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Original Article

Internal Medicine Section

Prevalence and Clinical Characteristics of Nonalcoholic Liver Disease in Type 2 Diabetes Mellitus Patients: A Cross-sectional Study

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ABSTRACT

Introduction: A refined diagnostic and classification strategy incorporating phenotypic characteristics of patients with Type 2 Diabetes Mellitus (T2DM) along with their blood glucose profile, lipid levels and evidence of Nonalcoholic Fatty Liver Disease (NAFLD) will help in identifying high risk population.

Aim: To determine the prevalence and assess the clinical characteristics of NAFLD in T2DM patients from August 2016 to February 2017.

Materials and Methods: This cross-sectional analysis was conducted on 100 T2DM patients with no history of alcohol intake, at the time of their screening. Physical examination and anthropometric measurements such as Body Mass Index (BMI) and Waist to Hip Ratio (WHR) were calculated. Fasting Blood Glucose (FBG), Post-Prandial Blood Glucose (PPBG), glycated haemoglobin (HbA1c), serum bilirubin, liver enzymes, lipid profile and ultrasound of the abdomen to diagnose NAFLD were done. Statistical analysis was carried out using student's t-test and Statistical Package for the Social Sciences (SPSS) Version 19.

Results: The prevalence of NAFLD in T2DM patients was 52%. The mean age was 52.27±1.82 years, with 40% males in the study cohort. There was a significant statistical correlation between the higher BMI ($p<0.001$), higher WHR ($p=0.046$), prevalence of upper body obesity ($p<0.001$) and the presence of NAFLD. The glycaemic control was poorer in patients with NAFLD with higher FBG ($p=0.0027$), PPBG ($p=0.0027$) and HbA1c $p<0.001$) than the non-NAFLD group. The serum cholesterol, triglycerides, Serum Glutamic Pyruvic Transaminase (SGPT), Serum Glutamic Oxaloacetic Transaminase (SGOT) were significantly higher in the NAFLD group. Duration of diabetes was not significantly different among the groups.

Conclusion: The incidence of NAFLD is common in T2DM patients with poor glycaemic control, dyslipidaemia, and obesity being associated factors. Duration of diabetes is not a significant predictor of NAFLD.

Keywords: Insulin resistance, Metabolic syndrome, Nonalcoholic hepatic steatosis, Steatosis

INTRODUCTION

The Nonalcoholic Fatty Liver Disease (NAFLD) , rarely recognised as a clinical entity before 1980, has rapidly moved to the clinical forefront, with a prevalence of 25% in the adult population of the world [1]. NAFLD is defined as the hepatic fat accumulation of greater than 5% to 10% by weight, often estimated as the percentage of fat-laden hepatocytes visualised on light microscopy in individuals without significant alcohol consumption [2].

Nonalcoholic Steatohepatitis (NASH) is strongly associated with metabolic conditions, including central obesity, Insulin Resistance (IR), dyslipidaemia, Diabetes Mellitus (DM), and hypertension. NAFLD is considered the hepatic manifestation of metabolic syndrome. IR is regarded as a hallmark and a causal factor of NAFLD, even in the absence of obesity and diabetes mellitus [3].

Increased adiposity, as often found in NAFLD and T2DM, is associated with adipocyte IR and dysfunction [3,4]. The excess Free Fatty Acids (FFA) released into the bloodstream predisposes to lipotoxicity i.e., when FFA overflow from adipose tissue leads to excess lipid uptake by tissues such as the liver, pancreas or muscle [4].

Diabetes, particularly T2DM is highly heterogeneous with regards to clinical presentation and progression. It is therefore inadequate to look at diabetes with respect to one metabolite alone such as blood glucose [5]. A refined diagnostic and classification strategy incorporating phenotypic characteristics of patients (age, height, weight, BMI, WHR, Waist Circumference (WC) with diabetes along with their blood glucose profile, lipid levels and Ultrasonography (USG) evidence of NAFLD will help in identifying high risk population [6-9].

