Hepatic Steatosis among Obese Children and Adolescents

R SHELIMa, F MOHSINb, T BEGUMc, MA BAKId, S MAHBUBAe, R ISLAMf

Summary:
Background: Chronic liver disease, known as non-alcoholic fatty liver disease (NAFLD) is a metabolic complication of obesity. Hepatic steatosis is an entity in the spectrum of NAFLD, ranges from simple steatosis to advanced fibrosis and cirrhosis. Objective: To identify prevalence of hepatic steatosis and to assess correlation between hepatic steatosis and anthropometry, SGPT and metabolic abnormalities of obese children and adolescents. Methodology: This cross sectional study included 50 obese children and adolescents, attending the Endocrine OPD of Dept. of Paediatrics in BIRDEM from June 2009 to December 2009. BMI ≥ 95th centile for age and sex was used as an anthropometric marker to diagnose obesity. Obesity with any dismorphism, endocrine or chromosomal abnormalities were excluded. Fasting blood samples were collected for measurement of SGPT, blood glucose, lipid profile, FT4 & TSH. Sonographic findings of fatty liver include increased echogenicity of liver, blurring of vascular margins and increased acoustic attenuation. Results: Mean age of the children was 11.24 (8-18) years. High SGPT level was prevalent among 36% of obese children. The most prevalent abnormal lipid profile was high TG (78%) followed by high cholesterol level (68%). The prevalence of hepatic steatosis was 36% with male predominance (M 72.2%, F 27.8%). Mild hepatic steatosis was 72% followed by moderate 28%. High SGPT, high cholesterol and LDL were more prevalent in children with hepatic steatosis in comparison to children without steatosis (P <0.004, <0.05 and <0.04 respectively). Conclusion: Hyperlipidemia with raised SGPT are important signs of liver dysfunction in obese children with hepatic steatosis. Prevention of obesity and identification of children with an increased risk of NAFLD are important steps in preventing irreversible liver damage.

Key words: Obesity, Non alcoholic fatty liver disease, Steatosis, SGPT, Hyperlipidemia.

Introduction:
Obesity is a global nutritional concern. The increasing prevalence of overweight, obesity and its consequences prompted the WHO to designate obesity as a global epidemic. Based on data from the 1999-2000 National Health and Nutrition Examination Survey (NHANES IV) in United States, in all ranges prevalence of obesity has increased compared with that in the previous report (1988-1994) and the most change, from 11% to 15%, occurred among 6 to 19 years of age group. The prevalence of obesity and overweight in affluent school children in Dhaka was found to be 17.9% and 23.6% respectively. Obesity plays a central role in the insulin resistance syndrome, which includes hyperinsulinemia, hypertension, hyperlipidemia, and type 2 diabetes mellitus (DM). Important health problems related to obesity are obstructive sleep apnea, degenerative joint disease, cholecystitis, depression, reproductive cancers and infertility.

A less well recognized association with childhood obesity is chronic liver disease, known as nonalcoholic fatty liver disease (NAFLD). This disorder was first described in adults in the late 1970s and in children in the mid 1980s. NAFLD represents fatty infiltration of the liver in the absence of alcohol consumption and is considered to be a hepatic consequence of metabolic syndrome. According to the American Association for
the Study of Liver Diseases (AASLD), NAFLD is defined as fat accumulation in the liver exceeding 5% to 10% by weight, determined by the percentage of fat-laden hepatocytes on light microscopy. The prevalence of NAFLD in obese children has been reported to range from 20% to 77%. Most cases of NAFLD occur in preadolescent and adolescent age group with male predominance. Certain ethnic groups such as Hispanic and Asian may be more susceptible.

