RESEARCH PAPER

Prevalence of Nonalcoholic Fatty Liver Disease in Normal-weight and Overweight Preadolescent Children in Haryana, India

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Objective: To document the prevalence of non-alcoholic fatty liver disease (NAFLD) and metabolic parameters among normal-weight and overweight schoolchildren.

Study design: Cross-sectional study.

Setting: Thirteen private schools in urban Faridabad, Haryana.

Participants: 961 school children aged 5-10 years.

Methods: Ultrasound testing was done, and 215 with fatty liver on ultrasound underwent further clinical, biochemical and virological testing.

Outcome measures: Prevalence of fatty liver on ultrasound, and NAFLD and its association with biochemical abnormalities and demographic risk factors.

Results: On ultrasound, 215 (22.4%) children had fatty liver; 18.9% in normal-weight and 45.6% in overweight category. Presence and severity of fatty liver disease increased with body mass index (BMI) and age. Among the children with NAFLD, elevated SGOT and SGPT was observed in 21.5% and 10.4% children, respectively. Liver enzyme derangement was significantly higher in overweight children (27% *vs* 19.4% in normal-weight) and severity of fatty liver (28% *vs* 20% in mild fatty liver cases). Eleven (8.1%) children with NAFLD had metabolic syndrome. Higher BMI (OR 35.9), severe fatty liver disease (OR 1.7) and female sex (OR 1.9) had strong association with metabolic syndrome.

Conclusions: 22.4% of normal-weight and overweight children aged 5-10 years had fatty liver. A high proportion (18.9%) of normal-weight children with fatty liver on ultrasound indicates the silent burden in the population.

Key words: *Fatty Liver Disease, Metabolic Syndrome, NAFLD.*

Non-alcoholic fatty liver disease (NAFLD) is defined as the accumulation of fat in the hepatocytes (>5-10% by weight) in the absence of any known liver pathology or excessive alcohol consumption [1]. NAFLD is the commonest cause of chronic liver disease in young people in the developed countries [2,3]. Paralleling overweight/obesity epidemiology, NAFLD report is also rising. Prevalence of fatty liver in the general adult population of India is in the range of 5% to 28%, with higher prevalence among the overweight and diabetics [4-6]. Prevalence of childhood NAFLD globally is in the range of 9 to 37% [7,8]. Further, the prevalence of NAFLD in normal-weight children and overweight/obese children is reported to range about 3-10% and 8-80%, respectively [9]. Presence of NAFLD varies according to the methodology and diagnostic criteria used [10]. Overweight/Obesity, dyslipidemia, insulin resistance and metabolic syndrome, ethnicity, gender and familial clustering are documented as risk factors for NAFLD in adults and children [9,11,12].

The increasing burden of obesity and non-communicable diseases across all ages warrants documentation of NAFLD burden. There is limited information about NAFLD among Indian preadolescent children. We undertook this study to document the prevalence of NAFLD among urban normal-weight and overweight school children in a northern Indian state, and its association with insulin resistance and other components of metabolic syndrome.

METHODS

This was a cross-sectional study that included urban school children aged ≥5 years and ≤10 years from Faridabad district, Haryana. We adopted intelligent two

stage sampling: (1) selection of schools and (2) selection of suitable children from the schools. Thirteen private schools were identified randomly from the list of schools with District Education Office. After obtaining informed written consent from parents, all the children in eligible age group were screened for weight, height and blood pressure. Weight and height were measured using electronic weighing scale (precision 100 grams) and Leicester Stadiometer (precision 0.1 cm), and Body mass index (BMI) calculated. Blood pressure was measured using electronic sphygmomanometer after resting for 10 minutes. Three measures for child each were obtained and mean of the measures was used. Date of birth was verified from the school register. Using the International Obesity Task Force (IOTF) reference for BMI, the children were categorized into underweight, normal-weight and overweight (BMI corresponding to <18.5, ≥18.5-<25 and ≥25 at 18 years of age, respectively) [13,14]. Children falling in the underweight category were excluded to avoid influence of fatty liver associated with undernutrition.

