ORIGINAL ARTICLE

ASSOCIATION OF LOW GFR AND NON-ALCOHOLIC HEPATOSTEATOSIS ON FIBROSCAN OF LIVER

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Background: Chronic kidney disease (CKD) and non-alcoholic fatty liver disease (NAFLD) are becoming a health concern, owing to their increasing incidence and prevalence. Both entities are linked to poor outcomes and increased costs, hence greatly impacting the healthcare system and economy. Therefore, it is imperative to establish the link between the two, so as to prevent disease progression and complications. **Methods:** The study was an observational retrospective study done in Karachi, from November 2021 to May 2022. It was conducted on 255 patients who were diagnosed with NAFLD, and the presence of CKD was then determined by calculating their GFRs. **Results:** Out of the 255 patients diagnosed with hepatosteatosis, 76% had a normal GFR, 20% had a mild decrease and 4% were noted to have a moderate reduction in their GFR. When cross-tabulated with CAP score, it was found that 28% had S1 grade steatosis, out of which 85% had a normal GFR, 13% had a mild decrease and 2% had a moderate decrease in GFR. 22% had S2 grade steatosis, out of which 76% had a normal GFR, 18% had a mild decrease and 6% had a moderate reduction in GFR. 50% patients had S3 grade steatosis, out of which 70% had a normal GFR, 25% had a mild decrease and 5% had a moderate reduction in GFR. **Conclusion:** There is an association present between NAFLD and the development of low GFR. Therefore, it is important that patients diagnosed with NAFLD are regularly screened for CKD, so as to prevent its development and complications.

Keywords: Chronic kidney disease; Liver steatosis; Nonalcoholic fatty liver disease; NAFLD

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INTRODUCTION

Chronic kidney disease (CKD) is defined as decreased glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 or kidney damage for at least 3 months.[1] There has been an increase in the worldwide prevalence of CKD which is associated with an increase in associated risk factors like hypertension, diabetes and aging.[2] Therefore, CKD has become a major public health issue and is posing a substantial burden on the costs of healthcare.[3] Moreover, CKD poses an increased risk for all-cause mortality as well as cardiovascular diseases (CVDs).[2]

Nonalcoholic fatty liver disease (NAFLD) is defined as fat accumulation (>5%) in the hepatic cells without the excessive intake of alcohol or other causes of liver disease including viral hepatitis, drug-induced or autoimmune hepatitis. The spectrum of NAFLD varies histologically from simple steatosis to non-alcoholic steatohepatitis (NASH), liver fibrosis, and cirrhosis.[1] It is now widely accepted that NAFLD involves a number of extrahepatic organs, and is thus a multi-systemic disease entity, especially involving the kidney and the heart, particularly due to the pathogenic cross-talk between inflamed adipose tissue and the liver.[4] The initiation of extrahepatic diseases, including CVD and CKD, has been reported to be increased by NAFLD.[5] In recent studies, an increased prevalence and incidence of CKD is associated with NAFLD.[6]

Owing to their rising incidence and prevalence, NAFLD and CKD have become major public health problems and are associated with poor outcomes and high costs. CKD affects up to ~10–15%, and NAFLD affects up to ~25–30% of the adult population globally.[1] Since NAFLD and CKD often occur along with other metabolic conditions, such as metabolic syndrome or type 2 diabetes, and are very common diseases, trying to find out what impact NAFLD has on the risk of incident CKD presents a question for researchers.[1]

The similarity in risk factors for NAFLD and CKD including obesity and diabetes make it difficult to delineate a direct association between the diagnosis of fatty liver disease and the development and progression of renal disease. Inflammation and oxidative stress are suggested to be the key factors involved in the inflammatory mechanisms and pathways linking NAFLD to CKD and responsible for both the pathogenesis and the progression of CKD in patients with NAFLD.[7] It could also be attributed to co-existing co-morbidities, for instance, uncontrolled

DM which can in itself lead to glomerulosclerosis and the development of diabetic nephropathy. Other risk factors might include the presence of obesity and hypertension. These add to the stress on kidney and activate the renin angiontensin aldosterone system (RAAS). Chronic activation of RAAS leads to endothelial dysfunction and further progression to CKD. Many large cross-sectional hospital-based and population-based studies involving both diabetic patients and non-diabetic patients have shown that the prevalence of CKD is increased in patients with NAFLD.[8] The establishment of a link between liver and kidney injury would help with the earlier identification of CKD, and allow for the treatment selection targeting both kidney and liver disease, with potentially relevant implications for preventive and therapeutic measures.[9] The ultimate aim of identifying patients with definite but also with early CKD would be to prevent the progression of disease and to minimize complications, in order to improve quality of life and promote survival rates.[10]

Keeping in view the aforementioned considerations, this study was done to determine the presence of CKD in patients diagnosed with NAFLD.

