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A CONTINUED STUDY TO DERTERMINE THE ASSOCIATION BETWEEN CHRONIC KIDNEY DISEASE AND NON-ALCOHALIC FATTY LIVER DISEASE AND ITS EFFECT ON eGFR

Dr. Arvind Gupta	Professor, Department of Internal Medicine, Motilal Nehru Medical College, Prayagraj, UP, India.
Dr. Poonam Gupta	Professor and Head of department of Internal Medicine, Motilal Nehru Medical College, Prayagraj, UP, India.
Dr. Anubha Srivastava	Associate Professor, Department of Internal Medicine, Motilal Nehru Medical College, Prayagraj, UP, India.
Dr. Amit Kumar Panday*	Junior Resident, Department of Internal Medicine, Motilal Nehru Medical College, Prayagraj, UP, India. *Corresponding Author

ABSTRACT

Background: The present study was conduct in Motilal Nehru Medical College, Swaroop Rani Nehru Hospital Prayagraj, a tertiary care center and data was collected over a period from January 2019 to April 2020. All 78 patients of CKD attending OPD & IPD of General Medicine and Nephrology, diagnosed by suggestive symptoms and confirmed by physical examination and laboratory investigations were taken , Among the subjects, those having NAFLD were grouped as cases. Patients of Chronic Kidney disease not having NAFLD were grouped as controls.

Aim & Objective: To study the prevalence of NAFLD in patients of CKD and establish the association between NAFLD and CKD by studying the effect of NAFLD on eGFR.

Methodology: This was a 16 month case control study. Total 78 patients with age 18-65 years , Either sex with Chronic kidney disease diagnosed by USG, KFT, physical examination and having NAFLD Patients with known diagnosis of metabolic syndrome, diabetes and/or hypothyroidism. Those on hepatotoxic medication (amiodarone, barbiturates, glucocorticoids, etc.). The data so collected was entered into computer using Microsoft Excel 2013 software and was subjected to statistical analysis.

Result : The findings of present study thus reaffirm the observations of previous studies that highlight a high prevalence of NAFLD in CKD patients and link it to the deranged metabolic factors. In present study we could not found a convincing evidence supporting a relationship between NAFLD and its severity with progression of CKD, probably owing to three major factors – first, owing to Discussion 71 limitation of study population in only CKD stage 3 and secondly, owing to absence of retrospective data tracing the time of development of NAFLD in these patients and thirdly, inability to carry out long-time follow-up of patients. In present study, though minor changes in eGFR values in patients were seen, however, during the limited period of follow-up no shift from Stage 3 to other stages of CKD was observed. All the patients were regular in follow-up and had a good medical compliance and in general did not show a phenomenal deterioration in renal function within the short span of study. Keeping in view these limitations, further studies are recommended on a larger sample size with inclusion of patients from different stages of CKD spanning over a longer duration of follow-up to see whether NAFLD presence and its severity has a relationship with long-term progression of CKD.

Conclusion: The present study showed that, CKD patients had a high prevalence of NAFLD. The findings also show that FIB-4 scores are useful noninvasive methods for detection of NAFLD in CKD patients. The findings showed a possible significant association between NAFLD and lower eGFR rates. One of the limitations of the present study was presence of only Stage 3 CKD patients, owing to which the linear correlations between eGFR and NAFLD severity could not be assessed properly. Further studies on larger sample size with inclusion of patients with other CKD stages too are recommended.

KEYWORDS : chronic kidney disease (CKD), glomerular filtration rate (GFR), end-stage renal disease (ESRD), Non-Alcoholic Fatty Liver Disease (NAFLD).

INTRODUCTION

Kidney is one of the most important organs of body. It plays an important role in homeostasis by maintaining overall fluid balance, regulation and filtration of minerals from body, filtering waste and toxic material from ingested food and creating hormones that play an important role in production of red blood cells, promotion of bone health and regulation of blood pressure. The relationship of kidney with heart, lung, gastrointestinal system and brain is well established[1]. Of the two, chronic kidney disease (CKD) because of its long-term impact has gained high attention. Globally, its prevalence is reported to range from 11 to 13% with majority in Stage 3 of disease[2] , in the United States has risen markedly in the past few decades[3]. Globally, both the prevalence as well as mortality associated with CKD is showing an increasing trend since the year 1990, showing an increase of 29.3% in all-stage prevalence and 41.5% increase in mortality[4].

