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# NAFLD is a risk factor for the development of diabetic nephropathy in patients with $T_2DM$

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## ABSTRACT

**Background:** Non-alcoholic fatty liver disease (NAFLD) and diabetes are two common health problems of global concern. Diabetic nephropathy (DN) is also a microvascular complication of diabetes. However, there is little knowledge about the relationship between NAFLD and DN. **Aims and Objectives:** The aim of this study was to know the association between NAFLD and DN in type 2 diabetes mellitus (T2DM) patients. **Materials and Methods:** A cross-sectional study was conducted on 136 patients of T2DM admitted to Sanjay Gandhi memorial Hospital, Rewa. Using abdominal ultrasonography, patients were grouped as patients, with NAFLD and patients without NAFLD. Then, patients were screened for DN (microalbuminuria) using the dipstick method. Liver and kidney function tests and complete blood count were performed along with FBS, PPBS, and HbA1c. Data were analyzed by appropriate statistical tests by Wizard 2® (Version 2.0.12 (259)) software. $P<0.05$ was considered significant. **Results:** In this study, 61 (44.85%) patients were found to have NAFLD, and 30 (49.81%) also had DN. Out of 75 (55.14%) non-NAFLD patients, 21 (28%) had DN. The data were statistically significant (OR: 2.4885, 95%, $P=0.0120$). The mean estimated glomerular filtration rate (eGFR) (mL/min/1.73 $m^2$) among subjects with FIB4 score $\geq 2.67$ was $77.33 \pm 9.54$ and was less as compared to the mean eGFR among subjects with FIB4 score $<2.67$ ($104.12 \pm 5.23$) (student t-test, $t(134)=2.247$, $P=0.026$). **Conclusion:** NAFLD might be a risk factor for the development of DN in T2DM patients.

**Key words:** Non-alcoholic fatty liver disease (NAFLD); Diabetic nephropathy; Type 2 diabetes mellitus

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## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most widespread liver disease in Western nations, affecting roughly 35% of the general population and about 75–90% of particular categories, such as obese and diabetic individuals.[1,2] According to epidemiological research, the prevalence of NAFLD in the general Indian population ranges from 9 to 32%, with a higher frequency among patients who are overweight, obese, or have diabetes or pre-diabetes.[3]

NAFLD is characterized by increased triglyceride accumulation in the liver (>5% of liver weight), which is not brought on by excessive alcohol use or other steatosis-related factors.[4,5] Hepatocellular carcinoma, non-alcoholic steatohepatitis, liver cirrhosis, and non-alcoholic fatty liver are all included in the illness spectrum.[6]

NAFLD and type 2 diabetes mellitus (T2DM) can affect each other. NAFLD increases mortality among patients with T2DM, while T2DM also increases progressive liver fibrosis up to 3 times and hepatocellular carcinoma up to 2 times and is an independent predictor of all causes and liver mortality in patients with NAFLD.[7,8] Insulin resistance is the condition that connects the two; hence, NAFLD is the liver component of metabolic syndrome. In T2DM and NAFLD, compensatory hyperinsulinemia results in abnormalities in lipid metabolism and hepatic triglyceride buildup. This also explains why T2DM and NAFLD are closely related and why those with NAFLD have a higher risk of developing T2DM.[9,10]

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It has been demonstrated that NAFLD and the macrovascular consequences of diabetes (coronary artery disease) are closely related.[11] On the other hand, nothing is known regarding the potential link between NAFLD and the microvascular consequences of diabetes. One of the most prevalent microvascular problems linked to T2DM is diabetic nephropathy (DN). However, there are not many clinical symptoms in the early stages of this illness, and kidney damage is typically irreparable if albuminuria persists. Monitoring those who have risk factors for DN is therefore crucial. An approach like this would make it easier to spot DN patients early on and might even aid the prognosis. A number of studies have linked NAFLD in adults to an increased incidence and prevalence of chronic renal disease.[12-16] Some other studies, however, found no correlation.[17]

This study was done to explore the association between NAFLD and the development of DN in patients with T2DM.

### Aims and objectives

1. To study the association between NAFLD and diabetic nephropathy in $T_2DM$ patients.
2. To know the prevalence of DN in $T_2DM$ patients, with and without having NAFLD.

## MATERIALS AND METHODS

Patients with T2DM were taken and stratified into two groups based on abdominal ultrasonography (USG), that is, patients with FLD and without FLD, and then, both the groups were evaluated for DN by detecting spot urinary microalbuminuria by dipstick method. The diagnosis of diabetes mellitus was based on the American Diabetic Association criteria for T2DM.

All adults with a diagnosis of T2DM with or without NAFLD and patients consenting to the study were included in the study.

Patients who were previously diagnosed with cases of T2DM, patients not consenting to the study, those who are under intensive care, proven chronic kidney disease patients/pre-existing kidney disease, proven acute kidney disease patients, history of alcohol intake, and patient on hepatotoxic and nephrotoxic drugs, were excluded from the study.

