mellitus for more than 5 years and had Ultrasonography findings suggestive of fatty liver disease. Those who had Type 1 DM, seropositivity for Hepatitis B, C and HIV, or had significant daily alcohol consumption (men >20 g and women >10 g), history of congestive heart failure or other secondary causes of hepatic steatosis (e.g., drugs use like amiodarone, tamoxifen etc.), or any major systemic illness or unwilling to give consent for participation were excluded from the study.

For the purpose of sample size estimation, study used is **Kalra S et al (2022)[1].**

Sample size formula used is:

$$n = ([Z_{\alpha/2}]^2 * p(1-p))/d^2$$

- **Zα/2** -critical value of the normal distribution at α/2 (for a confidence level of 95%, α=0.05 and the **critical value is 1.96**)
- **p=** Proportion of diabetic patients who have developed steatosis or fibrosis (value is 72.4%)
- **d:** Margin of error for desired precision (value is 0.01)

To estimate the desired outcome in this study, significant with 95% confidence interval and power of 80%, the required minimum sample size will be **318 patients.** With 5 % non-response rate, the final sample size was 335 diabetics with fatty liver disease.

Data Collection

After a written and informed consent of study participants. Diabetics, diagnosed for more than 5 years, Ultrasonography (USG) for hepatic steatosis and liver size (span) was performed in all patients after an overnight fast lasting atleast 8 hours, and the patient resting in supine position for at least 15 minutes. Liver span was measured as the largest craniocaudal diameter of the liver at the right mid clavicular line during inspiration in a supine position. All those patients who had a positive finding of fatty liver on USG, Fibroscan was performed after which patients were classified as Liver steatosis and Liver fibrosis group.

Liver stiffness and CAP were measured using transient elastography and FibroScan®. Initially, the M probe was utilized to assess liver stiffness (LSM) and measure the controlled attenuation parameter (CAP). When the M probe failed, the XL probe—designed for obese patients—was utilized. The following CAP cut-off values for liver steatosis (S) were taken from the Kamali et al. study: (17)

(1) <237 dB/m (S0, no steatosis),
(2) 237.0-259.0 dB/m (S1, mild steatosis),
(3) 259.0-291.0 dB/m (S2, moderate steatosis), and
(4) 291.0-400.0 dB/m (S3, severe steatosis).

The cut-off values for fibrosis (F) were also adopted from the same study as follows: [17]

(1) <5.5 kPa (F0, no fibrosis),
(2) 5.5-8.0 kPa (F1, mild fibrosis),
(3) 8.0-10.0 kPa (F2, moderate fibrosis),
(4) 11.0-16.0 kPa (F3, severe fibrosis), and
(5) >16.0 kPa (F4, cirrhosis) [6].

Blood samples were drawn and sent for tests such as fasting blood glucose (FBG), fasting insulin levels, and liver biochemistry, which included triglycerides (TG), total cholesterol, glycated hemoglobin (HbA1c), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, gamma-glutamyl transferase (GGT), and direct and total bilirubin (TB) and glycated hemoglobin (DB). Elevation of TG ≥150 mg/dL, total cholesterol ≥200 mg/dL, or both, or low HDL cholesterol (<50 mg/dL in females, <40 mg/dL in men) were considered indicators of dyslipidemia. 18]

Insulin resistance was calculated by using the HOMA (Homeostatic Model Assessment) model [HOMA-IR = fasting insulin (μIU/mL)*fasting glucose (mmol/L)/22.5] [19] and HOMA-IR ≥ 3.0 was chosen as a cut-off. [20]

Data Analysis: The data was analysed using SPSS version 24.0. Descriptive summary using frequencies, percentages, graphs, mean, and standard deviation were used to present the study results. Probability (p) was calculated to test statistical significance at the 5% level of significance. Categorical variables were analysed between steatosis and fibrosis using chi square test. Continuous variables were compared

between the two groups using independent t test. Linear regression analysis was done to establish association between independent and dependent variables.