The clinicopathologic spectrum of NAFLD ranges from steatosis or fatty liver, a reversible disorder to steatosis with inflammation and fibrosis - nonalcoholic steatohepatitis (NASH) to cirrhosis or hepatocellular carcinoma. The progression of steatosis to steatohepatitis is two hit process, proposed by Day and James in 1998. Fat accumulation in the liver is the first hit; a consequence of the imbalance between triglyceride accumulation on one hand and lipid beta-oxidation and export on the other. Insulin resistance is widely implicated in the initiation of NAFLD. Insulin resistance leads to hepatic steatosis, lipolysis and hyperinsulinemia. Lipolysis increases circulating free fatty acid and while increase uptake of FFA by liver leads to mitochondrial beta-oxidation overload and therefore leading to accumulating fat in the liver. Hyperinsulinemia increases synthesis of fatty acid in the liver by glycolysis and favouring hepatic accumulation of triglyceride by decreasing Apo-B production. Fat in the liver makes it vulnerable to the second hit. Factors involved in delivering the second hit are thought to include oxidative stress and subsequent lipid per oxidation, proinflammatory cytokines and adipokines. Increased hepatic FA oxidation can generate reactive oxygen radicals (ROS) that may promote mitochondrial dysfunction, lipid peroxidation and/or cytokine secretion. Cytokines are capable of producing all the classical histological features of NASH resulting in hepatocyte injury, inflammation and fibrosis.

The gold standard of diagnosis is liver biopsy but this investigation is not frequently performed in the paediatric population. In the absence of liver biopsy, presumed NAFLD is conventionally diagnosed by classical ultrasonographic hepatic appearances together with an elevated serum level of alanine aminotransferase (SGPT). Identification of children with an increased risk of NAFLD is an important step in preventing irreversible liver damage. This study will help us in early detection of steatosis in obese children and adolescents and to provide early intervention strategies to prevent further progression of hepatic steatosis to its complications.

Aims and Objectives:
The aims of our study were: (1) to determine the prevalence of hepatic steatosis among obese children and adolescents (2) to assess the correlation between ultrasonographic hepatic steatosis and anthropometry, SGPT and metabolic abnormalities.

Methods:
This was a cross sectional study done in BIRDEM from June 2009 to December 2009. Obese children and adolescents, 8 to 18 years of age, attending Paediatric endocrine outpatient department were included in our study. Body mass index was used as an anthropometric marker to diagnose obesity. According to official centers for disease control (CDC), children with BMI $\geq 95^{th}$ for age and sex were diagnosed as obese. Obese children having any dismorphism, endocrine or chromosomal abnormalities or diagnosed case of chronic hepatitis due to metabolic, infectious or autoimmune cause were excluded from study. A predesigned data collection sheet was used for each subject and information regarding history, clinical examination and investigations were recorded.

Weight was measured by spring scale in kilogram to the nearest 100 gram; standing height was measured by stadiometer to nearest 0.1 cm. The Body mass index (BMI) was calculated as weight in kilogram divided by square of height in meter. Waist circumference was measured at the level midway between the lower rib margin and the iliac crest, at level of umbilicus (in centimeter) with the person breathing out gently and hip circumference was measured at the maximum width over the buttocks at the level of greater trochanter by measuring tape (in centimeter).

All subjects had blood samples taken in the morning, after an overnight fast, for the estimation of blood glucose (by OGTT), SGPT, lipid profile, FT4 & TSH. During OGTT, fasting glucose 6.1-7.0 mmol/L, 2 hr plasma glucose $<11.1$ mmol/L but $\geq 7.8$ mmol/L signified IGT and fasting blood glucose $\geq7$ mmol/L or 2-hr plasma glucose $e^{"}11.1$ mmol/L was considered as DM. In 8-15 years of age group, triglyceride (TG) level $e^{"}100$ mg/dl was considered high while in 15-18 years of age group TG $\geq125$ mg/dl was considered high. Hypercholesterolemia was defined as serum cholesterol $\geq170$mg/dl. SGPT $\geq35$ U/L was defined as high SGPT.

Real-time abdominal USG examination was performed to rule out fatty liver by 3.5 MHz curvilinear transducer.
using SONO ACE 8000 and Sonoline Antares ultrasound machine following 6-hours fast. In USG, a hyperechogenic (bright liver) indicated steatosis. Informed consent was taken from the parents. SPSS, version 12.0 for Windows software was used for data recording and analysis. Chi-square test and Students t-test were used for comparing group ratios and group averages respectively. A P value less than 0.05 was considered significant.

