Prevalence and risk factors for nonalcoholic fatty liver disease in obese children in rural Punjab, India

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Abstract:

BACKGROUND: Pediatric nonalcoholic fatty liver disease (NAFLD) is associated with insulin resistance, hypertension, metabolic syndrome, cardiovascular problems, and increased risk of chronic liver disease and Type II diabetes mellitus. The aim of the study was to assess the metabolic profiles and associated risk factors of NAFLD in obese children.

MATERIALS AND METHODS: Children with a body mass index (BMI) of >27 kg/m^2 an adult equivalent cutoff (Indian Academy of Paediatrics, 2015 guidelines) aged 5–18 years presenting to the pediatric outpatient unit of PGIMER Satellite Centre, Sangrur, India, were retrospectively recruited over a 1-year period. Anthropometry, lipid profile, thyroid levels, liver function test, fasting blood sugar, and blood pressure were measured. Ultrasonography was used to diagnose NAFLD. Logistic regression was used to assess the risk factors.

RESULTS: A total of 100 children participated in the study. The mean age was 10.6 ± 2.6 years and the mean BMI-Z score was 2.6 ± 0.5. The prevalence of NAFLD was 62%. Alanine transaminase (ALT) was significantly elevated in all the children with NAFLD. Lipid levels and BMI Z-score were similar in both groups. Unadjusted odds ratio shows statistically significant association of ALT (2.058 [1.11–1.01]) and waist circumference (1.089 [1.19–0.99]) with NAFLD. With adjusted odds ratio only, ALT (1.12 [1.24–1.01]) was found to be significantly associated with NAFLD.

CONCLUSION: There is quite a high prevalence of nonalcoholic fatty liver in obese Indian children. All children with raised liver enzymes should undergo sonography to rule out NAFLD.

Keywords:

Association, nonalcoholic fatty liver, obesity, risk factors

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as hepatic fat infiltration of >5% by liver biopsy in the absence of any liver pathology and alcohol abuse.[1] It can range from fatty infiltration alone to a triad of fatty infiltration, inflammation, and fibrosis known as nonalcoholic steatohepatitis. Pediatric NAFLD has a strong association with obesity, and children with NAFLD have a high prevalence of associated insulin resistance, Type II diabetes mellitus, hypertension, metabolic syndrome, and cardiovascular problems. These children are also at an increased risk of developing chronic liver disease and liver failure.[2] The prevalence of pediatric NAFLD worldwide is in the range of 9%–37%.[3,4] The increasing prevalence of fatty liver disease in children in developing countries has been noted as parallel to the increase in the prevalence of obesity in this part of the world. Potential interventions such as lifestyle and dietary modifications early in the course of disease can help in the prevention and/or reversal

of the changes as some imaging studies suggest. This can help in halting its progression to chronic liver disease.[5]

There are limited data on the prevalence and other aspects of this disease from the developing world, particularly from India.[2,6,7] In recent studies from India, a wide ranging prevalence of 26%–62.5% using ultrasonography (USG) as a diagnostic tool has been reported of pediatric NAFLD in obese children.[2,6] A high proportion of overweight children with fatty liver on ultrasound indicates the increasing burden of this disease in the Indian pediatric population.[6]

Although histopathology is the gold standard for detecting fatty liver changes, it is invasive with a high risk of associated complications. USG, a cheap and feasible in a low-resource setting, is a noninvasive method for the detection of the severity of steatosis and the grading of fatty infiltration in the outpatient department (OPD). The aims of the present study were to assess the metabolic profiles and associated risk factors of NAFLD in obese children using noninvasive screening methods.

Materials and Methods

A retrospective, observational assessment of a database of a pediatric outpatient unit of PGIMER Satellite Centre, Sangrur (Punjab), India, with a total of 100 children (aged between 5 and 18 years) was done over a 13-month period, between September 1, 2018, and October 31, 2019. Ethical approval was obtained from the Institutional Review Board/Ethics Committee (PGIMER, Chandigarh, functioning under the Ministry of Health and Family Welfare, Government of India) to conduct this retrospective study (record-based observational assessment), and written informed consent was taken from the parents of all participants in the study. Children aged between 5 and 18 years, resident in the Punjab for the last 5 years, with body mass index (BMI) of >27 kg/m² adult equivalent cutoff based on revised Indian Academy of Paediatrics (IAP) 2015 reference percentiles, and with all assessment details were included in the study.

