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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 m^2 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.[1-4] 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.[5] 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.[6] 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.[7,8] This suggests a possibility of a potential therapeutic window in which occurrence of nephropathy may be prevented or delayed.[9] 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.[10] 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.[11] 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.

eGFR = (175 x 9 (Scr)-1.234 x (Age)-0.179x (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 m^2 and/or ACR ≥30 mg/g (>3 mg/mmol).[12]

NAFLD was diagnosed by lack of secondary causes of hepatic fat accumulation such as significant alcohol consumption, long term use of a steatogenic medication. Abdominal ultrasonography scan was used for detection of steatosis.[13]

- 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).[14]

- >7 kPa- Early fibrosis (≥F2 METAVIR 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/m^2)	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 m^2)	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/m^2)	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	
Model	**OR (95% CI)**	**P value**
Model 1[a]	2.14 (1.03-4.54)	0.046
Model 2[b]	2.76 (1.18-5.94)	0.01
Model 3[c]	2.88 (1.1-6.78)	0.03

[a]Unadjusted, [b]adjusted for age, sex, current smoking and physical inactivity, [c]adjusted for age, sex, current smoking and physical inactivity plus history of hypertension, serum high-density lipoprotein and serum fasting glucose.

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.[19] Targher G et al, followed 1760 type 2 diabetics 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 JC 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 prognosis 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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