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Prevalence of Non-alcoholic Fatty Liver Disease and its Association with Chronic Kidney Disease among Type-2 Diabetic Patients with the help of Ultrasonography

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ABSTRACT

The primary aim of our study was to investigate whether an association exists between chronic kidney disease (CKD) and the heightened severity of Non-alcoholic fatty liver disease (NAFLD) among individuals diagnosed with type-2 diabetes. Building upon previous research suggesting a potential connection, we undertook a cross-sectional study using non-probability sampling over a three-month period from July to September 2023 at Life Care Lab and Medical Diagnostic Center Rawalpindi. Our study encompassed Type-2 diabetic patients, regardless of age or gender, and focused on determining the grade of fatty liver disease through ultrasonographic assessments, categorized as Grade 1, 2, or 3. Notably, our study exclusively enrolled Type-2 diabetics who developed fatty liver disease in the absence of alcohol consumption, specifically excluding those whose fatty liver disease resulted from other causes such as Hepatitis B & C, Jaundice, or drug-related factors. Chronic kidney disease was defined based on various parameters, including glomerular filtration rate (GFR), Urine AlbuminCreatinine ratio (UACR), and Hemoglobin A1c levels. Importantly, we excluded patients with kidney disease attributable to factors other than diabetes. Our study cohort consisted of 300 Type-2 diabetes patients, comprising 63% males and 37% females. We categorized them into four age groups: 35-45 years, 46-55 years, 56-65 years, and >66 years. From the total population of our study there are 28% patients of chronic kidney disease and 54% have Nonalcoholic fatty liver disease while there were a 58% individuals of CKD who were suffering from NAFLD. To analyze our findings, we employed statistical tools within SPSS, revealing a Chi-square prevalence value of $p = 0.034$. This value strongly indicates the existence of a relationship between Non-alcoholic fatty liver disease and chronic kidney disease in Type-2 diabetics. Furthermore, our results suggest that these patients often share few things in common that elevate their susceptibility to these conditions like advanced age, a higher grade of fatty liver disease. This research sheds light on the intricate interplay between CKD, NAFLD, and Type-2 diabetes, offering valuable insights for both clinical practice and future investigations in this field.

Keywords: Type-2 Diabetes, Non-alcoholic Fatty Liver Disease (NAFLD), Chronic Kidney Disease (CKD), Ultrasound.

Introduction

Among one of the earliest illnesses that humans have ever encountered is possibly diabetes mellitus. Approximately three thousand years prior, an Egyptian book perhaps was the initial publication to mention it. Type-1 and type-2 of diabetes mellitus were evidently distinguished in 1936. The metabolic disorder originally included Type-2 diabetes mellitus being a part of it in 1988. The one which is more prevalent is type of diabetes, Type-2 diabetes sometimes referred to as diabetes without a dependency on insulin, and has features marked primarily as high blood sugar levels, intolerance to insulin, as well as a corresponding insulin deficit. The interplay of behavioral, external variables and

hereditary danger indicators leads to Type2 diabetes mellitus. Individuals with Type-2 diabetes mellitus are considerably prone to a variety of both immediate and ongoing problems, which frequently result in early mortality. The frequency of Type-2 diabetes mellitus, a long-term metabolic condition, seems to be continuously rising throughout the globe. The entire world is seeing an increase in the overall incidence of diabetes of Type-2, approximately 80 percent of those affected residing in nations with low or intermediate incomes. Around 2030, a whopping 439 million individuals are anticipated to be suffering from Type-2 diabetes. Because of ecological and behavioral risk elements, there have been significant regional differences in the development of Type-2 diabetes. In the course of the next twenty years, it is expected that the incidence of diabetes in the aged individuals of which Type-2 diabetes mellitus is growing more prevalent will rise, with a large portion of that growth taking place in emerging nations in which a large number of those suffering from diabetes are around the age of forty-five and sixty-four.

