

FREQUENCY OF NON-ALCOHOLIC FATTY LIVER DISEASE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract

Objectives: To determine the frequency of non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus in medical B Unit of Khyber Teaching Hospital, Peshawar. **Materials and Methods:** This cross-sectional study was conducted in Medical B Unit of Khyber Teaching Hospital, Peshawar, from 1st April, 2014 to 15th November, 2014. The study population comprised of male and female patients who were diagnosed as having type 2 diabetes mellitus based on their fasting and random blood sugar levels. All patients had abdominal ultrasounds carried out. Frequency and percentages were calculated for categorical variables like sex and non-alcoholic fatty liver diagnosed on abdominal ultrasound. Non-alcoholic fatty liver was stratified among the age, sex and duration of type-2 diabetes mellitus to see the effect modifiers. All the results were presented as tables and graphs, with the data being entered and analyzed using SPSS version 17. **Results:** Out of one hundred and forty five patients, 74 (51%) were female and 71 (49%) were male. Mean age of the patients was 47.93 ± 8.57 years. Fifty one (35.17%) of the diabetic patients had fatty liver. Most of the patients (53.7%) fell in age group 40-49. Fatigue was present in 53, generalized weakness in 46, heaviness right upper abdomen in 32 and pain right upper abdomen in 42 of fatty liver patients. Corresponding figures in Non Fatty Liver Patients were 47, 47 and 32 respectively. Itching was noted in 32 patients with fatty liver and 22 with non-fatty liver. Serum triglyceride levels more than 160 mg/dl were seen in 47 (92.15%) patients with fatty liver while serum cholesterol levels more than 200mg/dl were seen in 24 (47.05%) patients. Alanine aminotransferase (ALT) more than 40u/l was noted in 6(4.1%) fatty liver patients while serum albumin and serum bilirubin were within normal range in all fatty liver and non-fatty liver patients. **Conclusion:** Non-alcoholic fatty liver disease (NAFLD) is more commonly seen in Type-2 diabetic patients. Serum triglyceride and serum cholesterol are significantly raised in NAFLD patients. Diabetic patients having heaviness or pain right upper abdomen with raised serum triglycerides and cholesterol should be more closely observed for NAFLD and liver complications.

Keywords: Non-alcoholic fatty liver disease (NAFLD), Type-2 diabetes mellitus, Alanine aminotransferase.

Introduction

Type 2 diabetes mellitus (T2DM) and cardiovascular diseases represent a serious threat to the health of the population worldwide. Although overall adiposity and particularly visceral adiposity are established risk factors for these diseases, in the recent years fatty liver emerged as an additional and independent factor.¹

Diabetes by most estimates is now the commonest cause of liver disease in the U.S. Cryptogenic cirrhosis of which diabetes is by far the most common cause has become the third leading indication for liver transplantation in the U.S.²

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver condition characterized by insulin resistance and hepatic fat accumulation in the absence of other identifiable causes of fat accumulation such as alcohol abuse, viral hepatitis, autoimmune hepatitis, alpha-1 antitrypsin deficiency, or medications like corticosteroids and estrogens.³ Hepatic steatosis may range from a 'benign' indolent deposition of fat to severe lipotoxicity-induced steatohepatitis i.e. Non-alcoholic steatohepatitis (NASH). NASH is frequently associated with fibrosis and approximately 10% of the patients develop cirrhosis. There is also increased risk of hepatocellular carcinoma.⁴ Diabetes, dyslipidemia, hypertension and cardiovascular diseases occur more frequently in individuals with NAFLD.⁵ NAFLD may also be associated with a greater risk of renal disease in patients with T2DM.⁶

However, recent work has broadened our understanding of the disease and offered new treatments, suggesting that it will not be long before screening for fatty liver disease either non invasively or in selected cases with a liver biopsy, will be incorporated into

our routine evaluation of patients in the same way that we currently do for other chronic complications of diabetes.⁷

Non-alcoholic fatty liver disease has high prevalence of 60.8% in a local study.⁸ Much work has been done on NAFLD and NASH in the western world but its presentation and etiology have not been well studied in the Asian population because of its asymptomatic presentation.⁸

The rationale of this study is to determine the frequency of Non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus on the basis of Ultrasound. NAFLD is usually asymptomatic and it is not routinely screened like diabetic retinopathy, nephropathy and neuropathy. Having known that NAFLD may range in severity from simple fatty liver to NASH, followed by cirrhosis and ultimately hepatocellular carcinoma, it is important to know the frequency of this serious but ignored aspect of T2DM. Unfortunately very little work has been done locally on this problem as many clinicians think NAFLD is a benign condition of no clinical significance. The benefit of this study would be to give us the frequency of NAFLD in our local population and by timely diagnosing NAFLD using the easily available, cheap and non-invasive method i.e. ultrasound abdomen. If the frequency of NAFLD in T2DM is found to be significant compared to international and other local studies, clinicians will be suggested to intervene early thereby preventing its progression to cirrhosis and hepatocellular carcinoma. Moreover this study will provide basis for further studies regarding preventive and treatment strategies for this important issue.