MATERIAL AND METHODS

It is relevant to discuss the stages of CKD so as to categorise the patients in their respective degree of renal function. CAP score is discussed so as to divide the patients according to their degree of steatosis and then correlate it with the renal function. BMI was evaluated to see if it is a risk factor for the development of CKD in patients with NAFLD.

According to the guidelines of the National Kidney foundation, a normal GFR was taken to be >90 mL/minute. Mild reduction in GFR was taken to be between 60–89 mL/min and this also indicated Stage II kidney disease. A GFR of 30–59 mL/min was taken to be as moderate reduction in GFR, and Stage III kidney disease.

CAP (controlled attenuation parameter) score is a measurement of fat accumulation in the liver, seen on a fibroscan. Its unit of measurement is in decibels/ meter (Db/m). It ranges from 100–400 dB/m. It is divided into 3 grades:

- S1 grade steatosis or less than 33% fatty change in liver.
- The second category indicates an S2 grade steatosis with a fatty change of 34–66% seen in the liver.
- The third category indicates an S3 grade steatosis, with greater than 67% fatty change seen in the liver.

Body mass index (BMI) is based on height and weight and is a measure of body fat, and applies to adult women and men. It is measured in kg/m2.

The study was an observational retrospective study done by seeing the records of the patients at the Ziauddin University Hospital, Clifton Campus, Karachi. This hospital caters to a large number of people from Karachi, as well as from other parts of the province. The study duration was from November 2021 to May 2022. A total of 255 patients were part of the study. All patient records visiting the Hepatology OPD, in this time duration were checked. A proforma was made which included patient's demographics, BMI, liver and renal function tests, grade of renal failure, US findings, liver fibrosis and steatosis score on fibroscan, and severity of steatosis on fibroscan. Their GFR level was calculated using the MDRD equation. The study was approved by the Ethical Review Committee and Institutional Review Board. Given the observational nature of the study, informed consent was waived however confidentially was maintained throughout the study.

All patients who were already diagnosed with NAFLD were included in the study, and their GFR was calculated to see the presence of chronic kidney disease. All patients included in the study were aged 18 years and above.

Patients already diagnosed with CKD prior to NAFLD diagnosis were not included in the study.
The data was then entered in the SPSS version 20.

Age and gender frequencies were calculated. Then the frequency of patients falling in each category of GFR (that is patients with either normal GFR or mild or moderate reduction in GFR) was calculated. Subsequently, the GFR categories were cross-tabulated with the CAP score and BMI.

RESULTS

A total of 255 patients were part of the study, with maximum age recorded at 78 years and minimum recorded at 18 years. Almost 63% of the patients were male and 37% were females.

A total of 255 patients were included in the study. All patients were formally diagnosed with NAFLD based on liver fibrosis and steatosis score on fibroscan. Their GFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation. The Modification of Diet in Renal Disease (MDRD) Study equation, has been accepted widely, and when a measurement of serum creatinine is required, an estimation of GFR using this equation is reported by most clinical laboratories worldwide.[11] The patients were then divided into 3 categories having either a normal GFR, or as having kidney disease with mild or a moderate decrease in GFR. Out of 255 patients, 193 were found to have a normal GFR, or almost 76% of the patients were found to have a normal GFR. Fifty-two patients or 20% of the patients were found to have a mild decrease in GFR or Stage II

kidney disease. On the other hand, 10 patients or almost 4% of the patients were found to have a moderate reduction in GFR, indicating the presence of Stage III kidney disease.

In this study, the CAP score was divided into three categories. The first category included those patients who fell under the range of 247–279, and it indicated S1 grade steatosis. The second category ranged from 280–299, ad indicated S2 grade steatosis. The third category has a CAP score of 300 or more. The CAP score and GFR of each patient were then cross-tabulated.

A total of 71 patients (28%) had S1 grade steatosis or a CAP score of 247–279. Out of these, 61 patients (85%) had a normal GFR, 9 patients (13%) had a mild decrease in GFR and 1 patient (2%) had a moderate decrease in GFR. A total of 55 patients (22%) fell under the second category of CAP score, ranging from 280–299. Forty-two of these patients or 76% had a normal GFR, 10 patients or 18% had a mild decrease in GFR and 3 patients or 6% had a moderate reduction in GFR. On the other hand, A total of 129 patients (50%) had a CAP score of 300 or more, out of which 90 patients (70%) had a normal GFR, whereas 33 patients (25%) had a mild decrease in GFR and 6 (5%) had a moderate decrease in their GFR.

