Original Article

A study of occurrence of non-alcoholic steatohepatitis in children with obesity and overweight

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in children and its increasing prevalence is associated with concomitant rise in obesity. Anthropometric measurements and non-invasive tests (liver function tests and USG abdomen) help in early recognition of non-alcoholic steatohepatitis (NASH) and reduce consequent morbidity and mortality. Aim: This study aims to study the occurrence of NASH in obese and overweight children and to derive the correlation of NASH with clinical and biochemical parameters in overweight and obese children. **Methods:** This hospital-based prospective study included children (age ≤18 years) who met the inclusion criteria. Diagnosis of NASH was based on USG abdomen. Measurements included anthropometry, ultrasonography, fasting glucose, alanine aminotransferase (ALT), lipid profile and additional parameters of blood pressure, fasting insulin, and homeostatic model assessment of insulin resistance (HOMA-IR). The variables were compared between children with and without NASH. **Results:** A total of 146 patients (female: 51.4%, male: 48.6%) were enrolled in the study. The most common age group affected was 11–18 years (50.7%) followed by 6–10 years (43.2%) and <5 years (6.2%). The occurrence of NASH in the study group was 63% of obese and overweight children. Mean weight, body mass index (BMI), waist circumference, waist–hip ratio, blood pressure (BP), serum glutamic-pyruvic transaminase (SGPT), fasting insulin level, and HOMA-IR were significantly higher in children with NASH. There was a significant association between SGPT and NASH. Elevated SGPT of 79.3% and 1.9% was observed among the subjects with and without NASH, respectively. **Conclusion:** Anthropometric indices and biochemical parameters were more elevated in NASH group showing its direct correlation with hepatic steatosis.

Key words: Metabolic syndrome, Nash, Non-invasive tests, Obesity

Among the chronic liver diseases in children, non-alcoholic fatty liver disease (NAFLD) is the most common one and is prevalent in overweight or obese children [1]. It can range from fatty liver alone to a triad of fatty infiltration, inflammation, and fibrosis, termed non-alcoholic steatohepatitis (NASH).

The best diagnostic method for NAFLD is a liver biopsy, but it is difficult to perform in the pediatric obesity clinic due to cost, complications, and ethical considerations [2]. Ultrasonography (USG) is the most widely used method for NASH screening. The quantitative severity of hepatic steatosis measured by USG, correlated with the histological degree of steatosis on liver biopsy [3].

Waist circumference directly reflects abdominal fat and is closely related to the cardiovascular and metabolic complications of obesity [4-6]. Abdominal adiposity induces insulin resistance and free fatty acid accumulation through lipolysis [7]. The increased substrate for hepatic lipogenesis and relative hyperinsulinemia accelerates liver fat storage, leading to NASH [8,9]. The screening alanine transaminase (ALT) for elevation in today's youth (SAFETY) study recently reported that among otherwise healthy children, the 95th percentile for ALT is ~26 U/L for boys and ~23 U/L for girls, suggesting much lower ALT thresholds should be used to initially screen for chronic liver disease in children [10]. Children with NASH have a high prevalence of concomitant metabolic syndrome, increased risk for developing type 2 diabetes, and progression to end-stage liver disease [11]. The risk factors for NASH include obesity, diabetes, insulin resistance (IR), and hypertriglyceridemia [12].

In spite of the availability of noninvasive tests such as liver function tests and USG abdomen that help in early recognition

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Table 1: Mean anthropometry distribution

Variables	Mean±Standard deviation
Age	10.5±3.04
Height (cm)	139.59±16.07
Weight (kg)	52.23±16.45
Body mass index (kg/m^2)	26.19±3.79
Waist circumference (cm)	81.74±10.27
Hip circumference	87.88±11.07
Waist–hip ratio	0.93±0.04
Waist–height ratio	0.58±0.06
Systolic blood pressure	123.83±11.86
Diastolic blood pressure	77.48±8.88

of NASH, there is a lack of data from Indian studies. The current study was undertaken to know the magnitude of disease burden and clinical course in Indian children.