Materials and Methods

This cross-sectional study was conducted in Medical unit B of Khyber Teaching

Hospital, Peshawar, from 1st April, 2014 to 15th November, 2014. The study population comprised of 145 patients, of whom 74 (51%) were female and 71 (49%) were male. All non-alcoholic patients above 30 years of age, and having Type II diabetes mellitus of any duration were included in the study. Persons consuming alcohol for any duration (by history), patients with positive viral markers (detected by HCV Ab and HBs Ag in blood), already diagnosed cases of hemochromatosis, Wilson's disease and autoimmune hepatitis (by clinical record), use of certain drugs like steroids, oral contraceptive pills use in females, amiodarone and T2DM patients using statins and pioglitazones (clinical record and history), pregnancy (by history), insulin dependent diabetes mellitus (history of insulin injections) were excluded from the study. After getting approval from the hospital ethical committee to conduct the study, data was collected from all those patients with Type 2 diabetes mellitus (fasting glucose of ≥ 126 mg/dl, random glucose ≥ 200 mg/dl) of any duration presenting to medical OPD. They were admitted in medical department of KTH for further evaluation. An informed written consent was taken from patients who fulfilled the inclusion criteria. Patients with type 2 diabetes mellitus of any duration were worked up with detailed history and clinical examination. Imaging examination of all patients was done with abdominal ultrasound (Sonoline 450 (siemens), B-mode, Probe 3.5Mhz) for non-alcoholic fatty liver disease. All information was recorded in a pre- designed proforma. Exclusion criteria were followed strictly to control bias in the study results. All the data collected through design proforma was entered and analyzed in SPSS version 17. Frequency and percentages were calculated for categorical variables like sex and Non-alcoholic fatty liver. Mean \pm SD was calculated for

continuous variables like age. Non-alcoholic fatty liver was stratified among the age, sex and duration of type-2 diabetes mellitus to see the effect modifiers. All the results were presented as tables and graphs.

Results

A total of one hundred and forty five patients of either sex having type 2 diabetes mellitus attending out-patient department or admitted in Medical Unit B of Khyber Teaching Hospital Peshawar were included in the study. Out of these, 74(51%) were female and 71 (49%) were male (Figure No. 1).

Age varied from 40-70 years and mean age of the patients was 45.93 ± 8.57 years. Seventy four (51%) (Figure No. 2) of these patients had fatty liver. Age wise distribution was intense in age group 40-50 for diabetics (Table No.1), while fatty liver presentation was also intense in this group; almost 55(74.3%). The mean duration of diabetes was 8.85 ± 6.18 years, mean BMI was 30 ± 5.5 kg/m², and HbA1c was 7.9 ± 1.1 %.

Seventy four patients belonged to Peshawar while 22 patients came from Afghanistan for the treatment of diabetes (Figure No 3). Out of these 74 patients, 46 (62 %) were female and 28 (38%) were male. Patients presented with various complaints as shown in (Table No. 2). The major complaints were fatigue, generalized weakness and itching. Fatigue was noted as chief complaint in 100 diabetics; out of these 53 were fatty liver patients. Generalized weakness was seen in 93, out of which 46 were having NAFLD. Heaviness in right upper abdomen was seen in 32 patients, while pain in right upper abdomen was present in 42 patients with fatty liver. Serum albumin and serum bilirubin were normal in all the study patients while other biochemical derangements in NAFLD patients are given in Table No. 3. Subjects without NAFLD were significantly more likely to be male,

older, and ex or current smokers, compared with those who developed NAFLD. Seventy two (49.6%) subjects had hepatomegaly as assessed by ultrasound, which was mild in two-third of them. None of the patients without NAFLD had hepatomegaly. The average liver size was 17.2 ± 3.1 cm in patients with fatty infiltration and 13 ± 2.4 cm in non-NAFLD patients. Subjects with NAFLD were more likely to be obese and correspondingly had a higher mean body mass index (BMI). There was no significant difference in prevalence of other features including hypertension, hypertriglyceridemia, or low high-density lipoprotein cholesterol levels. Similarly, there was no difference in the apparent severity of diabetes with HbA1c values between the two groups. Furthermore, the treatment regimens for diabetes and use of medication for hypertension and hyperlipidemia were similar between the two groups.