Genetics and lifestyle factors are the main causes of Type-2 diabetes, common lifestyle factors include unhealthy living, excessive alcohol use, smoking, and lack of physical activity. It has been ascertained that roughly 55% of Type-2 diabetes mellitus cases are caused merely due to obesity. Type-2 diabetes is strongly inherited genetically. The most well-known variables associated with insulin resistance that advance Type-2 diabetes mellitus are obesity, age, βcell malfunction, tissue lipid buildup, oxidative stress, endoplasmic reticulum stress in β-cells, tissue inflammation, and insufficient physical activity (1).

Non-alcoholic fatty liver disease (NAFLD) is a hepatic component of a set of diseases connected to metabolism related disorders.The neologism non-alcoholic steatohepatitis was first used in 1980 by Ludwig and colleagues. Steatosis in more than 5 percent of hepatocytes despite concomitant chronic liver diseases or heavy alcohol use is what is known as nonalcoholic fatty liver disease (≥30 g per day for men and ≥20 g per day for women). Examples of these metabolic risk factors are type 2 diabetes and being overweight. Non-alcoholic fatty liver disease is a condition that's capable of exhibiting histologically in a number of manifestations, which incorporates steatosis containing or refraining from limited inflammation (Non-alcoholic fatty liver disease), together with a necroinflammation particular type (Non-alcoholic steatohepatitis) that somewhat additionally has characteristics defined primarily by an outbreak of hepatic necrosis.

Non-alcoholic fatty liver disease is usually experienced by persons who've had health issues like overweight and obese people, Type-2 Diabetes Mellitus (T2DM), the condition of metabolic syndrome, or any of its distinct aspects, and is frequently absent from symptoms at the time it preliminary develops. Hepatomegaly, fatigue, and tenderness in the most prominent right quadrant, together with a condition known as acanthosis nigricans that has a higher incidence in adolescents, are among the many prevalent indicators and manifestations. In juxtaposition to individuals refrain from steatosis, those suffering from non-alcoholic fatty liver disease exhibited larger body mass indexes (BMIs), bigger waistline circumferences, and were typically overweight. In addition, they consumed metformin more extensively, had greater levels of triglycerides in their blood, and showed a smaller incidence of nephropathy caused by diabetes than individuals lacking steatosis. Individuals with non-alcoholic fatty liver disease reported ALT levels that were significantly greater than the average. The most significant correlation was found with being overweight; those overweight individuals had a seven times a higher vulnerability of developing nonalcoholic fatty liver disease. The likelihood of being diagnosed with steatosis on ultrasonography heightened 2.7 times for elevated-normal ALT levels and a four-fold for those subjects with excessive levels of triglycerides, accordingly. In fact, an overwhelming number of those suffering from non-alcoholic fatty liver disease get noticed through inadvertently higher levels of liver enzymes or radiological analysis and criminal proceedings which reveal hepatic steatosis (5).

The co-existence of Non-alcoholic Fatty Liver Disease (NAFLD), Chronic Kidney Disease (CKD), and Type-2 Diabetes is a substantial health risk. These disorders are known to be linked and have a significant influence on patient health and healthcare expenditures. Understanding the incidence of these illnesses and their relationships is critical for establishing effective preventative and management methods. The findings from this study have the potential to improve patient care, contribute to public health efforts, and advance the knowledge in the field of diabetes and kidney disease management.

The main goal of the study is to determine the prevalence of non-alcoholic fatty liver disease among Type-2 diabetic patients. Additionally it aims to study the association between nonalcoholic fatty liver disease with the prevalence of chronic kidney disease among those Type2 diabetic patients using ultrasound.