Ultrasonography (USG) abdomen was done at Indraprastha Apollo hospital by a radiologist using Sonosite (Fujifilm Sonosite Inc.) machine with 3.5 MHz convex-type transducer among randomly selected children from the above. All the ultrasound images were saved and reviewed by senior radiologist, and repeated in 10% of the children. Ultrasound findings were categorized into absent, mild, moderate and severe fatty liver disease, as per Needleman criteria [15].

Parents of the children with fatty liver on ultrasound were approached for consent for second part of study for detailed clinical examination and anthropometry, blood biochemistry, and virological evaluation. Waist circumference and hip circumference were measured using non-stretchable tape (Seca 201). Waist circumference above 90th percentile for the age and gender was considered as abnormal [16]. Children with hypertension were identified using the BP reference given by Manu Raj, *et al.* [17]. Fasting venous blood sample (6 mL) was drawn for all enrolled children, serum was separated within 2 hours and analyzed within 24 hours. Blood glucose, liver function tests and lipid profile were measured. Serum ceruloplasmin was analyzed by the immunoturbidimetry method. Hepatitis B antigen (HBsAg) and Anti-hepatitis C (HCV) assays were done by ELISA using kits (VIDAS Biomeriex, France and Orthodiagnostics, USA, respectively). Internal and external quality control protocols for continuous quality assurance was adopted in the laboratory. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >40 IU/L were considered as raised. Metabolic syndrome was defined by abnormality of any three of the parameters: fasting glucose >100 mg/dL, triglyceride >110 mg/dL, high-density lipoprotein (HDL) <38 mg/dL, hypertension (blood pressure >95th percentile for systolic blood pressure/diastolic blood pressure/mean arterial blood pressure) and obesity (>95th percentile BMI) [18].

Assuming prevalence of NAFLD in normal-weight and overweight children to be in the range of 12% and 55% (relative admissible error ±20%) at 95% confidence level, the sample size needed was 704 and 80, respectively. Considering the estimated prevalence of overweight in the range of 12-15%, a sample size of 960 children for ultrasound was planned.

The study protocol was approved by the Institutional Ethics Committees of both Inclen Trust International and Indraprastha Apollo Hospital. Data analysis was done by STATA using descriptive statistics (means and standard deviations), Mann-Whitney Test, unpaired t-test and chi-square test. A *P* value less than 0.05 was considered significant.

RESULTS

A total of 3560 children aged ≥5 and <10 years (2087 boys and 1473 girls) were screened. Out of the children screened, 2092 were normal-weight, 402 were overweight and 154 were obese. A total of 961 children (528 boys) underwent ultrasound examination (***Fig.* 1**), out of which 836 were in normal-weight category and 125 in overweight category. There was comparable representation from age-bands among the children who underwent ultrasound and those which did not.

Out of these 215 (22.4%; boys 25.6% and girls 18.5%) had fatty liver on ultrasound. Out of the 215 children with fatty liver, 110 had mild degree and 25 had moderate degree and none had severe degree. The prevalence of fatty liver increased with age in both boys and girls, from 13.1% in 5-6 years to 31% in 9-10 years age-group (***Fig.* 2**). Boys had a higher risk of fatty liver (OR 1.5; 95% CI 1.3-1.8).

Proportion of fatty liver among overweight children was 45.6%, twice than the normal-weight children (18.9%); which was similar in both boys (48.5% and 22.3%, respectively) and girls (42.4% and 14.7%, respectively). Higher BMI was observed to be a risk factor for fatty liver in both sexes [boys, OR 3.28 (95% CI 2.96-3.64); girls, OR 4.26 (95% CI 3.96-4.52); all children OR 3.59 (95% CI 2.9- 4.5)]. Only few children had any symptoms and/or signs like pain abdomen (6.4%), jaundice (2.8%) or vomiting (2.1%). Family history of hypertension, diabetes and liver disease were

