Study of Non-Alcoholic Fatty Liver Disease and Its Association with Coronary Artery Disease

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Abstract: Introduction: Non-alcoholic fatty liver disease (NAFLD) is a type of fatty liver which occurs when fat is deposited in the liver due to causes other than excessive alcohol use. Data suggests that NAFLD is also an independent risk factor of cardiovascular disease, which remains the commonest cause of mortality in such patients. Aims: This study was conducted to estimate the prevalence of NAFLD diagnosed by ultrasound examination of the liver in type 2 diabetes mellitus (DM) and to assess the association between NAFLD and coronary artery disease (CAD) in type 2 DM. Settings and Design: This is an observational study conducted at Department of General Medicine of a tertiary care centre for 2 years. Methods: 500 adult patients (age >18 years) of type 2 DM were evaluated for NAFLD, CAD and other cardiovascular risk factors. Statistical analysis used: Microsoft Excel® and SPSS® 20 for Windows® were used for data storage and analysis. Results: The incidence of NAFLD was 44% in all diabetics, among them males were affected more (50%) than females (40%). Mean BMI was 27.8 and 27.2 among males and females respectively. NAFLD subjects had higher incidence of smoking, hypertension, obesity, dyslipidemia, uncontrolled sugar and CAD than Non-NAFLD group subjects. These differences were statistically significant. Conclusions: Clinicians should look for NAFLD in diabetics, especially in the presence of the metabolic syndrome. Once found, aggressive management of risk factors for CAD should be the primary goal, given the greater odds of developing CAD and the high prevalence of CAD in diabetics with NAFLD. [A Singhai, Natl J Integr Res Med, 2018; 9(2):76-80]

Key Words: Fatty liver, diabetes mellitus, coronary artery disease

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Introduction: Non-alcoholic fatty liver disease (NAFLD) is one of the types of fatty liver which occurs when fat is deposited (steatosis) in the liver due to causes other than excessive alcohol use. NAFLD is the most common liver disorder in developed countries[1,2] NAFLD is related to insulin resistance and metabolic syndrome and may respond to treatments originally developed for other insulin-resistant states (e.g. diabetes mellitus type 2) such as weight loss, metformin, and thiazolidinediones.[3] Up to 80% of obese people have the disease.[4] Non-alcoholic steatohepatitis (NASH) is the most extreme form of NAFLD, and is regarded as a major cause of cirrhosis of the liver of unknown cause.[5] Most people have a good outcome if the condition is caught in its early stages.[6]

Most people with NAFLD have few or no symptoms. Patients may complain of fatigue, malaise, and dull right-upper-quadrant abdominal discomfort. Mild jaundice may be noticed although this is rare. More commonly NAFLD is diagnosed following abnormal liver function tests during routine blood tests. NAFLD is associated with insulin resistance and metabolic syndrome (obesity, mixed hyperlipidemia, diabetes mellitus, and hypertension). Data suggests that NAFLD is also an independent risk factor of cardiovascular disease, which remains the commonest cause of mortality in such patients. This study was conducted to estimate the prevalence of NAFLD diagnosed by ultrasound examination of the liver in type 2 diabetes mellitus (DM) and to assess the association between NAFLD and coronary artery disease (CAD) in type 2 DM.

Subjects and Methods:

Study Design: This is an observational study.

Study Setup: This study is conducted at Department of General Medicine of a tertiary care centre.

Study Duration: The duration of study was two years; November-2014 to October-2016.

Sampling: Purposive sampling technique is used for selection of desired samples according to inclusion criterion.

Sample Size: 500 adult patients (age >18 years) of type 2 DM were evaluated for possible inclusion in this study.

Inclusion criteria: All adults who fulfill criteria of DM by American Diabetes Association criteria or already on treatment for DM were included in this study.

Exclusion criteria: The exclusion criteria were patients of viral hepatitis (positive for hepatitis B surface antigen and anti-hepatitis C virus), history of alcohol ingestion (> 30 gm/day for men and > 20 gm/day for women), history of drug use reported to cause steatosis (steroids, estrogens, tamoxifen, amiodarone, valproic acid, diltiazem, or methotrexate), improved steatosis (metformin, statins, or glitazones) within 3 months of enrollment, or history of any other chronic liver disease.

