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Prevalence of ischemic heart disease among subjects with type 2 diabetes mellitus with or without nonalcoholic fatty liver disease.

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Abstract: - Objectives: To study the prevalence of NAFLD in type 2 diabetes mellitus by ultrasonography, and than the prevalence of IHD among type 2 diabetes mellitus with or without NAFLD assesed using Rose Questionnaire for angina, ECG changes (Minnesota coding system), Echocardiography changes.
Methods: Total 170 patients of type 2 diabetes were recruited. History and physical examination were recorded. Laboratory investigations included fasting and 2-hour post-prandial blood glucose, blood urea, serum creatinine, liver function tests, lipid profile, and. NAFLD was diagnosed on the basis of ultrasound assessment of the liver. The presence of IHD was assessed by Rose Questionnaire for angina, ECG changes (Minnesota coding system), Echocardiography changes.
Results: The study group (n=170) was divided into a NAFLD group (n=86) and a non-NAFLD group (n=84). The prevalence of NAFLD was 50.6%. IHD was more prevalent in the NAFLD subgroup (75%) compared to the non-NAFLD subgroup (23.8%). The NAFLD subgroup had higher prevalence of hypertension, obesity (measured by BMI), central obesity (measured by waist circumference and waist hip ratio), higher Triglyceride and cholesterol levels and lower HDL level.
Conclusion: Our results suggest that IHD is extremely common in people with type 2 diabetes and is associated with higher prevalence of NAFLD. It is a surrogate and fairly reliable marker of risk for IHD amongst type 2 diabetic patients. Ultrasonographically detected NAFLD is a simple, cheap, and safely assessable parameter for coronary risk stratification in type 2 diabetics.

Keywords: *Non alcoholic fatty liver disease (NAFLD), Type 2 Diabetes mellitus, ischemic heart disease(IHD).*

I. INTRODUCTION

The world wide prevalence of diabetes has risen dramatically for last two decades and prevalence of type 2 Diabetes Mellitus (Type 2 DM) is raising more rapidly [1] Non Alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver disorder ranging from simple steatosis to steatohepatitis, which can progress to end stage liver disease. NAFLD is commonly associated with Type 2 DM, dyslipidemia and Insulin resistance, all of which are components of Metabolic Syndrome. This strongly supports that NAFLD is the Hepatic manifestation of the syndrome [2-4]Prevalence of NAFLD ranging from 15-30% in general population of various countries and 70-90% among Diabetes or Obese [5] Because of the high risk of atherosclerosis in patients with NAFLD, even without metabolic syndrome, assessment of NAFLD may be helpful for cardiovascular risk stratification.[6] NAFLD could not merely be a marker of cardiovascular disease (CVD), but may also be actively involved in its pathogenesis, which includes a release of pro-atherogenic factors from the liver (C-reactive protein, fibrinogen, plasminogen activator inhibitor-1, IL-6 and other inflammatory cytokines), hepatic insulin resistance, subclinical inflammation and atherogenic dyslipidemia which together lead to increased oxidative stress and endothelial dysfunction, finally promoting CAD.[7]However if correct this data suggest that the identification of NAFLD in Type 2 DM may help in IHD prediction with important management implication. Identifying people with NAFLD would also high light a sub group of Diabetic patient that should be targeted with more intensive therapy to decrease their risk of future IHD event.The main purpose of this study is to determine the prevalence of IHD among subjects with Type 2 DM with or without NAFLD.

II. MATERIAL AND METHODS

Study was conducted in the 0ut patient department (OPD) of medicine department, Agartala Government Medical College and GBP Hospital. Study subjects were male and female, diagnosed as type 2Diabetes mellitus . Total sample size estimated around 170. Age more than 35 years under treatment of type 2 diabetes mellitus and teetotalers were included. Patients having known hepatic disease, history of Ingestion of hepatotoxic drugs and patients having alcoholic liver disease were excluded. Approximately 3500 diabetic patients attended in diabetic clinic at Agartala Government Medical College & GBP, for the year 2011-2012. To recruit 170 study subjects from the patients with type 2Diabetes mellitus, approximately monthly fifteen(15) study subjects were recruited. Approximately (150-200) diabetic patient attending OPD monthly, from which 15 study subjects were selected randomly, one subject in alternate day. After obtaining informed consent and

Institutional ethical committee approval the Study was conducted. Detail history and physical examination was done with emphasis on Brachial BP, height, weight, BMI, Waist/Hip ratio. Blood pressure was measured with a standard mercury manometer, sitting position, right arm. Hypertension was diagnosed as blood pressure 140/90 mmHg or the taking of antihypertensive drugs. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Laboratory investigation were include Blood glucose both fasting and Post Prandial by oxidase-peroxidase method(fasting reference range,100-125 mg/dl and post prandial reference range,140-199mg/dl), Liver Function Test[bilirubin by jendrassik & grof method,reference range,0.2-1mg/dl,alanine aminotransferase(ALT) and aspartate aminotransferase(AST) by enzyme kinetic method, reference range 7-41u/l and 12-38u/l
respectively] and Lipid profile(LDL cholesterol by friedewald's equation, reference range LDL 100-129mg/dl HDL >40mg/dl total cholesterol <200mg/dl).