MATERIALS AND METHODS

The present study was carried out in the Department of Pediatrics, Mahadevappa Rampure Medical College, Kalaburagi. Patient attenders were informed about the purpose of study and written consent was taken before initiation of the study. Ethical clearance was obtained by the ethical clearance committee of the institution. The study included the study of occurrence of NASH in children with obesity and overweight during the period from October 2018 to April 2020.

The inclusion criteria were children <18 years of age of either sex with obesity (BMI > 95th percentile) or overweight (BMI > 85th percentile but <95th percentile) according to revised Indian Academy of Pediatrics (IAP) growth chart. The exclusion criteria were obesity caused by endocrine or genetic disorders, and those with previously diagnosed diabetes mellitus or primary liver disorders were excluded from the study.

Anthropometric and laboratory assessments were as follows: BMI was calculated as weight (kg)/height^2 (m^2). Waist circumference was measured at the midpoint between the inferior border of the rib cage and the superior aspect of the iliac crest at the end of normal expiration. Hip circumference was measured at the level of the greater trochanter. The waist-to-height ratio (WHtR) was calculated as waist circumference (cm) divided by height (cm). The waist-to-hip ratio (WHR) was calculated as waist circumference (cm) divided by hip circumference (cm). Waist circumference was >90th percentile for age and gender [13]. WHR was considered to be high if >0.95 (boys) and >0.85 (girls) [14]. WHtR not only incorporates waist circumference as a measure of abdominal adiposity but also adjusts for an individual's size. It is an age-independent index and does not necessitate age-specific diagnostic references. NASH is higher in obese male children with a waist circumference >90th percentile and a WHtR >0.56 [15]. Hypertension was diagnosed at systolic BP ≥130 mmHg and/or diastolic BP ≥85 mmHg [16]. Metabolic syndrome in adolescents was diagnosed using the International Diabetes Federation criteria [16]. Elevated ALT was defined as >26 U/l for boys and >23 U/l for girls [17]. Revised IAP growth charts 2015 were used to define obese (BMI >95th percentile) or overweight (BMI >85th percentile

Table 2: Clinical, demographic, and anthropometric parameters of children

Variables	Subgroups of the variables	Count	Percentage
Age	<5 years	9	6.2
	6–10 years	63	43.2
	11–15 years	66	45.2
	>15 years	8	5.5
Sex	Female	75	51.40
	Male	71	48.60
Acanthosis nigricans	Absent	16	11.00
	Present	130	89.00
BMI percentile	Obese	133	91.10
	Overweight	13	8.90
Waist circumference percentile	>95th	52	35.60
	90–95th	74	50.7
WHR distribution	Females >0.85	60	81.10
	Males >0.95	40	56.30
Waist–height ratio	<0.56	48	32.9
	>0.56	98	67.1
SBP and DBP distribution	SBP >130	52	35.60
	DBP >85	51	34.90
Fatty liver on ultrasonography (USG)	Absent	54	37.00
	Grade 1	68	46.60
	Grade 2	23	15.80
	Grade 3	1	0.70
SGPT	Increased	74	50.7
	Normal	72	49.3
Lipid profile distribution	Total count >200	7	4.80
	Triglycerides >150	34	23.30
	High-density lipoprotein (HDL) >40	76	52.10
	Low-density lipoprotein (LDL) >130	6	4.10
FBG, GTT 2 h, fasting insulin, and HOMA-IR distribution	<100	122	83.60
Fasting blood glucose (FBG)	>100–<126	24	16.40
Glucose tolerance test (GTT)	2 h <140	142	97.30
	>140	4	2.70
Fasting insulin	<20	91	62.30
	>20	55	37.70
HOMA-IR	≥3.2	96	65.8
	<3.2	50	34.2

