Original Article

Hepatobiliary dysfunction in Type-2 diabetes mellitus

Piyush Manoria[1], Sameer Inamdar[2], Ravindra Kumar[3]

Departments of [1]Gastroenterology and [2]Medicine, Sri Aurobindo Medical College and PG Institute, [3]Central Research Laboratory, Sri Aurobindo Medical College and PG Institute, Indore, Madhya Pradesh, India

Abstract

Objective: Nonalcoholic fatty liver disease (NAFLD) and gallstones are frequently present in diabetics, but its exact prevalence is not well studied in India. We have done a prevalence study of hepatobiliary involvement in Type-2 diabetes mellitus (T2DM) and also studied the other risk factors of NAFLD. **Materials and Methods:** Two hundred diabetics and 200 controls underwent anthropometric measurements, abdominal ultrasonography, (USG) and biochemical tests at a tertiary care hospital. Univariate and multivariate logistic regression analyses were done. **Results:** One hundred and thirty (65%) diabetics and 47 (23.50%) controls were having USG evidence of fatty liver (odds ratio [OR] = 6.046, 95% confidence interval [CI]: 3.904–9.363 [$P < 0.0001$]). Raised liver enzymes were present in 42 (21%) diabetics and 16 (8%) controls [OR = 3.057, 95% CI: 1.654–5.648 [$P < 0.004$]). Gallstones were present in 32 (16%) diabetics and 10 (5%) controls (OR = 2.825; 95% CI: 1.850–4.315 $P < 0.0001$). In addition, waist circumference (WC) and body mass index (BMI) were significantly more in diabetics, but lipid profile was not significantly deranged as compared to controls. Then, all patients with fatty liver were compared with patients with normal liver, and we found that fatty liver group was having raised BMI, WC, liver enzymes, and more dyslipidemia. Multivariate analysis was done which shows the presence of T2DM, elevated liver enzymes, obesity, and elevated WC as independent risk factors of fatty liver. **Conclusion:** The prevalence of NAFLD and gallstones was higher in diabetics as compared to healthy population. In addition, the presence of T2DM, elevated liver enzymes, obesity, and elevated WC are independent predictors of NAFLD.

Keywords: Dyslipidemia, fatty liver, gallstone, nonalcoholic fatty liver disease, Type-2 diabetes mellitus

Introduction

Nonalcoholic fatty liver disease (NAFLD) which develops in the absence of alcohol abuse is now recognized as one of the major health burden. The 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. With increasing incidence and prevalence of NAFLD, the perception of it being a benign condition is rapidly changing. It includes steatosis (increased liver fat without inflammation) and nonalcoholic steatohepatitis (NASH) (increased liver fat with inflammation). Simple steatosis is not dangerous for the patient, but NASH may progress to end-stage liver disease (cirrhosis), liver failure, and hepatocellular carcinoma.[1] The pathogenesis of NASH is poorly understood, but lipid peroxidation and oxidative stress are the leading culprits.[2] Patients with NAFLD appear to have a higher all-cause mortality in addition to liver-related cause of death and an increased risk for cardiovascular disease.[1] There is an epidemic of Type-2 diabetes mellitus (T2DM) affecting 285 million people worldwide in 2010, and this number is expected to rise to 439 million by 2030.[3] Numerous studies show that NAFLD is the hepatic component of metabolic syndrome. NAFLD is becoming the most common liver disorder worldwide with a median prevalence of around 20% in general population[4] and 42%–70% in T2DM.[5] Its prevalence in India is studied in only few studies. Gallbladder emptying abnormalities are also found in diabetic patients who may predispose them to

Address for correspondence: Dr. Ravindra Kumar, Central Research Laboratory, Sri Aurobindo Medical College and PG Institute, Indore Ujjain Highway, Indore - 453 111, Madhya Pradesh, India.
E-mail: ravindrachhabra@gmail.com

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/2249-4863.222018

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Manoria P, Inamdar S, Kumar R. Hepatobiliary dysfunction in Type-2 diabetes mellitus. J Family Med Prim Care 2017;6:563-7.

cholelithiasis, but obesity and hyperlipidemia may be contributing factors. Thus we conduct our study to know the prevalence of NAFLD and gallstones in patients with T2DM coming to our institute and to compare it with normal healthy individuals. In addition, we have compared anthropometric measurements and various biochemical tests between the two. We have also compared anthropometric and biochemical variables between patients having fatty liver with patients not having it.