Materials and method:

The study was undertaken in Life Care Lab and Medical Diagnostic Center Rawalpindi and it took six months for completion. After getting written agreement, all patients who met the inclusion criteria were enrolled in our study. A thorough history of the reported concerns was compiled. The patient was asked to lie down on the examination table in the supine position. The examination was made with Toshiba Medical Systems through ultrasound imaging, steatosis was identified as having hyperechoic liver surrounding tissues, closely packed tiny echoes, and posterior beam attenuation. Steatosis vulnerability was categorized as mild, moderate, or severe, a curvilinear probe of frequency 3.5 MHz was used. The abdomen underwent ultrasonography using an ultrasound probe. Then a trained medical expert applied a particular gel to stomach before the test. The sonographer then touches the gel with the probe. As the patient is laying back on the exam table, the probe quickly delivers high frequency in the direction of the ROI. High-frequency sound waves are transmitted through the skin via the probe, and they are reflected off soft tissues like liver and kidney. Then real-time images are shown on a nearby computer screen.

Ethical Consideration:

The study was carried out following the approval granted by the Institutional Review Board (IRB) of the Lab where the research was conducted.

Inclusion Criteria: All outdoor patient's samples of those patients who were presented clinically with Type-2 diabetes and underwent abdominal ultrasound were included irrespective of age and gender.

Exclusion Criteria: Kidney disease having cause other than that of Diabetes • Liver Disease due to Hepatitis B & C • Type-1 Diabetic patients • Alcohol Consumption • Pregnancy • Jaundice

Results:

While talking about the gender distribution of our study population. We divided the individuals on the basis of their gender into two groups, male and female. From the 300 participants of our study there are 189 male which makes 63% percent of total and remaining 37% are female. From our study it had been made evident that both genders are prone to development of such associated diseases of CKD and NAFLD depending on the presence of other contributing factors.

Gender	Frequency	Percentage
Male	189	63.0
Female	111	37.0
Total	300	100.0

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Depending on the age of the participants the total population had been divided among four age groups. First group includes those individuals having age between 35-45 years that makes 8% of our study individuals, similarly 25.7% of participant's lies in the 46-55 years age group and 45% falls between 56-65 years group while the rest 21.3% are above 66 years.

Age groups	**Frequency**	**Percentage**
35-45 Years	24	8.0%
46-55 Years	77	25.7%
56-65 Years	135	45.0%
> 66 Years	64	21.3%
Total	300	100.0%

One of the risk factor for non-alcoholic fatty liver disease that's mostly common having association with chronic renal disease, non-alcoholic fatty liver disease among Type-2 diabetics is shown in the table below 62.3% of those with the illness are obese. Additionally, 37.7% of people do not have obesity. The majority of patients had obesity, which is a risk factor in type-2 diabetic patients and then it further leads to Non-alcoholic fatty liver disease.

