Original Research Article

**Association of non-alcoholic fatty liver disease with chronic kidney disease in type 2 diabetes mellitus**

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**ABSTRACT**

**Background:** Non-alcoholic fatty liver disease (NAFLD) is closely associated with metabolic syndrome. NAFLD is considered a disease of no consequence. Data on the effect of NAFLD on renal dysfunction in T2DM is sparse. Author aimed to study the association of NAFLD with CKD in Indian T2DM subjects.

**Methods:** In an observational cross-sectional study at Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan, India from February 2017 to March 2018. 197 out of 268 randomly selected type 2 diabetes mellitus (T2DM) subjects were selected for the study after considering the inclusion and exclusion criteria. CKD was defined as estimated GFR <60 ml/min per 1.73 m² and/or albumin to creatinine ratio ≥30 mg/g. NAFLD was diagnosed using ultrasonography. The association between NAFLD and CKD was analyzed using SPSS (version 24.0).

**Results:** On ultrasonography 133 (67.5%) T2DM subjects had NAFLD. Diabetic with NAFLD (133, 67.51%) had significantly more history of hypertension (p 0.006), higher systolic (p 0.03) and diastolic BP (p 0.009), higher BMI (p <0.001), waist circumference (p <0.001), fasting glucose (p 0.03), triglyceride (p<0.001) and higher urinary albumin-to-creatinine ratio (p <0.001). Diabetics with CKD (61, 30.96%), were older (p 0.03), hypertensive (p <0.001) and had higher fasting glucose (p 0.003). Subjects with CKD had a higher prevalence of underlying NAFLD (78.69% vs 62.5%, p 0.03) as compared with diabetics with no CKD. T2DM subjects with NAFLD had more than two times (OR 2.88 (1.1-6.78), p 0.03) the risk of developing CKD after multivariate analysis as compared to subjects without NAFLD.

**Conclusions:** NAFLD is a risk factor for development of CKD in patients of type 2 diabetes mellitus. Screening and early preventive measures may go long way in reducing morbidity.

**Keywords:** CKD, NAFLD, Type 2 diabetes

**INTRODUCTION**

Metabolic syndrome is not only highly prevalent in patients with NAFLD, also increase the risk of developing NAFLD.¹ ¹ NAFLD is regarded as the hepatic manifestation of metabolic syndrome. The spectrum of NAFLD includes nonalcoholic fatty liver (NAFL), nonalcoholic steatohepatitis (NASH), liver cirrhosis and hepatocellular carcinoma.² NAFLD is the most common liver disease in world, affects more than a quarter of the
general population, with an even higher prevalence in patients with diabetes mellitus and metabolic syndrome. An independent relationship of NAFLD with impairment of renal function and mild kidney function damage (MKFD), which occurs before development of chronic kidney disease (CKD) has been suggested. This suggests a possibility of a potential therapeutic window in which occurrence of nephropathy may be prevented or delayed. Indian subjects with NAFLD are significantly different from their Western counterparts in being less obese and having lower frequency of diabetes mellitus and metabolic syndrome. India is projected to be the next capital of diabetes in world. The prevalence of diabetes has increased tenfold from 1.2% to 12.1%, between 1971 and 2000. It is estimated that the prevalence it’s projected to increase from 61.3 million in 2011 to 101.2 million by 2030. There is extremely limited Indian data on association NAFLD and CKD in type 2 diabetes mellitus subjects.

METHODS

In an observational cross-sectional study conducted at Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan, India from February 2017 to March 2018, 268 diagnosed cases of type 2 diabetes mellitus (American Diabetes Association criteria) with age more than 30 years were evaluated. Author excluded patients with ultrasound suggestive of cirrhosis, high liver stiffness measurement (LSM) ≥13 kPa, history of decompensation of liver disease, pregnant females and those with alternate etiology for liver disease. All subjects included in the study were nonalcoholic had negative viral markers (HBsAg, anti-HCV), negative autoimmune hepatitis markers, negative serology for celiac disease and had normal serum ceruloplasmin and normal iron work up. After applying the exclusion criteria 197 type 2 diabetes mellitus (T2DM) subjects were included in the study. Signed informed consent was obtained from all subjects. Patient’s clinical profiles were reviewed, and information was procured pertaining to demographic aspects, past medical history. A detailed anthropometric examination was done.