Methods: Demographic characters like age, sex, height, waist circumference and weight of all subjects were noted. Detail history was recorded, general physical examination was done and detailed systemic examination was done. Routine investigations including complete blood counts, peripheral smear examination, fasting blood glucose (FBG), 2-hr postprandial blood glucose (PPBG), HbA1c, kidney function tests, liver function tests, Lipid profile, and ultrasound of abdomen were done. CAD is diagnosed on the basis of ECG, cardiac enzymes, echocardiography or coronary angiography. All patients underwent ultrasound of the abdomen to detect fatty changes in the liver, performed by a single experienced sonologist. Metabolic syndrome is diagnosed when a patient has at least 3 of the following 5 conditions: FBG>100 mg/dl (or on antidiabetic drug), BP> 130/85 mm Hg (or on antihypertensive drugs), triglycerides >150 mg/dl (or on lipid lowering drugs), HDL-C< 40 mg/dl in men or <50 mg/dl in women (or on lipid lowering drugs), waist circumference≥102 cm in men or ≥88 cm in women.

Ethical Consideration: Prior to conduct of the present study, the protocol of the study was submitted to ethical and scientific committee of hospital. After getting due approval from these two committees, the present study was initiated. Also prior to conduct of study related procedure / investigation, a voluntary written informed consent was taken from the patient /legally acceptable representative.

Statistical Technique: Microsoft Excel® and SPSS® 20 for Windows® were used for data storage and analysis. The qualitative data were expressed in percentages and quantitative data were expressed as mean ± standard deviation. Student's t test and Chi-Square test were used to determine statistical difference between variables. Correlations between CAD severity and NAFLD degree were analyzed using Pearson's correlation analysis.

Results: Total 500 diabetic subjects were included in this study, among them 300 (60%) were female and 200 (40%) were male. Mean age of subjects was 48.8 ±12.8 years. (Table 1) Male diabetic subjects had higher incidence of hypertension, dyslipidemia, metabolic syndrome and CAD. The incidence of NAFLD was 44% in all diabetics, among them males were affected more (50%) than females (40%). Mean BMI was 27.8 and 27.2 among males and females respectively. (Table 2) NAFLD subjects had higher incidence of hypertension, obesity, dyslipidemia, uncontrolled sugar and CAD than Non-NAFLD group subjects. These differences were statistically significant. (Table 3)

On multiple regression analysis, male gender, BMI, raised HbA1c and raised HDL-C did not have influence on the presence of CAD (p>0.05), whereas age [OR:1.03 (95% CI), p=0.002], Smoking [OR:3.28 (95% CI),p=0.006], and NAFLD [OR:2.38 (95% CI), p=0.03] have independent effects.(table 4)

Table 1: Demographic measures and biochemical values of All subjects

Characteristics	Type 2 DM
Number	500
Gender % (Female)	60
Incidence of NAFLD	44%
Age (Mean ± SD)	48.8 ± 12.8 years

Table 2: Various parameters among male and female diabetics

Characteristics	Male Diabetic Subjects	Female Diabetic subjects
History of Smoking	21%	0%
BMI (Mean ±SD)	27.8 ±4.1 kg/m^2	28.2 ±3.9 kg/m^2
History of Hypertension	45%	42%
FBG (Mean ±SD)	108 ±28.4 mg/dl	105.4 ±19.8 mg/dl
PPBG (Mean ±SD)	220.4 ±94.4 mg/dl	254.3 ±108.5 mg/dl
HbA1c (Mean ±SD)	7.3 ±1.9	7.9 ±2.1
Presence of CAD	12%	11%
LDL-C	139 ±12.9	134 ±21.8 mg/dl

(Mean ±SD)	mg/dl	
HDL (Mean ±SD)	45.9 ±5.2 mg/dl	42.8 ±6.5 mg/dl
Triglyceride (Mean ±SD)	189.8 ± 20.9 mg/dl	190.2 ±23.9
Presence of Metabolic Syndrome	28%	27%
Incidence of NAFLD	50%	40%

Table 3: Various parameters among NAFLD and Non-NAFLD group subjects

Characteristics	NAFLD Group	Non-NAFLD Group	P value
History of Smoking	8.3%	7.8%	P=0.09
History of Hypertension	79.3%	22.8%	P<0.005
Incidence of Obesity	87.5%	12.8%	P<0.005
Incidence of dyslipidemia	76.8%	21.3%	P<0.005
HbA1c	8.9 ±2.1	6.9 ±1.9	P<0.005
Incidence of CAD	12.9%	9.8%	P<0.005