Hepatic IR is a feature of NALFD and the recent cluster analysis by Ahlqvist E et al., shows an increased incidence of NAFLD in the Severe Insulin Resistant Diabetes (SIRD) cluster [10]. It is not plausible to measure fasting and stimulated C-Peptide and Homeostatic Model Assessment (HOMA) Insulin Resistance (IR)/HOMA-β (Beta) for risk stratification of patients with T2DM in small tertiary care centres in India. Therefore, plotting simple clinical features and a bedside ultrasound assessment can provide a practical tool for precision medicine in diabetes so that physicians can tailor the management on the basis of clinical features of IR and NAFLD [11].

The study aimed to determine the prevalence of NAFLD in T2DM patients by a non-invasive technique, viz., ultrasonography, and the correlation between anthropometric measurements, glycaemic control, lipid profile, and NAFLD in these patients.

MATERIALS AND METHODS

This was a cross-sectional analysis, carried out between August 2016 to February 2017, at a tertiary care centre in southern India. The study was carried out after an approval from the Institutional Ethics Committee (HDHCR/IEC/letter no: 2016143 dated 12th June 2016). An informed consent was obtained from each participant before the study. The participants were ensured about the privacy and confidentiality of the exercise. The data of T2DM patients reporting into the diabetes clinic were screened for alcohol intake history.

Inclusion criteria: The patients with presence of T2DM for over six months and no history of alcohol intake as reported by the participant or the next of kin were included in the study.

Exclusion criteria: Patients with a history of jaundice, ascites, and features of liver cell failure, or those patients medicated with any drugs known to have hepatotoxic effects such as methotrexate, amiodarone, glucocorticoids, synthetic oestrogens, and nucleoside analogs were excluded from the study. Moreover, patients with chronic renal failure, chronic cardiac conditions of any nature, history of diabetic ketoacidosis, and major abdominal surgeries were not enrolled in the study. Finally, Hepatitis B surface Antigen (HBsAg) positive individuals were excluded from the study.

Sample size calculation: The prevalence of NAFLD was assumed to be 35% in nonalcoholic diabetic patients visiting the clinic over the period of six months (n=150) and a margin error of 5% was considered. A sample size of 100 was calculated at a 95% confidence interval (z score=1.96).

One hundred patients with no history of alcohol intake underwent physical examination, anthropomorphic measurements and laboratory tests in addition to an ultrasound of the abdomen to diagnose NAFLD. A detailed history was taken to elicit information on the known duration of diabetes, symptoms referable to liver disease, alcohol consumption, surgical, and drug history. A general physical examination was carried out that included the measurements of height, weight, Waist Circumference (WC), hip circumference, and examination of the abdomen for the liver, spleen for any free fluid in the abdomen. BMI was calculated in kg/m^2. WC was measured in standing position at the level of the umbilicus. Waist Hip Ratio (WHR) was calculated. Systolic and diastolic blood pressure was measured with a standard mercury manometer.

Venous blood was drawn after an overnight fasting for eight hours or more. Serum chemistry encompassing FBG, serum bilirubin, Serum Glutamic-Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT), Alkaline Phosphate (ALP), Serum Total Proteins (STP), and lipid profile were measured by standard laboratory procedures. HbA1c was also measured. PPBG was measured 2 hours after breakfast.

Hepatic ultrasonography was performed in all patients by a trained operator using a Logi tech EP5 with a 4 MHz probe. Hepatic steatosis was diagnosed as the presence of an ultrasonographic pattern consistent with "bright liver" with evident ultrasonographic contrast between hepatic and renal parenchyma, vessel blurring, focal sparing and narrowing of the lumen of the hepatic veins. Liver size >15 cm in the longitudinal plane was considered to represent hepatomegaly [12].