Children with known liver pathology, history of familial hyperlipidemia, storage disorder; children with obesity secondary to genetic, chromosomal, major endocrinal, metabolic syndrome; or children with psychological disorders, Children on medications that account for steatosis and those who were obviously short in stature were excluded from the study.

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Sample size was calculated using the formula: $n = z^2 P (1 - p)/d^2$.[7] The prevalence of pediatric NAFLD in overweight children had been estimated as about 45.6% as per an Indian study done in Haryana.[7] Considering an absolute margin of error of 10% at 95% confidence interval with 90% power, the total sample size was 100. We enrolled consecutive 100 patients who fulfilled the inclusion criteria from the database for the study.

Baseline data on demographic and clinical characteristics were collected retrospectively throughout the study on a predesigned pro forma. Anthropometric assessments recorded were weight (kg), height (m), BMI (kg/m²), and waist circumference. BMI was measured as weight in kg divided by height in m². BMI Z-scores were calculated using revised IAP 2015 reference percentiles.[8]

Obesity was defined as a BMI >27 kg/m² adult equivalent cutoff presented in the revised IAP 2015 BMI charts that had been proposed for Indian children, as Asian children are known to be prone to cardiovascular complications at lower BMI.[8] BMI Z-scores were calculated. Waist circumference above 90th percentile for age and gender was considered as abdominal obesity.[9] Blood pressure (BP) readings were recorded from the data analyzed. Children with raised BP were labeled as hypertensive based on the BP reference given by Raj *et al*.[10] Blood glucose, liver function tests, lipid profile, and thyroid profile readings were recorded from the data. ALT >26 U/l for boys and >23 U/l for girls were considered raised.[11] Fasting and random sugar were considered elevated if they were ≥100 and 140 mg/dl, respectively.[12] Triglycerides, total cholesterol, and low-density lipoprotein were considered high if ≥150 mg/dl, >200 mg/dl, and 130 mg/dl, respectively, and high-density lipoprotein (HDL) was considered low if <40 mg/dl in children of either gender.[13] Normal values for thyroid hormones for the study were taken as per the pediatric reference intervals given by Kapelari *et al*.[14] Abdominal ultrasound results were analyzed from the data retrospectively. Ultrasound Abdomen was done as a part of the routine workup for obese children presenting in the OPD. Ultrasound was done using Mindray DC 60 with 2–5 MHz convex probe on all obese children to determine the fatty changes in the liver, based on echogenicity of the liver in comparison to kidney, portal vein, and diaphragm. The size of the liver was also recorded from the data. Severity of fatty liver was routinely graded on USG reports in our institute as follows: Group A - normal liver, Group B - mild, Group C – moderate, and Group D - severe (as per the Needleman Criteria).[15]

The data were entered in MS excel and analyzed using SPSS version 20 (IBM Corp., Armonk, NY, USA). Descriptive statistics (percentage, mean, median, and

mode) were calculated. Normality of data was calculated by Shapiro–Wilk test. Association of NAFLD with other risk factors was assessed by Chi-square test/McNemer's test (categorical variable), Student's *t*-test, and Mann–Whitney U-tests. Binary logistic regression was applied to calculate the odds ratio. Receiver operating characteristic (ROC) curve was constructed to discover the sensitivity and specificity of the screening tool. The level of significance was fixed at <0.05 at 95% confidence interval (CI).