III. RESULTS

Out of 335 patients, 206 had Liver steatosis and 129 had Liver fibrosis on Fibroscan. The mean age of participants in steatosis and fibrosis group was 52.34 ±10.2 and 59.2 ±5.83 years, which was statistically highly significant (p value- 0.0001). the distribution of gender amongst the 2 groups, BMI was also statistically significant (p value- 0.023, 0.046 respectively). Mean difference in history of diabetes among the 2 groups i.e. 8.64 ±2.36 and 11.28 ±3.18 years, was also highly significant (p value- 0.0001). (Table 1)

There was a statistically significant difference in the blood investigations like fasting blood glucose, HbA1c, fasting insulin, triglycerides, cholesterol, LDL, HDL, ALF, AST and GGT levels across the 2 groups. The HOMA-IR across the 2 groups was also statistically significant (p value-0.0001). 40.3% steatosis patients and 60.5% of fibrosis patients had HOMA-IR ≥ 3 (p value-0.04). (Table 2)

27.7% (57/206) of steatosis patients had severe grade steatosis i.e., CAP values 290-400 dB.m. 18.6% (24/129) of fibrosis patients had severe grade fibrosis i.e., LSM values 11 to 16 kPa. 4 patients had cirrhosis of liver i.e., F4 grade fibrosis on LSM findings. (Table 3)

A linear regression analysis was done to ascertain the correlation of age, BMI, waist circumference, history of diabetes, fasting blood sugar, HbA1c, fasting insulin and HOM-IR with the development of fibrosis. Linearity assumption was tested using Durbin-Watson and pseudo-R square statistics. The model was a good fit to the observed data (f value= 0.524, p=0.667). With increase of BMI by 0.09 units, the fibrosis score will increase by one unit. With increase of fasting blood glucose by 2.51 units, the fibrosis score increases by one unit. With increase in HbA1c by 1.78 units, the fibrosis score increases by one unit. With decrease in fasting insulin levels by 0.32 units, the fibrosis score increases by one unit. Lastly with increase in HOM-IR by 4.78 units, the fibrosis score increases by one unit. (Table 4)

IV. DISCUSSION

The clinical range of non-alcoholic fatty liver disease (NAFLD) is wide, spanning from cirrhosis to simple steatosis [15,21]. Insulin resistance, metabolic and oxidative stress, inflammation, apoptosis, fibrogenesis, genetic predisposition, and environmental variables are some of the pathophysiologic processes that NAFLD and T2D have in common. 23–24] Thus, there is a markedly elevated risk of liver cirrhosis and HCC when NASH is developed. [25]

It is widely known patients with type 2 diabetes frequently exhibit symptoms of NAFLD which is a multisystem illness that affects several organs, including the cardiovascular, hepatic, and cerebrovascular systems. [26] Furthermore, T2D is thought to be a risk factor for the development of cirrhosis, liver fibrosis, and potentially HCC in NAFLD. In [27] According to Lomonaco et al., at least 15% of T2D patients have moderate-to-advanced fibrosis (F2 or above), which is a known risk factor for cirrhosis and overall mortality. [28]

Similar to our research, a number of other studies have demonstrated that in individuals with NAFLD and T2D, age is a factor that influences the onset and severity of liver fibrosis. [26, 29-33] As people age, the problems of chronic liver disease worsen. Aging causes changes in metabolism and encourages the buildup of fat in the liver. Insulin resistance and hyperinsulinemia also cause obesity and the start of liver fibrosis when physical activity levels decrease with age. [34] Thus, aging is a potential indicator of liver fibrosis in T2D patients with NAFLD.