The study was approved by the Institutional Ethics Committee (reference no. 468/IEC/MC/2020).

### Procedure plan

Taking informed consent from each patient and demographic and clinical variables data was collected from each subject. Known cases of T2DM or newly detected cases with T2DM were examined for RBS and HbA1C. Fasting venous blood samples (5 mL) were collected and analyzed and an USG abdomen was done. Based on the USG abdomen, the patients were categorized into two groups, patients with FLD, and those with no FLD. Then, subjects from both groups were evaluated for renal function test (RFT) and microalbuminuria. For RFT, liver function test and lipid profile 3 mL venous sample were withdrawn and sent for testing in the biochemistry department in SGMH Rewa. For detecting microalbuminuria to diagnose DN, morning urine samples collected from the patient in a sterile urine container were tested by dipstick method. Microalbuminuria was graded based on albuminuria level as 0 (<30 mg/dL), 1 (30 mg/dL), 2 (100 mg/dL), and 3 (300 mg/dL).

CBC, liver function test, RFT, lipid profile, FBS, PPBS, HbA1C, urine examination for microalbuminuria, and USG ABDOMEN were done for each patient.

Data were entered on an Excel® worksheet. Data were analyzed by appropriate statistical tests by Wizard 2® (Version 2.0.12 (259)) software. $P<0.05$ was considered significant in this study.

## RESULTS

In this study, 136 patients with T2DM were evaluated, of which 75 (55.14%) were male, and 61 (44.90%) were female subjects. NAFLD was found in 53.57% (61) of diabetic patients. Among 61 NAFLD cases, 30 (49.18%) had DN, whereas DN was found in 28% (21) of non-FLD (75) patients, as shown in Table 1.

The mean estimated glomerular filtration rate (eGFR) among subjects with FIB4 score ≥2.67 was 77.33±9.54 (mL/min/1.73 $m^2$) and was less as compared to the mean eGFR among subjects with FIB4 score <2.67. ($P=0.026$), as depicted in Table 2. A negative correlation was found between the patients' FIB4 score and eGFR, as shown in Chart 1. Table 3 shows that patients with FIB score ≥2.67 had a higher (60%) prevalence of DN ($P=0.010$).

## DISCUSSION

In the present study, out of 136 total subjects with T2DM, 61 (53.57%) subjects were found with FLD among which 30 (49.18%) subjects also had DN. Subjects without FLD were of a total 75 (55.14%), of which 21 (28%) had DN (Table 1).

**Table 1: Relation between FLD and diabetic nephropathy in T2DM patients**

| FLD status | Number of subjects | Percentage | Diabetic nephropathy | | | |
|---|---|---|---|---|---|---|
| | | | Present | | Absent | |
| Present | 61 | 44.85 | 30 | 49.18% | 31 | 50.82% |
| Absent | 75 | 55.14 | 21 | 28.0% | 54 | 72.0% |
| Total | 136 | 100 | 51 | | 85 | |

OR: 2.4885, 95% CI 1.2218–5.0685, P=0.0120

**Table 2: Relation between FLD staging (FIB4) and eGFR**

| FIB4 score | Number of patients | eGFR (mL/min/1.73 $m^2$) |
|---|---|---|
| | (n=136) | Mean±SE |
| <2.67 | 111 | 104.12±5.23 |
| ≥2.67 | 25 | 77.33±9.54 |

Student's t-test, t (134)=2.247, P=0.026

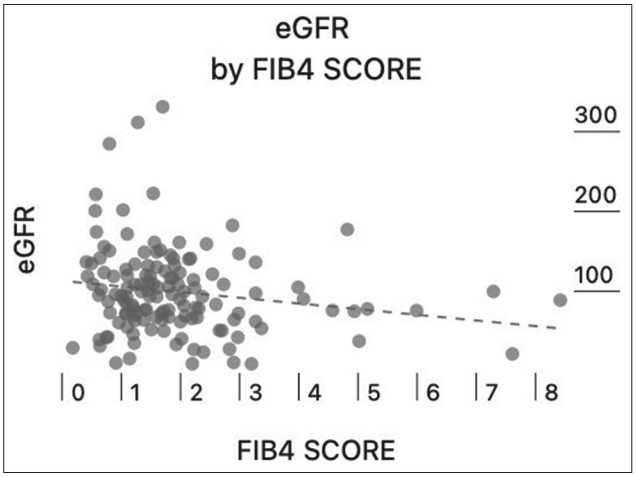


**Chart 1:** Negative correlation between FIB4 SCORE (liver fibrosis) and eGFR product- moment correlation, r (134)=0.194, P=0.024

The correlation between the prevalence of DN with and without FLD in T2DM patients was found to be significant (OR: 2.4885, 95% CI 1.2218–5.0685, P=0.0120).

