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Original Research Article

Renal morbidity in type 2 diabetes mellitus patients with and without non-alcoholic fatty liver disease

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is independently associated with with prevalent as well as incident cardiovascular diseases (CVD), type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD) and Metabolic syndrome (MetS). Awareness of Renal Morbidity and full understanding is work at progress. Hence it was determined to assess the Renal morbidity as measured by eGFR in patients of T2DM with and without NAFLD.
Methods: Patients with T2DM (ICMR 2018 criteria) with proper informed and valid consent and satisfying essential inclusion and exclusion criteria were screened for presence of fatty liver by ultrasound and were divided into two groups; those with NAFLD and without NAFLD. All patients were investigated for renal morbidity in terms of eGFR using MDRD formula.
Result: Diabetic patients with NAFLD had lower eGFR levels compared to diabetics without NAFLD ($p<0.05$). Patients with diabetes and NAFLD has significantly higher BMI, WHR, duration of diabetes compared to Diabetes patients without NAFLD.
Conclusions: Group of diabetics with NAFLD have to be closely monitoring for serum creatinine levels and BMI is required for early intervention and optimisation of treatment. Elderly patients required more prompt monitoring.

Keywords: NAFLD, T2DM, Renal diseases, Alcohol, Obesity

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is an emerging condition that currently affects about 25 out of every 100 adults world-wide.[1] T2DM, metabolic syndrome (MetS) and Obesity are all associated with NAFLD, which increases the risk of CVD and renal diseases.[2] NAFLD is a multifaceted illness. Patients with progressive NAFLD have an increased risk of both hepatic and extra-hepatic pathologies apart from increased overall morbidity and mortality. Recently there is increased evidence showing that the risk, clinical profile, and burden of NAFLD disease is being altered by genetic, epigenetic differences and life-style changes along with environmental factors, inflammatory states, well-being of intestinal microbes and hormonal balance.[3]

The entity NAFLD has been identified long time ago as a liver related feature in the spectrum of MetS. Steatosis a part of spectrum of NAFLD. Non-alcoholic steatohepatitis (NASH) results due to elevated triglycerides (TG) and their accumulation in the hepatocytes.[4] This may progress to cause hepatic fibrosis followed by cirrhosis and even hepatocellular carcinoma if not treated in time.[5] NAFLD is also considered an independent risk factor for Renal morbidity especially in diabetic patients.[6] Liver is the main organ that is responsible for the regulation of carbohydrate and lipid metabolism and is the main source of inflammatory mediators and cytokines that result in cardiovascular and renal morbidity. A high-fat, low-nutrition, high-sodium diet and a sedentary way of life are also regarded as risk factors for NAFLD. Additionally, CKD can

be induced by the use of nephrotoxic medications, glomerular, infectious, and other disorders, in addition to diabetes mellitus and hypertension.[10] The prevalence of CKD is also influenced by age and sex. Age >65 years and female gender were the two groups with the highest prevalence of CKD, suggesting that elderly women should concentrate on early diagnosis of renal function impairment. The risk of CKD in NAFLD patients is typically predicted by markers of NAFLD severity, elements of metabolic syndrome, and few renal function related markers. Additionally, the risk factors that are each separately linked to the development of CKD and NAFLD should not be disregarded. A thorough analysis of these variables has some influence on how clinical practice should be performed.[11] It has also been suggested that stimulation of the RAAS contributes to the decline in renal function in patients with NAFLD. All RAAS components are produced by fat cells, which also contribute up to 30% of the circulatory angiotensin II levels, which encourages the creation of pro-inflammatory molecules and lipogenesis.[12] On the one hand, it can accelerate the advancement of NAFLD; on the other hand, it can cause ectopic lipid deposition to constrict the glomerular efferent arteriole, which in turn triggers inflammatory and oxidative stress, which in turn eventually results in the formation of glomerular sclerosis.

