Document heading doi: 10.21276/apjhs.2020.7.1.16 **Original Research Article**

Prevalence of Nonalcoholic Fatty liver Disease (NAFLD) and its association with Cardio-metabolic risk factors in Type 2 Diabetes Mellitus

Priyanka Choudhary[1], Akash Rajender[2*], Pankaj Mathur[1], Deepak Gupta[3], Puneet Rijhwani[3], Ganesh Narain Saxena[3]

[1]Resident, Department of General Medicine, Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan, India

[2] Assistant Professor, Department of Gastroenterology, Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan, India

[3] Professor, Department of General Medicine, Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan, India

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) and Nonalcoholic fatty liver disease (NAFLD) have risen globally to epidemic proportions. The study was aimed to determine the prevalence of NAFLD and its association with cardio-metabolic risk factors in T2DM subjects. **Method:** In a case control study, 212 consecutive, T2DM subjects with age ≥ 30 years, were evaluated from December 2017 to December 2018 at Mahatma Gandhi Medical College &Hospital, Jaipur, Rajasthan. Subjects with history of significant alcohol consumption, evidence of cirrhosis, hepatotoxic drugs, and other known causes of fatty liver were excluded. The T2DM subjects were divided into (1) NAFLD - patients with USG evidence of fatty changes in the liver (2) Non-NAFLD – patients without any USG evidence of fatty changes in the liver. Coronary artery disease was screened by any past medical history of CAD or electrocardiographic or angiography evaluation. Continuous variables were expressed as mean with standard deviation. Comparison of continuous data between subgroups was done by using Independent student's t-test or Mann Whitney U test. All statistical analysis was carried out by SPSS version 25. **Result:**55.66% diabetics had comorbid NAFLD. Both study groups had comparable mean age (p 0.719) and gender distribution (p 0.482). Subjects with NAFLD had significantly higher BMI (p 0.0001), mean waist circumference (p <0.001), waist hip ratio (p <0.001), systolic BP (p 0.001), diastolic BP (p 0.024), HbA1c (p 0.021), total cholesterol (p 0.0426) & triglyceride (p 0.02). Mean LDL (p 0.054), VLDL (p 0.235) & HDL (p 0.113) values were comparable in two study groups, suggesting no significant association with NAFLD. 32 (15.09%) subjects had coronary artery disease (CAD). Diabetics with NAFLD had significantly higher CAD (22.03% vs 9.57%, p 0.02).**Conclusion:** Diabetics with NAFLD had significantly higher cardio-metabolic risk factors, leading to increased associated risk of CAD.

Key words: NAFLD, Diabetes, CAD

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a disorder characterized by fat accumulation in the liver which is closely associated with insulin resistance and Type 2 diabetes (T2DM). [1-3]

Address for Correspondence
Dr. Akash Rajender
Assistant Professor, Department of Gastroenterology, Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan, India.
E-mail: drakash5@gmail.com

NAFLD is a spectrum of liver disease that encompasses simple fatty infiltration in >5% of hepatocytes (steatosis), fatty infiltration plus inflammation (Nonalcoholic steatohepatitis), fibrosis and ultimately cirrhosis, in the absence of excessive alcohol consumption (a threshold of <20 g/day for women and <30 g/day for men). [4] The prevalence of NAFLD has been reported as 15-20% in general population & 50–87.1% in Type 2 Diabetics.[5-8] Adoption of a sedentary lifestyle and globalization of Western diet is associated with an increase in the prevalence of NAFLD in developing nations. In many

parts of the world NAFLD has become the predominant cause of chronic liver disease and subsequently for liver transplantation. [9]It is estimated that by the year 2025, three-quarters of the world's diabetics will be in non-industrialized countries and almost a third in India and China alone. [10] Already 4.3–13.9% of the urban and 2.7–3.7% of the rural Indian population are diabetic. [11, 12]The high prevalence of NAFLD in Western countries is probably due to the contemporary epidemic of obesity and associated metabolic complication. Obesity, Type 2 diabetes, and hyperlipidemia are recognized as risk factors for NAFLD. Accumulating evidence suggests that NAFLD can be regarded as part of or, indeed a hepatic manifestation of metabolic syndrome. Also, NAFLD as a syndrome is an optimal biological milieu in which T2DM can develop. NAFLD influence the severity of hepatic insulin resistance and may precede development of Type-2 diabetes and cardiovascular disease.[13,14]NAFLD has been associated with markers of subclinical atherosclerosis (such as impaired flow-mediated vasodilatation), endothelial dysfunction, increased arterial stiffness and carotid artery intima–media thickness.[15] By present trends, India has been predicted to face an epidemic of T2DM & NAFLD in near future, which makes it pertinent to study association of both these disorders. It remains important to define cardio-metabolic factors which are associated with the presence of NAFLD in Indian diabetic patients.