Results

A total of 100 children were enrolled in the study. Of those, 62(62%) were males and 38 (38%) were females. The mean age of males and females was 11.17 ± 2.8 and 9.93 ± 2.2 years, respectively, the mean BMI Z-score was 2.6 ± 0.5, and there was preexisting acanthosis nigricans in 78% of the patients. Twelve patients (12%) were found to have associated hyperglycemia while hypertension and subclinical hypothyroidism were found in 20% and 22% of the patients, respectively. Mean or median values of various biochemical and radiological parameters are presented in Table 1. The prevalence of NAFLD was 62% (presence of fatty infiltration on USG), of which 46% of patients had mild and 16% had moderate fatty infiltration. None of the patients was found to have severe fatty liver. A family history of obesity, diabetes, and hypertension was present in 42%, 34%, and 38% of the children, respectively [Table 1].

The risk factors found to have significance in relation to NAFLD were waist circumference and ALT level, whereas all other factors such as age, sex, and BMI were found to be statistically insignificant. Family history of obesity, diabetes, and hypertension was found not to be significant. Children with NAFLD had significantly raised levels of ALT and albumin as compared to children without NAFLD. But levels of total serum proteins, AST(Aspartate transaminase) and ALP(Alkaline phosphatase) were comparable in both the groups. Statistically no significant difference was found in the mean serum fasting sugars, thyroid hormones levels, and lipid levels between the two groups [Table 2]. Unadjusted odds ratio showed statistically significant association of ALT 26 U/l for boys and >23 U/l for girls (2.058 (1.11–1.01]) and waist circumference >90 centile for age and gender (1.089 [1.19–0.99]) with NAFLD. With adjusted odds ratio only, ALT (1.12 [1.24–1.01]) was found to be significantly associated with NAFLD [Table 3].

To evaluate the potential of ALT (>28.5 U/l) and waist circumference above 90th percentile for age and gender as a screening tool for NAFLD, an ROC curve was constructed. The area under the ROC curve for waist circumference >90th centile for age and gender was

Table 1: Characteristics of the study participants (*n*=100)

Characteristics	N (%)
Age (years) Mean±SD	10.6±2.6
Age- pubertal (9+ years)	69 (69.0)
BMI *Z* score Mean±SD	2.6±0.5
Comorbidities	
Hyperglycemia	12 (12.0)
Hypertension	20 (20.0)
Subclincal hypothyroidism	22 (22.0)
Preexisting acanthosis nigricans	78 (78.0)
Biochemical parameters and liver size	
Total serum cholesterol (mg/dl), Median (IQR)	187.5 (155.7-206.2)
HDL (mg/dl) Median (IQR)	37.5 (34-43)
LDL (mg/dl) Median (IQR)	143 (115.75-156)
VLDL (mg/dl) Median (IQR)	34 (30-39)
Triglycerides (mg/dl) Median (IQR)	184.5 (157.75-198)
AST (U/L) Median (IQR)	40.50 (32.75-54)
ALT (U/L) Median (IQR)	44 (37.75-54.25)
Fasting blood sugar (mg/dl) Mean±SD	79.9±7.2
ALP (U/L) Median (IQR)	217 (177.5-293.3)
Total protein (g/dl) Mean±SD	6.9±0.8
Albumin (g/dl) Mean±SD	4.24±0.6
TSH (µIU/mL) Mean±SD	4.13±1.6
Total bilirubin (mg/dl) Mean±SD	0.45±0.2
Liver size (cm) Mean±SD	14.06±2.2
NAFLD grading by USG	
Normal	38 (38.0)
Mild	46 (46.0)
Moderate	16 (16.0)
Severe	0 (0)
Family history	
Hypertension present	38 (38.0)
Diabetes present	34 (34.0)
Obesity present	42 (42.0)
Play hours/day	
1	46 (46.0)
2	54 (56.0)

SD=Standard deviation, BMI=Body mass index, AST=Aspartate transaminase, ALT=Alanine aminotransferase, ALP=Alkaline phosphatase, HDL=High-density lipoprotein, LDL=Low density lipoprotein, NAFLD=Nonalcoholic fatty liver disease

0.67 (95% CI 0.52–0.82, *P* = 0.05) and gave a sensitivity of 90% and a specificity of 84% for predicting NAFLD. The area under the ROC curve for ALT was 0.69 (95% CI 0.55–0.84, *P* = 0.02) and the cutoff of ALT ≥28.5 gave a sensitivity of 90% and a specificity of 90% for predicting NAFLD [Figures 1 and 2].