The complex biochemical interactions between the fat tissue (i.e., adipose tissue), kidney and the liver makes it challenging to differentiate and understand the particular process of CKD seen in patients with NAFLD. Alterations in activation of renin-angiotensin system and deranged anti-oxidant defence mechanisms and deranged lipogenesis provide increasing evidence of liver and kidney interactions and highlight the scope and need for research in this area. Knowing about these mechanisms helps us to identify modifiable risk factors and therapeutic targets for the occurrence and management of NAFLD and CKD.[7] Prevalence of CKD (eGFR<90 ml/min/1.73 m^2) reportedly ranges from 20% to 55% in case of NAFLD whereas it is 5% to 30% in case of non-NAFLD population as reported by Mantovani et al.[8] Cardiovascular morbidities in the same study was put at 21% in patients with T2DM and 40% in T2DM with NAFLD.[9] Presence of NAFLD in T2DM patients has been independently linked to occurrence of CKD and also to higher cardiovascular morbidity as above.

The present study was conducted to evaluate kidney function using estimated glomerular filtration rate (eGFR) using MDRD formula, in patients of (T2DM) with and without NAFLD.

METHODS

The study type was comparative, observational, and cross sectional study conducted at out-patient as well as in-patient department of medicine at Dr. D. Y. Patil medical college hospital and research institute, Kolhapur. All the necessary ethical permissions were taken from the institutional research committee. Data collection was from January 2021 to July 2022. Total 160 patients with T2DM-80 T2DM with NAFLD and 80 T2DM without NAFLD were included in the study. Patients who had T2DM (ICMR guidelines 2018), belonging to both the genders, who had alcohol consumption <10 gm/day for females and 20 gm/day for males and those who revealed fatty liver on ultrasonography (for diagnosis of NAFLD) were included for the study. While, the patients who were known case of acute or CKD, obstructive kidney diseases, CVD, peripheral vascular disease were excluded from the study. Also, patients who had no other liver disease in past 6 months, conditions with accelerated atherosclerosis, autoimmune diseases, those on anti-cancer drugs, immune suppressants, steroids, COX 2 NSAIDS, known malignancy patients, patients with oliguria and polyuria of any etiology other than T2DM, and patient on nephrotoxic drugs were also excluded from this study. Proper valid written informed consent was taken from the patients in their local language. All the study Participants were screened for presence of Fatty liver by Ultrasound and were divided into two groups those; T2DM with NAFLD and T2DM without NAFLD. Renal morbidity was assessed using serum creatinine and eGFR. eGFR was calculated using automated calculation based on equation for modification of diet in renal disease (MDRD) study.

Also, the demographic data like age, sex, gender and Anthropometric data like height, weight, waist-hip ratio, body mass index (BMI) were collected and compiled using Microsoft excel worksheet for analysis.

Table 1: Reference values (cut-off values).

Parameters	Reference values
BMI (Kg/m^2)	>24.99
Hypertension (mm HG)	>140/90
Random blood sugar* (mg/dl)	>200
Fasting blood sugar* (mg/dl)	>126
Post prandial blood sugar* (mg/dl)	>200
HbA1c (gm%)*	>6.5
Estimated glomerular filtration rate (eGFR) (ml)	90-120

*According to the ICMR guidelines for management of type 2 diabetes 2018.

RESULTS

Age

Table 3 presents anthropometric and demographic data of total study participants and also of the two groups (with and without NAFLD).

Significantly higher duration of DM, BMI and WHR was noted in participants with NAFLD as compared to those without NAFLD (all p<0.05) (Table 3).

Table 2: Mean age of both genders in two groups (with and without NAFLD).

Variables	NAFLD	Non-NAFLD	P
Male	57.71±11.23	54.18±12.80	<0.05
Female	57.64±15.11	57.48±12.59	

Table 3: Demographic and anthropometric data of study population.

Variables (Mean ± SD)	Total	NAFLD	Non-NAFLD	P
Age (Years)	55.9± 13.80	57.68± 12.80	54.11± 14.58	0.10
Duration of diabetes	6.96± 4.95	7.88± 5.21	6.02± 4.49	0.02*
Duration of HTN	3.75± 1.71	7.82± 4.88	6.16± 3.46	0.13
SBP	122.5± 12.74	121.5± 12.93	123.5± 12.53	0.32
DBP	77.0± 9.70	77.12± 12.93	76.87± 9.22	0.87
BMI (Kg/m^2)	26.8± 3.11	27.75± 3.35	25.95± 2.55	0.00*
WHR (cm)	89.0± 9.18	1.05± 0.06	1.03± 0.05	0.03*
HBA1C	7.84± 1.46	8.06± 1.50	7.62± 1.39	0.06

*Indicates significant p value (<0.05)

Comparison analysis

Table 4 presents the eGFR of study participants with and without NAFLD in 3 groups; with reduced filtration (<90 ml/kg/1.73 m^2), normal filtration (90-120 ml/kg/1.73 m^2) and hyper filtration (>120 ml/kg/1.73 m^2) groups.