MATERIAL AND METHOD

In a case control study, 212 consecutive, Type 2 diabetes mellitus (American Diabetes Association ADA criteria, presenting in OPD or IPD at Department of Medicine, Mahatma Gandhi Medical College &Hospital, Jaipur from December 2017 to December 2018 subjects were evaluated. T2DM subjects with age ≥ 30 years were evaluated. Subjects with history of significant alcohol consumption were excluded (significant alcohol consumption be defined as >21 standard drinks per week in men and >14 standard drinks per week in women in previous 2 year period). A standard alcoholic drink defined as any drink that contains about 14 g of pure alcohol. Subjects with history or evidence of cirrhosis, hepatotoxic drugs, drugs known to cause fatty liver and other known cause of liver disease by following etiologies- Hepatitis B & C (HbsAg/Anti HCV antibody), Autoimmune (ANA) were excluded. We also excluded subjects with cirrhosis, other known causes of fatty liver (history of rapid weight loss, starvation, surgical procedures-biliopancreatic diversion, extensive small bowel resection, jejunoileal bypass, inflammatory bowel disease) and subjects with significant unstable physical illness (eg. Acute myocardial infarction, Diabetic ketoacidosis, Hyperglycemic hyperosmolar coma). NAFLD was further classified based on standard ultrasonographic imaging criteria as: Grade I (Mild Steatosis) - increased echogenicity of the liver along with visible periportal and diaphragmatic echogenicity; Grade II (Moderate Steatosis) - increased echogenicity of the liver along with invisible periportal echogenicity, without diaphragmatic fading and Grade III (Severe Steatosis) - increased echogenicity of the liver along with invisible periportal echogenicity, with diaphragmatic fading. Further, the T2DM patient study group was divided into 2 subgroups: NAFLD - patients with USG evidence of fatty changes in the liver (Cases). Non-NAFLD – patients without any USG evidence of fatty changes in the liver (Controls).

Detailed physical examination was carried out with emphasis on blood pressure, height, weight, and waist-hip ratio. Laboratory investigations included HbA1c, lipid profile (total cholesterol, LDL, HDL, VLDL, and triglycerides) and liver function tests. BMI was calculated by dividing weight in kilograms by height in meters squared. Waist circumference was measured at the level of the umbilicus. Coronary artery disease (CAD) was screened by any past medical history of CAD or electrocardiographic or angiography evaluation. Continuous variables were expressed as mean with standard deviation (S.D.). Comparison of continuous data between subgroups was done by using Independent student's t-test or Mann Whitney U test. All statistical analysis was carried out by SPSS version 25[Table 1,Figure 1].The study was approved by the institutional ethics committee.

RESULTS

Among 212 T2DM subjects studied, approximately half of the studied diabetics had comorbid NAFLD (55.66%, 118). The mean age in T2DM subjects with NAFLD was 57.59±11.22 years; as compared to 57.14±11.19 years in subjects without NAFLD (p 0.719). Both study groups had comparable gender distribution (p 0.482). Subjects with NAFLD had significantly higher mean BMI (34.59±4.83) as compared to subjects without NAFLD (25.73±2.92). The difference was statistically significant (p 0.0001).In diabetic subjects with NAFLD mean waist circumference was significantly higher (91.6 ±4.83 cm) as compared to DM (85.6±7.61 cm) group. (p <0.001). The mean waist hip ratio of T2DM subjects with NAFLD was significantly higher than subjects with NAFLD (p <0.001). The mean systolic BP in subjects

with NAFLD was 127.49±23.82 mmHg as compared to 115.14±18.14 mmHg in subjects without NAFLD. This difference was significant (p 0.001). The mean diastolic BP in T2DM subjects with NAFLD was 79.04±11.37 mmHg as compared to 75.42±10.93 mmHg in subjects without NAFLD. This difference was significant (p 0.024). The mean HbA1c in diabetic subjects with NAFLD was higher (7.07±1.96), as compared to diabetics without NAFLD (6.02±1.74). The difference was statistically significant (p 0.021). Total cholesterol (p 0.0426) & triglyceride (p 0.02) levels were significantly higher in T2DM subjects with NAFLD as compared to T2DM subjects without NAFLD. Mean LDL (p 0.054), VLDL (p 0.235) & HDL (p 0.113) values were comparable in two study groups, suggesting no significant association with NAFLD. 32 (15.09%) subjects had coronary artery disease, including 22.03% of diabetics with NAFLD and 9.57% without comorbid NAFLD (p 0.02).