STATISTICAL ANALYSIS

All the data were entered in Microsoft Excel 2016 and then exported to SPSS version 19 (Chicago, Illinois, USA). Statistical analysis was performed using student's t-test. Significance was accepted at p<0.05.

RESULTS

Of the total of 100 T2DM patients 40 were male. The age of the study population ranged from 38 years to 75 years. (52.27±1.82 years). Their duration of diabetes ranged from 2 to 20 years (5.06±0.81 years). Among the 52 with NAFLD, 18(34.60%) were men while 34(65.40%) were women. There was no statistical significance with age and gender and the prevalence of NAFLD. The demographic and clinical parameters are shown in [Table/Fig-1].

Seventy-one percent (n=37) had no symptoms referable to the hepatobiliary system. Malaise was the most common symptom being present in 12 patients (23%), followed by right upper quadrant discomfort in nine patients (17.3%) the patients. 2 cases (3.8%) complained of abdominal distension. Jaundice was present in none. Hepatomegaly on clinical examination was present in 4 cases (7.7%). None had splenomegaly or free fluid in the abdomen.

Fatty liver alone was present in 38% (n=38), while it was present together with hepatomegaly in another 14% (n=14). Thus, the overall prevalence of fatty liver, i.e., NAFLD in the study population was 52%.

Characteristics (unit)	T2DM* patients with NAFLD† (n=52)	T2DM patients without NAFLD (n=48)	p‡-value
Male, n (%)	18 (45)	22(55)	0.312
Age, (mean±SD) 52.27±1.82 years			
Anthropometric measurements			
BMI(kg/m^2)	25.23±1.48	22.45±1.19	**0.001**
Waist to Hip Ratio	0.93±0.04	0.91±0.02	**0.046**
Upper body obesity, n (%)	30 (57.7)	8 (16.67)	**0.001**
Serum chemistry			
FBG (mg%)	160.58±23.60	145.79±22.45	**0.0027**
PPBG (mg%)	218.88±38.08	195.19±35.22	**0.0027**
Serum Total Cholesterol (mg%)	216.40±15.48	198.5±19.18	**0.001**
TGL (mg%)	218.33±59.08	170.04±52.82	**0.001**
HDL (mg%)	47.87±5.13	48.98±4.76	0.245
HbA1c (%)	7.42±0.46	7.05±0.47%	**0.001**
Liver function tests			
Serum Bilirubin (mg%)	0.83±0.11	0.82±0.15	0.703
SGOT (IU/L)	22.52±6.20	18.90±8.14	**0.046**
SGPT (IU/L)	25.12±7.15	18.73±6.80	**0.001**
ALP (IU/L)	129.08±41.54	116.19±37.45	0.317
STP (G%)	6.44±0.17	6.49±0.35	0.317
Diabetic status			
Duration of diabetes (years)	5.13±1.30	4.98±0.79	0.712

[Table/Fig-1]: Clinical characteristics of Type 2 DM (T2DM) patients in the study cohort N=40.
NAFLD: Nonalcoholic fatty liver disease; Type 2 DM: Type 2 diabetes mellitus; BMI: Body mass index; FBG: Fasting blood glucose; PPBG: Post prandial blood glucose; TGL: Serum triglycerides, HDL: Serum high density lipoprotein; HbA1c: Haemoglobin; SGOT: Serum glutamic-oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; ALP: Alkaline phosphate; STP: Serum total protein; *Type 2 diabetes defined as: 1) fasting blood glucose ≥126 mg%; 2) HbA1c ≥6.5%; or 3) existing clinical diagnosis of type 2 diabetes; †Nonalcoholic Fatty Liver Disease confirmed by ultrasonographic evaluation of hepatic steatosis in patients with no history of alcohol consumption; ‡p-value determined by statistical analysis using student t-test

The duration of diabetes in diabetics with NAFLD ranged from 2 years to 15 years (5.13±1.30 years), while that in diabetics without NAFLD ranged from 3 years to 20 years. (4.98±0.79 years) (p= 0.712).