Discussion

The prevalence of NAFLD in obese pediatric patients in our study was 62% on ultrasound. Pawar *et al*. found the prevalence of NAFLD as 66.1% in overweight and obese children in a school-based cross-sectional study in Mumbai, which is consistent with our study.[16] Irshad *et al*. and Das *et al*. documented NAFLD as 26% in obese

Table 2: Comparisons of clinical and biochemical parameters in children with and without nonalcoholic fatty liver disease

Parameters	Children without NAFLD (*n*=38) N (%)	Children with NAFLD (*n*=62) N (%)	*P*-Value
Age (years) Mean±SD	9.32±2.4	10.52±2.2	0.077
Age (years)			
<9	18 (52.9)	16 (47.1)	0.105
≥9	20 (30.3)	46 (69.7)	
Sex			
Male	22 (40.7)	32 (59.3)	0.445
Female	16 (34.8)	30 (65.2)	
Family H/O HTN			
Absent	10 (32.3)	21 (67.7)	0.221
Present	9 (47.4)	10 (52.6)	
Family H/O DM			
Absent	20 (30.3)	46 (69.7)	0.105
Present	18 (52.9)	16 (47.1)	
Family H/O obesity			
Absent	24 (41.4)	34 (58.6)	0.390
Present	14 (33.3)	28 (66.7)	
Weight (kg) Mean±SD	46.43±12.2	54.2±14.4	0.056
Height (cm) Mean±SD	131.32±12.3	137.63±13.1	0.096
Waist circumference (cm) Mean±SD	72.08±6.0	76.73±8.6	0.045
BMI Z-score Mean±SD	2.58±0.04	2.54±0.4	0.783
BMI Mean±SD	26.41±2.9	28.10 (3.2)	0.065
Liver size Mean±SD	13.89±1.4	14.16±2.5	0.679
TP (g/dl) Mean±SD	6.83±0.6	6.9±1.0	0.764
Albumin (g/dl) Median (IQR)	4.1 (3.7-4.3)	4.5 (3.9-4.7)	0.017
AST/SGOT (IU/L) Median (IQR)	36 (34-53)	43 (32-56)	0.337
ALT/SGPT (IU/L) Median (IQR)	39 (36-45)	51 (38-67)	0.024
ALP (IU/L) Median (IQR)	209 (170-274)	237 (187-308)	0.208
T3 (ng/dl) Mean±SD	6.53±2.0	1.44±0.25	0.203
T4 (ug/dl) Mean±SD	6.41±2.0	6.47±3.2	0.94
TSH (uIU/ml) Mean±SD	4.47±1.8	3.93±1.4	0.222
Serum cholesterol (mg/dl) Median (IQR)	200 (155-217)	172 (156-204)	0.384
HDL (mg/dl) Median (IQR)	37 (34-43)	38 (34-43)	0.881
LDL (mg/dl) Median (IQR)	145 (118-156)	136 (109-156)	0.280
TGs (mg/dl) Median (IQR)	187 (168-192)	178 (156-199)	0.682
FBS (mg/dl) Mean±SD	79.47±7.1	80.16±7.4	0.748

Statistical tests used: Independent *t*-test for comparison of means, Chi-square test/McNemer's test for comparison of proportions, Mann-Whitney U-tests for median and IQR. IQR=Interquartile range, SD=Standard deviation, HTN=Hypertension, DM=Diabetes mellitus, BMI=Body mass index, TP=Total protein, AST=Aspartate transaminase, SGOT=Serum glutamic-oxaloacetic transaminase, ALT=Alanine aminotransferase, SGPT=Serum glutamic pyruvic transaminase, ALP=Alkaline phosphatase, TSH=Thyroid-stimulating hormone, HDL=High-density lipoprotein, LDL=Low-density lipoprotein, TGS=Triglycerides, FBS=Fasting blood sugar, NAFLD=Nonalcoholic fatty liver disease, H/O=History of

