

Original Article

Prevalence of Non Alcoholic Fatty Liver Disease in Type 2 Diabetes Mellitus and Association with Metabolic Syndrome

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Abstract

Background

Non alcoholic fatty liver disease- a recently recognized entity, is being increasingly reported in general population and commonly associated with type 2 diabetes mellitus. NAFLD is also commonly associated with obesity, dyslipidemia, and insulin resistance, all of which are components of the metabolic syndrome-strongly supporting the notion that NAFLD is the hepatic manifestation of the syndrome.

Aims and objectives

To determine prevalence of NAFLD in type 2 diabetes mellitus, and comparing the prevalence of NAFLD in cases with that of age and gender matched non diabetic controls and its association with metabolic syndrome and various components of metabolic syndrome.

Methods

In this Case control hospital based study 100 Cases of type 2 diabetes mellitus(WHO criteria) attending out patient clinic having age more than 40 years were included. While conditions affecting liver were excluded. All cases(n=100) and controls(n=100) were subjected to abdominal ultrasound for prevalence of fatty liver.

Results

Prevalence of NAFLD was significantly more in cases of type 2 DM (62%) than controls(22%)Parameters (Hypertension, BMI, Waist circumference)suggestive of central obesity was observed in significantly higher number of cases (69%) as compared to (35%) of controls. Univariate analysis demonstrated significant association of NAFLD in cases of type 2 diabetes mellitus with smoking, hypertension dyslipidemia, central obesity & BMI ($p<0.0001$), Lab parameters like ALT, AST and albuminuria also showed significant association($p<0.002$). Metabolic syndrome was found to be significantly associated with NAFLD in cases of type 2 diabetes mellitus(OR 8.16, 95% CI 2.98-22.70, $p<0.0001$) Multiple logistic regression analysis revealed independent association of NAFLD with Obesity, Increased waist circumference Hypertriglyceridemia & ALT.

Conclusions

Non Alcoholic Fatty Liver Disease is prevalent in type 2 diabetes mellitus. NAFLD in type 2 diabetes mellitus is associated with metabolic syndrome.

Key words: NAFLD, Diabetes mellitus, metabolic syndrome

Introduction

Non-alcoholic fatty liver disease (NAFLD), a practically unheard entity before 30 years, is now considered as one of the most common liver disorders in the US and a leading cause of cirrhosis in adults.^{1,2} NAFLD represents a spectrum of clinical-pathological features ranging from simple steatosis, i.e. fatty infiltration, to non-alcoholic steatohepatitis (NASH), which is characterised by inflammation and hepatocellular injury with or without fibrosis and cirrhosis^{3,4}. The prevalence of NAFLD has

increased in parallel with the epidemics of obesity and type 2 diabetes, which are risk factors for NAFLD. NAFLD is commonly associated with obesity, type 2 diabetes mellitus, dyslipidemia, and insulin resistance, all of which are components of the metabolic syndrome, strongly supporting the notion that NAFLD is the hepatic manifestation of the syndrome⁵

The prevalence of NAFLD has been reported to be in the 15–30% range in the general population in various countries and is almost certainly increasing. It has been estimated that 70–75% of type 2 diabetic patients may have some form of NAFLD; however, the “precise” prevalence of NAFLD in type 2 diabetes mellitus is unknown. The few available studies have been small and performed in highly selected populations or have estimated only the prevalence of abnormal amino

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transferase levels, which are a poor proxy measure of NAFLD.⁶