The BMI of the diabetics with NAFLD was significantly higher than that of the patients without any signs of fatty liver disease. Similarly, overall obesity was prevalent in both the subgroups (13.46% vs 16.66%). The incidence of upper body obesity and the WHR was significantly higher in the NAFLD cohort.

The glycaemic control was better in patients without NAFLD than those with NAFLD. The fasting blood glucose in diabetics with NAFLD ranged from 90 mg% to 269 mg% (160.58±23.60 mg%), while that in diabetics without NAFLD ranged from 89mg% to 317 mg% (145.79±22.45 mg%) (p=0.0027).

The PPBG in diabetics with NAFLD ranged from 142 mg% to 402 mg% (218.88±38.08 mg%), while that in diabetics without NAFLD ranged from 122 mg% to 374 mg% (195.19±35.22 mg%) (p=0.0027). HbA1c was significantly higher in the NAFLD cohort.

The lipid profile amongst the two groups were also comparable. Serum cholesterol in diabetics with NAFLD ranged from 152 mg% to 363 mg%, (216.40±15.48 mg%), while that in diabetics without NAFLD ranged from 137 mg% to 324 mg% (198.5±19.18 mg%) (p<0.001).

The serum triglycerides in diabetics with NAFLD ranged from 67 mg% to 449 mg% (218.33±59.08 mg%), while that in diabetics without NAFLD ranged from 68 mg% to 358 mg% (170.04±52.82 mg%) (p<0.001).

There was no significant difference between the rest of the liver function tests serum bilirubin, SAP and STP amongst the two study cohorts. The duration of diabetes did not vary between the NAFLD and the non-NAFLD group.

DISCUSSION

The aim of this study was to determine the occurrence of NAFLD in the type 2 diabetics in a small tertiary centre setting with the help of simple clinical features and an ultrasound examination of the abdomen. In the Indian population, a high prevalence of all the components of metabolic syndrome in cases of NAFLD has been reported [13,14]. Several authors have reported the prevalence of NAFLD in the general population, in obese individuals and in those undergoing specialised surgeries in India [15,16]. However, there exists a paucity of data in terms of prevalence of NAFLD in the Indian diabetic cohort especially when NAFLD is viewed as a component of metabolic syndrome.

Matteoni CA et al., stated that the prevalence of NAFLD in diabetics ranged from 25 to 75% or even higher [17]. The prevalence of NAFLD in diabetics in the present study was 52%. This high occurrence indicates the importance of management and early evaluation of NAFLD in T2DM patients.

Of the 40 men, 18 (45%) had NAFLD; on the other hand, of the 60 women, 34 (56.67%) had NAFLD, a difference that was not statistically significant. However, among the 52 with NAFLD, 18 (34.60%) were men while 34 (65.40%) were women. Women far outnumbered men in a ratio of 1.9:1 in diabetics with NAFLD. However, in large meta-analyses globally, the prevalence of NAFLD was significantly higher in male T2DM patients than female T2DM patients [18,19]. Gender differences in the prevalence of NAFLD in T2DM patients could be attributed to the gender differences in hormone levels and lipid levels [18]. Clark JM et al., observed that men have a higher prevalence of NAFLD than women (5.7% *vs* 4.6%, respectively) however, there was no significant difference in either gender in IR as calculated by Homeostasis Model Assessment (HOMA) or exercise level in their study [20]. Conducting a HOMA to measure IR for all diabetics might not be feasible in tertiary care setups in India.

Seventy one percent of the subjects had no symptoms referable to the hepatobiliary system. Malaise was the most common symptom being present in 23%. As for physical signs, hepatomegaly was the only physical finding noted in the present study and it was present in 7.7% of the subjects studied. Several authors have also noted that an enlarged liver is the only sign noted at physical examination [21,22]. Given the insidious nature of the disease, it is not surprising to see malaise being the most common symptom in less than one-quarter of the study population. The most frequent symptoms are fatigue and right upper quadrant pain or dullness, although many patients have no symptoms [3]. Mild or moderate hepatomegaly is reported to be one of the most common physical examination findings [20-22].