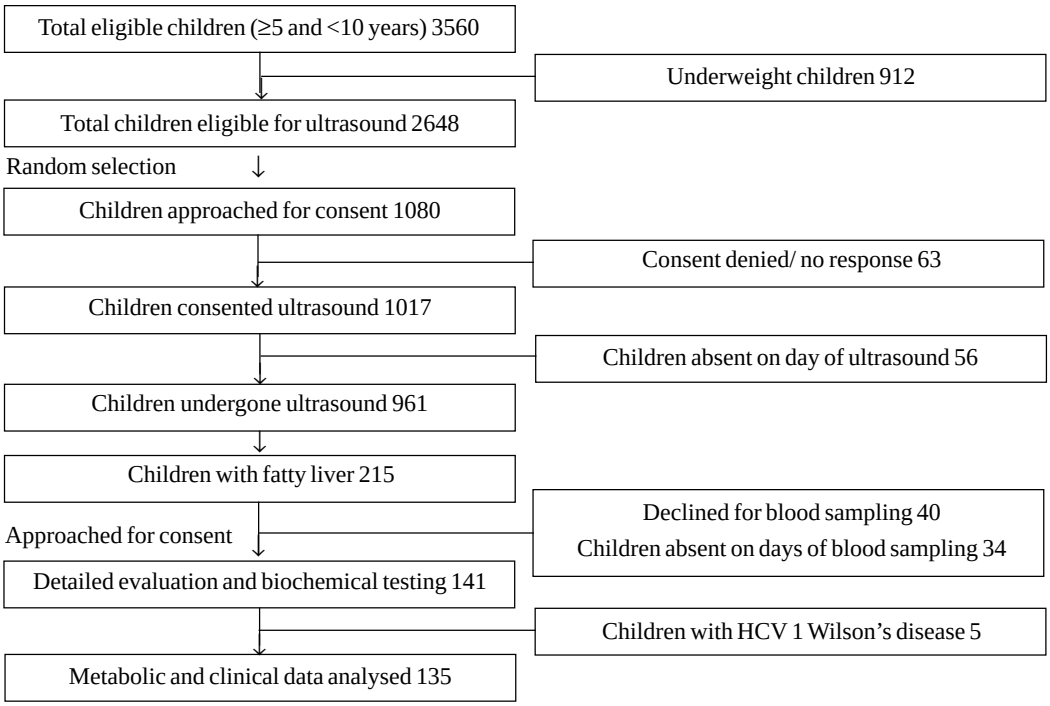
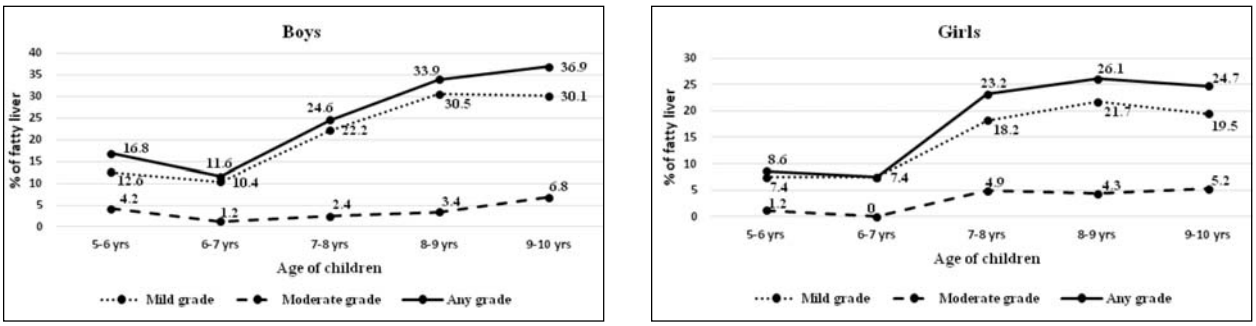


FIG. 1 *Study participation flow chart.*



(a) *(b)*

FIG. 2 *Severity of fatty liver diagnosed on ultrasound in (a) boys; and (b) girls.*

present in 12.8%, 6.4% and 3.5% of children, respectively and there was no relationship with severity of fatty liver.

Detailed biochemical evaluation could be done in 141 children. AST and ALT levels were raised in 29 (21.5%) and 14 (10.4%) children, respectively. AST level was elevated in 19.4% of normal-weight children and 27% of the overweight children. SGPT level was elevated in 35% of overweight children and 1% of the normal-weight children.