Materials and Methods

A total of 200 patients of Type-2 DM attending the Outpatient Department of Medicine for routine checkup at a tertiary care institute were studied for the presence and type of hepatobiliary dysfunction between January 2012 and September 2013. Patients with alcohol intake more than 20 g/day, positive hepatitis B surface antigen, positive anti-hepatitis C virus, having significant comorbidities (sepsis, organ failure, malignancy, etc.), positive antinuclear antibody and taking hepatotoxic drug for more than 3 consecutive months were excluded from the study. A total of 200 nondiabetic volunteer age- and sex-matched healthy controls were also recruited for comparison. Exclusion criteria for controls were same as that for patients. All subjects gave informed consent, and the study protocol was approved by the Ethics Committee of Institute.

A thorough medical history and physical examination were performed including measurement of height, weight, and waist circumference (WC). 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 <90 cm for men and <80 cm for women. BMI between 23 and 24.9 kg/m^2 are overweight and >25 kg/m^2 are obese.

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.

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. Lipid profile and liver enzymes were analyzed using automated biochemistry analyzer. HbA1C was measured using chemiluminescence analyzer (Elecsys 2010 Systems, Hitachi, Japan).

Statistical analysis

All data were stored in Microsoft Excel format and were analyzed using IBM SPSS version 20.0 software (SPSS, Chicago, Illinois, USA). P <0.05 was considered statistically significant. 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.

Results

Baseline characteristic of cases and controls are shown in Table 1. The mean age of cases was 55.75 ± 14.53 years, of which 113 were male and 87 were female. The mean age of controls was 53.71 ± 13.42 years, of which 115 were male and 85 were female. 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) [Table 1]. Out of 130 diabetic with NAFLD patients, eighty patients had Grade 1 NAFLD, thirty patients had Grade II NAFLD whereas Grade III

Table 1: Clinical and laboratory characteristics of cases and controls

Variables	Diabetics (*n*=200)	Controls (*n*=200)	95% CI	OR	*P*
Mean age	55.75±14.53 years	53.71±13.42 years	-	-	0.144
Sex (male/female)	113/87	115/85	0.646-1.426	0.960	0.919
Fatty liver	130	47	3.904-9.363	6.046	<0.0001
Obesity (BMI >25 kg/m^2)	135	89	1.725-3.890	2.590	<0.0001
Elevated liver enzymes	42	16	1.654-5.648	3.057	0.004
Elevated liver enzymes + fatty liver	40	12	1.987-7.722	3.917	<0.0001
Elevated waist circumference	174	154	1.179-3.388	1.999	0.0134
Raised cholesterol	90	70	1.016-2.273	1.519	0.525
Raised LDL	113	101	0.8857-1.888	1.273	0.272
Low HDL	139	116	1.093-2.491	1.650	0.221
Raised TG	102	84	0.9686-2.133	1.437	0.083
Gallstones	32	10	1.850-4.315	2.825	<0.0001

CI: Confidence interval; OR: Odds ratio; BMI: Body mass index; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglyceride

NAFLD was observed in twenty diabetic patients [Table 2]. Patients having more duration of diabetes have more incidence of Grade III NAFLD as compared to patients with lesser duration ($P < 0.0001$) [Table 3]. Diabetic patients were also found to have higher risk of obesity, high WC, elevated liver enzymes, and occurrence of gallstones. Among the lipid profile, no variable was found to be significantly altered in diabetic patients as compared to nondiabetic.

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 5].