Histological examination of the liver is gold standard for diagnosis of NAFLD and only way to distinguish between fatty liver and hepatic fibrosis, but to do biopsy for everyone suspected of having NAFLD would not be practically feasible. Ultrasonography is simple, non-invasive, cost effective and can be easily performed with high sensitivity⁷ Whereas the association of type 2 diabetes with microvascular complications and macrovascular disease is well established, the association of type 2 diabetes mellitus with NAFLD is more recently recognized and probably less well-known to physicians. Furthermore, because patients are usually asymptomatic and routine blood tests are often normal, it may be a diagnosis that is overlooked in patients with type 2 diabetes mellitus. Recent data suggest that the presence of NAFLD in type 2 diabetes may also be linked to increased cardiovascular disease (CVD) risk independently of components of the metabolic syndrome, although this hypothesis needs verification in larger studies. However, if correct, these data suggest that the identification of NAFLD in type 2 diabetes may help in CVD risk prediction with important management implications. Identifying people with NAFLD would also highlight a subgroup of diabetic patients who should be targeted with more intensive therapy to decrease their risk of future CVD events⁸

Methods

In this present case control hospital based study. 100 cases of type 2 Diabetes mellitus (diagnosed by WHO criteria) attending diabetic out patient clinic of the institution were enrolled & compared with 100 age and gender matched controls. The aims and objectives of the study were to determine prevalence of NAFLD (assessed by abdominal ultrasound) in type 2 diabetes mellitus, comparing the prevalence of NAFLD in cases with that of non diabetic controls and its association with metabolic syndrome and various components of metabolic syndrome. (hypertension, dyslipidemia and obesity). Cases diagnosed as hepatitis B, hepatitis C, Autoimmune hepatitis, Wilson's disease, haemochromatosis, connective tissue disorders, pregnant diabetic patients, patients on Amiodarone, Methotrexate, Tamoxifen, estrogens, cases with acute medical illness and cases of type 2 diabetes mellitus consuming alcohol > 20 grams per day were excluded from the study. Controls were selected from healthy, non diabetic & non alcoholic subjects who visit the hospital. All cases underwent detailed history, clinical examination including measurement of blood pressure, height, weight, BMI, waist circumference and for

signs and symptoms of DM, NAFLD or complications of type 2 DM. Biochemical investigations included fasting and post prandial blood sugar, glycated hemoglobin, 24 hours urine albumin serum creatinine, lipid profile (total cholesterol, LDL, triglycerides and HDL cholesterol). Liver function tests estimation included ALT, ALT, serum bilirubin and serum proteins. Written consent from all study subjects was obtained & approval of the ethic committee of the institution was also taken.

All cases and controls were subjected to abdominal ultrasound independently by 2 experienced radiologists blinded to subject details using a high resolution B-mode ultrasonography system. Fatty liver was defined as the presence of an ultrasonographic pattern consistent with "bright liver" "with evident ultrasonographic contrast between hepatic and renal parenchyma, vessel blurring and narrowing of the lumen of the hepatic veins in absence of findings suggestive of chronic liver disease. NAFLD was defined as any degree of fatty liver in the absence of alcohol intake. NAFLD, if present, was classified based on standard ultrasonographic RUMAC criteria. Sensitivity of ultrasonography was 90% to 94% and a specificity of 84% in detection of moderate and severe hepatic steatosis, when hepatic infiltration on liver biopsy is 30%⁹

Metabolic syndrome was defined by NCEP-ATPIII guidelines

At least three of the following five should be present

- 1) Waist circumference: >102 cm in mens (>90CM in South Asian) 88 cm in female (>80 cm in South Asian)
- 2) Hypertriglyceridemia: >150 mg per dl or specific medication
- 3) Low HDL cholesterol: <40 mg per dl in men <50 mg per dl in female
- 4) Blood pressure: >130mm Hg systolic >85 mm Hg diastolic or specific medication
- 5) Impaired fasting glucose >100 mg/dl or previously diagnosed type 2 DM. Statistical analysis results were analysed using software STATA version 10.0 for data analysis.