Diagnosis of hypertension was considered if patient was currently receiving antihypertensive medication or else if the blood pressure was consistently ≥130/85 mmHg.

For diagnosis of CKD, kidney function was estimated using the simplified modification of diet in renal disease (MDRD) study equation.

\[ \text{eGFR} = \frac{175 \times 9 \times (\text{Scr} - 1.234) + 0.179 \times (\text{Age} - 0.79)}{\text{if female, 0.79)}}, \]

Urinary albumin excretion rate (ACR, mg/g) was measured as the albumin to creatinine ratio. CKD was defined as eGFR < 60 ml/min per 1.73 m² and/or ACR ≥30 mg/g (>3 mg/mmol). NAFLD was diagnosed by lack of secondary causes of hepatic fat accumulation such as significant alcohol consumption, long term use of a statogenic medication. Abdominal ultrasonography scan was used for detection of steatosis.

- Grade I- Minimal diffuse increase in hepatic echogenicity with normal visualization of diaphragm and intrahepatic borders.
- Grade II- Moderate diffuse increase in hepatic echogenicity with slightly impaired visualization of intrahepatic vessels and diaphragm.
- Grade III- Marked increase in echogenicity with poor penetration of posterior segment of right lobe of liver and poor or no visualization of hepatic vessels and diaphragm.

Liver stiffness measurement (LSM) was done using transient elastography (Fibroscan).

- >7 kPa- Early fibrosis (≥F2 META VIR stage),
- >8.7 kPa - Advanced fibrosis (≥F3),
- ≥13 kPa- Overt cirrhosis (excluded from the study),

Severity of NAFLD was assessed non-invasively by grading of steatosis on ultrasonography and presence and degree of hepatic fibrosis as measured by transient elastography.

Statistical analysis

SPSS (version 24.0) was used for analyses and calculations. Data was shown as mean±standard deviation (SD) if they had a normal distribution. Median and interquartile range (25-75th percentiles) were used to show continuous variables. Student’s t test was used for continuous variables and Chi-square test was used for categorical variables. Logistic regression analysis was done. Results are expressed as odds ratios (OR) with 95% confidence intervals (95% CI). Three multivariate logistic regression models were performed were model 1 is unadjusted, model 2 adjusted for age, sex, current smoking and physical inactivity and model 3 adjusted for age, sex, current smoking and physical inactivity plus history of hypertension, serum high-density lipoprotein and serum fasting glucose. P values <0.05 were considered statistically significant.

RESULTS

About 268 subjects with T2DM were evaluated, 197 subjects were included in the study in accordance with the inclusion and exclusion criteria. On ultrasonography, 133 (67.5%) T2DM subjects had NAFLD. Study sample was studied in two groups one with NAFLD and T2DM (n=133) and other of T2DM without NAFLD (n=64). Diabetic subjects with NAFLD were significantly associated with history of hypertension (p 0.006), higher systolic (p 0.03) and diastolic BP (p 0.009), higher BMI (p <0.001), waist circumference (p <0.001), fasting glucose (p 0.03), triglyceride (p <0.001) and higher urinary albumin-to-creatinine ratio (p <0.001) (Table 1).
Table 1: Study variables in NAFLD and non NAFLD groups.

