Journal of Cardiovascular Disease Research

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 11, 2024

Study of Hepatobiliary dysfunction in Type-2 diabetes mellitus

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Abstract

Background: Diabetes mellitus is a chronic lifestyle endocrine disorder, often referred as "silent killer" with numerous microangiopathic and macroangiopathic complications, including retinal, renal, and liver dysfunction, cardiovascular disease, peripheral neuropathy, and poorly controlled glycemic index, leading to obesity and metabolic syndrome.Type 2 diabetic patients may experience hepatic involvement ranging from steatosis to NAFLD, NASH, cirrhosis, or hepatocellular carcinoma.In advent of same, the present study was designed to study the prevalence of hepatobiliary involvement in Type 2 diabetes mellitus (T2DM).

Materials and Methods: After approval from institutional IEC, the present cross-sectional study was conducted on 100 patients aged ≥18 years with Type 2 Diabetes mellitus visiting the OPD at Department of Medicine, SAIMS & PG institute, Indore. Patients qualifying the inclusion criteria were enrolled after taking a written informed consent. After clinical evaluation, routine haematological and radiological investigations in type 2 diabetic patients, mainly liver function tests, CBC, sonography of the abdomen, ECG, urine analysis, anthropometric measurements, etc were noted. Data was statistically analyzed using SPSS software version 20.0.

Results: Duration of diabetes was significantly correlated with the presence of fatty liver in USG abdomen. 25 (25%) patients of T2DM had symptoms of dull aching pain and 15 (15%) patients had hepatomegaly on palpation which was clinically significant. Fatty liver was diagnosed in 30% of the total participants with 26.7% of the patients having diabetes less than 5 years, 40% of the patients having diabetes for more than 10 years and 33.3% of patients in the duration range of 6-10 years show evidence of fatty liver on ultrasound of abdomen. In addition, WC and BMI were significantly more in diabetics. Further, fatty liver patients had raised BMI, WC, liver enzymes, and more dyslipidemia. Presence of T2DM, elevated liver enzymes, obesity, and elevated WC are found to be independent risk factors of fatty liver.

Conclusions: This study found a significant correlation between increased BMI, deranged blood sugar levels, early nephropathy, and retinopathy in patients with type 2 diabetes. Liver dysfunction was also detected on abdomen sonography. A significant correlation was found between fasting blood sugar and BMI, indicating that glycemic control management is crucial for preventing diabetes complications.

INTRODUCTION

Diabetes mellitus is a chronic lifestyle endocrine disorder often referred as "silent killer" presenting with numerous microangiopathic and macroangiopathic complications, including retinal, renal, liver

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 11, 2024

dysfunction, cardiovascular disease, peripheral neuropathy, and poorly controlled glycemic index, leading to obesity and metabolic syndrome. [1,2]

Diabetes mellitus can alter hepatic morphology and physiology and can be exacerbated by hepatic diseases.[2] The most common clinical presentation being hepatomegaly with most patients having normal or only mildly abnormal transaminases and normal bilirubin. [1]

Hepatic involvement in a type 2 diabetic patients can range anywhere between clinically asymptomatic with steatosis to NAFLD, NASH, cirrhosis or rarely hepatocellular carcinoma. Cirrhosis was the fourth leading cause of death and accounted for 4.4% of diabetes-related deaths. [2,3] Further, Nonalcoholic fatty liver disease (NAFLD) is recognised as a major health issue which develops in the absence of alcohol abuse. Further, increasing prevalence of obesity, insulin resistance, and the metabolic syndrome has significant implications for the development of chronic liver disease which is characterized by abnormal fat accumulation in liver cells and histologically resembling alcohol induced liver damage. It is characterized by abnormal fat accumulation in liver cells and liver damage resembling alcohol-induced damage. The perception of NAFLD as benign is changing, with steatosis and nonalcoholic steatohepatitis (NASH) being the two types. NASH can progress to end-stage liver disease, liver failure, and hepatocellular carcinoma. [4]

The pathogenesis of NASH is poorly understood, but lipid peroxidation and oxidative stress are leading culprits. Patients with NAFLD have higher all-cause mortality, liver-related deaths, and an increased risk for cardiovascular disease. [4]The global T2DM epidemic affects 285 million people, with NAFLD becoming the most common liver disorder. Gallbladder emptying abnormalities in diabetic patients may predispose them to cholelithiasis, with obesity and hyperlipidemia contributing factors.[5] Thus, it is imperative to have necessary biological markers and investigations for the early detection and diagnosis of liver dysfunction in this condition. [2]