Our study also showed significant difference in BMI of patients with T2DM who developed steatosis and fibrosis. Similar to our study, earlier researches have also shown that among T2D patients, having a high BMI is a separate potential risk factor for liver fibrosis. [26, 31, 33, 35] There has been a suggestion that there is a causal connection between the development of extra fat, insulin resistance, and liver fibrosis. Over 90% of obese T2D patients also have NAFLD. Obesity and hyperglycemia are risk factors for NAFLD. [36] Inflammation, lipotoxicity, and hepatocyte fat storage are all facilitated by obesity, which also plays a role in the development of insulin resistance and increased adiposity. [36] The advancement of non-alcoholic fatty liver disease (NAFLD) from simple steatosis to NASH and fibrosis can be caused by hyperglycemia and toxic lipids through a number of processes, including as oxidative stress, endoplasmic reticulum stress, and abnormalities of the mitochondria. [34]

Patients with fibrosis had significantly increased liver enzyme levels, dyslipidemia, and insulin resistance. In a study conducted by Sanyal D et al., it was discovered that T2D patients with NAFLD had considerably greater ALT and AST activity than T2D patients without NAFLD. (37) In T2D patients with NAFLD, other earlier research has similarly shown a favorable correlation between AST activity and liver fibrosis. [31,38,39] Serum AST and ALT activity are readily available and inexpensive tools for detecting liver damage, making them valuable indicators for determining if liver fibrosis is present in T2D patients with NAFLD.

It is commonly known that advanced fibrosis is a reliable indicator of developing cirrhosis in the future. [41, 40] Adults with DM who have advanced fibrosis (F ≥ 3) and are at high risk of developing cirrhosis need to be identified by NASH screening. [42, 41] However, doctors rely on steatosis or ALT to identify patients at risk of developing NASH with fibrosis since noninvasive diagnostic panels or imaging methods cannot consistently diagnose steatohepatitis. [41] Our study had 27.7% (57/206) of steatosis patients had severe grade steatosis and 18.6% (24/129) of fibrosis patients had severe grade fibrosis. Liver cirrhosis was also seen in 4 out of 129 patients.

Some lower incidence was seen in French patients with T2DM, 12.7%, 7.3% and 2.1% of them showed significant/advanced fibrosis or cirrhosis (LSM<8 kPa, <9.6 kPa, <13 kPa respectively). [43] Another research conducted by Tuong TTK et al. found that 73.3% of 307 Vietnamese patients with T2DM had NAFLD (20.5%, 21.8%, and 30.9%, respectively, for mild, moderate, and severe steatosis). (35) Similar frequency of 18.6% of cases with severe or advanced fibrosis from the same geographic area was reported by Gupta A et al. In [44]

We also observed high impact of dyslipidemia and insulin resistance in severity of steatosis and insulin resistance. We found that with increase of BMI by 0.09 units, the fibrosis score will increase by one unit. With increase of fasting blood glucose by 2.51 units, the fibrosis score increases by one unit. With increase in HbA1c by 1.78 units, the fibrosis score increases by one unit. A study by Gupta A et al., also found that an increase of 1 unit of BMI above 23 kg/m2 led to 19.6 times increased risk of hepatic steatosis in T2DM patients aged 50 years and above. SGOT and GGTP were significant predictors of any degree of hepatic fibrosis. [44]

Specifically for NASH, insulin resistance is a major contributing factor to NAFLD. It influences several processes, including endothelial dysfunction, hyperglycemia, activation of oxidative stress and inflammation, dyslipidemia, and ectopic lipid accumulation, all of which work together to create a pro-atherogenic milieu that is favorable to the development of CVD as well. [45] Patients with non-alcoholic fatty liver disease (NAFLD) may or may not have atherogenic dyslipidemia, which is characterized by plasma hypertriglyceridemia, increased small dense LDL particles, and reduced HDL-C levels. [46]

Due to liver's involvement in the synthesis and/or removal of all lipoprotein particle types, it plays a key component in lipoprotein metabolism. Apart from its function in lipoprotein particle metabolism, the liver plays a significant role in the metabolism of its substituent triglycerides, particularly cholesterol. As a result, there is a complex relationship between modified lipoprotein metabolism and composition and hepatic metabolic dysfunction in non-alcoholic fatty liver disease. [46]

A few limitations of this study include that being a cross-sectional design, it was impossible to distinguish the cause and impact of NAFLD across age and gender. Second, we were unable to confirm the NAFLD results on USG and FibroScan with histological investigations using liver biopsies. To identify any significant differences between the groups, the research observations must also be contrasted with those of normoglycemic persons (controls) who do not have hepatic steatosis as well as with T2DM patients who do not have hepatic steatosis. Nevertheless, an adequate number of samples and noteworthy insights are obtained from the research data.