Obesity	**Frequency**	**Percentage**
Yes	187	62.3
No	113	37.7
Total	300	100.0

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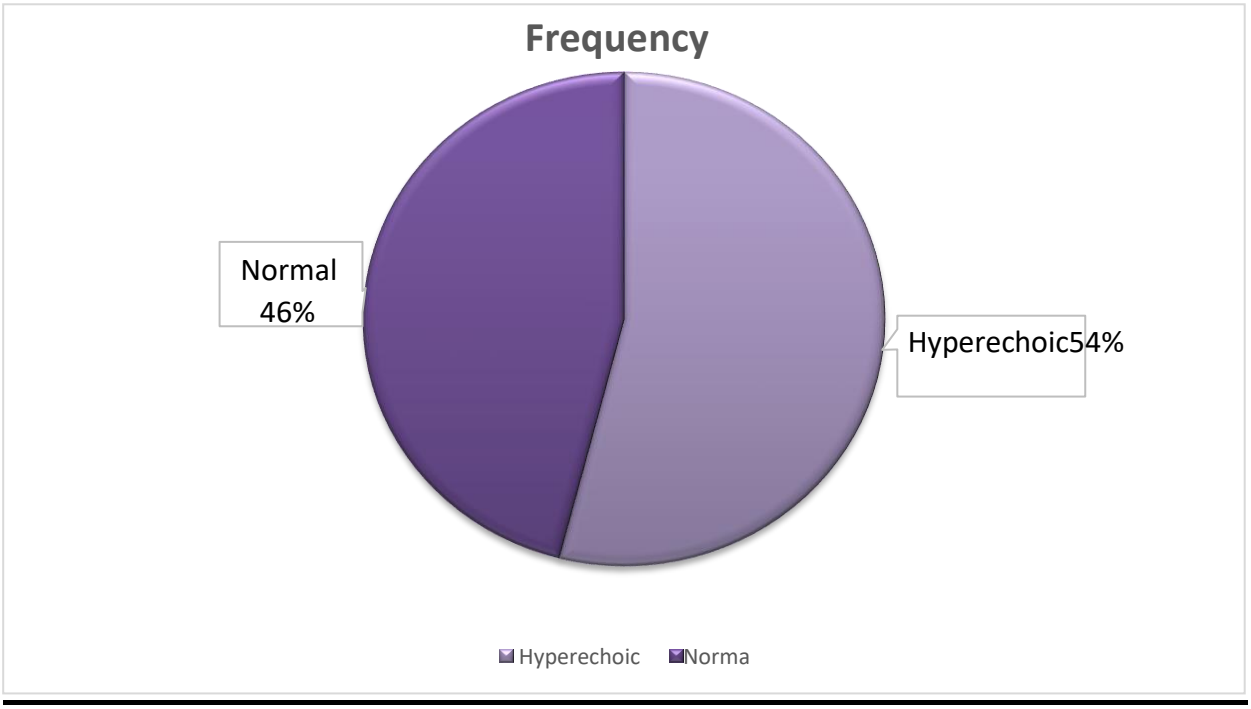
This chart displays the sonographic appearance of fatty liver disease. There are two possible appearances: hyperechoic and normal. On ultrasonography, fatty liver appeared hyperechoic in 162 patients that's 54.0% of the total. Furthermore, 46.0% from the total 300 patients had normal appearance of liver on ultrasonography



The grade of fatty liver disease is displayed in this table. The severity of the condition increases with grade. This data indicates that overall 54% of patients have NAFLD and by dividing them into grades it's been shown that 27.7% of the patients have grade 1. 19.3% of patients had grade 2 fatty liver disease. 7.0% of patients had fatty liver disease at grade 3. And 46% are normal among the total population of 300 patients in our studyThe above table shows that among 300 patients, number of those with Chronic Kidney Disease (CKD) who had a positive test for chronic renal disease (28% of patients). They are affected by this illness. Additionally, 72% are free of chronic renal disease. This indicates that the vast majority of people do not have chronic renal disease among our total population of

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300individuals. There were 36 patients of CKD in 56-65 years age group while 21 in > 66 years group while 20 of them were in 46-55 years and 35-45 years age group had 7 patients.

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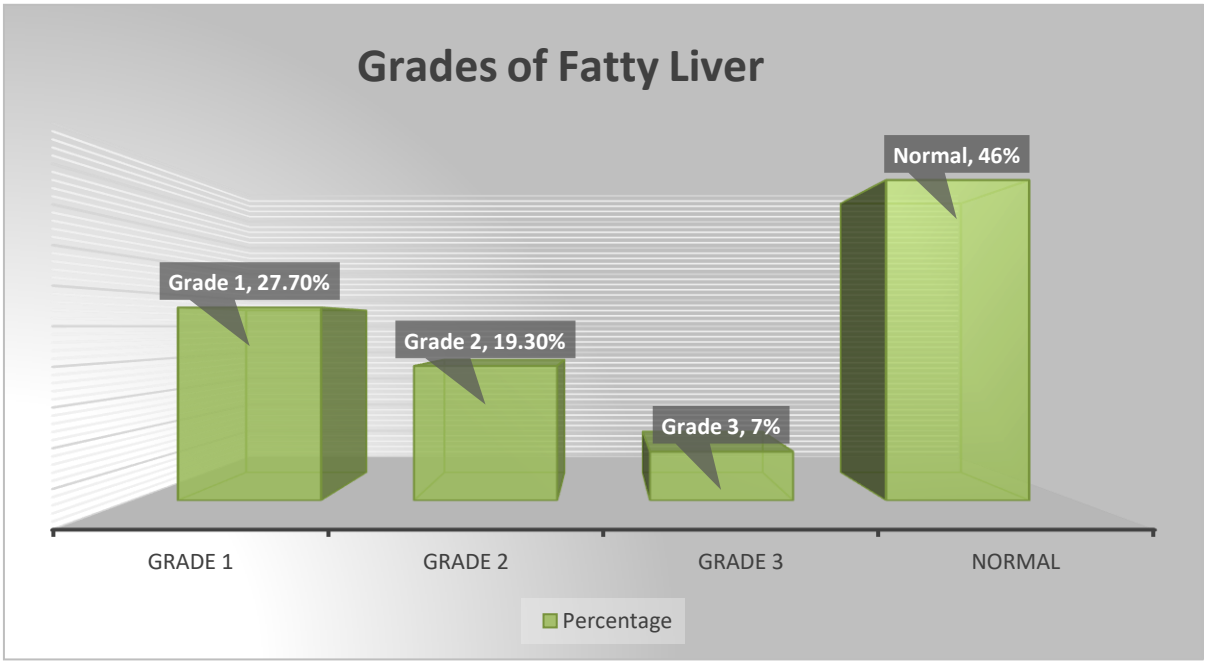