| Characteristics                        | NAFLD (N=133) | Non NAFLD (N=64) | p value |
|----------------------------------------|----------------|------------------|---------|
| Age (year)                             | 57.67±9.8      | 59.71±9.4        | 0.8     |
| No. of males (%)                       | 64 (48.12)     | 26 (40.63)       | 0.4     |
| **Clinical characteristics**           |                |                  |         |
| History of coronary heart disease (%)  | 12 (9.02)      | 2 (3.13)         | 0.36    |
| Hypertension (%)                       | 57 (42.86)     | 16 (25)          | 0.006*  |
| Current smoking (%)                    | 18 (13.53)     | 6 (9.38)         | 0.61    |
| Body mass index (kg/m²)                | 26.76±3.62     | 22.84±3.1        | <0.001* |
| Waist circumference (cm)               | 95.35±9.94     | 85.25±8.83       | <0.001* |
| Systolic blood pressure (mm Hg)        | 141.1±17.35    | 132.13±19.47     | 0.03*   |
| Diastolic blood pressure (mm Hg)       | 86.36±10.54    | 78.42±12.65      | 0.009*  |
| Physical inactivity (%)                | 86 (64.66)     | 40 (62.5)        | 0.88    |
| **Laboratory parameters**              |                |                  |         |
| Fasting glucose (mg/dl)                | 118.57±13.23   | 108.44±14.66     | 0.03*   |
| Serum cholesterol (mg/dl)              | 216.52±29.67   | 202.73±26.83     | 0.26    |
| Serum triglyceride (mg/dl)             | 158.11±12.72   | 103.27±13.49     | <0.001* |
| Serum high-density lipoprotein (mg/dl) | 54.78±9.45     | 59.54±9.02       | 0.34    |
| Serum low-density lipoprotein (mg/dl)  | 126.63±19.88   | 120.72±18.93     | 0.58    |
| Estimated glomerular filtration rate (ml/min/1.73 m²) | 94.57±20.86 | 93.32±16.81 | 0.7 |
| Chronic kidney disease (%)             | 47 (35.34)     | 14 (21.87)       | 0.02*   |
| Urinary albumin-to-creatinine ratio (mg/g) | 13.6 (6.2-34.48) | 9.4 (5.2-12.6) | <0.001* |

*p <0.05.

CKD was significantly more common in subjects with NAFLD (35.34% vs 21.87%, p 0.02). Variable like age, sex, current smoking and history of coronary heart disease were equally distributed among two study groups. Subjects with CKD were older (p 0.03), hypertensive (p <0.001), higher fasting glucose (p 0.003). Subjects with CKD had a higher prevalence of underlying NAFLD (78.69% vs 62.5%, p 0.03) as compared with diabetics with no CKD (Table 2).

Table 2: Study variables in CKD and non-CKD participants.

| Characteristics                        | CKD (N=61)     | Non CKD (N=136) | P value |
|----------------------------------------|----------------|-----------------|---------|
| Age (year)                             | 64.34±11.22    | 59.36±9.19      | 0.03*   |
| No. of males (%)                       | 30 (49.18)     | 56 (41.18)      | 0.47    |
| **Clinical characteristics**           |                |                  |         |
| History of coronary heart disease (%)  | 5 (8.2)        | 9 (6.62)        | 0.8     |
| Hypertension (%)                       | 39 (63.93)     | 34 (25)         | <0.001* |
| Current smoking (%)                    | 8 (13.11)      | 16 (11.76)      | 0.7     |
| Body mass index (kg/m²)                | 23.86±4.17     | 24.04±3.92      | 0.85    |
| Waist circumference (cm)               | 92.28±9.47     | 89.26±9.83      | 0.2     |
| Physical inactivity (%)                | 38 (62.3)      | 88 (64.47)      | 0.74    |
| Fasting glucose (mg/dl)                | 124.56±14.54   | 106.38±13.85    | 0.003*  |
| NAFLD (%)                              | 48 (78.69)     | 85 (62.5)       | 0.03*   |

*p<0.05.

Most T2DM subjects had moderate steatosis (55.64%), 41 (30.83%) had mild steatosis and 18 (13.53%) severe steatosis. Severity of hepatic fibrosis was assessed by transient elastography (Fibroscan), no fibrosis (LSM ≤5.7 kPa) in 63 (47.37%) patients, significant fibrosis (LSM >7 kPa) in 45 (33.83%) patients and advanced fibrosis in 25 (18.8%) patients (Table 3). T2DM subjects with NAFLD were at approximately two-fold the risk of CKD.
as compared to subjects without NAFLD. As suggested in model 1-unadjusted (OR 2.14 (1.03-4.54), p 0.046), model 2-adjusted for age, sex, current smoking (2.76 (1.18-5.94), p 0.01), model 3-adjusted for all above plus history of hypertension, serum high-density lipoprotein, serum fasting glucose (2.88 (1.1-6.78), p 0.03) (Table 4).