Discussion

The prevalence of NAFLD and its associated complications (NASH and cirrhosis) are increasing worldwide and are expected to more than double by the year 2025⁹. Understanding the mechanisms responsible for the ethnic differences in the prevalence of hepatic steatosis and steatosis-related liver injury may provide clues to the development of new therapeutic approaches for the prevention and treatment of this disorder. As NAFLD is common and generally asymptomatic in patients with diabetes mellitus, the clinical significance of NAFLD has traditionally been overlooked. A study from Karachi, Pakistan conducted by Luxmi et al.⁸ in 120 diabetic patients described the frequency of NAFLD as 60.8%. Another study from Japan in apparently healthy individuals has reported the prevalence of NAFLD as 29%¹⁰ while an Italian study reported it to be 20%¹¹. The frequency of NAFLD reported in general

population of USA is 20%¹² and Akber et al from Saudi Arabia reported it to be 55% in Type-2 diabetics¹³ while Gupta et al from India report it to be 49% in diabetics¹⁴.

It is possible that some subjects were falsely diagnosed with fatty liver; however, as ultrasound has a high (>90%) sensitivity and specificity for the detection of fatty liver and as the diagnosis required clinical confirmation by the managing physician, we feel this is unlikely.

In present study frequency of NAFLD is 51% which is close to the finding from India and Pakistan. It is pertinent to say that we have taken abdominal ultrasonography as a tool for detection of NAFLD which can only detect NAFLD if the fat content of the liver is more than 33% and sensitivity of ultrasonography for detection of fatty liver is poor if the patient has fat content less than 33% of the liver weight. The frequency of NAFLD actually might have been high if we had done liver biopsy for the diagnosis of NAFLD.

Various studies describe NAFLD as asymptomatic which may be true in initial phase of NAFLD but patients may present with fatigue and heaviness in right upper abdomen later on. In our study fatigue was noted as chief complaint in 145 diabetics, out of these 53 were fatty liver patients. Generalized weakness was seen in 93, out of which 46 (31.7%) were having NAFLD. Here it is difficult to say whether these complaints were purely due to NAFLD or underlying diabetes mellitus as our study population was type 2 diabetic patients. Heaviness right upper abdomen was seen in 32 (64.70%) and pain right upper abdomen in 42 fatty liver patients. A study by Wingkin syn et al described fatigue as an important symptom and pain right upper abdomen in 33% of the patients¹⁵. Heaviness and pain in right upper abdomen are due to stretching of the liver capsule which is correlated with the amount of fat

present in the liver^{16,17}. Diabetes mellitus is an important risk factor for NAFLD.

It is established that diabetes mellitus through insulin resistance leads to increased free fatty acid load to the liver consequently high triglyceride synthesis and increased secretion of triglyceride rich very low density lipoprotein by the liver. Hypertriglyceridemia is strongly correlated with NAFLD and our study also supports this. Serum triglycerides were raised in 86 patients. Similarly serum cholesterol was raised in 42 patients. The study by Luxmi et al⁸ also reported raised serum triglyceride level in patients with fatty liver and same is the result from our study.

Subjects with NAFLD were significantly heavier and had a higher prevalence of obesity than subjects without NAFLD. Obesity is an established risk factor for a range of malignancies¹⁸. In addition, hepatic steatosis increases hepatic insulin resistance and may exacerbate hyperinsulinemia^{19,20}.

In vitro studies have shown that insulin is mitogenic to colonic mucosa²¹ and hyperinsulinemia has recently been identified as an independent risk factor for colorectal malignancy at a population level²². Subsequently, the metabolic features associated with NAFLD may have increased the risk of malignancy.

Serum alkaline phosphatase was raised in 13 of our study patients. Raised Alkaline phosphatase has been described in fatty liver patients especially in old females²². ALT was raised in only 12 patients and six were fatty liver patients, however raised ALT have been reported in significant number of fatty liver patients in other studies^{23,24}. Raised ALT level is important finding in fatty liver patients¹ while raised ALT was not seen in significant number of NAFLD patients in our study and these findings support the study by Luxmi et al⁸. Normal ALT has also been reported in NAFLD by other studies¹⁶. Mofrad reported that

histologic spectrum is not significantly different in patients with raised or normal ALT and normal values did not confirm freedom from steato-hepatitis²⁵.

Recently, Targher et al. have reported that 35.1% of patients with type II diabetes seen in a single tertiary care medical center in Italy suffered from cardiovascular disease, as defined by the sum of coronary heart disease and cerebral and peripheral vascular disease. Similarly, 77% (1,349/1,749) of the total cohort of patients with type II diabetes in the Italian series²⁶ suffered from NAFLD as compared with 51% in our series. In addition, the prevalence of several features of the metabolic syndrome was significantly higher among the patients with NAFLD in the Italian series, but was not significantly different between patients with and without NAFLD in our series. All these differences between the two series can easily be explained by differences in the study design, leading to the inclusion of different patient populations. For instance, the Italian report²⁷ was a cross-sectional study with the prevalence of cardiovascular disease, NAFLD, and components of the metabolic syndrome determined at a single point in time after several years of suffering from diabetes, whereas the prevalence of all those conditions in our series was determined at the time of diabetes diagnosis. The cumulative incidence of cardiovascular disease and the components of the metabolic syndrome, and most likely the development of NAFLD as well, were expected to increase as the duration of diabetes lengthens. In this same cohort of diabetic patients, the Italian group recently reported that presence of NAFLD was associated with a 53% higher risk for the development of cardiovascular events within a 5-year follow-up period²⁸.