renal disease. This indicates that the vastmajority of people do not have chronic renal disease among our total population of 300 individuals. There were 36 patients of CKD in 56-65 years age group while 21 in > 66 years group while 20 of them were in 46-55 years and 35-45 years age group had 7 patients.

Chronic Kidney Disease	**Frequency**	**Percentage**
Present	84	28.0
Absent	216	72.0
Total	300	100.0

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The results given in the below tables after the application of SPSS for the calculation of Chisquare test gives the p = 0.034 which lies in the significant region. As we have found that value in our acceptance region thus we would accept our null hypothesis that non-alcoholic fatty liver disease and chronic kidney disease are closely associated among Type-2 diabetics. There are total 49 patients of NAFLD and CKD in common from which 18 lies in Grade 1 fatty liver and 25 of them have Grade 2 fatty liver disease while 6 are those having Grade 3 of fatty liver.

Table 07: NAFLD and CKD Cross-tabulation

NAFLD Grade	Chronic Kidney Disease		Total
	Present	Absent	
Grade 1	18	65	83
Grade 2	25	33	58
Grade 3	06	15	21
Normal	35	103	138
Total	84	216	300

Chi-Square Test:

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	8.683[a]	3	0.034
Likelihood Ratio	8.249	3	0.041
Linear-by-Linear Association	.036	1	0.849
Number of Valid Cases	300		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 5.88.

DISCUSSION

Since there is a link between non-alcoholic fatty liver disease and chronic kidney disease in Type-2 diabetic patients and a 6.4% world-wide incidence of these patients, it was required to establish a calculation of the percentage of conjunction among these people. According to prior study findings, 10% of people have chronic kidney disease and 40% of those suffering from NAFLD are found globally. Similarly, data shows that among T2DM patients, 50-70% acquire non-alcoholic fatty liver disease and roughly 40% have chronic kidney disease when discussing the overall incidence and connection of Type-2 diabetes, NAFLD, and CKD globally, Atan NAD et al., (2017) (33). Our research's objective is to study an association between these ailments. 300 Type-2 diabetic patients participated in the study, which was conducted in the Life Care Lab and Medical Diagnostic Center in Rawalpindi. The condition is more prevalent in older and obese people, with 63% of patients being men and 37% being women, 62.3% were obese in our study. We divided the individuals into four groups depending on their age as following 35-45 years having 8% and others 46-55 years, 56-65 years and >66 years containing 25.7%, 45% and 21.3% respectively. Our main finding demonstrated a comparatively elevated risk of chronic kidney disease in a group of people with Type-2 diabetes when Non-Alcoholic Fatty Liver Disease, detected through patient medical records, blood tests, and distinctive sonographic attributes was preexisting.