Table 1: Comparison of characteristics of Type 2 Diabetes mellitus patients with and without NAFLD

Variable	DM+NAFLD(n 118)	DM(n 94)	P value
Age (Years)	57.59±11.22	57.14±11.19	0.719
Sex (% Males)	57.63	62.77	0.482
BMI (Kg/m^2)	34.59±4.83	25.73±2.92	0.0001
Waist Circumference (in cm)	91.6 ±4.83	85.6±7.61	< 0.001
Waist hip ratio	0.96±0.02	0.87±0.09	<0.001
Systolic BP (mmHg)	127.49±23.82	115.14±18.14	0.001
Diastolic BP (mmHg)	79.04±11.37	75.42±10.93	0.024
HbA1c	7.07±1.96	6.02±1.74	0.021
Total Cholesterol (mg/dl)	217.3±19.42	193.66±17.90	0.043
TG (mg/dl)	133.56±20.23	109.00±21.32	0.02
HDL (mg/dl)	44.55±14.82	47.65±13.25	0.113
LDL(mg/dl)	122.80±25.53	116.10±24.35	0.0540
VLDL (mg/dl)	27.96±11.49	29.90±12.26	0.235

values are mean ± SD

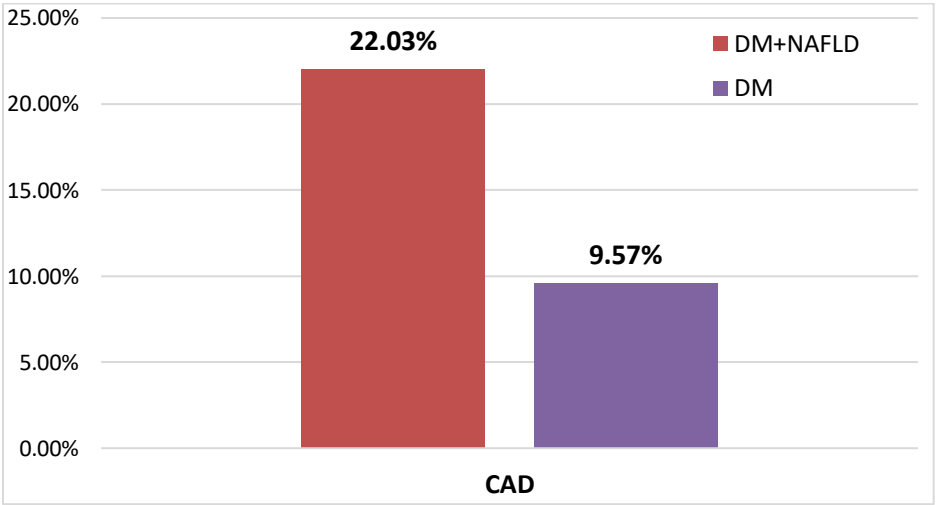

Figure 1: Prevalence of CAD in diabetics with NAFLD

DISCUSSION

Among the 212 T2DM subjects studied, 55.66% (118) had NAFLD. Kalra S *et al* (2013) in SPRINT study in 189 Indian centers, evaluated 924 T2DM subjects, identified 56.5% subjects to have NAFLD.[16] Prashanth M *et al* (2009) found 62.25% [17],Mohan V *et al* (2009) 54.5% [18] Chandel K *et al* (2016) 55.68% [19] of study subjects to have NAFLD. Several studies have suggested that age having no association with presence of NAFLD in T2DM subjects, similar to our study. [17, 20, 21,22] Male predominance among subjects with NAFLD was also noted in several similar studies. [16, 18,