Table 4: Multiple logistic regression analysis for the presence of CAD

	Odds ratio	P value
Age	1.03	0.002
Male Gender	1.48	0.52
Smoking	3.28	0.006
BMI	0.98	0.12
Raised HbA1c	1.32	0.55
Raised HDL-C	0.98	0.18
NAFLD	2.38	0.03

Discussion: Our results demonstrate that NAFLD is a significant predictor of CAD independent of traditional risk factors in Indians. The prevalence of NAFLD in normal weight individuals without the presence of metabolic risk factors is reported to be around 16%[7] rising to 43-60% in patients with diabetes[8,9], 91% in obese patients undergoing bariatric surgery[10], and up to 90% in patients with hyperlipidaemia.[11,12] The prevalence of NAFLD also increases with age from less than 20% under the age of 20 to more than 40% in over the age of 60[13] and indeed older age has been shown to be an independent risk factor for hepatic steatosis and progression to fibrosis and cirrhosis. The male gender has been regarded as a risk factor for progression to NASH and fibrosis.[14] These findings were similar to our study.

Wong et al[15] evaluated the interaction between fatty liver and cardiovascular outcomes using coronary angiograms in a prospective cohort study and demonstrated that fatty liver is associated with CAD independently of other metabolic factors, which is consistent with our results. Arslan et al.[16] also reported that NAFLD is independently associated with presence of CAD.

The pathogenesis of NASH is currently not well defined but is hypothesized to involve complex interactions of genetics and environmental factors. The early 'two-hit' model of NASH proposed that the 'first hit' involves accumulation of lipids in the form of triglycerides.[6] This lipid-rich environment then provides the optimum setting for oxidative stress constituting the 'second hit' that triggers hepatocellular injury, inflammation, and fibrosis.

The pathophysiological mechanisms that link NAFLD with CAD are incompletely understood. The concept so far was that in patients with NASH, there was an increase in systemic and hepatic insulin resistance which in turn caused the accumulation of atherogenic dyslipidemia, characterized by high triglycerides, low HDL and high VLDL. In NASH, there seemed to be increased production of many pro-inflammatory markers such as uric acid and C-reactive protein (CRP)[16], IL-6, TNF-α as well as profibrogenic markers such as tumor growth factor-β, endothelin 1 and insulin like growth factor-1 which can lead to CAD.[17] Epidemiological studies performed in United States and Japan showed that NAFLD is associated with increased risk of CAD and is a predictor of CAD independent of the presence of other metabolic syndrome risk factors such as hypertension, diabetes, dyslipidemia, obesity and insulin resistance.[18] The RISC (Relationship between Insulin Sensitivity and Cardiovascular disease) study showed that patients with NAFLD had an increased 10 year CAD risk score even when only considering those at perceived low risk patients (i.e. without diabetes or hypertension).[19] The study also showed that subjects with NAFLD are more prone to early carotid atherosclerosis in the absence of coexisting metabolic syndrome risk factors.[20] Recent phase II trials assessing coronary atherosclerotic plaque in patients with NAFLD have

showed that such patients are more likely to have advanced high risk coronary plaque, independent of traditional cardiovascular risk factors as compared with patients without NAFLD.[21] The worst prognosis was seen in patients with stage 3 or 4 fibrosis at baseline.[22] In another study of patients with a Framingham cardiovascular risk score 20%, the presence of advanced fibrosis was predictive of cardiovascular events.[23]

Although weight loss through lifestyle modifications including dietary changes and increased physical exercise remains the backbone of management of NASH, it has proved challenging for patients to achieve and maintain weight loss goals. Thus, it is often necessary to couple lifestyle changes with another pharmacologic treatment for NASH. Insulin sensitizers including the biguanides (metformin), thiazolidinediones (pioglitazone), and glucagon-like peptide-1 receptor agonists (exenatide) are large groups of medications that have been studied for the treatment of NASH. Other agents with anti-inflammatory, anti-apoptotic, or anti-fibrotic properties which have been studied in NASH include vitamin E, pentoxifylline, betaine, and ursodeoxycholic acid.

Conclusion: Clinicians should look for NAFLD in diabetics, especially in the presence of the metabolic syndrome. Once found, aggressive management of risk factors for CAD should be the primary goal, given the greater odds of developing CAD and the high prevalence of CAD in diabetics with NAFLD.

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