BMI: Body mass index, WHR: Waist–hip ratio, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SGPT: Serum glutamic-pyruvic transaminase, HOMA-IR: Homeostatic model assessment of insulin resistance and <95th percentile). Fasting and 2 h blood glucose were considered elevated if ≥100 and 140 mg/ dl, respectively [18], and HOMA-IR (HOMA-IR = fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5) was considered high if ≥3.2 [19]. Triglyceride (TG) was considered high if ≥150 mg/dl; high-density lipoprotein (HDL) was considered low if <40 mg/dl, total count (TC) and low-density lipoprotein (LDL) cholesterol were considered elevated if >200 and 130 mg/dl, respectively [20]. Acanthosis nigricans over the neck was classified as absent, mild (if visible on close visual inspection and limited to the base of skull), and moderate to severe (if extending to lateral margins of the neck or further anteriorly) [21].

All the included patients were assessed by a single sonographer following not <8 h fasting using FFsonic UF-4100 apparatus with abdominal; convex linear probe 3.5 MHz. Longitudinal, subcostal, and oblique scans were performed. The liver size and echo pattern were evaluated. Liver echo pattern was graded as follows [22]: Grade 1 (mild): A slightly diffuse increase in fine echoes in the hepatic parenchyma with normal visualization of the diaphragm and intrahepatic vessel borders. Grade 2 (moderate): A moderate diffuse increase in fine echoes with slightly impaired visualization of the intrahepatic vessels and diaphragm. Grade 3 (marked): A marked increase in fine echoes with poor or no visualization of the intrahepatic vessel borders, diaphragm, and posterior portion of the right lobe of the liver.

Statistical analysis: Data were analyzed by IBM SPSS 20.0 software. For qualitative data analysis, we applied Chi-square test, Student's *t*-test, and ANOVA test were used for quantitative data analysis. $P < 0.05$ was considered as statistically significant.

The etiological evaluation of 146 children was done by detailed history, physical examination, anthropometry, BP measurement, and routine investigations including complete blood count (CBC), liver function tests (LFTs), USG, lipid profile, oral glucose tolerance test (OGTT), fasting insulin levels, and HOMA-IR were performed. Weight and BMI of children were assessed by revised IAP growth chart 2015.

RESULTS

A total of 146 children (female: 51.4%, male: 48.6%) who met the inclusion criteria were included in the study. The clinical, demographic, and anthropometric distributions of the study population are detailed in Tables 1 and 2.

Table 3: Comparison among obese and overweight children with and without NASH

Variables	NASH						*P* value
	No NASH		Mild NASH		Moderate NASH		
	Mean	SD	Mean	SD	Mean	SD	
Age	9.67	2.9	11.03	3.04	10.87	3.05	0.038*
Height (cm)	136.87	16.01	140.81	16.58	142.26	14.45	0.275
Weight (kg)	47.23	13.96	52.61	16.58	62.42	17	0.001*
BMI (kg/sq.m)	24.73	3.19	25.93	3.03	30.19	4.29	<0.001*
Waist circumference (cm)	78.87	10.21	82.68	10.14	85.52	9.39	0.017*
Hip circumference	88	12.28	87.1	10.5	89.79	9.89	0.592
Waist–hip ratio	0.89	0.05	0.95	0.03	0.95	0.03	<0.001*
Waist–height ratio	0.57	0.05	0.58	0.05	0.6	0.06	0.149
HB (g/dl)	12.66	1.52	13.21	1.39	12.8	1.15	0.091
SGPT (IU/L)	17.87	3.92	34.81	14.94	47.11	19.26	<0.001*
Total count (mg/dl)	148.09	28.42	151.36	31.79	148.6	20.68	0.809
Triglycerides (mg/dl)	118.9	48.44	122.05	73.02	141.16	53.38	0.322
HDL (mg/dl)	41.03	6.62	40.97	8.9	36.65	9.23	0.063
LDL (mg/dl)	84.33	24.66	86.09	27.44	83.83	17.89	0.897
VLDL (mg/dl)	24.24	9.44	25.18	14.16	26.5	10.41	0.741
TG/HDL	2.98	1.44	3.17	2.25	3.74	1.69	0.265
LDL/HDL	2.14	0.64	2.15	0.7	2.42	0.75	0.203
Creatinine (mg/dl)	0.53	0.14	0.53	0.17	0.54	0.2	0.959
FBG (mg/dl)	88.33	10.02	90.87	9.34	92.25	12.37	0.215
GTT 1 h (mg/dl)	110.13	24.71	118.26	26.73	127.83	28.38	0.021*
GTT 2 h (mg/dl)	104.59	13.1	110.35	20.3	111.71	21.57	0.144
Fasting insulin (uIU/ml)	18.29	10.46	21.84	14.69	26.3	14.72	0.046*
HOMA-IR	4.01	2.38	5.06	3.56	6.24	4.03	0.018*
HBA1c	0.08	0.11	0.07	0.09	0.06	0	0.527