FIB4 score was calculated to assess the risk for advanced fibrosis among patients, and it was found that the prevalence of DN increased as the risk for fibrosis increased and patients with a high risk of advanced fibrosis (FIB4 score) ≥2.67 had a 60% prevalence of DN (Chi-square test, z=2.572, P=0.010). The mean eGFR among subjects with significant fibrosis (FIB4 score ≥2.67) was 77.33±9.54 and was less as compared to the mean eGFR among subjects with FIB4 score <2.67(104.12±5.23) (student t-test, t (134)=2.247, P=0.026).

Jia et al., observed that increased liver fat content was associated with increased occurrence of albuminuria and decreased GFR. Elevated liver fat content could be associated with a higher DN burden.[18] The present study observed similar findings that a high risk of advanced fibrosis could be associated with the prevalence of DN and a decrease in eGFR. Kaur et al., studied 75 type 2 diabetic patients and found that out of 31 (41.33%) patients with DN, NAFLD was present in 25 (33.33%) patients.[19] Similar findings were also obtained in a study by Targher et al., in which NAFLD was associated with increased rates of CKD (odds ratio 1.87; 95% CI 1.3–4.1, P=0.020). They concluded that NAFLD is associated with an increased risk of DN independent of several other confounding factors.[12]

Jia et al., in their retrospective study, divided T2DM patients into two groups based on NAFLD status (with NAFLD=group A; without NAFLD=group B), and observed a higher cumulative incidence of DN in patients from Group A (58.58%) than in Group B (37.22%) (P=0.005). Their study also observed that NAFLD might be a risk factor for Diabetic Nephropathy[18] Zhan et al., assessed the incidence of diabetic nephropathy in 413 type 2 diabetic patients, by testing the 24 h urinary albumin excretion rate. The NAFLD was diagnosed based on the patient's medical history and liver ultrasound. A total of 363, out of 413 type 2 diabetic patients, were enrolled in this study. The incidences of NAFLD and DN in participants were approximately 56% (202/363) and 38% (137/363), respectively, and there was no significant difference in the prevalence of DN between patients with, and without NAFLD (37.1% vs. 38.5%, P=0.787).[17]

Heidari and Gharebaghi investigated the association between NAFLD and DN in 255 patients. A cross-sectional study was conducted on 255 patients with T2DM with a minimum age of 30 years. Fatty liver was diagnosed in patients who consumed very little or no alcohol, and fatty infiltration was seen on USG, with mildly deranged liver enzymes and urine albumin to creatinine ratio showing microalbuminuria. Out of 255 patients, 221 patients (86.66%) had NAFLD and DN was seen in 33% of subjects. NAFLD was not considered a risk factor for diabetic nephropathy.[20]

Kasim et al., in their cross-sectional study on 134 subjects (67 NAFLD subjects and 67 non-NAFLD subjects), found that NAFLD subjects had more proportion of eGFR <60 mL/min/1.73 $m^2$ than non-NAFLD subjects (40.3% vs. 16.4%, P=0.002). Correlation analysis between NAFLD and proteinuria did not show significant results (P=0.051).[21]

**Table 3: Relation between high risk of advanced fibrosis and diabetic nephropathy**

| FIB 4 score | Number of subject | Percentage | Diabetic nephropathy | | | |
|---|---|---|---|---|---|---|
| | | | Present | | Absent | |
| <2.67 | 111 | 81.6 | 37 | 32.4% | 75 | 67.6% |
| ≥2.67 | 25 | 18.4 | 15 | 60.0% | 10 | 40.0% |
| Total | 136 | 100 | 51 | | 85 | |

Chi-square test, z=2.572, P=0.010

A study conducted by Yilmaz et al., concluded that microalbuminuria was present in 16% of the patients with NAFLD.[22]

A study conducted by Sinn et al., found that the incidence of diabetic nephropathy was significantly higher in patients with NAFLD.[23]

Kasapoglu et al., in their study, found that patients with NAFLD had significantly greater albumin creatinine ratio than those without.[24] In a study by Yeung et al., T2DM patients with NASH had more significant albuminuria than those patients without NASH.[25]

### Limitations of the study

This study had several limitations. First, the sample size was small to represent a large disease population. Second, NAFLD and DN are part of the natural history of chronic disease T2DM, a follow-up study could have been more informative. Moreover, due to the paucity of resources, it was difficult to rule out all other causes of fatty liver as well as nephropathy.

## CONCLUSION

NAFLD and DN are the common complications of T2DM. Our study found that NAFLD might be a risk factor for the occurrence of DN and is supported by various previous studies. There is a negative correlation between the risk of advanced fibrosis and the eGFR of the patient. The prevalence of DN is higher in patients with a high risk of advanced fibrosis.

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**Authors Contribution:**
**UMH-** Definition of intellectual content, Concept, design, review of literature, data analysis and interpretation, discussion, manuscript review; **KSK-** Concept, design, study protocol, data analysis and interpretation, discussion, manuscript preparation, manuscript review; **RSS-** Literature survey, Prepared first draft of the manuscript, implementation of the study protocol, data collection, data analysis, manuscript preparation and submission of the article.

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