Discussion

The result of our study showed that patients with T2DM have significantly higher prevalence of NAFLD on abdominal ultrasonography as compared to healthy controls (130/200 vs. 47/200 [$P < 0.0001$]). Worldwide prevalence of NAFLD ranges from 6.3% to 33% with a median of 20% in the general population.[4] In Indian population, its prevalence is around 9%–32%.[6-12] 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.[13] 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.[14] The overall prevalence of NAFLD in T2DM in Indian population is reported to be in range of 12.5%–87.5%.[8-10,12,15] Hence, the results of our study are consistent with the studies done previously.

Similar to our study, elevated transaminases have been found in 2.8%–13.3% in general population[16,17] and 7.8%–31.5% in T2DM.[18-23] The extent of elevated liver enzymes in Indian T2DM patients is not clear.[15]

Obesity is a well-known risk factor for NAFLD which was also observed in our study. The study done by Wanless and Lentz[24] in 351 patients showed that 70% of obese patients have liver steatosis and degree of steatosis was proportional to degree of obesity. An Italian study[25] also showed that steatosis was 4.6-folds more common in obese persons. Also in persons undergoing bariatric surgery, its prevalence can exceed 90%.[4] Kalra *et al.*[15] have found that in Indian T2DM patients, obese individuals have 14% higher risk for NAFLD.

In our study, dyslipidemia was more common in NAFLD patients. NAFLD is present in around 50% of dyslipidemia patients attending lipid clinics.[26] Hyperlipidemia and specifically high levels of triglycerides and low levels of high-density lipoprotein (HDL)-cholesterol are strongly associated with NAFLD. In a study done by Marchesini *et al.*,[27] hypertriglyceridemia and low HDL-cholesterol level were present in 64% and 30%–42% of NAFLD patients, respectively. In a study done by Duseja.,[28] in Indian subjects, abnormal cholesterol, TG, and HDL were present in 36%, 53%, and 66%, respectively. Silaghi *et al.* showed that sex, ALT, low-density lipoprotein (LDL) cholesterol were significantly and independently associated with the presence of NAFLD in T2DM subjects.[29]

Table 2: Grading of fatty liver in cases and controls

Fatty liver	Diabetics	Controls
Grade I	80	31
Grade II	30	12
Grade III	20	4
Total	130	47

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

Fatty liver	Duration of DM (years)				
	<5	5-10	10-20	>20	*P*
Grade 1	23	18	30	9	<0.0001
Grade 2	1	5	12	12	
Grade 3	0	2	9	9	

DM: Diabetes mellitus

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

Variables	Fatty liver (*n*=177)	Normal liver (*n*=223)	95% CI	OR	*P*
Diabetics	130	70			
Obesity (BMI >25 kg/m^2)	150	103	3.977–10.534	6.472	<0.0001
Elevated liver enzymes	52	6	6.282–36.036	15.045	<0.0001
Elevated waist circumference	172	161	5.194–33.784	13.247	0.0001
Raised cholesterol	75	85	0.798–1.785	1.194	0.388
Raised LDL	108	106	1.158–2.578	1.728	0.007
Low HDL	123	128	1.116–2.562	1.691	0.013
Raised TG	95	82	1.108–2.456	1.650	0.013
Gallstones	28	14	1.428–5.511	2.805	0.0028

CI: Confidence interval; OR: Odds ratio; BMI: Body mass index; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglyceride

Table 5: Multivariate regression analysis of variables to predict nonalcoholic fatty liver disease

Variables	*B*	OR	95% CI	*P*
T2DM	1.569	4.800	2.836-8.124	<0.0001
Elevated liver enzymes	2.796	16.377	5.638-47.574	<0.0001
Obesity (BMI >25 kg/m^2)	1.964	7.127	3.897-13.035	<0.0001
Elevated waist circumference	2.387	10.884	3.997-29.641	<0.0001

CI: Confidence interval; OR: Odds ratio; NAFLD: Nonalcoholic fatty liver disease; T2DM: Type 2 diabetes mellitus; BMI: Body mass index