All these tests were done by fully automated biochemical analyzer XL-300 in the department of biochemistry AGMC&GBP hospital. Serological tests done for viral hepatitis B & C. All patients were undergone USG of abdomen for detection of Fatty liver, performed by a Radiologist using B mode. Fatty liver was defined as the presence of an ultrasonography 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 the 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 criteria as:

Grade 1 (mild steatosis): slightly increased liver echogenicity with normal vessels and absent posterior attenuation.

Grade 2 (moderate steatosis): moderately increased liver echogenicity with partial dimming of vessels and early posterior attenuation.

Grade 3 (severe steatosis): diffusely increased liver echogenicity with absence of visible vessels and heavy posterior attenuation.The presence of IHD was assessed by Rose Questionnaire for angina, ECG changes (Minnesota coding system), Echocardiography changes.Resting 12-lead ECG was performed in all study subjects. ECG changes recorded as Minnesota coding system Conventional trans-thoracic echocardiography was performed at rest. Standard positions of the chest wall for echo window in the left para-sternal, apical,sub costal, right para-sternal were used. Wall motion at rest, any Regional wall motion abnormality(RWMA) Ejection Fraction, E/A ratio were recorded. Fraction of <55% was taken as systolic dysfunction. E/A ratio<1 was taken as a criteria for diastolic dysfunction. Echocardiography changes (RWMA, and/or Diastolic dysfunction) was taken as IHD.Patient having abnormality in any of the methods, Rose Questionnaire for angina, ECG changes and Echocardiographic changes was taken as IHD.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Science (SPSS). The categorical variables were shown as numbers of cases with percentage, and the continuous variables were shown as mean ± standard deviation (SD). A *P* value of ≤0.05 was considered statistically significant.

III. RESULTS

A total of 170 study subjects with type 2 diabetes mellitus were included. Out of 170 patients, 101 men and 69 women. Out of 170 study subjects, 86(50.6%) were found to be NAFLD and 84(49.4%) patients having Non NAFLD. out of 86(50.6%) patients of NAFLD, men having a marginally higher prevalence (27.7%) of NAFLD as compared to women (22.9%).In this study, GradeI, GradeII and GradeIII NAFLD was present in 34%, 50%, and 16% of type 2 diabetics, respectively.Now subjects were divided into two groups,[Group 1, partients with NAFLD,n-86 and Group 2, patients without NAFLD, n-84], and were compared(Table 1&2).

Table 1: Comparison of baseline parameters between patients with and without NAFLD(n=170)

Variable (Mean ± S.D.)	**Group I NAFLD patients (N=86)**	**Group II Non-NAFLD Patients (N=84)**	**p value**
Age (yrs)	52.55±9.27	52.02±12.07	0.7486
Duration of diabetes (yrs)	8.48±3.63	5.23±3.23	0.0005
BMI (kg/m2)	26.830±2.366	26.1230±2.4014	0.0548
WHR	0.97 ± 0.15	0.93 ±.06	0.087
SBP	143.33± 10.14	133.83±10.34.	<0.0001
DBP	90.14 ± 6.97	84.95±6.96	<0.0001
FBG	161.3 ± 64.44	168.88 ± 63.9	0.517
PPBG	165.35 ± 40.86	155.62 ± 38.79	0.1134
CHOLESTEROL	171.85 ± 42.30	155.85±31.19	0.0057

LDL	97.99 ± 33.72	88.15±29.85	0.0459
HDL	34.30 ± 10.95	35.07±9.84	0.6299
TG	199.85 ± 72.80	166.36±46.40	0.0005
AST	31.73 ± 14.23	28.13±11.30	0.0692
ALT	35.34 ± 18.88	27.51 ±11.62	0.0014
Prevalence Of IHD	75%(65)	23.8%(20)	< 0.0001

Table 2: Prevalence of individual abnormalities between NAFLDand non-NAFLD groups(n=170)