Liver biopsy is the gold standard diagnostic test for hepatic disease, but it's not suitable for screening due to its invasive nature. Thus, its reserved for situations with conflicting diagnosis. [6] Liver ultrasonography (USG) is a non-invasive, feasible tool that is more affordable and effective in detecting hepatic involvement in type 2 diabetes. Biochemical markers like AST/ALT, alkaline phosphatase, and total bilirubin are used to detect hepatic involvement in type 2 diabetes. Kalra S et al. reported that NAFLD prevalence is 9-32% in the general Indian population, with higher incidence in obese and diabetic patients.[3] However, there are only a few studies that have evaluated the prevalence of hepatobiliary involvement in Type 2 diabetes mellitus (T2DM) on Indian population.

In advent of same, the present study was aimed to study the prevalence of hepatobilary dysfunction including NAFLD and gallstones in patients with T2DM. The present study, is a step towards recognising and understanding which tool can be used as a feasible marker for diagnosis of hepatic involvement in T2DM.

MATERIAL AND METHODS

After approval from institutional IEC, the present cross-sectional study was conducted on 100 patients aged $\geq$18 years with Type 2 Diabetes mellitus visiting the OPD at Department of Medicine, SAIMS & PG institute, Indore for routine checkup and the presence and type of hepatobiliary dysfunction was evaluated. Patients qualifying the inclusion criteria were enrolled after taking a written informed consent.

Inclusion criteria

- Type-2 diabetic adult of either sex or age >18 years and asymptomatic for liver disease.

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- Patients consenting for the study

Exclusion criteria

- All patients with type-1 diabetes mellitus, past/present history of chronic alcohol consumption i.e., alcohol intake more than 20 g/day, current history of Anti-Koch's therapy, past history of hepatitis or other hepatobiliary disease, positive hepatitis B surface antigen, positive anti-hepatitis C virus, significant comorbidities (sepsis, organ failure, malignancy, etc.), positive antinuclear antibody and taking hepatotoxic drug for more than 3 consecutive months and history of congestive cardiac failure, renal failure were excluded.
- Patients having significant comorbidities (sepsis, organ failure, malignancy, etc.),
- Patients who did not consented for the study

Procedure

A preinformed written consent was obtained from all the patients after explaining the study protocol in their vernacular language. A detailed personal and medical history was recorded and any present clinical symptoms especially dull aching pain in right hypochondriac region were noted. In general examination measurement of height, weight and waist circumference was done andbody mass index (BMI), waist to hip ratio (WHR), acanthosis nigricans were noted. Body mass index (BMI) was calculated by the formula weight (kg)/height (m^2) and WC was measured midway between the uppermost border of iliac crest and lower border of the rib cage. The normal BMI for Asian Indians is 18–22.9 kg/m^2, and normal WC is 25 kg/m2 are obese. In systemic examination, emphasis was given to presence of hepatomegaly, if any.

Patients were grouped according to their duration of diabetes as group 1 (=<5 years), group 2 (6-10 years) and group 3 (more than 10 years). Five milliliters venous blood (2 ml in ethylenediaminetetraacetic acid and 3 ml in plain vacutainer) was drawn under aseptic condition from all patients and controls after minimum of 8 h of fasting. Biochemical parameters including Hb, CBC, liver function test (AST/ALT/total bilirubin), fasting blood sugar & postprandial blood sugar, s. cholesterol, s. triglycerides, lipid profile, liver enzymes, urine – routine and microscopy especially for presence of albuminuria as a marker of early nephropathy. Lipid profile and liver enzymes were analyzed using automated biochemistry analyzer. HbA1C was measured using chemiluminescence analyzer (Elecsys 2010 Systems, Hitachi, Japan).

ECG, fundoscopy for evidence of retinopathy and USG abdomen for assessment of extent of fatty liver or cirrhosis were also performed. Ultrasound (USG) abdomen was done in all the patients as well as controls for any evidence of hepatobiliary involvement. In ultrasonography, the right kidney echogenicity was used for the determination of liver parenchyma echogenicity. With the kidney cortex and liver parenchyma echogenicity being the same, it is evaluated as normal. Fat infiltration in liver is described in 3 ultrasonographic stages. Mild (Grade 1): Minimal diffuse increase in hepatic echogenicity. Diaphragm and intrahepatic vessel contours seem normal. Medium (Grade 2): Medium grade diffuse increase in hepatic echogenicity. There was mild deterioration in the image of diaphragm and intrahepatic vessels. Severe (Grade 3): Apparent increase in echogenicity. Posterior segment of the right hepatic lobe is difficult to display. Intrahepatic vessel structure and diaphragm contours are vague or not seen. All the baseline data was recorded on a prestructured proforma.