The mean duration of diabetes in the NAFLD subgroup was 5.13±1.30 years (range 2-15 years) and did not differ significantly from those without NAFLD. A negative correlation between the prevalence of NAFLD and the duration of diabetes has been observed in several studies [23,24]. This negative correlation can be attributed to the greater degree of hyperinsulinemia in early T2DM driving the uptake of Free Fatty Acids (FFAs) by hepatocytes [24].

Prevalence of NAFLD in patients with obesity or T2DM can be as high as 80-90% [19]. In the current study, while overall obesity was prevalent similarly in both the subgroups (13.46% vs 16.66%), upper body obesity was present in a significantly higher percentage of diabetics with NAFLD. The WHR was higher in the NAFLD population with a statistical significance. Visceral fat has been considered as a direct predictor than subcutaneous fat for Nonalcoholic Steatohepatitis (NASH) and is related to the severity of NAFLD. WC is an alternative marker for the visceral fat and is strongly associated with triglyceride accumulation in liver cells, liver inflammation and, liver fibrosis [25].

The glycaemic control reflected by FBG, PPBG, and HbA1c was poorer in diabetics with NAFLD compared to diabetics without NAFLD. Similar observations have been made by other concomitant studies [26,27].

Similarly, total cholesterol, triglycerides, and LDL-cholesterol were significantly higher in diabetics with NAFLD compared to diabetics without NAFLD. Dyslipidaemia and hypercholesterolemia have been considered as direct predictors of NAFLD in several other studies [27-29]. In fact in recent times, NAFLD is considered as the hepatic manifestation of the metabolic syndrome.

Serum Bilirubin was within normal limits in diabetics with and without NAFLD and did not differ significantly between the two groups. The transaminases, even though within normal limits, were significantly higher in those with NAFLD compared to those without NAFLD. Systemic Arterial Pressure was within normal limits in both the subgroups and was similar. STPs, while being within normal limits, was lower in those with NAFLD. Mild elevations of liver enzymes in the upper normal range are associated with features of metabolic syndrome and NAFLD [30]. The high prevalence of metabolic syndrome and hyperlipidaemia in NAFLD patients suggests that risk stratification and aggressive treatment is needed to control the risk of cardiovascular diseases in these patients [1]. The typical biochemical pattern in hepatic steatosis due to NAFLD is, increased levels of transaminases, Alanine Aminotransferase (ALT) levels higher than Aspartate Aminotransferase (AST). This helps in differentiating between NAFLD from alcoholic liver injury, with the latter normally associated with a high AST:ALT ratio [31].

Limitation(s)

The study was conducted on a limited sample size of 100 patients. The second limitation is the self-reported alcohol consumption record during the initial screening.

CONCLUSION(S)

It is concluded that NAFLD is common in T2DM being present in a little over a half of all diabetics and that poor glycaemic control, dyslipidaemia, and overall as well as regional adiposity are significantly associated with its development. Further, WC and WHR are easy to measure predictors of NAFLD. Ultrasound is a relatively inexpensive, non-invasive and accessible, compared to other diagnostic techniques, for screening for the presence of fatty liver in clinical settings and, especially in population studies. Therefore, plotting simple clinical features and a bedside USG assessment can provide a practical tool for precision medicine in diabetes so that physicians can tailor the management on the basis of clinical features of IR and NAFLD.

In India, there is a lack well designed prospective studies profiling large cohorts of patients with well-characterised NAFLD who are followed for long periods. Studies of this kind will provide the type of evidence needed to encourage clinicians, researchers, and health policy experts to focus on NAFLD as one of the most common chronic human diseases.

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