Frequency of metabolic syndrome among newly detected type 2 diabetic patients with non-alcoholic fatty liver disease and high serum alanine aminotransferase levels

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Abstract

Background: *Non-alcoholic fatty liver disease (NAFLD) is emerging as one of the most common causes of chronic liver disease world-wide. It has strong association with obesity, type 2 diabetes mellitus (T2DM) and metabolic syndrome. We aimed to investigate the prevalence of metabolic syndrome in newly detected T2DM patients having NAFLD with high serum alanine aminotransferase (ALT) level.*

Methods: *In this cross-sectional study, 110 newly detected T2DM patients with high serum ALT level were evaluated. To find out the etiology of high serum ALT level, abdominal ultrasonography was done to detect NAFLD cases along with other relevant investigations. All NAFLD cases then underwent further evaluation for the prevalence of metabolic syndrome.*

Results: *Out of 110 study subjects, NAFLD was detected in 80 (72.7%) individuals. According to International Diabetic Federation (IDF) criteria, metabolic syndrome was detected in 56 (56/80, 70%) of NAFLD cases. Among the 56 patients with NAFLD, male were 24 (42.9%) and female were 32 (57.1%) and 14 (14/56, 25%) cases had all five components of metabolic syndrome. Metabolic syndrome was found in all female NAFLD subjects (32, 100%). Mean age of patients with metabolic syndrome was 43.11±10.77 years and mean body mass index (BMI) was 27.87±3.72 kg/m^2. Hypertension was found in 37.5% cases. High BMI (e"25 kg/m^2) was found in 87.5% cases. Mild, moderate and severe fatty liver were found in 28.6%, 46.4% and 25% cases respectively. Dyslipidemia was found in all (56, 100%) NAFLD subjects with metabolic syndrome. Metabolic syndrome had significant correlation with BMI (p 0.00), abdominal obesity (p 0.00) and serum triglyceride level (p 0.04).*

Conclusion: *Over two-thirds of T2DM patients having NAFLD had metabolic syndrome in this study.*

Key words: *alanine aminotransferase, body mass index, non-alcoholic fatty liver disease, metabolic syndrome.*

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Introduction

Diabetes mellitus (DM) is a global public health issue. Patients with type 2 DM (T2DM) often have asymptomatic elevation of serum alanine amino-transferase (ALT) level. In the United States, non-alcoholic fatty liver disease (NAFLD) is replacing alcoholic hepatitis and viral hepatitis as the most common etiology of chronically elevated serum ALT in both diabetic and non-diabetic individuals.[1] NAFLD is the most common cause of chronic liver disease in many developed countries[2,3] and is closely associated with obesity[4] and cardiovascular diseases.[5,6] Moreover, NAFLD has also been reported as risk factor, independent of the traditional risk factors, for subclinical atherosclerosis[7,8], T2DM[9] and increased mortality.[10] Furthermore, NAFLD is expected to become an even

more serious public health issue because of the increasing prevalence of obesity and aging.[11,12] The presentation of the disease is mostly silent, considered as "silent liver disease".[13] Approximately 10-25% of patients with "silent liver disease" develop non-alcoholic steatohepatitis (NASH) and 5-8% of those will develop liver cirrhosis within 5 years.[14]

Metabolic syndrome is a cluster of metabolic abnormalities that is a precursor to cardiovascular disease, T2DM and chronic kidney disease. Patients with NAFLD are anticipated for the future development of the metabolic syndrome. Many cross-sectional studies have demonstrated that NAFLD is strongly associated with metabolic syndrome.[15,16] So, NAFLD is often regarded as the hepatic component of the metabolic syndrome[17] and makes the metabolic syndrome a relevant condition in clinical practice and a major public health concern worldwide.[18-20] Nevertheless, very few studies were published internationally addressing specifically the prevalence of metabolic syndrome and associated factors in T2DM patients having NAFLD with raised serum ALT level. To the best of our knowledge, no study was done focusing this special issue in our country. So, we aimed to investigate the frequency of metabolic syndrome in this special group of patients.