Diabetics were having more gallstones in a statistically significant manner in the present study. There is a long-standing debate that whether T2DM predisposes toward gallstone formation. Sodhi *et al.* done a case-control study involving 450 T2DM patients with >2 years of duration and observed that patients with T2DM had higher probability of having gallstone (17.7%) as compared to the general population (5.8%).[30]

Bodmer *et al.*,[31] 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. Hence, some studies have shown that a higher prevalence of gallstones among diabetics compared with nondiabetics while in others, there was no association. Our study showed a significant correlation between gallstones and T2DM.

The limitation of our study is that 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.

Hence, to conclude that prevalence of fatty liver and gallstones was high among T2DM patients. Liver enzymes were also more raised in diabetics as compared to nondiabetics. In addition, both these conditions, i.e., hepatic steatosis and raised liver enzymes were more common in diabetics compared to nondiabetics. BMI and WC have positive correlation with NAFLD as both these variables were more in patients with fatty liver. Dyslipidemia also has a positive correlation with NAFLD. LDL and TG were more, and HDL was less in patients with fatty liver. The presence of T2DM, BMI >25 kg/m^2, elevated WC, and elevated liver enzymes are independent predictors of occurrence of fatty liver.

Conclusion

Since in the present study, T2DM patients have found at risk for NAFLD and raised liver enzymes, family care physician should counsel and advise their patients for monitoring for NAFLD, liver enzymes, and lipid profile. Family physician should also counsel for dietary and lifestyle changes that may prevent the NAFLD.[32]

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Torres DM, Harrison SA. Diagnosis and therapy of nonalcoholic steatohepatitis. Gastroenterology 2008;134:1682-98.
2. Reid AE. Nonalcoholic steatohepatitis. Gastroenterology 2001;121:710-23.
3. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010;87:4-14.
4. Vernon G, Baranova A, Younossi ZM. Systematic review: The epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 2011;34:274-85.
5. Ahmed MH, Husain NE, Almobarak AO. Nonalcoholic fatty liver disease and risk of diabetes and cardiovascular disease: What is important for primary care physicians? J Family Med Prim Care 2015;4:45-52.
6. Duseja A. Nonalcoholic fatty liver disease in India – A lot done, yet more required! Indian J Gastroenterol 2010;29:217-25.
7. Majumdar A, Misra P, Sharma S, Kant S, Krishnan A, Pandav CS. Prevalence of nonalcoholic fatty liver disease in an adult population in a rural community of Haryana, India. Indian J Public Health 2016;60:26-33.
8. Gupte P, Amarapurkar D, Agal S, Baijal R, Kulshrestha P, Pramanik S, *et al.* Non-alcoholic steatohepatitis in type 2 diabetes mellitus. J Gastroenterol Hepatol 2004;19:854-8.
9. Amarapurkar D, Kamani P, Patel N, Gupte P, Kumar P, Agal S, *et al.* Prevalence of non-alcoholic fatty liver disease: Population based study. Ann Hepatol 2007;6:161-3.
10. Mohan V, Farooq S, Deepa M, Ravikumar R, Pitchumoni CS. Prevalence of non-alcoholic fatty liver disease in urban South Indians in relation to different grades of glucose intolerance and metabolic syndrome. Diabetes Res Clin Pract 2009;84:84-91.
11. Uchil D, Pipalia D, Chawla M, Patel R, Maniar S, Narayani, *et al.* Non-alcoholic fatty liver disease (NAFLD) – the hepatic component of metabolic syndrome. J Assoc Physicians India 2009;57:201-4.
12. Prashanth M, Ganesh HK, Vima MV, John M, Bandgar T, Joshi SR, *et al.* Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus. J Assoc Physicians India 2009;57:205-10.
13. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, *et al.* Prevalence of hepatic steatosis in an urban population in the United States: Impact of ethnicity. Hepatology 2004;40:1387-95.
14. Forlani G, Giorda C, Manti R, Mazzella N, De Cosmo S, Rossi MC, *et al.* The burden of NAFLD and its characteristics in a nationwide population with type 2 diabetes. J Diabetes Res 2016;2016:2931985.
15. Kalra S, Vithalani M, Gulati G, Kulkarni CM, Kadam Y, Pallivathukkal J, *et al.* Study of prevalence of nonalcoholic fatty liver disease (NAFLD) in type 2 diabetes patients in India (SPRINT). J Assoc Physicians India 2013;61:448-53.
16. Lazo M, Clark JM. The epidemiology of nonalcoholic fatty liver disease: A global perspective. Semin Liver Dis