Operational definitions:

a) Hepatic Steatosis:
Hepatic steatosis is a pathological condition characterized by abnormal excessive accumulation of lipids mainly triglyceride in liver.9

b) Degree of fatty infiltration was graded as mild, moderate and severe according to ultrasonic appearance of liver echotexture. The severity of echogenesity was graded as follows:
- mild steatosis - slight, diffuse increase in fine echoes in liver parenchyma with normal visualization of diaphragm and intrahepatic vessel borders.
- Moderate steatosis - moderate, diffuse increase in fine echoes with slightly impaired visualization of intrahepatic vessels and diaphragm.
- Severe steatosis - marked increase in fine echoes with poor or nonvisualisation of the intrahepatic vessel borders, diaphragm, and posterior right lobe of the liver.13

Results:
A total of 50 obese children and adolescents were enrolled in the study. This was comprised of 30 boys and 20 girls of 8-18 years of age. 33 children (66%) belonged to 8-12 years age group while 17 children (34%) belonged to 13-18 years age group. The mean age of the subjects was 11.24 years. Male: Female ratio was 1.5:1. Mean weight of the children was 55.79±17.62 kg, mean height was 144.45±11.84 cm, mean BMI was 29.88±6.06 kg/m², mean Waist circumference (cm) was 69.77±31.79, mean Hip circumference (cm) was 60.36±39.36, mean waist: hip ratio was 0.93:1. Among biochemical parameters, mean level of SGPT was 35.93±19.56 U/L, triglyceride (TG) 165.80±58.07 mg/dl, cholesterol 181.58±30.73 mg/dl, low density lipoprotein (LDL) 111.0±30.53, high density lipoprotein (HDL) 37.18±9.34, fasting blood glucose 4.83±0.50, 2 hours after glucose 7.39±1.49.

The most prevalent abnormal lipid profile was high TG and that was detected in 78% children followed by high cholesterol level (68%) and high LDL (50%). High SGPT was prevalent among 36% of obese children as shown in table-I.

Table-I

<table>
<thead>
<tr>
<th>Metabolic abnormalities among obese children and adolescents (n=50)</th>
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<tr>
<td>Metabolic abnormalities</td>
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<tr>
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<tr>
<td>High Triglyceride (TG)</td>
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<tr>
<td>High Cholesterol</td>
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<tr>
<td>High Low Density lipoprotein (LDL) Cholesterol</td>
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<tr>
<td>Low High Density Lipoprotein (HDL) Cholesterol</td>
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<tr>
<td>Diabetes Mellitus (DM)</td>
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<tr>
<td>Impaired Glucose Tolerance (IGT)</td>
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<tr>
<td>High SGPT</td>
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</table>

In total, 18 obese children had ultrasonographic evidence of hepatic steatosis. The prevalence of hepatic steatosis was 36% which is shown in figure-I

Fig.-1: Distribution of the patients according to presence of hepatic steatosis.

Thirteen children (72%) were found to have mild steatosis while five (28%) had moderate hepatic steatosis. There was no evidence of severe degree of hepatic steatosis. Out of twenty girls, five had hepatic steatosis as did thirteen boys. Prevalence of steatosis was high among male (72.2%) compared to female (27.8%). The mean age of children having steatosis was 11.67 years. There is no statistically significant difference in age (P=0.34) and anthropometric measurement including BMI (P=0.29) and Waist: Hip ratio (P=0.46) between children with or without hepatic steatosis as shown in table- II.

The mean level of SGPT in obese children with hepatic steatosis was 49.07(± 23.81) while 28.53(± 11.72) in
children without steatosis. The mean level of triglycerides was 186.39 (± 42.24) in obese children with hepatic steatosis and 154.22 (± 62.99) in children without steatosis. The mean level of cholesterol in children with or without steatosis was 191.56 (± 28.57) and 175.97 (± 30.89) respectively shown in table III.

Table IV showed comparison of metabolic abnormalities in between these two groups. A correlation was evident between High SGPT, cholesterol, LDL and hepatic steatosis. High SGPT, high cholesterol and LDL were significantly common in obese children with hepatic steatosis than children without steatosis (P < 0.004, < 0.05 and < 0.04 respectively).