Methods

In this cross-sectional study, 110 newly detected T2DM patients were selected at medicine outpatient department (MOPD) of Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) General Hospital, Dhaka, Bangladesh, from August to October, 2009. Informed written consent was taken from every patient after explaining the purpose and procedure. A standard questionnaire was filled up. Every patient was evaluated clinically and supplemented by necessary laboratory investigations. Newly diagnosed, adult (≥18 years), T2DM subjects with serum ALT ≥1.5 times upper limit of normal were included in this study. Patients with history of regular alcohol intake more than 30 grams/day in males and more than 20 grams/day in females, diagnosis of acute hepatitis/chronic liver disease, history of hepatotoxic drug intake were excluded. Anthropometric measurement included weight and height. Body mass index (BMI) was calculated as body weight in kilogram divided by height in meters square. Waist circumference was measured in cm at the horizontal plane mid-way between anterior superior iliac spine and lower costal margin at the narrowest part of the waist line while the patient was standing and at the end of normal expiration. Hip circumference was measured at a horizontal plane passed through the greater trochanter of femur on both sides in standing position. Hypertension was leveled with blood pressure ≥130/85 mm Hg and/or on regular use of anti-hypertensive medication. Biochemical tests included oral glucose tolerance test (OGTT), fasting lipid profile, serum ALT level, viral markers like hepatitis B virus surface antigen (HBsAg) and antibody against hepatitis C virus (anti-HCV) and ultrasonography (USG) of hepatobiliary system and pancreas. Additional investigation was done as required.

Dyslipidaemia was defined according to National Cholesterol Education Programme (NCEP) Adult Treatment Panel (ATP) III Guideline: plasma triglyceride (TG) ≥150 mg/dl, plasma total cholesterol (TCH) ≥200 mg/dl, plasma low density lipoprotein cholesterol (LDL-C) >100 mg/dl, plasma high density lipoprotein cholesterol (HDL-C) <40 mg/dl in male or <50 mg/dl in female.

Metabolic syndrome was defined according to International Diabetic Federation (IDF) criteria: central obesity (waist circumference ≥90 cm for male and ≥80 cm for female as for Asian-Indian) plus any two of the following four criteria: (1) raised plasma TG level ≥150 mg/dl or ≥1.7 mmol/L or specific treatment for this lipid abnormality, (2) low plasma HDL-C <40 mg/dl or <1.03 mmol/L for males or < 50 mg/dl or < 1.29 mmol/L for females or specific treatment for this lipid abnormality, (3) high blood pressure (BP): systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg and (4) fasting plasma glucose ≥5.6 mmol/L or 100 mg/dl or use of medication for hyperglycemia. Abdominal USG was performed in a fasting state for at least 8 hours by a single sonographer using SIEMENS Sonoline Antares. NAFLD was classified according to the standard criteria accepted by American Gastroenterology Association (AGA) as follows: grade-1 (mild steatosis) – slight diffuse increase in the fine echoes in the hepatic parenchyma with normal visualization of diaphragm and intrahepatic vessel borders, grade-2 (moderate steatosis) – moderate diffuse increase in the fine echoes with slightly impaired visualization of the intrahepatic vessels and diaphragm, grade-3 (severe steatosis) – marked increase in the fine echoes with poor or no visualization of intrahepatic vessel borders, diaphragm and posterior portion of the right lobe of the liver. Statistical analysis was done by statistical package for social scientists (SPSS) version

21. Data were expressed as mean, standard deviation (SD), percentage etc. Chi-square test (χ^2) was used for the comparison of qualitative data. Independent sample t-test was used for comparison between two groups. Results were considered statistically significant at p value <0.05.

Results

Among the 110 patients, 80 (72.7%) had NAFLD and 56 (50.9%) fulfilled criteria for metabolic syndrome, which was 70% of NAFLD (56/80, 70%) patients. Among the 56 NAFLD patients who had metabolic syndrome, 25% had all the components of metabolic syndrome and all the female subjects (32) with NAFLD had metabolic syndrome. Twenty one (21/56, 37.5%) of NAFLD patient with metabolic syndrome had hypertension and 16 (28.6%), 26 (46.4%) and 14 (25%) had mild, moderate and severe form of NAFLD respectively. High TG, TC and LDL were present in 69.6%, 51.8% and 76.8% cases respectively and 85.7% had low HDL. Comparison of base-line characteristics of NAFLD patients with and without metabolic syndrome is shown in Table I.