Table 3: Imaging characteristics of NAFLD subjects.

| Steatosis on ultrasound | NAFLD (N 133) |
|-------------------------|--------------|
| Grade I (Mild)          | 41 (30.83)   |
| Grade II (Moderate)     | 74 (55.64)   |
| Grade III (Severe)      | 18 (13.53)   |

| Fibrosis on transient elastography | |
|-----------------------------------|--|
| No fibrosis (LSM ≤5.7 kPa) n %    | 63 (47.37) |
| Significant (≥F2, LSM >7 kPa) n % | 45 (33.83) |
| Advanced (≥F3, LSM >8.7 kPa) n %  | 25 (18.8) |

Table 4: Association of NAFLD with chronic kidney disease.

| Chronic kidney disease | OR (95% CI) | P value |
|------------------------|-------------|---------|
| Model 1a                | 2.14 (1.03-4.54) | 0.046   |
| Model 2b                | 2.76 (1.18-5.94) | 0.01    |
| Model 3c                | 2.88 (1.1-6.78) | 0.03    |

DISCUSSION

Present observational cross-sectional study specifically aimed at assessing the association between NAFLD with CKD in T2DM subjects. In this study, type 2 diabetics with NAFLD were closely associated with hypertension, obesity and hyperlipidemia, which have consistently been suggested in several studies. Present results were consistent with previous data.15-19 NAFLD and CKD share many common characteristics including visceral obesity, diabetes mellitus, metabolic syndrome and insulin resistance.15 Targher G et al, followed 1760 type 2 diabetes for 6.5 years, suggest that nonalcoholic fatty liver disease is associated with an increased incidence of CKD (hazard ratio 1.49, 95% confidence interval 1.1 to 2.2, P <0.01).15 A Korean study Ahn AL et al, suggested positive association between NAFLD and CKD among population aged 50 years or older.19 In this study, 35.34% T2DM subjects with NAFLD had CKD. Though Indian literature is lacking several cross-sectional studies from the West have suggested the prevalence of CKD in NAFLD patients to be 14% to 47%.20-24 Chang Y et al, found that subjects with NAFLD had a relative risk 2.18 (95% confidence interval (CI), 1.75-2.71) for development of impaired renal function.7 In this study, after multivariate regression analysis adjusting for confounding factors, type 2 diabetics with NAFLD were more than two times prone to develop CKD (OR 2.88 (1.1-6.78), p 0.03). Whereas Sirota IC et al, found no association between NAFLD and CKD in individuals with diabetes.21 The possible mechanisms for the association may be through inflammation and oxidative stress. Several cytokines and inflammatory mediator such as IL-6, TGF-b and TNF-are released in NAFLD22, which promote the progress of the proteinuria.23 The liver-kidney crosstalk in NAFLD includes altered renin-angiotensin system (RAS) and activated protein kinase (AMPK) activation, impaired antioxidant defense, and excessive dietary fructose intake, which affects renal injury through altered lipogenesis and inflammatory response. In turn, kidney reacts by promoting further RAS activation, increased angiotensin II and uric acid production in a vicious cycle leading to fibrosis.24

Diagnosis of NAFLD in this study was based on the presence of hepatic steatosis on ultrasound along with exclusion of other causes of hepatic steatosis. It has a sensitivity of 89% and a specificity of 95% in detecting moderate and severe steatosis, but this sensitivity is reduced when hepatic fat infiltration upon liver biopsy is less than 33%.25,27,28 Author also used transient elastography which is now an established modality for presence of significant fibrosis and the severity of liver disease. But liver biopsy is ideal diagnostic tool for quantification and assessment of progression in NAFLD.29 Exposing clinically asymptomatic subjects to invasive procedure like liver biopsy poses an ethical dilemma.

CONCLUSION

NAFLD increases the risk more than two folds for development of CKD in patients of type 2 diabetes mellitus.