Chronic kidney disease (CKD) is the new and universally accepted term for the condition earlier known as chronic renal failure (CRF). It is a term used to denote a chronic decay in renal function. Technically, it is defined as either kidney damage or a decreased glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 for at least 3 months[7,8] . It is induced by a progressive loss of nephrons and reduction of functional renal mass which after reaching a certain threshold leads to initiation of a process of irreversible sclerosis in remaining nephrons that leads to a progressive decline in the GFR[9].

As per KDIGO guidelines, chronic kidney disease can be categorized into five stages depending upon the declining glomerular filteration rate. As per the guidelines, individuals with GFR ≥90 ml/min/1.73 m^2 are categorized into first stage where the kidney functions normally, 60–89 ml/min/1.73 m^2 falls in the second stage with mildly decreased function. The third stage is sub divided into two; people with 45–59 ml/min/1.73□□m^2 and 30–44 ml/min/1.73 m^2, where the GFR is mildly to severely decreased. In stage 4, the GFR decreases to 15– 29 ml/min/1.73□□m^2 and in the fifth stage (GFR) kidney fails to function. Stages 4 and 5 together are also termed as End-Stage disease. The early stages are asymptomatic and

the end-stage is treated by dialysis or transplantation[10]. Diabetes, hypertension, cardiovascular diseases (CVD), and cigarette smoking are the common risk factors of chronic kidney disease (CKD)[11,12] . An evaluation of these risk factors shows similarity of these risk factors with risk factors of other lifestyle disorders too.

Changing demographics, increasing affluence and sedentary lifestyles have led to the increasing prevalence of non-communicable lifestyle diseases like diabetes mellitus (DM), obesity, hypertension (HTN), cardiovascular disease (CVD) and chronic kidney disease (CKD), even in developing countries like India. It is estimated that 80% of chronic disease deaths now occur in low- and middleincome countries[13]. CKD is important among this group as, apart from its own morbidity, mortality and high risk for progression to end-stage renal disease (ESRD), it has also been found to be an important independent risk factor for CVD[14,15] .

Owing to a strong physiological and pathological link between the liver and the kidney. Kidney disease, vis-à-vis, liver disease have a mutual impact on the other organ too. Chronic kidney disease, being the most important kidney disease, which is also considered to be a lifestyle disease, has shown relationship with liver diseases, particularly Non-Alcoholic Fatty Liver Disease (NAFLD), which is considered to be the most common cause of chronic liver disease, as an interaction of physiological and pathological relationship between liver and kidney. Moreover, NAFLD has shown a number of similarities with chronic liver disease. Like CKD, NAFLD also shares the inflammatory disorders as the dominant factor playing role in pathogenesis. Moreover, obesity, renin-angiotensin system, and dysregulation of fructose metabolism and lipogenesis have been recognized as the other common factors playing a role in the development of both disorders[25]. Like CKD, NAFLD has also been shown to be responsible for endothelial dysfunction and an increased risk of CVD26,[27,28] . the correlation between CKD severity and NAFLD stage has also shown a considerable difference across different studies . Hence it is important to study the Introduction 5 relationship between CKD and NAFLD in local perspective and to understand as to how ethnic, geographical, dietary, lifestyle and other factors influence the relationship between CKD and NAFLD in our population.

MATERIAL AND METHODOLOGY

STUDY DESIGN- This Cohort study was conducted in SRN Hospital, MLN Medical College, Allahabad, U.P. India.

CASES: All the patients of CKD attending OPD & IPD of Gen. Medicine and Nephrology, diagnosed by suggestive symptoms and confirmed by physical examination and laboratory investigations were taken as thesis subjects. Among the subjects, those having NAFLD were grouped as cases.

CONTROLS - Patients of Chronic Kidney disease not having NAFLD were grouped as controls.

INCLUSION CRITERIA - Age 18-65 years , Either sex with Chronic kidney disease diagnosed by USG, KFT, physical examination and having NAFLD.

EXCLUSION CRITERIA - Patients with known diagnosis of metabolic syndrome, diabetes and/or hypothyroidism. Those on hepatotoxic medication (amiodarone, barbiturates, glucocorticoids, etc.).