Statistical Analysis

The collected raw data of 100 patients was entered in Microsoft excel spread sheet and analyzed statistically using SPSS version 20.0 software (Chicago, USA). Numerical and Categorical variables will be given as mean ± SD and percentage, respectively. Descriptiveresults were expressed as frequency and percentage. Correlation coefficient was used to test for significant relationships between categorical

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variables. Comparison of continuous variables was carried out using unpaired Student's t-test. Chi-square test was applied to compare between the categorical variable. Statistical tests were based on two-tailed probability. Multinomial logistic regression was also done. A p value less than 0.05 was considered statistically significant.

RESULTS.

A total of 100 patients were evaluated in the study. The mean age of cases was 55.65 ± 14.23 years, of which 42 were male and 58 were female.The mean fasting blood sugar was 193.44 mg/dl and mean post-prandial blood sugar was 277.46 mg/dl. 25 (25%) patients of T2DM had symptoms of dull aching pain and 15 (15%) patients had hepatomegaly on palpation which was clinically significant. Baseline characteristic of participants are shown in Table 1.

Using USG abdomen, fatty liver was diagnosed in 65% of the total participants with 23% of the patients having diabetes less than 5 years, 26.1% of the patients having diabetes for more than 10 years and 50.9% of patients in the duration range of 6-10 years show evidence of fatty liver on ultrasound of abdomen. Diabetic patients were at significantly higher risk for the occurrence of NAFLD with odds ratio of 6.046, (95% confidence interval = 3.904–9.363, P < 0.0001). Out of 65 diabetics with NAFLD patients, 40 patients had Grade 1 NAFLD, 15 patients had Grade II NAFLD whereas Grade III NAFLD was observed in 10 diabetic patients Patients having more duration of diabetes have more incidence of Grade III NAFLD as compared to patients with lesser duration (P < 0.0001). [Table 2, Graph 1].

Diabetic patients were also found to have higher risk of obesity, high WC, elevated liver enzymes, and occurrence of gallstones [10(15.45%)] had gallstones. A statistically non-significant correlation was observed between liver enzymes (AST, ALT, Sr. bilirubin) and duration of diabetes (P>0.05). A statistically positive correlation was observed between presence of fatty liver and levels of fasting blood sugar (FBS) which was demonstrated by spikes in the level of FBS in cases with fatty liver. There is a positive correlation between BMI and deranged fasting and postprandial blood sugars p value <0.0001 in both cases thus being extremely significant. An association of BMI derangement with hepatic involvement was seen. The correlation of FBS with waist: hip ratio was found to be statistically significant (p=0.0001). 50 (77%) patients with hepatic involvement had obesity, 28 (43%) had raised LDL and 35(53.8%) had raised TG which are the markers of metabolic syndrome. [Table 3]

All the subjects were also grouped according to the presence of NAFLD or not, and we observed that patients with NALFD had higher incidence of obesity, high WC, elevated liver enzymes and gallstones as compared to non-NAFLD group. Lipid profile was also significantly deranged in NAFLD group as compared to non-NAFLD [Table 4]. Multinomial logistic regression analysis was performed to see the independent risk factors for NAFLD. The presence of T2DM, obesity, high WC, and elevated liver enzymes were observed as independent risk factor for the development of NAFLD [Table 3].