### Table II

Comparison of mean of age and anthropometric measurements in obese children and adolescents with and without hepatic steatosis.

<table>
<thead>
<tr>
<th>Anthropometric Measurements (Mean)</th>
<th>Hepatic Steatosis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=18)</td>
<td>No (n=32)</td>
</tr>
<tr>
<td>Age</td>
<td>11.67 (± 2.25)</td>
<td>11.0 (± 2.37)</td>
</tr>
<tr>
<td>Height</td>
<td>148.32 (± 8.78)</td>
<td>142.28 (± 12.88)</td>
</tr>
<tr>
<td>Weight</td>
<td>61.78 (± 16.78)</td>
<td>52.42 (± 17.44)</td>
</tr>
<tr>
<td>BMI</td>
<td>31.08 (± 42.73)</td>
<td>29.20 (± 6.15)</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>72.98 (± 33.79)</td>
<td>67.97 (± 31.01)</td>
</tr>
<tr>
<td>Hip circumference</td>
<td>57.40 (± 42.73)</td>
<td>62.02 (± 37.09)</td>
</tr>
<tr>
<td>Waist-Hip ratio</td>
<td>0.93 (± 0.05)</td>
<td>0.92 (± 0.06)</td>
</tr>
</tbody>
</table>

### Table III

Mean biochemical parameters in obese children and adolescents with and without hepatic steatosis.

<table>
<thead>
<tr>
<th>Biochemical parameters</th>
<th>Hepatic steatosis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=18)</td>
<td>No (n=32)</td>
</tr>
<tr>
<td>SGPT</td>
<td>49.07 (± 23.81)</td>
<td>28.53 (± 11.72)</td>
</tr>
<tr>
<td>TG</td>
<td>186.39 (± 42.24)</td>
<td>154.22 (± 62.99)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>191.56 (± 28.57)</td>
<td>175.97 (± 30.89)</td>
</tr>
<tr>
<td>LDL</td>
<td>119.33 (± 33.25)</td>
<td>106.31 (± 28.35)</td>
</tr>
<tr>
<td>HDL</td>
<td>34.77 (± 5.78)</td>
<td>39.97 (± 10.85)</td>
</tr>
<tr>
<td>FBG</td>
<td>4.93 (± 0.51)</td>
<td>4.77 (± 0.49)</td>
</tr>
<tr>
<td>2HAG</td>
<td>7.62 (± 1.59)</td>
<td>7.27 (± 1.44)</td>
</tr>
</tbody>
</table>
Discussion:
Liver disease is a serious complication of childhood obesity. Although much to be learned about NAFLD, it is already evident that children with NAFLD, having high risk of progressive liver damage.\textsuperscript{5} In recent years, physicians have become increasingly interested in childhood obesity and accompanying steatohepatitis, and many studies have been published about these topics.\textsuperscript{5,14,15}

Male preponderance in obesity has been reported in most of the studies in Bangladesh and in neighboring countries.\textsuperscript{3,16,17} In the present study, male: female ratio was found 1.5:1 which was similar to the previous study done in BIRDEM, showing male: female ratio 1.3:1 and also with other studies.\textsuperscript{5,16,17} Among 50 obese children and adolescents, the most prevalent abnormal lipid profile was high TG followed by high cholesterol and LDL level. All these figures were much higher than the previous record in BIRDEM.\textsuperscript{15} In our study, prevalence of IGT was 12% which was consistent with 17.1% and 11.2% in different studies done in Bangladesh\textsuperscript{17} and abroad.\textsuperscript{18} The prevalence of diabetes mellitus was 6%, this figure was also consistent with other studies where it was 4%.\textsuperscript{19}

In present study, the prevalence of high SGPT among obese children was 36%. The prevalence of high SGPT was 25%, 48% and 47.1%, found in different studies done abroad.\textsuperscript{15, 20, 21} The Third National Health and Nutrition Examination Survey data have shown that 6% of overweight and 10% of obese adolescents have elevated ALT levels.\textsuperscript{22}