METHODS - The clinical study was started after obtaining Institutional Ethical Committee approval. All the patients fulfilling the inclusion criteria were invited to participate in the study. Only those providing informed consent and not falling in exclusion criteria were enrolled in the study. After enrolment, demographic information was obtained, personal habits were enquired and presenting signs and symptoms were noted. All the patients underwent anti HCV and HBsAg antigen profiling to rule out viral hepatitis. Body weight and height were measured and body mass index was calculated. Blood pressure measurements were done. Subsequent to this, a 2 ml blood sample was obtained under aseptic conditions for hematological assessment (Hb, TLC, platelet count), liver function tests (ALT, AST), Renal function assessment (S. creatinine) and HbA1c. Estimated glomerular filteration rates (eGFR) were calculated. Urinary samples were analyzed for proteinuria. Liver fibrosis was assessed using FIB-4 score. FIB-4 scores were calculated using the following formula75: FIB-4 = Age (years) x AST (U/L) / Platelet count (109/L) x ALT (U/L) All the patients thereafter underwent abdominal ultrasound for diagnosis of NAFLD. Presence and grade of NAFLD was noted. The patients were subsequently followed up at 1, 3 and 6 months intervals. Changes in eGFR and S. creatinine levels were assessed.

The data so collected was entered into computer using Microsoft Excel 2013 software and was subjected to statistical analysis.

RESULTS

A total of 78 patients were enrolled in the study. Age of these patients ranged from 36 to 65 years with a mean age of 51.19±6.34 years. Majority of patients were aged 51-60 years (53.8%) followed by those aged 41-50 years (34.6%), 60 years (5.1%) respectively. There was a dominance of males (69.2%) over females (30.8%). Sex ratio of the study population was 2.25.

BMI of patients ranged from 14.7 to 35.8 kg/m^2. Mean BMI of study population was 24.81±3.41 kg/m2 . Mean systolic and diastolic blood pressure values were 138.38±6.68 and 94.08±5.23 mmHg respectively. Hemoglobin levels ranged from 8.7 to 14.9 g/dl with a mean of 10.89±1.54 g/dl. Mean TLC and platelet counts were 8.07±1.54 thousands/cumm and 2.64±0.64 lacs/cumm respectively. Mean AST and ALT levels of study population were 46.00±21.46 and 41.10±19.05 IU/L respectively. Serum creatinine levels ranged from 1.12 to 2.20 mg/dl and eGFR values ranged from 34.1 to 4.17 ml/min/1.73 m2 . Mean Serum creatinine and eGFR levels were 1.50±0.19 mg/dl and 48.76±4.17 ml/min/1.73 m2 respectively. A total of 32 (41%) patients had proteinuria. Hepato-renal impairment as measured by FIB-4 scores ranged from 0.54 to 2.86 with a mean of 1.52±0.67. HbA1c levels ranged from 4.9 to 6.8% with a mean of 6.04±0.36%, A total of 50 (64.1%) patients had non-alcoholic fatty liver disease (NAFLD). Out of these, maximum (n=22/50; 44%) had Grade 2, followed by Grade 3 (n=17; 34%) and Grade 1 (n=11; 22%) NAFLD.

Table 1: BMI, Hemodynamic, Hematological and Biochemical Profile of patients and USG finding

SN	Characteristic	Mean	SD	Minimum	Maximum
Body mass index					
1.	BMI (kg/m^2)	24.81	3.41	14.7	35.8
Hemodynamic					
2.	SBP (mmHg)	138.38	6.68	128	156
3.	DBP (mmHg)	94.08	5.23	84	106
Hematological					
4.	Hb (g/dl)	10.89	1.28	8.7	14.9
5.	TLC (Thousands/cumm)	8.07	1.54	1.3	10.8
6.	Platelet counts (lacs/cumm)	2.64	0.64	1.42	3.94
Liver functions					
7.	AST (IU/L)	46.00	21.46	24	98
8.	ALT (IU/L)	41.10	19.05	16	88
Renal Functions (All were stage 3 CKD)					
9.	S. creatinine (mg/dl)	1.50	0.19	1.12	2.20
10.	eGFR (ml/min/1.73 m^2)	48.76	4.17	34.1	56.6
11.	Proteinuria	32 (41.0%)			
Hepato-renal Impairment (FIB-4)					
12.	FIB-4	1.52	0.67	0.54	2.86
Glycemic Profile					
13.	HbA_{1c} (%)	6.04	0.36	4.9	6.8
USG Abdomen for NAFLD					
14.	NAFLD	50 (64.1%)			
	Grade 1	11			
	Grade 2	22			
	Grade 3	17			