Table 1. Clinical and laboratory characteristics of participants

Variables	Diabetics (n=100)	95% CI	OR	P
Mean age	55.65+14.23 years	-	-	0.142
Sex (male/female)	42/58	0.646-1.426	0.960	0.921
Fatty liver	65	3.904-9.363	6.046	<0.0001
Obesity (BMI >25 kg/m2)	62	1.725-3.890	2.590	<0.0001
Elevated liver enzymes	21	1.654-5.648	3.057	0.003
Elevated liver enzymes + fatty liver	20	1.987-7.722	3.917	<0.0001

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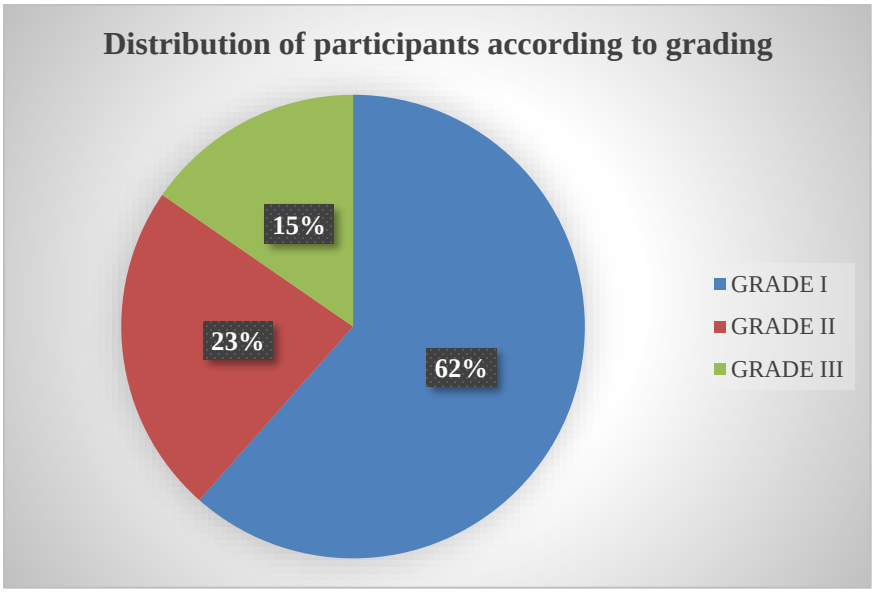
Elevated waist circumference	87	1.179-3.388	1.999	0.0123
Raised cholesterol	45	1.016-2.273	1.519	0.565
Raised LDL	56	0.8857-1.888	1.273	0.224
Low HDL	70	1.093-2.491	1.650	0.242
Raised TG	51	0.9686-2.133	1.437	0.081
Gallstones	16	1.850-4.315	2.825	<0.0001



Graph 1: Grading of fatty liver in participants

Table 3: Relationship of duration of diabetes mellitus with grading of fatty liver

Fatty liver	Duration of DM (years)			
	<5	**6-10**	**>10 years**	**P**
Grade 1	13	11	16	<0.0001
Grade 2	2	3	10	
Grade 3	0	3	7	

Table 4: Clinical and laboratory characteristics of patients with fatty liver and normal liver

Variables	**Fatty liver (n=65)**	**Normal liver (n=35)**	**95% CI**	**OR**	***P***
Obesity (BMI >25 kg/m^2)	50	10	3.947–10.434	6.442	<0.0001
Elevated liver enzymes	19	16	6.372–36.126	15.105	<0.0001
Elevated waist circumference	63	1	5.134–32.754	13.517	0.0001
Raised cholesterol	28	30	0.785–1.735	1.134	0.384
Raised LDL	40	15	1.128–2.558	1.718	0.005
Low HDL	45	18	1.126–2.542	1.621	0.003
Raised TG	35	21	1.218–2.326	1.560	0.011
Gallstones	10	12	1.388–5.633	2.785	0.0018

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DISCUSSION

Diabetes mellitus (DM) is an extensively researched and studied subject mainly because of two factors: its, often silent spread among the community and the wide range of complications associated with it. One of them being hepatic dysfunction, the spectrum of which ranges from clinically asymptomatic with steatosis to NASH, NAFLD, cirrhosis and rarely, hepatocellular carcinoma.

The result of our study showed that patients with T2DM have significantly higher prevalence of NAFLD on abdominal ultrasonography i.e., 65% (130/200 [$P < 0.0001$]). Worldwide prevalence of nonalcoholic fatty liver disease (NAFLD) in the general population is between 6.3% and 33%, with a median of 20%. In India, the reported prevalence is around 9%-32%. In Dallas Heart study, one-third of the population had hepatic steatosis, whereas 62% of subjects who were known diabetics or fasting glucose >110 mg/dl had hepatic steatosis.[7] Forlani et al. in 2016 done a nationwide study in 160 diabetic clinics of Italy and observed a 59.6% prevalence of NAFLD in T2DM patients.[8] The overall prevalence of NAFLD in T2DM in Indian population is reported to be in range of 12.5%–87.5%.[9-13] Hence, the results of our study are consistent with the studies done previously. Contrasting results were reported by Karande et al. who reported an incidence of 28% for fatty liver which is lower than present study. [1]