children and 45.6% in overweight, respectively.[2,7] The range of prevalence of NAFLD found in obese children in other developed countries varied widely from 26.0% to 85% in studies done by Yu *et al*. and Jimenez-Rivera *et al*. using USG and liver enzymes as screening tools.[17,18] The wide ranging prevalence in these studies could be attributed to the different definitions of abnormal liver enzymes and different diagnostic criteria used in various studies. In our study, children with NAFLD were found to have significantly elevated ALT compared to children without NAFLD [Table 2]. The results of our studies also agreed with those of previous studies that evaluated the diagnostic accuracy of alanine aminotransferase (ALT) for NAFLD in children with obesity.[2-7,16-18] Das *et*

al concluded that liver enzymes derangement was significantly higher in overweight children as compared to normal weight children in their study. Whereas ALT level was elevated in 35% of overweight children ,only 1% of the normal-weight children had elevated ALT.[7] Jimenez-Rivera *et al*. found that ALT was elevated in 61% of patients with NAFLD.[18] Therefore, all children with raised liver enzymes should undergo sonography to rule out NAFLD.

Similar to findings observed by Jain *et al*., in the present study, lipid levels were not statistically significantly different in the children with and without NAFLD[6] though the Jain *et al*.'s study found lower levels of HDL

Table 3: Association of various factors with nonalcoholic fatty liver disease

Factors	Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
ALT/SGPT (IU/L)	2.058 (1.11-1.01)	0.03	1.12 (1.24-1.01)	0.03
Total cholesterol (mg/dl)	0.996 (1.09-0.99)	0.50	0.989 (1.01-0.97)	0.37
HDL (mg/dl)	1.019 (1.12-0.93)	0.68	0.918 (1.09-0.77)	0.33
LDL (mg/dl)	0.988 (1.01-0.97)	0.21	0.975 (1.01-0.94)	0.17
Triglycerides (mg/dl)	1 (1.02-0.98)	0.96	1.02 (1.06-0.98)	0.35
Age <9 years	0.386 (1.29-0.12)	0.12	0.4 (4.94-0.03)	0.48
Male sex	0.776 (2.45-0.25)	0.67	0.646 (4.52-0.09)	0.66
Waist circumference (cm)	1.089 (1.19-0.99)	0.05	1.167 (1.42-0.96)	0.13
BMI Z-score	0.836 (2.99-0.24)	0.77	0.785 (7.75-0.08)	0.84
TSH (uIU/ml)	0.79 (1.15-0.54)	0.22	0.894 (1.56-0.51)	0.69

SD=Standard deviation, BMI=Body mass index, ALT=Alanine aminotransferase, SGPT=Serum glutamic pyruvic transaminase, TSH=Thyroid-stimulating hormone, HDL=High-density lipoprotein, LDL=Low-density lipoprotein, CI=Confidence interval, OR=Odds ratio
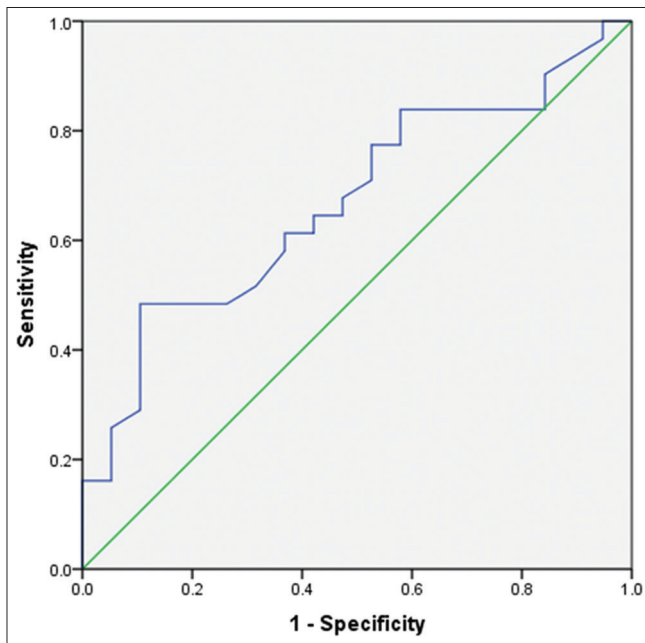