Table I Base-line characteristics of NAFLD patients with (N=56) and without MS (N=24)

Characteristic	NAFLD with metabolic syndrome	NAFLD without metabolic syndrome	p value
Age (years)	43.11±10.77	44.13±11.56	0.706
BMI (kg/m2)	27.87±3.72	24.17±2.75	0.000
Systolic BP (mm Hg)	127.32±18.16	126.46±16.25	0.841
Diastolic BP (mm Hg)	80.71±10.11	80.83±8.42	0.960
WC (cm)	94.01±8.67	85.00±6.50	0.000
WHR	1.01±0.08	0.95±0.05	0.003
ALT (U/L)	104.91±61.55	92.83±31.30	0.366
FBG (mmol/L)	11.91±4.15	11.79±4.20	0.910
TG (mg/dL)	203.03±99.63	184.50±108.01	0.459
TC (mg/dL)	203.35±52.36	201.66±43.85	0.890
LDL (mg/dL)	127.39±39.74	137.18±41.49	0.322
HDL (mg/dL)	36.05±8.32	36.79±7.93	0.714

[WC = Waist circumference, WHR=waist hip ratio]

All the patients were diabetic and a comparison of components of metabolic syndrome in patients with and without metabolic syndrome are presented in Table II.

Table II Comparison of components of metabolic syndrome in NAFLD patients with (N=56) and without metabolic syndrome (N=24)

Variables	NAFLD with metabolic syndrome (n-56) N (%)	NAFLD without metabolic syndrome (n-56) N (%)	p value
BMI (kg/m^2)			
18.5 – 24.9	7	15	0.000
25-29.9	30	7	
=30	19	2	
Systolic BP (mmHg)			
<130	35	17	0.611
=130	21	7	
Diastolic BP (mmHg)			
<85	37	17	0.797
=85	19	7	
WC (cm) (male)			
<90	0	22	0.000
=90	24	2	
WC (cm) (female)			
<80	0	0	---
=80	32	0	
TG (mg/dL)			
<150	17	13	0.040
=150	39	11	
HDL (mg/dL) (male)			
<40	19	15	0.341
=40	5	9	

Discussion

In this study, 70% of NAFLD subjects had metabolic syndrome according to the IDF criteria using Asian-Indian standards for waist circumference. It was much higher than two studies done by Duseja A et al (50%) and Uchil D et al (47.1%).[21,22] Among the NAFLD

subjects with metabolic syndrome, 57.1% were female which was lower than that reported by Gaharwar R (61.1%).[23] Over two-thirds (71.4%) of NAFLD subjects with metabolic syndrome had moderate to severe (grade 2 to 3) fatty liver which was lower than that reported by Gaharwar R (83.3%).[23] The mean age of NAFLD subjects with metabolic syndrome of present study was higher than that reported by Bajaj S et al.[24] The BMI and WC of NAFLD subjects with metabolic syndrome was significantly higher than those of NAFLD subjects without metabolic syndrome in our study. Similar observation was reported by Gaharwar R.[23] Hypertension was found in 37.5% of NAFLD subjects with metabolic syndrome which was lower than that reported by Bajaj S et al (48.72%).[24] In NAFLD subjects with metabolic syndrome, 69.6% had high TG which was significantly higher than findings of Uchil D et al (43.6%)[22] and 85.7% had low HDL levels which was lower than that described by Gaharwar R (94.4%).[23]

The diagnosis of NAFLD was based only on USG imaging. The sensitivity of USG in detecting NAFLD may vary between 60% and 94% and the USG finding can be reported as normal in case of hepatic fibrosis.[25] Magnetic resonance spectroscopy (MRS) can be used to confirm the grading of hepatic steatosis demonstrated by USG.[26] The gold-standard technique for the diagnosis of NAFLD is liver biopsy.[27] MRS or liver biopsy was neither feasible nor practical in such a cross-sectional study. Another limitation of our study was short duration of study period and small sample size.

In conclusion, **s**eventy percent of newly diagnosed T2DM subjects with raised ALT and NAFLD had metabolic syndrome in this study. The components of metabolic syndrome were more prevalent in T2DM patients having NAFLD. Therefore, whenever these parameters are encountered in the clinical setting, patients should be evaluated for the presence of NAFLD. Early detection of NAFLD would modify the disease course and also play a role in modifying components of metabolic syndrome thus also benefit cardiovascular risk factors.

Conflicts of interest: Nothing to declare.

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