Table 2: Clinical course of renal functions

SN	Follow-up	Mean	SD	Change from baseline			Statistical significance	
				Mean	SD	% Change	't'	'p'
eGFR (ml/min/1.73 m²)								
1.	Baseline	48.76	4.17					
2.	FU 1	48.32	5.67	-0.44	5.30	-0.90	0.731	0.467
3.	FU 2	47.96	5.14	-0.80	4.82	-1.64	1.471	0.145
4.	FU 3	49.34	12.22	0.58	12.18	1.19	0.419	0.676
S. Creatinine (mg/dl)								
1.	Baseline	1.504	0.193					
2.	FU 1	1.539	0.227	0.035	0.179	2.33	1.73	0.089
3.	FU 2	1.524	0.181	0.019	0.161	1.26	1.06	0.291
4.	FU 3	1.573	0.417	0.069	0.426	4.59	1.42	0.159

Both systolic and diastolic blood pressure values of NAFLD patients were significantly higher as compared to non-NAFLD patients ($p < 0.05$). Mean hemoglobin levels and platelet counts were significantly lower while mean TLC levels were significantly higher in NAFLD as compared to non-NAFLD patients ($p<0.001$). Mean Serum AST levels were significantly higher in NAFLD as compared to nonNAFLD patients ($p<0.001$), however, there was no significant difference between two groups with respect to Serum ALT levels ($p=0.972$).

Serum creatinine levels were significantly higher in NAFLD cases (1.55±0.21 mg/dl) as compared to non-NAFLD cases (1.42±0.12 mg/dl) ($p=0.003$). Mean eGFR levels of NAFLD cases were lower (48.07±4.47 ml/min/1.73 m2) as compared to that of non-NAFLD patients (50.00±3.30 ml/min/1.73 m2), the difference between two groups was marginally non-significant ($p=0.051$). Mean FIB-4 score of NAFLD patients was 1.92±0.47 which was significantly higher as compared to that of non-NAFLD patients (0.80±0.15) ($p <0.001$). Though mean HbA1c levels of NAFLD cases were higher (6.08±0.34%) as compared to non-NAFLD patients (5.98±0.40%) yet this difference was not significant statistically ($p=0.273$).

DISCUSSION

Chronic kidney disease is a condition in which damage to kidney takes place over a prolonged period of time. Racial, genetic and lifestyle factors play an important role in causation of chronic kidney disease. A number of chronic health conditions like diabetes, hypertension and dyslipidemia also play an important role in the pathogenesis of chronic kidney disease76. Chronic kidney disease, is not limited to kidney only, but is associated with a number of serious complications, viz., cardiovascular disease, hyperlipidemia, anemia and metabolic bone disease77 . CKD not only impairs the renal function but also affects functioning of other organs. Apart from others, CKD has also been shown to affect the functioning of liver. The frequency of liver diseases is quite high in patients of CKD78 . Conversely, kidney disease is a common complication in patients with liver disease79 . In view of this interrelationship between chronic kidney disease and liver disease, the prevalence of non-alcoholic fatty liver disease, a metabolic disorder, seems to be of high interest and enquiry among CKD patients.

Hence, the present study was carried out with an aim to study the prevalence of NAFLD in patients of CKD and to establish the association between NAFLD and CKD by studying the effect of NAFLD on eGFR.

For this purpose, a total of 78 CKD patients were enrolled in the study. All the patients had Stage 3 CKD (eGFR in 30-60 ml/hr/1.73 m2 range). The prevalence of NAFLD in study population was 64.1%. The prevalence of NAFLD in CKD patients has shown a considerable variability in literature.

In present study, it was found that older age, symptomatic manifestation, obesity (higher BMI), hypertension (increased systolic and diastolic blood pressure), low hemoglobin and platelet count, inflammatory activity (as indicated by higher mean TLC), higher AST, S. creatinine and FIB-4 scores and proteinuria were associated with NAFLD. NAFLD patients also had lower mean eGFR values as compared to non-NAFLD patients at baseline and all the follow-up intervals.