V. CONCLUSION

NAFLD, which is a multisystem disease that affects multiple organs, including hepatic, cardiovascular, and cerebrovascular systems, often presents in T2D patients. Age, BMI, Insulin resistance and dyslipidemia significantly impacts the severity of liver steatosis and fibrosis in patients of Type 2 Diabetes Mellitus.

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Table 1- Basic Demographic and Anthopometric profile of study participants across both groups

Variables		Liver Steatosis N=206	Liver Fibrosis N=129	P value
Mean Age (yrs)		52.34 ±10.2	59.2 ±5.83	**0.0001**
Sex	**Male**	137 (66.5%)	84 (66.6%)	
	Female	69(33.5%)	45	**0.023**
Mean BMI (kg/m^2)		28.45 ±4.16	29.34 ±3.63	**0.046**
BMI > 30		63	38	0.923
Waist circumference		103.1 ±11.2	104.6 ±12.7	0.258
H/O of Diabetes (yrs)		8.64 ±2.36	11.28 ±3.18	**0.0001**

Table 2- Biochemical profile of study participants across both groups

Variables		Liver Steatosis (N=206)	Liver Fibrosis (N=129)	P value
Mean fasting Blood Glucose		136 ±21.67	152 ± 24.78	0.0001
HbA1c		7.8 ±2.3	9.6 ±1.8	0.0001
Mean fasting Insulin		30.2 ±3.87	36.7 ±3.45	0.0001
Mean HOM-IR		2.4 ±1.2	3.2 ± 0.7	0.0001
HOMA-IR ≥ 3		83 (40.3%)	78	0.004
Lipid Profile	**Triglycerides**	124.3 ±23.8	143.7 ±32.6	0.0001
	Cholesterol	189.9 ±32.74	206 ±42.3	0.0001
	LDL	113.9 ±25.9	125.6 ±24.3	0.0001
	HDL	46.2 ±11.8	38.2 ±7.6	0.0001
LFT	**ALT**	34 ±16.8	43.5 ±21.9	0.0001
	AST	40.75 ±13.5	51.1 ±19.4	0.0001
	GGT	36.29 ±8.9	46.7 ± 11.2	0.0001

Table 3- Distribution of study participants according to basis of grades of steatosis and fibrosis

Variables		N (%)
CAP (dB/m)	S1 (237-259)	53 (25.7%)
	S2 (259-291)	96 (46.6%)
	S3 (291-400)	57 (27.7%)
LSM (kPa)	F1 (5.5-8)	45 (34.9%)
	F2 (8 -10)	56 (43.4%)
	F3 (11-16)	24 (18.6%)
	F4 (>16)	4 (3.1%)

Table 4- Linear Regression analysis for predictors of severe fibrosis

Variables	Standardized Beta	95% CI		P value
		Lower	Upper	
Age (yrs)	0.0879	0.231	1.457	0.321
BMI (kg/m^2)	1.0559	1.001	21.943	**0.042**
Waist circumference	0.6112	0.345	2.567	0.787
H/O of Diabetes (in years)	0.6806	0.257	2.450	0.672
Fasting Blood Glucose	2.551	1.491	32.013	**0.002**
HbA1c	1.787	1.324	19.012	**0.001**
Fasting Insulin	-0.342	-.0021	-0.482	**0.0001**
HOM-IR	4.781	2.056	8.091	**0.031**