Figure 1: Receiver operating characteristic curves for waist circumference. Area under receiver operating characteristic curve for waist circumference = 0.67
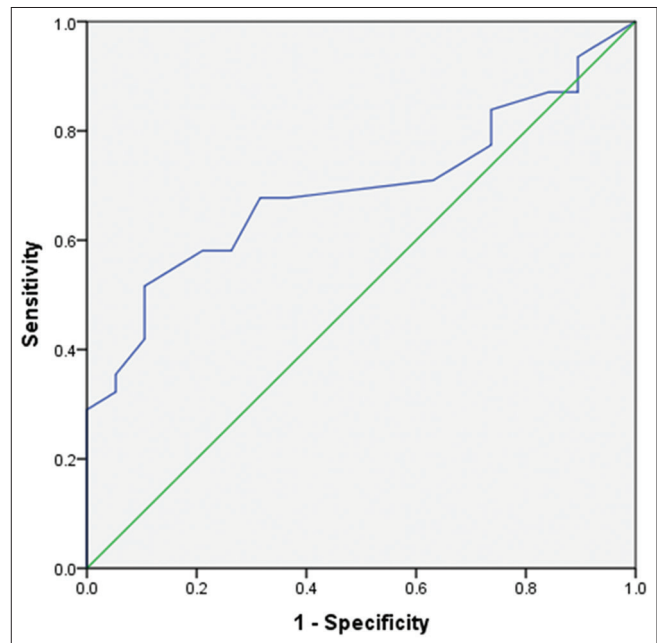

Figure 2: Receiver operating characteristic curves for alanine transaminase. Area under receiver operating characteristic curve for alanine aminotransaminase = 0.67

cholesterol in the adolescents with moderate or severe fatty liver. In the index study, 12% and 20% of the patients had associated hyperglycemia and hypertension. Findings are in agreement with the previous literture.[16,19] In addition, 22% of children had deranged thyroid profile in the form of subclinical hypothyroidism, a result which is in agreement with studies the done by Stichel *et al*. and Reinehr *et al*., which also reported moderately increased peripheral thyroid hormones (T3 and T4) and TSH levels in obese children.[20,21] However, as per a recent meta-analysis, TSH level could be an important risk factor for the development and progression of NAFLD, independent of thyroid hormones.[22] In view of the conflicting results of previous studies regarding thyroid dysfunction in NAFLD, further research is recommended to determine the relationship between thyroid dysfunction and NAFLD and the underlying mechanisms.[23]

Jain *et al*. found that the waist circumference standard deviation score SDS cutoff >1.4 had the highest discriminating ability, with the area under the ROC curve of 0.73 (95% CI 0.66–0.80), for predicting the risk of NAFLD similar to our study (area underthe curve 0.67 [95% CI 0.52–0.82, *P* = 0.05]).[6] Although waist circumference was found not to be a significant predicting risk factor on adjusted odds ratio in our study [Table 3], this could be the result of the small sample size. This needs further evaluation as several earlier studies have also recognized waist circumference as a simple and effective screening tool for abdominal obesity and a means of identifying children at a higher risk of metabolic syndrome and cardiovascular diseases.[24-27]

The relatively small sample size and the nonavailability of the confirmatory tests such as liver biopsy and MRI are

some of the limitations of present study. Although liver biopsy could have confirmed diagnosis of NAFLD, as the majority of the patients were asymptomatic and none was found with severe fatty infiltration on USG, liver biopsy was not indicated as per the treating physician.

Conclusion

The prevalence of nonalcoholic fatty liver in obese Indian children aged 5–18 years is rising ,trend observed similar to the western countries. Early detection using various simple screening tools can go a long way in the prevention of chronic liver disease and associated comorbidities in the obese children. However, more population-based studies are recommended to find out the exact prevalence of the problem and definitive associations with various clinical and biochemical parameters.

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Conflicts of interest
There are no conflict of interest.

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