Variable	**Group I NAFLD patients (N=86)**	**Group II Non-NAFLD Patients (N=84)**	**p value**
BMI >25 kg/m^2	82(97%)	68(80%)	0.0075
HTN >140/90mmHg	65(75%)	28(33%)	<0.0001
Total cholesterol > 200 mg%	23(27%)	12(14%)	0.0689
LDL >130mg%	14(16%)	10(11%)	0.5494
HDL <40mg%	64(74%)	10(12%)	<0.0001
S. Triglyceride > 150mg%	72(84%)	63(75%)	0.2239
WHR(≥0.95-males; ≥0.85-females)	51 (59%)	35 (41%)	0.0319
Prevalence Of IHD	65(75%)	20(23.8%)	< 0.0001

IHD was more prevalent in the NAFLD subgroup (75%) as compared to the non-NAFLD subgroup (23.8%).

Table 3: Comparison of baseline parameters among patients of various grade of NAFLD. (n=170)

Variable (Mean ± S.D.)	**Group I NAFLD Grade I patients (N=28)**	**Group II NAFLD Grade II patients (N=45)**	**Group III NAFLD Grade III patients (N=13)**	**p value**
Age (yrs)	49.00± 8.79	52. 33 ±8.85	60.92 ± 6.53	0.0004
Duration of diabetes (yrs)	6.00 ± 3.50	9.16± 3.13	11.46 ±2.03	0.0001
BMI (kg/m2)	26.782 ± 1.666	26.524± 2.476	27.992± 3.019	0.14
SBP	143.82± 11.16	140.42 ± 7.58	152.31 ± 10.89	0.0006
DBP	89.43 ± 7.18	90.40± 5.84	90.77± 9.98	0.80
PPG	170.07 ± 47.76	159.31 ± 26.63	176.08 ± 61.47	0.33
CHOLESTEROL	158.64 ± 25.43	177.11± 44.15	182.08 ± 58.73	0.12
HDL	32.36 ± 7.43	35.78± 11.80	33.38± 14.02	0.41
LDL	90.79± 25.01	101.44± 36.56	101.54 ± 39.59	0.39
TG	168.75± 55.26	212.62 ± 74.88	222.62 ±81.71	0.019
SGPT	31.54 ± 11.72	39.51± 23.44	29.08± 7.80	0.091
SGOT	27.82± 9.13	35.56 ±17.09	26.92 ± 7.78	0.031
Prevalence of IHD	43%	67%	100%	0.0001

In this study Rose Questionnaire for angina, ECG (Minnesota codes), Echocardiography done for all 170 patients for detection of IHD. On the basis of the test 85(50%) patients did not having any abnormality, 36 patients having Rose angina positive, 73 patients having abnormal ECG changes and 85 patients having diastolic dysfunction(Table 4).

Table No 4: Distribution of abnormal individual test among patients (n=170)

Name of test	NAFLD(86)	NON NAFLD(84)	Total(170)
Rose Questionnaires	30(34.8%)	6(7.1%)	36(21.1%)
ECG	55(63.9%)	18(21.4%)	73(42.9%)
ECHOCARDIOGRAPHY	65(75%)	20(25%)	85(50%)

IV. DISCUSSION

There is a pressing unmet need to determine the prevalence of NAFLD in type 2 diabetic population and to evaluate its association with IHD. The prevalence of NAFLD based on abdominal ultrasound examination in our study group was 50.6%. This is similar to other studies which have reported the prevalence of NAFLD among DM patients at approximately 50% (range: 21-78%).[2] In a study by Mohan *et al* the prevalence of NAFLD (54.5%) was significantly higher in patients with diabetes compared to those with pre-diabetes (IGT or IFG) (33%), isolated IGT (32.4%), isolated IFG (27.3%) and normal glucose tolerance (NGT) (22.5%).[8] The prevalence of NAFLD was 50.6%, with men having a marginally higher prevalence (55%) as compared to women (45%). The prevalence of NAFLD among men and women varied in different clinical studies. In some studies, NAFLD was considered to be more common among women,[64,65] whereas it was reported to be more prevalent among men in others.[66,67]The prevalence of mild, moderate, and severe NAFLD was present in 34%, 50%, and 16% of type 2 diabetics, respectively in our study.Gupte *et al* found that mild, moderate, and severe NAFLD was present in 65.5%, 12.5%, and 9.35% of otherwise asymptomatic type 2 diabetics, respectively.[9]

Prashanth *et al* found a high prevalence of NAFLD and NASH in type 2 diabetics which increased with multiple components of the metabolic syndrome.[10] The mean age of patients in both the NAFLD and non-NAFLD groups was 52.55±9.27 and 52.02±12.07 respectively which was not statistically different (p=0.7486). We also compared the frequency of NAFLD among different age groups which showed that maximum patients of NAFLD belongs to 45-54 years.