In present study, mean FIB-4 scores of NAFLD patients were found to be significantly higher as compared to non-NAFLD patients. However, no significant difference in mean FIB-4 scores could be seen among different grades of NAFLD. This finding in turn indicates that there is no absolute correlation between pathological changes (fibrosis) and functional changes in NAFLD. This finding has also been reported previously with presence of normal liver function tests in NAFLD patients with T2DM82. The findings imply that functional and pathological parameters imply changes of different type in NAFLD patients. Nevertheless, in present study we found that though FIB-4 scores did not correlate linearly with different grades within NAFLD patients, however, FIB-4 score >1.13 were found to be 100% sensitive and 100% specific in diagnosis of NAFLD.

The findings of present study thus reaffirm the observations of previous studies that highlight a high prevalence of NAFLD in CKD patients and link it to the deranged metabolic factors. In present study we could not found a convincing evidence supporting a relationship between NAFLD and its severity with progression of CKD, probably owing to three major factors – first, owing to Discussion 71 limitation of study population in only CKD stage 3 and secondly, owing to absence of retrospective data tracing the time of development of NAFLD in these patients and thirdly, inability to carry out long-time follow-up of patients. In present study, though minor changes in eGFR values in patients were seen, however, during the limited period of follow-up no shift from Stage 3 to other stages of CKD was observed. All the patients were regular in follow-up and had a good medical compliance and in general did not show a phenomenal deterioration in renal function within the short span of study. Keeping in view these limitations, further studies are recommended on a larger sample size with inclusion of patients from different stages of CKD spanning over a longer duration of follow-up to see whether NAFLD presence and its severity has a relationship with long-term progression of CKD.

CONCLUSION

The present study was carried out with an aim to determine the association between chronic kidney disease and non-alcoholic fatty liver disease. For this purpose, a total of 78 CKD patients were enrolled in the study and were subjected to thorough clinical, hematological, biochemical and USG assessment. Age of patients enrolled in the study ranged from 36 to 65 years. Mean age of patients was 51.19±6.34 years. Majority of patients were aged 51-60 years. All the patients had Grade 3 CKD (eGFR in 30-60 ml/hr/1.73 m2) range. Mean eGFR and serum creatinine levels at admission were 48.76±4.17 ml/hr/1.73 m2 and 1.50±0.19 mg/dl respectively. A total of 32 (41%) had proteinuria. NAFLD was diagnosed in 50 (64.1%) patients. Out of these, maximum (n=22/50; 44%) had Grade 2, followed by Grade 3 (n=17; 34%) and Grade 1 (n=11; 22%) NAFLD. Mean FIB-4 scores of study population were 1.52±0.67. No significant change in eGFR and S. creatinine levels were observed at different follow-up intervals. Baseline eGFR levels were lower in NAFLD as compared to non-NAFLD patients but the difference was marginally non-significant ($p=0.051$), however, at all the three

subsequent follow-up intervals, mean eGFR of NAFLD patients were significantly lower as compared to that of nonNAFLD patients. However, mean S. creatinine levels of NAFLD patients were significantly lower as compared to non-NAFLD patients at baseline as well as on all the three follow-up intervals. Mean eGFR levels of non-NAFLD patients were 49.99±3.30 ml/hr/1.73 m2 as compared to 45.82±7.02, 49.30±3.20 and 47.94±3.37 ml/hr/1.73 m2 respectively in Grades 1, 2 and 3 NAFLD patients. Statistically, intergroup differences were significant. It was seen that non-NAFLD patients had significantly higher mean values as compared to Grade 1 NAFLD patients. None of the other between group comparisons were significant.

The findings of present study showed that, CKD patients had a high prevalence of NAFLD. The findings also show that FIB-4 scores are useful noninvasive methods for detection of NAFLD in CKD patients. The findings showed a possible significant association between NAFLD and lower eGFR rates. One of the limitations of the present study was presence of only Stage 3 CKD patients, owing to which the linear correlations between eGFR and NAFLD severity could not be assessed properly. Further studies on larger sample size with inclusion of patients with other CKD stages too are recommended.

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