***Statistically significant, BMI: Body mass index, HB: Hemoglobin, SGPT: Serum glutamic-pyruvic transaminase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, FBG: Fasting blood glucose, GTT: Glucose tolerance test, HOMA-IR: Homeostatic model assessment of insulin resistance, HBA1c: Hemoglobin A1c or glycated hemoglobin**

Age and distribution of gender were similar in the two groups. Mean BMI, white cells (WCs), WHR, BP, SGPT, fasting insulin, HOMA-IR, and prevalence of acanthosis nigricans were higher in the adolescents with NASH compared to those without NASH. The anthropometric and biochemical parameters were further compared between the adolescents without NASH (n = 54), with mild NASH (n = 68), and with moderate or severe NASH (n = 24). The parameters that were significantly different among the adolescents in these three groups are presented in Table 3. A clear gradation of BMI, WC, acanthosis nigricans, SGPT, lipid profile, fasting insulin, and HOMA-IR was observed across the three groups, showing further the association between severity of obesity, insulin resistance, and NASH.

DISCUSSION

Childhood obesity is one of the primary predictors of obesity in adults. More than two-thirds of children with obesity will become obese adults [23]. NASH, metabolic syndrome, type 2 diabetes mellitus, obstructive sleep apnea, and cardiovascular disease are not only well-described complications of obesity in adults but are also becoming increasingly recognized conditions in children. Elevated serum aminotransferases activity gives evidence of inflammation and the death of hepatocytes [24].

Anderson *et al.* reported the prevalence of NAFLD in the general population as 7.8% and to surpass 30% in those who are obese [11]. In one more study done by Reetha *et al*. [25] showed that prevalence of NAFLD among obese children residing in North Kerala, to be 60% and 20% of these, had elevated level of alanine amino transferase. A total of 65 patients (age: 5–18 years) were enrolled in this annual study.

NASH can occur in very young children also, but it is more prevalent in adolescents. Factors responsible for higher rate of NASH in adolescents include the role of pubertal hormones, increasing obesity, unhealthy eating habits, and sedentary lifestyle. In the current study, majority of children were >11 years of age. Literature suggest that higher prevalence of NAFLD is associated with male gender, while estradiol affords some protection in females [26]. Our results showed occurrence of NASH slightly more in females (51.4%).

Higher mean weight, BMI, waist circumference, and waist–hip ratio were significantly associated with NASH in the present study, as observed in other studies [27,28]. The presence and severity of acanthosis nigricans were also observed to be significantly higher in the children with NASH compared to those without. In our present study, Acanthosis nigricans was observed to be significantly higher in children with NASH compared to those without NASH. Hence this was used as a clinical risk marker for complications of obesity.

A clear gradation of the observed clinical and biochemical variables (Table 3) across the three groups showed further association between severity of obesity, insulin resistance, and NASH. These results are similar to one Indian study by Vandana Jain *et al*. [29]. However, the study was conducted in a tertiary care center and serves as a referral center for childhood obesity.

CONCLUSION

There is a higher occurrence of NASH in obese and overweight children (63%) as observed in USG findings and abnormal ALT. Hence, all overweight and obese children should be screened for NASH, especially if one or more of the risk markers are present.

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