The mean duration of DM was in patients with NAFLD (8.48±3.63) as compared to patients without NAFLD (5.23±3.23), respectively, and p value equals 0.0005, means that this difference is statistically significant.The mean BMI of patients with NAFLD (26.830±2.366) as compared to patients without NAFLD(26.1230±2.4014), respectively which was statistically not significant(p=0.0548)

The prevalence of obesity (BMI >25 kg/m^2) in patients with NAFLD was 95%, as compared to 79% in non-NAFLD patients. Maximum patients of IHD belongs to Grade II obesity in our study. In our study, the waist/hip ratio was significantly different between the two groups (p=0.087). There was statistically significant difference in Systolic Blood pressure and Diastolic blood pressure, mean cholesterol, LDL, HDL and serum triglycerides between the two groups. The prevalence of dyslipeadimia (serum triglycerides>150mg/dl)in patients with NAFLD was 84%, as compared to 75% in non-NAFLD patients.(p=0.2239).

The prevalence of IHD was 75% in diabetics with NAFLD and 25% in diabetics without NAFLD(P value is less than 0.0001). So the correlation between NAFLD and IHD is considered to be extremely statistically significant. This result was same as the study where the prevalence of IHD was 60.5% in diabetics with NAFLD and 45.2% in diabetics without NAFLD.[11] In the present study which consisted of 170 patients with T2DM, the prevalence of IHD was 50% assessed by Rose Questionnaire for angina, ECG , and Echocardiography changes.

In our study, the prevalence of Rose Questionnaire for angina was 21.1%. This is similar to study of Fischbacher CM et al, which have reported the prevalence of IHD detected among DM patients by Rose Questionnaire at approximately 18%[12] The Rose questionnaires for angina was 38.8% sensitivity, 96.4% specificity, 91.6% positive predictive value and 61% negative predictive value in our study group. This is similar to study of Yatish TR et.al also found the Rose Questionnaire had 63.63% sensivity,97.5% specificity,73% positive predictive value, and 96% negative predictive value.[13]The prevalence of abnormal ECG at rest was 42.9% in our study group. This is similar to other studies of Ahto M et al, which have reported the prevalence of IHD detected among DM patients by ECG (Minnesota coding) at approximately 33.9% and 39.3% in men and women, respectively.[14]

The prevalence of Diastolic dysfunction detected by echocardiography at rest was 50% in our study group. Patil et al[15] in their study of 127 Type II diabetics found a significant incidence (54.33%) of diastolic dysfunction in diabetics. Sohail et al[16] in their study of 212 diabetic population found that 30.76% patients with Type II DM had diastolic dysfunction. Our study showed that IHD was more prevalent in male than female (male 59% vs female 41%). There is significant difference of mean Duration of diabetes (yrs), BMI(kg/m2).SBP,DBP, TG and Prevalence of NAFLD between IHD and Non-IHD group.Prevalence of IHD was 43% in grade 1 NAFLD, 67% in grade 2 NAFLD, and 100% in grade 3 NAFLD.IHD was more prevalent in grade 2 than in grade 1&2 NAFLD patients, and all patients with grade 3 NAFLD had IHD. . Patients with grade 2 NAFLD had greater dearrangements in lipid profile than grade1 patients. Liver enzymes were higher in grade 2 than in grade 1 NAFLD.

The limitation of our study is that the diagnosis of NAFLD was based on ultrasonography and was not confirmed by liver biopsy. Ultrasonography is by far the commonest method
of diagnosing NAFLD in clinical practice and has very good sensitivity and specificity. The sensitivity and specifi city of ultrasound for detecting hepatic steatosis varies from 60 to 94% and 88 to 95%, respectively.[17]

Overall, these findings might have possible clinical and public health implications. Our results indicate that the majority of patients with type 2 diabetes have NAFLD and previous studies also showed that type 2 diabetes mellitus is an independent predictor of advanced liver disease in NAFLD. Currently, it is not known whether improving NAFLD will ultimately prevent the development of CVD. However, it is notable that interventions that are known to be effective in preventing CVD in type 2 diabetic people, including weight reduction and treatment with insulin-sensitizing anti-diabetic agents, may possibly improve NAFLD.We should look for NAFLD in diabetics, especially in the presence of the metabolic syndrome. Once found, aggressive management of risk factors for IHD should be the primary goal, given the greater odds of developing IHD and the high prevalence of IHD in diabetics with NAFLD.

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