In this study, BMI was divided into 4 categories. Fort-five patients had a BMI of upto 25 kg/m^2, out of which 36 patients had a normal GFR, 7 patients had a mild decrease in GFR and 2 patients had a moderate decrease in GFR. 86 patients had a BMI ranging from 25.1 to 30 kg/m^2, out of which 66 patients had a normal GFR, 16 of these had a mild reduction in their GFR and 4 patients had a moderate decrease in GFR. A total of 76 patients had a BMI ranging from 30.1 to 35 kg/m^2, out of which 53 patients had a normal GFR, 20 patients had a mild decrease in GFR, and 3 of them had a moderate decrease in their GFR. 48 patients had a BMI of 35.2 kg/m^2 or more. Thirty-eight of these patients had a normal GFR, 9 patients had a mild reduction in their GFR and 1 patient had a moderate decrease in GFR.

DISCUSSION

The presence of NAFLD was determined using the liver function tests, and the degree of steatosis seen on fibroscan. Based on the data presented above, it is seen that almost 24% of the patients or 62/255 patients diagnosed with NAFLD had developed CKD, independent of other risk factors. Around 20% of the patients developed a mild reduction in their GFR, or CKD stage II. Whereas 3.9% of the patients developed CKD stage III or a moderate reduction in GFR. Furthermore, it was seen that with a rising CAP Score, the percentage of fatty change in the liver increased, and the number of people having reduced GFR also increased. For instance, out of the 52 patients diagnosed with CKD stage II, 9 of them had an S1 grade steatosis, 10 of them had an S2 grade steatosis whereas 33 of them had an S3 grade steatosis. Similarly, out of the 10 patients diagnosed with CKD stage III, 6 of them had an S3 grade steatosis. Therefore, we deduced that as the degree of steatosis increased, the number of relative patients having a reduced GFR also increased.

A study conducted in Pakistan also showed the impact of fasting lipid profile on CKD patients.[12] A prospective cohort study Shen ZW *et al.* conducted in China in 2017 also showed that NAFLD (that is top quartile of serum GGT levels) was independently associated with an increased risk of incident CKD (aHR 1.33, 95% CI 1.07–1.64). Similarly, Wilechansky RM *et al.*, United States, 2019, also showed that liver fat (measured by the average liver attenuation on CT) was significantly associated with incident microalbuminuria and CKD in age- and sex-adjusted models.[1] A study conducted in Japan in 2020 also established that around 13% of NAFLD patients developed CKD.[13] Similarly, a study in Taiwan in 2020 established that 17% NAFLD patients developed incident CKD.[14]

Studies have shown NAFLD as an independent risk factor and contributes to the development of CKD.[15] BMI was also evaluated. It shows that the majority of patients having a mild reduction in GFR or a stage II kidney disease, also had an increased BMI. Out of the 52 patients, 29 of them had a BMI of greater than 30 kg/m^2. Whereas, out of the 10 patients having a moderate decrease in GFR, 4 of them had a BMI of greater than 30 but 6 of them had a BMI of less than 30.

Therefore, it is important to implement strict prevention measures and lifestyle modification aiming toward weight loss and increased physical activity. The mainstay of management of NAFLD after its development, is lifestyle intervention, which includes modified diet and exercise with reduction in weight which is associated with an improvement.[16] Moreover, researchers concluded that CKD-NAFLD patients taking ACE-I or ARBs had a lower level of liver stiffness, compared to the patients not on medications (p=0.0005).[17] Also, the American Association for the Study of Liver Disease (AASLD) has published guidelines recommending pioglitazone and Vitamin E use in non-diabetic adults with NASH proven on liver biopsy.[18] Furthermore, creating awareness among physicians for CKD screening in patients with NAFLD may lead to sooner detection and treatment of this disease entity, thus improving outcomes in patients with liver steatosis, and with those with advanced liver fibrosis.

The study however had a limitation. The study was conducted in an urban setting and the majority of patients belong to high socio-economic background. This may lead to some disparity in results. Also, the study design does not establish a direct cause and effect relationship between CKD and NAFLD.

CONCLUSION

There is an association present between NAFLD and the development of low GFR. As the degree of steatosis increases, the number of patients having low GFR also increased. Therefore, it is important that patients diagnosed with NAFLD are regularly screened for CKD, so as to prevent its development and complications.

AUTHORS' CONTRIBUTIONS

KB: Designed the research methodology and revised the article critically. MM: Wrote the final draft of the manuscript. MA: Helped with writing the initial draft of the manuscript. SA: Collected the data for the study. NH: Contributed to the design and implementation of the research and revised the article critically. AW: Conducted the data analysis.

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