Table 4: Correlation of eGFR category with presence of NAFLD.

Variables	eGFR				P value
	<90	**90 to 120**	**>120**	**Grand total**	
Non NAFLD	13	62	5	80	0.00*
NAFLD	70	10	0	80	
Grand total	83	72	5	160	

*Indicate significant p value (<0.05)

Significant correlation was noted between the presence of NAFLD and the presence of reduced eGFR below 90 ml/min/1.73 m^2 (p=0.00). All patients in the study population with hyper filtration did not have the NAFLD.

DISCUSSION

The prevalence of spectrum of NAFLD in T2DM patients is increasing over the period of time. The common risk factors like sedentary life style, metabolic syndrome and overweight (obesity) might be the reason for the association. There is a greater need for study about these two progressive entities to prevent morbidity and resultant mortality, by finding proper association in order to pave way for early diagnosis and management. The prevalence of NAFLD among patients with type 2 diabetes is 59.67% according to the meta-analysis conducted by Dai et al.[13] This study was done by analysing the results of twenty-four studies involving 35,599 T2DM patients. The usage of ultrasonography modality for diagnosis of NAFLD has been supported in studies conducted by Gomercić et al and Hamaguchi et al in western population with 60 to 94% sensitivity and 84 to 95% specificity.[14] In this study USG was used for detection of fatty liver.

In the present study the patients with T2DM and NAFLD had higher body-mass index than the T2DM patients without NAFLD (Table 1) which was seen in the study of Fan et al conducted in 3203 individuals of Zhejiang city of China who stated that increased BMI is an independent risk factor NAFLD.[15] According to study of Khan A et al there is significant correlation between obesity and occurrence of NAFLD.[16]

In this study the Waist-hip ratio (WHR) is higher in the patients with Diabetes and NAFLD whereas it is slightly lower in patients with diabetes without NAFLD (Table 1). Similar results were seen in the study of Lin et al conducted in Japan, in 14,125 population taken from a health programme called “health dock”.[17]

The T2DM patients in this study with NAFLD had significantly lower values of eGFR implicating increased renal morbidity compared to patients without NAFLD. This was similarly shown by Chinnadurai et al European population with prevalence of 24-69.5%.[18] A study conducted by Hsieh et al in 96 Hispanic patients provides that there is association of impaired eGFR with increased fibrosis score in patients with NAFLD.[19]

The study which was conducted in the Middle-East by Al-Ozairi et al showed that there is 44% of prevalence of CKD in Diabetic patients.[20] It was suggested in study conducted by Byrne et al that the NAFLD itself is a non-dependent factor that contributes to the prevalence of CKD.[21] In that study, the T2DM was taken as a confounding factor. In this study the prevalence of renal morbidity in Diabetes with NAFLD patients is 87.5% (Table 2). Hence it suggests that renal morbidity is contributed by presence of both Diabetes and NAFLD.

It is evident that there is higher risk for Renal morbidity in patients those who have both, diabetes and NAFLD. This study emphasises in need for close monitoring, prevention strategies, early diagnosis and management of the risk factors so that the progression of renal morbidity can be controlled preventing the mortality.

Limitations

Study was conducted only at one centre. Not a multicentric study with variable population. Microalbuminuria can be better and earlier indicator of the renal morbidity in T2DM.

CONCLUSION

There is significant association between renal morbidity in diabetic patients with NAFLD compared to those without NAFLD. Results of this study support stricter implementation of prevention and monitoring efforts to pre-empt renal morbidity in T2DM patients with NAFLD as compared to those T2DM patients without NAFLD.

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