Results

Prevalence of NAFLD was 62% in cases and 22% in controls. The odds of cases of type 2 DM having NAFLD was 5.78 times higher than non diabetic controls (OR 8.16, 95% CI 2.98-22.70, $p < 0.0001$). (Fig. 1) It was also observed that cases of type 2 DM were associated with higher grades of NAFLD as compared with controls. Out of 62 cases with NAFLD, 32 (51.61%) had mild grade, 25 (40.32%) had moderate grade and 5 (8.06%) had severe grade fatty liver while in controls all 22 (100%) cases were

in mild grade group. None of the controls had moderate or severe grade fatty liver as assessed by ultrasonography ($\chi^2 = 16.55$, $p < 0.0001$). Age and gender did not reveal statistically significant difference in cases of type 2 DM with and without NAFLD ($p > 0.05$, and 0,394 resp)

Components of metabolic syndrome (viz. obesity-assessed by BMI and waist circumference, dyslipidemia and hypertension) were present significantly in higher number of cases as compared to controls. **(Table 1)** Metabolic syndrome was present in 61% cases compared to 32% controls with statistically significant difference between two (OR 3.32, 95% CI 1.78-6.20, (P value 0.001)

Present study did not demonstrate significant age and gender difference in cases of type 2 diabetes mellitus with or without NAFLD. BMI, Waist circumference systolic as well as diastolic blood pressures were significantly higher in cases with NAFLD) than those without NAFLD **(Table 2) & Fig. 2.**

Results of the univariate analysis demonstrated significant association of NAFLD in cases of type 2 diabetes mellitus with smoking, hypertension, dyslipidemia, central obesity (increased waist circumference male > 90 cm, female > 80 cm), BMI, ALT and AST. **(Table 3 & 4)**

Multiple logistic regression analysis revealed independent association of NAFLD with

1) Obesity: as assessed by Increased BMI > 25 kg/m² (OR 1.64, 95% CI 1.01-2.65, P value 0.044) and Increased waist circumference (OR 1.36, 95% CI 1.09-1.68, P value 0.005)
2) Hypertriglyceridemia (OR 1.09, 95% CI 1.03-1.17, P value 0.01 and 3) ALT (OR 2.05, 95% CI 1.39-3.02, P value 0.001) **(Table 5)**

Discussion

Prevalence of non alcoholic fatty liver disease, is increasing in the community. NAFLD has been reported to be more common in type 2 Diabetes mellitus as compared to general population. Metabolic syndrome is also found to be highly prevalent in type 2 Diabetes mellitus as well as NAFLD. Sharing a common determinant as insulin resistance, presence of NAFLD is associated with increased morbidity and mortality in case of type 2 diabetes mellitus, not only because of liver cirrhosis but also because of increased cardiovascular events and other vascular complications of Diabetes.

In the present study, prevalence of NAFLD in diabetes was found to be 62% while that in age and sex matched healthy control was 32%, with highly significant statistical difference (p , OR 5.78, 95% CI 2.97-11.34 value 0.0001). Reported prevalence of NAFLD in Type 2 DM in the various studies is in the range of 54-57% (S. Merat et al¹⁰, Mohan et al¹¹ & Agrawal et al,¹²) which was significantly

higher.

Results of the present study are well correlating with others. We observed that, cases with type 2 diabetes mellitus had higher grades of fatty liver disease as compared to controls. However, in the present study grading of NAFLD was done by ultrasonography. Differentiation of steatosis from fatty liver requires liver biopsy which was not performed in this study, as it may lead to life threatening complications. Sensitivity and specificity of ultrasonography for detection of NAFLD is 94% and 84% respectively as reported in literature¹³. Zobair M. Younossi Et al¹³, demonstrated Cirrhosis (histological or clinical) in 25% of patients with DM with NAFLD compared with only 10.2% of patients without DM with NAFLD ($P < 0.04$). Angulo et al¹⁴ found that, diabetes mellitus ($P < 0.009$), was significant predictor of severe liver fibrosis (bridging/cirrhosis).

Prevalence of Metabolic syndrome in Type 2 DM was significantly high as reported previously. Similar findings were observed in the present study (significantly higher number of cases With type 2 diabetes 61% as compared to controls 32% (OR 3.32. CI 1.78-6.20, (P value 0.0001) Mishra et al found the prevalence of metabolic syndrome and NAFLD to be 24% and 14.8% respectively, in non-alcoholic North Indian men.