2008;28:339-50.

17. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. Am J Gastroenterol 2003;98:960-7.
18. Yildirim B, Ozugurlu F, Sahin S, Ozyurt H, Atis O, Akbas A, *et al.* Association between elevated aminotransferase levels and the metabolic syndrome in Northern Turkey. Ann Hepatol 2010;9:161-5.
19. Harris EH. Elevated liver function tests in type 2 diabetes. Clin Diabetes 2005;23:115-9.
20. West J, Brousil J, Gazis A, Jackson L, Mansell P, Bennett A, *et al.* Elevated serum alanine transaminase in patients with type 1 or type 2 diabetes mellitus. QJM 2006;99:871-6.
21. Meybodi MA, Afkhami-Ardekani M, Rashidi M. Prevalence of abnormal serum alanine aminotransferase levels in type 2 diabetic patients in Iran. Pak J Biol Sci 2008;11:2274-7.
22. Judi L, Toukan A, Khader Y, Ajlouni K, Khatib MA. Prevalence of elevated hepatic transaminases among Jordanian patients with type 2 diabetes mellitus. Ann Saudi Med 2010;30:25-32.
23. Esteghamati A, Jamali A, Khalilzadeh O, Noshad S, Khalili M, Zandieh A, *et al.* Metabolic syndrome is linked to a mild elevation in liver aminotransferases in diabetic patients with undetectable non-alcoholic fatty liver disease by ultrasound. Diabetol Metab Syndr 2010;2:65.
24. Wanless IR, Lentz JS. Fatty liver hepatitis (steatohepatitis) and obesity: An autopsy study with analysis of risk factors. Hepatology 1990;12:1106-10.
25. Bellentani S, Saccoccio G, Masutti F, Crocè LS, Brandi G, Sasso F, *et al.* Prevalence of and risk factors for hepatic steatosis in Northern Italy. Ann Intern Med 2000;132:112-7.
26. Assy N, Kaita K, Mymin D, Levy C, Rosser B, Minuk G. Fatty infiltration of liver in hyperlipidemic patients. Dig Dis Sci 2000;45:1929-34.
27. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M, *et al.* Nonalcoholic fatty liver disease: A feature of the metabolic syndrome. Diabetes 2001;50:1844-50.
28. Duseja A. Nonalcoholic fatty liver disease in India – is it different? Trop Gastroenterol 2006;27:142-6.
29. Silaghi CA, Silaghi H, Colosi HA, Craciun AE, Farcas A, Cosma DT, *et al.* Prevalence and predictors of non-alcoholic fatty liver disease as defined by the fatty liver index in a type 2 diabetes population. Clujul Med 2016;89:82-8.
30. Sodhi JS, Zargar SA, Khateeb S, Showkat A, Javid G, Laway BA, *et al.* Prevalence of gallstone disease in patients with type 2 diabetes and the risk factors in North Indian population: A case control study. Indian J Gastroenterol 2014;33:507-11.
31. Bodmer M, Brauchli YB, Jick SS, Meier CR. Diabetes mellitus and the risk of cholecystectomy. Dig Liver Dis 2011;43:742-7.
32. Nseir W, Hellou E, Assy N. Role of diet and lifestyle changes in nonalcoholic fatty liver disease. World J Gastroenterol 2014;20:9338-44.