[20,23]In our study, subjects with NAFLD had significantly higher mean BMI (34.59±4.83) as compared to subjects without NAFLD (25.73±2.92) (p 0.0001). Leite NC *et al*[20] in a similar study had comparable results with mean BMI 27±3.6 in no-NAFLD group as compared to 31.3 ± 5.4 in NAFLD group (p<0.001).Our results were also similar to several other Indian studies. [21, 24, 25, 26] The mean waist circumference in diabetics with NAFLD was significantly higher (91.6 ±4.83 cm) as compared to DM (85.6±7.61 cm) group. Leite NC *et al* (2009)[20] Mohan V *et al* (2009)[18] and Uchil D *et al* (2009)[23] also suggested higher mean waist circumference to be significantly associated with NAFLD in diabetics. In our study, mean waist hip ratio of T2DM subjects with NAFLD was significantly higher than subjects without NAFLD (p 0.001). These results suggest that T2DM subjects with high waist hip ratio are at a higher risk of developing NAFLD. Similar results were found by Chandel K *et al* (2016).[19] In our study, the mean systolic BP in subjects with NAFLD was 127.49±23.82 mmHg as compared to 115.14±18.14 mmHg in subjects without NAFLD. This difference was significant (p 0.001). The mean diastolic BP in T2DM subjects with NAFLD was 79.04±11.37 mmHg as compared to 75.42±10.93 mmHg in subjects without NAFLD (p 0.024). Mohan V *et al* (2009) in similar study found systolic and diastolic BP to be significantly different in NAFLD and non NAFLD group in T2DM subjects. SBP (119±17 vs 124±17 mmHg, p <0.05), DBP (74 ± 11 vs 77 ± 10 mmHg, p <0.05)[18]Lv WS *et al* (2013) [26], Rajender A *et al* (2019)[27] had similar results. In our study, the mean HbA1c in diabetic subjects with NAFLD was higher (7.07±1.96), as compared to diabetics without NAFLD (6.02±1.74) (p 0.021). Viswanathan V *et al* (2010) suggested mean HbA1c to be significantly associated with NAFLD (9.7±2.1 vs 8.5±2.1, p 0.01).[24] Similar results were seen in studies by Patel H *et al* (2018)[22] Somalwar AM *et al* (2014) [25] Lv WS et al (2013) [26], Prabhakar A *et al* (2017). [28] Whereas very few studies suggested HbA1c not to be significantly associated with NAFLD in T2DM subjects. [20,21]In our study, total cholesterol (p 0.0426) & triglyceride (p 0.02) levels were significantly higher in T2DM subjects with NAFLD as compared to T2DM subjects without NAFLD. Mean LDL (p 0.054), VLDL (p 0.235) & HDL (p 0.113) values were comparable in two study groups, suggesting no significant association with NAFLD. The results have varied in several studies related to different types of lipid fractions. Mohan V *et al* (2008) suggested significantly higher total cholesterol and lower HDL in diabetic subjects with NAFLD. [18] Patel H *et al* (2018) suggested total cholesterol to be comparable in both groups, but triglycerides (p 0.42), LDL(p 0.03) and HDL (p 0.01) to be significantly different [22]. Chandel K et al (2016) [19],Uchil D *et al* (2009) [23], Somalwar AM et al (2014) [25] suggested total cholesterol, HDL, triglyceride to be significantly different in study groups. Agarwal AK et al (2011)[21] Viswanathan V *et al* (2010)[24] and Lv WS et al (2013)[26] also suggested triglycerides to be significantly higher in diabetics with NAFLD. In our study, 32 (15.09%) subjects had coronary artery disease (CAD), including 22.03% of diabetics with NAFLD and 9.57% without comorbid NAFLD suffered from coronary heart disease. Viswanathan V *et al* (2010) on evaluating 298 diabetics, suggested that CAD was significantly higher in subjects with NAFLD (11.5% vs 1.4%, p 0.01). [24] Agarwal AK *et al* (2011) on evaluating 124 T2DM subjects suggested that NAFLD was significantly correlated with CAD (p 0.016). [21] Somalwar AM *et al* (2014) also found a significant association between NAFLD and CAD in T2DM subjects (70.58% vs 21.11%, p<0.001). [25] Prabhakar A *et al* (2017) in 114 T2DM subjects, used binary logistic regression analysis to suggest that NAFLD is an independent predictor of CAD (p 0.002) [28]

CONCLUSION

NAFLD in type 2 diabetics is associated with several cardiometabolic risk factors and with increased risk of coronary artery disease.

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