Univariate analysis was performed to determine the association of NAFLD with components of metabolic syndrome, results of the analysis revealed that: Obesity { increased waist circumference (male > 90 cm, female > 80 cm) BMI > 25 kg/m²}, Hypertension, Fasting and post prandial blood glucose, Hb A1C Serum AST and ALT, Total cholesterol, LDL cholesterol, Hypertriglyceridemia, low HDL cholesterol, presence of metabolic syndrome, were significantly higher in cases with NAFLD as compared to cases without NAFLD. Results of the multiple logistic regression analysis demonstrated that factors viz Triglycerides, Waist circumference, BMI and Serum ALT to be independently associated with NAFLD

Similar kind of studies performed by various authors found strong association of components of metabolic syndrome, duration of DM & HbA1c with NAFLD^{15,16,17}. Present study demonstrated association of metabolic syndrome and its components with NAFLD in cases of type 2 diabetes mellitus.

Association of NAFLD with coronary artery disease has already been documented by Targher et al¹⁸. However, to demonstrate the exact association of NAFLD in type 2 diabetes mellitus – as a risk factor, or a complication – large sample sized prospective studies are needed.

Implications

Although Cardiovascular event is considered as one of the important factor for increased morbidity and mortality among cases of type 2 diabetes mellitus, NAFLD is being increasingly recognized as an additional important comorbidity. NAFLD in type 2 diabetes mellitus has also been mentioned as an important risk factor for coronary artery disease NAFLD and metabolic syndrome have been documented to increase the risk of vascular events in type 2 diabetes mellitus.

Obesity, in any form especially central has an important association with NAFLD. Whether NAFLD develops earlier or late in the natural history of type 2 DM is exactly not known. Lifestyle modification, weight reduction and treatment of obesity have been reported to be most promising interventions. As the prevalence of NAFLD is found to rising, even in adolescents and it is found high in DM, timely interventions are absolutely essential to prevent and treat this new disease entity.¹⁹

Ultrasonography is simple, non invasive, cost effective and highly sensitive method to detect NAFLD. It may be

recommended that cases of type 2 DM should be routinely and frequently screened for identifying NAFLD because of the high prevalence. However, whether it is really cost effective or not, needs to be evaluated in large sample sized, multicentric, prospective studies.

Limitations of study

Present study is a hospital based and Cross sectional study, has a Small sample size. Diagnosis of NAFLD in the present study is based on abdominal ultrasonography and liver biopsy has not been performed.

Conclusions

Non Alcoholic Fatty Liver Disease is prevalent in type 2 diabetes mellitus. NAFLD in type 2 diabetes mellitus is associated with metabolic syndrome & it's components. NAFLD is independently associated with waist circumference, BMI, serum triglycerides and ALT. Ultrasonography is simple, non invasive, cost effective and highly sensitive method to detect NAFLD. It may be recommended that cases of type 2 DM should be routinely and frequently screened for identifying NAFLD

1. Components of metabolic syndrome in cases and controls

Risk factors	Cases(%)	Controls(%)	OR	95% CI	P value
Hypertension	62 (62%)	33(33%)	3.31	1.78-6.17	0.0000
BMI>25 kg/m ²	60 (60%)	38(38%)	2.45	1.33-4.49	0.0019
WC (Males >90cm Females>80cm)	68 (68%)	35(35%)	3.94	2.10-7.42	0.0000
Dyslipidemia	58 (58%)	32(32%)	2.93	1.58-5.47	0.0002
Metabolic syndrome	61 (61%)	32(32%)	3.32	1.78-6.20	0.0000

Table2 . Comparison of clinical parameters in cases of type 2diabetes mellitus with and without NAFLD

Parameter	Cases with NAFLD(n=62)	Cases without NAFLD(n=38)	P VALUE
Mean BMI±SD(kg/m ²)	27.94±2.90	26.98±2.31	0.041
Mean waist circumference(cm)	95.48±8.68	88.76±	0.0001
Mean systolic blood pressure (mmHg)	147.38±18.32	129.89±	0.0001
Mean diastolic blood pressure (mmHg)	90.32±8.86	83.94±13.06	0.0045