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REFERENCES

1. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. Hepatol. 2016;64(1):73-84.
2. Byrne CD. Targher G NAFLD: a multisystem disease. J Hepatol. 2015;62(1):547-64.
3. Argo CK, Caldwell SH. Epidemiology and natural history of non-alcoholic steatohepatitis. Clin Liver Dis. 2009;13(4):511-31.
4. Younossi ZM, Stepanova M, Afendy M, Fang Y, Younossi Y, Mir H, et al. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. Clin Gastroenterol Hepatol. 2011;9(6):524-30.
5. Starley BQ, Calcagno CJ, Harrison SA. Non alcoholic fatty liver disease and hepatocellular
carcinoma: a weighty connection. Hepatol. 2010;51(5):1820–32.
6. Duseja A, Singh SP, Saraswat VA, Acharya SK, Chawla YK, Chowdhury S, et al. Non-alcoholic fatty liver disease and metabolic syndrome-position paper of the Indian national association for the study of the liver, endocrine society of india, Indian college of cardiology and Indian society of gastroenterology. J Clin Exp Hepatol. 2015;5(1):51–68.
7. Chang Y, Ryu S, Sung E, Woo HY, Oh E, Cha K, et al. Nonalcoholic fatty liver disease predicts chronic kidney disease in non hypertensive and nondiabetic Korean men. Metab. 2008;57(4):569-76.
8. Li G, Shi W, Hu H, Chan Y, Liu L, Yin D. Non-alcoholic fatty liver associated with impairment of kidney function in non-diabetes population. Biochem Med. 2012;22(1):92–9.
9. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Inter Med. 2003;139(2):137-47.
10. Duseja A, Das A, Das R, Dhiman RK, Chawla Y, Bhasali A, et al. The clinicopathological profile of Indian patients with nonalcoholic fatty liver disease (NAFLD) is different from that in the West. Dig Dis Sci. 2007;52(9):2368-74.
11. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diab Care. 2004;27(5):1047-53.
12. Levin A, Stevens PE, Bilous RW, Coresh J, De Francisco AL, De Jong PE, et al. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3(1):1-50.
13. Wilson SR, Rosen IE, Chin-Sang HB, Arenson AM. Fatty infiltration of the liver--an imaging challenge. J Can Assoc Radiol. 1982;33(4):227-32.
14. Musso G, Gambino R, Cassader M, Pagano G. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Ann Med. 2011;43(8):617-49.
15. Targher G, Chonchol M, Bertolini L, Rodella S, Zenari L, Lippi G, et al. Increased risk of CKD among type 2 diabetics with nonalcoholic fatty liver disease. J Am Soc Nephrol. 2008;19(8):1564-70.
16. Targher G, Pichiri I, Zoppini G, Trombetta M, Bonora E. Increased prevalence of chronic kidney disease in patients with Type 1 diabetes and non-alcoholic fatty liver. Diab Med. 2012;29(2):220-6.
17. Zhan YT, Zhang C, Li L, Bi CS, Song X, Zhang ST. Non-alcoholic fatty liver disease is not related to the incidence of diabetic nephropathy in type 2 diabetes. Int J Mol Sci. 2012;13(11):14698-706.
18. Yasui K, Sumida Y, Mori Y, Mitsuyoshi H, Minami M, Itoh Y, et al. Nonalcoholic steatohepatitis and increased risk of chronic kidney disease. Metab. 2011;60(5):735-9.
19. Ahn AL, Choi JK, Kim MN, Kim SA, Oh EJ, Kweon HJ, et al. Non-alcoholic fatty liver disease and chronic kidney disease in Koreans aged 50 years or older. Korean J Family Med. 2013;34(3):199.
20. Hwang ST, Cho YK, Yun JW, Park JH, Kim HJ, Park DI, et al. Impact of non-alcoholic fatty liver disease on microalbuminuria in patients with prediabetes and diabetes. Inter Med J. 2010;40(6):437-42.
21. Sirola JC, McFann K, Targher G, Chonchol M, Jalal DI. Association between nonalcoholic liver disease and chronic kidney disease: an ultrasound analysis from NHANES 1988–1994. Am J Nephrol. 2012;36(5):466-71.
22. Targher G, Chonchol M, Zoppini G, Abaterusso C, Bonora E. Risk of chronic kidney disease in patients with non-alcoholic fatty liver disease: is there a link?. J Hepatol. 2011;54(5):1020-9.
23. Navarro-González JF, Mora C, Muros M, Garcia J, Donate J, Cazana V. Relationship between inflammation and microalbuminuria in prehypertension. J Human Hypertension. 2013;27(2):119.
24. Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with non-alcoholic steatohepatitis. Hepatol. 1999;30(6):1356-62.
25. Adams LA, Angulo P, Lindor KD. Nonalcoholic fatty liver disease. CMAJ. 2005;172(7):899-905.
26. Day CP. Non-alcoholic fatty liver disease: current concepts and management strategies. Clin Med. 2006;6(1):19-25.
27. Tolman KG, Fonseca V, Dalpiaz A, Tan MH. Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. Diab Care. 2007;30(3):734-43.
28. Saadeh S, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterol. 2002;123(3):745-50.
29. Angulo P. Nonalcoholic fatty liver disease. New Eng J Med. 2002;346(16):1221-31.

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