Conclusion

Nonalcoholic fatty liver disease (NAFLD) is more commonly seen in Type-2 diabetic

patients. Serum triglyceride and serum cholesterol are significantly raised in NAFLD patients. Raised ALT and AST were not a common finding in our NAFLD study patients. Diabetic patients having heaviness or pain right upper abdomen with raised serum triglycerides and cholesterol should be more closely observed for NAFLD and liver complications. In summary Liver-related death was responsible for a substantial proportion of deaths among patients with NAFLD. Therefore, patients with diabetes should be evaluated for evidence of NAFLD and considered for therapy.

NAFLD is considered the hepatic manifestation of metabolic syndrome and clinicians should consider it as part of management of other components of this syndrome. The clinical spectrum of NAFLD warrants continued research to determine its pathogenesis and to improve diagnostic

modalities. It is hoped that improved imaging techniques and the discovery of serum biomarkers, as well as the development of clinical algorithms, will enable a more accurate diagnosis of NASH without the need for a liver biopsy.

Since no proven, effective treatment is currently available for NASH, well-designed clinical trials are needed to provide evidence-based recommendations for the treatment of these patients. So far, preliminary data suggest that weight loss can be beneficial and should be encouraged in overweight patients with NAFLD. As insulin resistance has a key role in the development of NAFLD, treating insulin resistance in the NAFLD population is a promising strategy. Although there is no current treatment for NASH, patients with NASH who have cirrhosis should be screened for esophageal varices and HCC.

Fig 1: Area wise distribution of patients

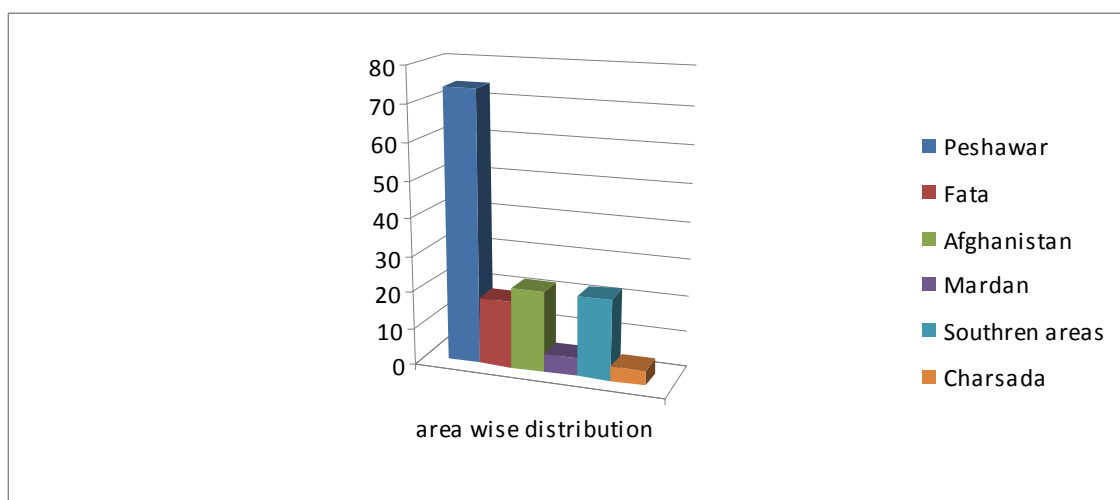


Table 1: Presenting complaints of fatty and non fatty liver diabetic patients

Complaints	Fatty liver patients (n=74)	Non fatty liver patients(n=71)	Total
Fatigue	53	47	100
Generalized weakness	46	47	93
Heaviness right upper abdomen	32	35	67
Pain right upper abdomen	42	41	83
Itching	32	22	54
Nausea	43	40	83
Anorexia	53	46	99

Table no. 2: Biochemical profile of fatty and non fatty liver diabetic patients

Investigation	Fatty liver patients	Non fatty liver patients
Triglycerides (>150 mg/dl)	47(32.4%)	39(26.8%)
Serum cholesterol (>200 mg/dl)	24(16.5%)	18(12.4%)
Serum alkaline phosphatase (>300 u/l)	8(5.5%)	05(3.4%)
Alanine Amino-transferases (>40 u/l)	6(4.1%)	6(4.1%)

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