Low HDL (38.5%) and hypertriglyceridemia (23.7%) were the commonest metabolic derangements observed (***Table* I**). The 11 children with metabolic syndrome had hypertriglyceridemia (100%), obesity (91%), and low HDL (82%) as prominent features. When compared across the BMI categories; low HDL level was comparable among normal-weight (37.8%) and overweight children (38.1%), but increased among obese children (43.8%; *P*=0.04). The hypertriglyceridemia proportion increased with BMI; 16.3% in normal-weight, 33.3% in overweight (*P*=0.04) and 56.3% in obese (*P*=0.005) categories. Similarly the prevalence of hypertension increased with BMI; 8.2% among normal-

WHAT IS ALREADY KNOWN?

- Prevalence of fatty liver and NAFLD is high in children with higher BMI (overweight or obese).

WHAT THIS STUDY ADDS?

- A high proportion of normal-weight children also have NAFLD and metabolic derangements.

weight, 14.3% in overweight (P=0.03) and 12.5% in obese (P=0.04) categories. Proportion of children with low HDL level and hypertension was higher with higher severity of fatty liver (***Table* I**). Higher BMI (OR 35.9; 95% CI 28.5-41.2), severe fatty liver disease (OR 1.7; 95% CI 1.32-1.96) and female sex (OR 1.9; 95% CI 1.4-2.24) had an association with metabolic syndrome.

DISCUSSION

This study documented fatty liver on ultrasound in 22.4% of selected children (45.6% in overweight children, 18.9% in normal-weight children). Presence of fatty liver increased with rise in BMI, and derangement in liver enzymes increased with fatty liver severity and BMI. Low HDL and hypertriglyceridemia were the commonest metabolic derangements observed.

Exclusion of under-weight children, including only private school students, and non-availability of liver biopsy findings for confirmation of NAFLD are some of the limitations of the present study.

Reports on NAFLD among Indian children are limited. Among 4-18 years old Kashmiri school children, NAFLD was documented in 7.4% in all children (26% in obese children) [19]. In a hospital-based study from Delhi, 3% of children aged 5-12 years had fatty liver [20]. NAFLD was documented on ultrasound in 33.9% normal-weight and 66.1% of overweight adolescents aged 11-15 years in Mumbai [21]. We documented higher proportion of NAFLD among normal-weight children, but the proportion in over-weight/obese children was comparable. Among Iranian children with NAFLD, raised liver enzymes were reported in 4.1% and 6.6% of the normal-weight children and 16.9% and 14.9% of the obese children (6-18 years), respectively [11]. Although higher proportion of liver enzyme derangement was observed in our study, the trend across the BMI category and severity of fatty liver was consistent. Proportion of metabolic syndrome with NAFLD was comparable to reports among children from China (32%), Japan (30%) and North America (26%) [22-24].

TABLE I METABOLIC PARAMETERS IN CHILDREN WITH FATTY LIVER

Parameters	*Fatty liver, n(%)*		
	Mild (n=109)	*Moderate (n=26)*	*Total (n=135)*
Obese	29 (26.6)	8 (30.8)	37 (27.4)
Hypertension	10 (9.2)	3 (11.5)	13 (9.6)
Hyperglycemia	13 (11.9)	3 (11.5)	16 (11.8)
Hypertriglyceridemia	26 (23.8)	6 (23)	32 (23.7)
Low HDL	39 (35.8)	13 (50)	52 (38.5)
*Metabolic syndrome	8 (7.3)	3 (11.5)	11 (8.1)

**Metabolic syndrome was defined as presence of any three of the five parameters.*

In conclusion, the present observation indicates high prevalence of fatty liver in normal-weight and overweight children aged 5-10 years. This early onset of NAFLD in childhood points towards rising prevalence coupled with increasing overweight/obesity, although the carry-over effect of transition from underweight to normal-weight or overweight cannot be ruled out. The current practice of NAFLD screening based on high BMI is likely to miss a sizable number of normal-weight children with NAFLD, who are also at risk for progression. Further research is needed to address the biological basis and associations with various risk factors and potential interventions to prevent and/or reverse NAFLD. Additionally, lack of appropriate cut-offs for various metabolic parameters in metabolic syndrome in Indian children makes comparison and trend analysis challenging. With high burden of undernutrition, the prevalence of fatty liver among children related to overweight and metabolic syndrome may be different from the published reports.

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