According to the level of severity of the condition, patients were divided into four groups and the grade of their fatty liver disease was assessed using ultrasonography. According to our study, Type-2 diabetics who are older than 50 years and obese are at increased risk of being diagnosed with NAFLD. Of these individuals, 27.70% have grade 1 fatty liver disease, 19.30% have grade 2, and 7% have grade 3, accordingly and 46% being normal. In our study among these non-alcoholic fatty liver disease patients 64% were obese. There is a significant connection between the development of chronic kidney disease and the severity of fatty liver in Type-2 diabetics; typically, those with higher severity of illness and those who are more susceptible to risk factors that increase the likelihood of renal failure are on the edge of developing both disorders concurrently. From 300 individuals of T2DM of our population, 28% patients have chronic kidney disease, 57% being male. It was unearthed that among these individuals 72% are overweight. In our case majority i.e. 29.85% of the CKD sufferers were found among Grade 2 fatty liver disease. In our investigation,

the findings of laboratory tests, such as the urine albumin-creatinine ratio, triglycerides level, estimated glomerular filtration levels, and ALT levels, were the source for examining the kidney function and liver activity as well.

Individuals with type 2 diabetes mellitus who also have non-alcoholic fatty liver disease are at a significantly higher risk of developing chronic kidney disease, with their likelihood being approximately double that of those without. In our case 58% patients of chronic kidney disease are those who have already developed non-alcoholic fatty liver disease. A few associated variables are similar between NAFLD and CKD, including Type-2 diabetes, male gender, being overweight, old age, decreased estimated glomerular filtration levels, and developing insulin resistance. These risks in our study are also few of them that were found to be related to these diseases in previous study of Singh G, et al., (2019) (25). Ultrasound being easily accessible and free of ionizing radiations proves to be one of the best modality for the detection of fatty liver disease. It appears to be hyperechoic on ultrasound and sharp echoes are seen radiating from liver making it the distinguishing feature for the diagnosis of fatty liver.

CONCLUSION

Our study population included 300 patients of Type-2 diabetic patients, 63% of which were male and 37% female. The individuals were divided into four age groups 35-45 years accommodated 8% of patients other consisted of 46-55 years = 25.7%, 56-65 = 45% and 21.3% in >66 years. Non-alcoholic fatty liver disease was present in 54% of individuals from which 27.70% lies in Grade 1 other includes 19.30% in Grade 2 and 7% in Grade 3 respectively. The disease was more common among male e.g. 63% from total participants, 62.3% individuals are obese and are more prone to develop chronic kidney disease. In our study 28% patients have chronic kidney disease. In both chronic kidney disease and nonalcoholic fatty liver disease majority of patients lies in 56-65 years age group e.g. 42.8% and 46% respectively. The diseases were more common among male and obese patients. 58% patients of chronic kidney disease participants are with non-alcoholic fatty liver disease having larger portion falling in Grade 2 NAFLD. Thus our study shows that there exist an association between CKD and NAFLD among Type-2 diabetic patients. Proper screening and knowing the underlying causes is one of the measure that one needs to take before it’s too late to tackle this morbid condition.

Limitations

In our research, patients underwent ultrasound screening to diagnose non-alcoholic fatty liver disease, a method known for its sensitivity of approximately 89% and specificity of around 95% in identifying moderate and severe steatosis. However, it's important to note that the sensitivity of this approach decreases when the hepatic fat infiltration is less than 33%, which is a limitation of this diagnostic method. Furthermore, our study had a relatively short duration, spanning only three months, which may have limited our ability to gather comprehensive data on these patients and potentially introduced some degree of error into our findings. The limited sample size in our study may have contributed to less precise results

Recommendations:

Use of liver biopsy for the diagnosis of non-alcoholic fatty liver disease may provide better overall results about severity and prognosis of this disease because ultrasound can’t differentiate between non-alcoholic steatohepatitis and any other forms non-alcoholic fatty liver disease. Additionally, we did not delve into other potential contributing factors to the progression of both CKD and NAFLD, which further needs to be investigated.

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