The exact prevalence of NAFLD is not well established. Information on its prevalence among children is scanty. In our study, the prevalence of hepatic steatosis was 36%. Pooling data from studies performed mainly in tertiary medical centers- the prevalence of NAFLD in obese children has been reported to range from 20-77\%.\textsuperscript{6} In an Italian multicentric study, 53% obese children had radiological fatty liver.\textsuperscript{15} In one study of school-aged children in northern Japan, overall prevalence of fatty liver was 2.6% and increased to 10-35% in obese children.\textsuperscript{14} Study conducted among Chinese obese children showed 77% had evidence of hepatic steatosis on sonography.\textsuperscript{23} In a small epidemiological study in India, prevalence of fatty liver was found 24%. \textsuperscript{24}
In one study in Pakistan and Iran, 7.52% and 2.3% of obese children had hyperechogenic fatty liver respectively.\textsuperscript{25,21} In present study 72% had mild, 28% had moderate hepatic steatosis, while no patient was identified to have severe steatosis. This finding is comparable to study done by Madana et al.\textsuperscript{21} among Iranian obese children and by DFY Chan et al.\textsuperscript{23} among Chinese obese children and adolescents, based on ultrasound score of fatty liver.

There had been male predominance (M 72.2%, F 27.8%) of hepatic steatosis found in our study with mean age of 11.67±2.25 years. In the studies of Franzese et al.\textsuperscript{15} and Tominaga et al.\textsuperscript{14} there was no difference between fatty liver prevalence between boys and girls. However, male predominance and younger age at presentation were postulated in different previous studies.\textsuperscript{23,21}

In ou study, when anthropometric measurements were compared among obese children and adolescents with or without hepatic steatosis, there was no significant difference between these two groups. This result was not similar to other study. Mandana Rafeey et al.\textsuperscript{21} and DFY Chan et al.\textsuperscript{23} showed in their studies, hepatic steatosis was positively correlated with BMI, waist and hip circumference, triglyceride and insulin resistance, indicate that higher adiposity may lead to a greater degree of fatty acid accumulation in the hepatocytes.

In the present study, high SGPT, high cholesterol and high LDL were more prevalent in children with hepatic steatosis in comparison to children without steatosis but there was no significant difference in TG, HDL and blood sugar level between these two groups. Nur Arslan et al.\textsuperscript{26} found a significant relationship between Serum TG and fatty liver in a study conducted among Turkish obese children. In another study among Iranian obese children and adolescents, total cholesterol and SGPT were significantly higher among hepatic steatosis group which is consistent with our findings.\textsuperscript{21}

The best enzyme marker for hepatic steatosis appears to be SGPT with a high sensitivity and specificity. Kawasaki et al.\textsuperscript{27} used SGPT as the predictor of fatty liver and found the correlation with of obesity to be the third best as compared to immunoreactive insulin and serum triglyceride. The strong association between the degree of steatosis and elevation of SGPT suggests that the greater degree of steatosis, the higher the chance for inflammatory change and possible development of more progressive disease.\textsuperscript{23}

**Limitation of the study:**
In our study we did not make correlation between predictors like socioeconomic status, exercise, dietary pattern or family history of dyslipidemia, DM, hypertension or fatty liver and hepatic steatosis whether these predictors resulted in steatosis in some obese children not in others. Sample size was small and duration of study was short. Patients with fatty liver did not undergo detailed evaluation for infective, metabolic and autoimmune hepatitis. In case of designing future researches in this field, special attention should be given to the above mentioned limitations.

**Conclusion:**
Our study concludes that hyperechogenic (bright) liver on USG with hyperlipidemia and raised SGPT are important signs of liver dysfunction in obese children with hepatic steatosis. In this study we attempted to find out the obese children having hepatic steatosis and related metabolic abnormalities so that we could make necessary affords for helping children avoid these serious liver problems as obesity with liver disease can get overlooked among the plethora of adverse outcomes related to childhood obesity. This may be helpful in the development of protocols designed to screen at-risk children and adolescents.

**References:**