The results of our study showed that a high prevalence of NAFLD in those who have had diabetes for a period of more than ten years, but this should be corroborated after extensive research with a larger sample size. Most of the diabetic patients are asymptomatic, but few may have symptoms of dull aching pain in right hypochondriac region as early presentation of fatty liver. It can be demonstrated clinically by palpation for hepatomegaly. From prevalence studies with data collected using USG abdomen, 65% of the total participants with 23% of the patients having diabetes less than 5 years, 26.1% of the patients having diabetes for more than 10 years and 50.9% of patients in the duration range of 6-10 years show evidence of fatty liver on ultrasound of abdomen.

In the present study raised liver enzymes was observed in 19 patients with fatty liver. However, a statistically non-significant correlation was observed between liver enzymes (AST, ALT, Sr. bilirubin) and duration of diabetes ($P>0.05$). Concurrent to our study, elevated transaminases have been found in 2.8%–13.3% in general population[14,15] and 7.8%–31.5% in T2DM.[16-21] The extent of elevated liver enzymes in Indian T2DM patients is not clear.[9]

Obesity is a significant risk factor for non-alcoholic fatty liver disease (NAFLD), with study done by Wanless and Lentz [22] reporting 70% of obese patients have liver steatosis, a condition proportional to obesity. As reported by Bellentani S is 4.6-fold more common in obese individuals and can exceed 90% in those undergoing bariatric surgery. Concurrent to our study, Kalra et al. [9] have found that in Indian T2DM patients, obese individuals have 14% higher risk for NAFLD.

In our study, Dyslipidemia is more common in NAFLD patients, with NAFLD present in around 50% of dyslipidemia patients. Hyperlipidemia, particularly high triglycerides and low HDL-cholesterol, is strongly associated with NAFLD ($P<0.05$). Anecdotal studies done by Marchesini et al. [23] have shown that hypertriglyceridemia and low HDL-cholesterol levels are present in 64% and 30%-42% of NAFLD patients, respectively. In a study done by Duseja.,[24] on Indian subjects, abnormal cholesterol, TG, and HDL levels were present in 36%, 53%, and 66%. Silaghi et al. [25] found significant associations between sex, ALT, and LDL cholesterol with NAFLD in T2DM subjects. Contrasting results were reported by Karande et al. who reported a statistical non-significant correlation of liver enzymes (AST, ALT, Sr. bilirubin) with duration of diabetes for all three liver enzymes tested (AST, ALT, Sr. biliribun). [1]

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The study found that diabetics have a significantly higher risk of developing gallstones [10(15.3%), a finding that contradicts the long-standing debate about whether type 2 diabetes (T2DM) predisposes to gallstone formation. A case-control study done by Sodhi et al. [26] involving 450 T2DM patients showed a 17.7% higher likelihood of gallstones. Also, study done by Manoria P et al. [4] reported an incidence of 15.81% which was similar to our study.Bodmer et al.,[27] retrospectively studied the prevalence of diabetes in subjects undergoing cholecystectomy and in four times group of controls and concluded that diabetes is not an independent risk factor for cholecystectomy. Our study found a significant correlation between gallstones and Type 2 Diabetes Mellitus (T2DM), despite some studies showing a higher prevalence of gallstones among diabetics.

The limitation of our study is that it has been conducted on a small scale and hence all the results before being extrapolated to the population have to be conducted on a larger scale. Further, liver biopsy was not done, but the studies have shown that USG is the most common method of diagnosing NAFLD and biopsy is seldom necessary. Further, we dint compared the study group with control group in our study.

CONCLUSION

The study concluded that T2DM patients have a high prevalence of fatty liver and gallstones, with higher liver enzyme levels and hepatic steatosis. These conditions are more common in diabetics. BMI and WC have a positive correlation with non-alcoholic fatty liver disease (NAFLD), with fatty liver patients having more LDL, TG, and HDL. T2DM, BMI >25 kg/m2, elevated WC, and elevated liver enzymes are independent predictors of fatty liver occurrence.

Glycemic control management is crucial for preventing diabetes complications like metabolic syndrome, central obesity, and hepatic involvement. Gradual weight loss and good blood glucose control are recommended for patients with steatohepatitis.

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