Table 3 Baseline biochemical characteristics of Cases with NAFLD and without NAFLD

Characteristics	Cases With NAFLD (n=62)	Cases Without NAFLD (n=38)	P value
Fasting Blood Glucose mean (mg%) Range	142.77±23.04 90-189	118.63±21.36 89-156	0.0000*
Post prandial Blood Glucose mean(mg%) Range	257.48±56.16 145-389	205.60±39.97 145-290	0.0000*
Glycated Hb (%) range	8.72±0.68 7.210	7.38±0.50 6.9-8.5	0.0000*
Total cholesterol mean (mg%) Range	203.58±17.32 162-254	187.36±14.36 154-205	0.0000*
LDL cholesterol mean (mg%) Range	107.58±14.89 85-134	99.05±8.72 85-128	0.0018*
HDL cholesterol mean(mg%) Range	40.03±6.41 32-55	45.28±5.33 35 -52	0.000†
Triglyceride mean(mg%) Range	170.4±17.08 134 196	149.55±10.39 139 -190	0.0000*

* Statistically significant

Table 4 . Association of NAFLD with components of metabolic syndrome

Component of metabolic syndrome	Cases With NAFLD (n=62)	Cases Without NAFLD (n=38)	OR	95% CI	P value
Hypertension	49(79.03%)	13(34.21%)	7.24	2.67-19.88	0.0000 HS
Dyslipidemia Triglyceride>150 mg/dl HDL m <40 mg/dl .f <50 mg/dl	48(77.41%)	12(31.57%)	7.42	2.74-20.38	0.0000 HS
Waist circumference m>90 cm f>80 cm	50(80.64%)	19(50%)	4.16	1.55-11.28	0.0013
Metabolic syndrome	49(79.03%)	12(31.57%)	8.16	2.98-22.70	0.0000 HS

HS = Statistically Highly significant

Table 5 Multiple Regression Analysis

Parameter	OR	95% CI	P value
ALT	2.05	1.39-3.02	0.000*
WC (>90 M , >80 F)	1.36	1.09-1.68	0.005*
Serum Triglyceride	1.09	1.03-1.17	0.003*
BMI >25	1.64	1.01-2.65	0.044

* Statistically significant

Fig. 1: Prevalance of NAFLD in cases and controls

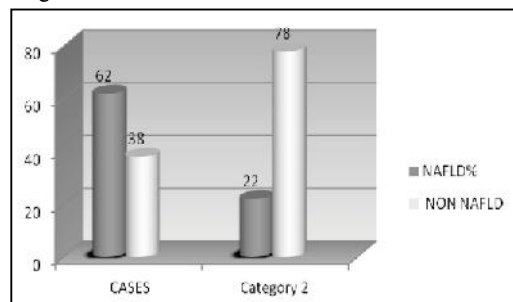
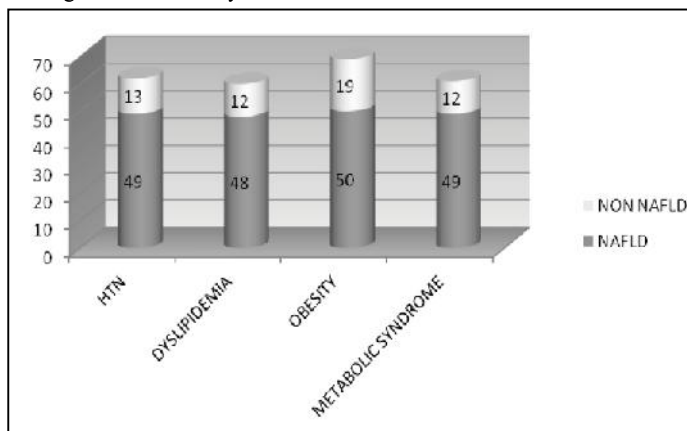


Fig. 2: Metabolic syndrome in cases with and without NAFLD



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