

Assessment of Non-Alcoholic Fatty Liver Disease in Adolescents with Malnutrition: A Cross-Sectional Study

Pawan Nimbhorkar¹, Rakesh Thamke², Vijay Kamale³, Akshai B.⁴

¹ Junior Resident, Department of Family Medicine, MGM Medical College & Hospital, Navi Mumbai
Corresponding Author E-mail ID: [pawannimbhorkar95\[at\]gmail.com](mailto:pawannimbhorkar95[at]gmail.com)
Contact No: 9561944606 / 8830908210

² Associate Professor & Head, Department of Family Medicine, MGM Medical College & Hospital, Navi Mumbai
E-mail ID: [rthamke\[at\]yahoo.com](mailto:rthamke[at]yahoo.com)

³ Professor & Head, Department of Pediatrics, MGM Medical College & Hospital, Navi Mumbai
E-mail ID: [drvijaynkamale\[at\]gmail.com](mailto:drvijaynkamale[at]gmail.com)

⁴ Senior Resident, Department of Pediatrics, MGM Medical College & Hospital, Navi Mumbai
E-mail ID: [akshaifreat\[at\]gmail.com](mailto:akshaifreat[at]gmail.com)

Abstract: ***Introduction:** NAFLD is the most common liver disorder and its increased worldwide prevalence in adolescents is associated with the global obesity epidemic. NAFLD is strongly associated with malnutrition (under nutrition as well as obesity). The prevalence of lean NAFLD or non-obese NAFLD is also increasing. NAFLD has a close association with obesity, CV disease, diabetes mellitus and hepatocellular carcinoma, thus increasing occurrence of NAFLD is a matter of concern, as it is associated with increased morbidity and mortality. Indian data is scarce; therefore, the present study was undertaken to assess NAFLD in adolescents with malnutrition (under nutrition as well as obesity). **Objectives:** To assess NAFLD in adolescents with malnutrition (under nutrition as well as obesity). **Material & Methods:** A cross sectional study was conducted at MGM Medical College & Hospital, Navi Mumbai and MGM School, Nerul including 60 adolescents between age group of 12 to 19 years. Demographic details and anthropometric measurements were done for the children with necessary permission before the start of the study. Anthropometry was done using standard guidelines and WHO charts were used for classification of obese and underweight. USG abdomen and biochemical investigations were done for diagnosis of NAFLD. **Result:** We included 60 study subjects in our study. The average age of study subjects was 18.43 ± 0.78 years ranged from 17 years to 19 years, among which 53.3% ($n=32$) were females. According to BMI for age, 50% ($n=30$) of subjects were obese and 50% ($n=30$) were underweight. Inpatients categorized according to BMI as an obese and underweight group, the SGOT and SGPT levels were significantly associated ($p=0.04$, $p=0.04$), whereas USG abdomen findings were not significantly associated ($p=0.12$). Similarly, in patients categorized according to WHR as normal, obese, and overweight, had a significant association with SGOT, SGPT levels and USG abdomen findings ($p=0.02$, $p=0.02$, $p=0.034$). **Conclusion:** BMI and WHR along with biochemical parameters can be used to predict the risk of NAFLD in adolescents in resource-poor setup.*

Keywords: Non-alcoholic fatty liver disease (NAFLD), obese adolescents, malnutrition, under nutrition, lean NAFLD.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a broad term used to express a spectrum of conditions including hepatic steatosis without inflammation (non-alcoholic fatty liver), non-alcoholic steatohepatitis (NASH), and cirrhosis [1]. It is the most common liver disorder and its prevalence in western nations ranges from 20 to 30% and around 34% of children are followed in obesity clinics [2] [3]. NAFLD has a close association with obesity, CV disease, diabetes mellitus and hepatocellular carcinoma, thus increasing occurrence of NAFLD is a matter of concern, as it is associated with increased morbidity and mortality [4] [5].

NAFLD is characterized by the deposition of fat in more than 5% of hepatocytes in the absence of other causes of steatosis [6]. Currently, the increased occurrence of NAFLD is

associated with the global obesity epidemic and is considered to be a hepatic manifestation of metabolic syndrome [7]. The prevalence of lean NAFLD or non-obese NAFLD is also increasing, such individuals may experience similar complications compared to obese NAFLD. Its occurrence in adolescents is ranging from 8% (in developed countries) to 16% (Asia Pacific region) [8] [9]. Moreover, urbanization, socioeconomic status and diet and physical activity are associated with the NAFLD [10].

Children with malnutrition are characterized by wasting, edema, hair discoloration, and hepatomegaly [11] and are known to have an electrolyte imbalance, increased oxidative stress, hepatic steatosis and decreased albumin synthesis [12] [13]. Compared to obese individuals, NAFLD is poorly characterized in adolescents with lean NAFLD and malnutrition. Therefore, the present study was undertaken to

assess NAFLD in adolescents with malnutrition (under nutrition as well as obesity).

2. Literature Survey

NAFLD is defined as the accumulation of fat in >5% of hepatocytes in absence of secondary causes including alcohol or drugs. It incorporates a spectrum of diseases from NAFL to NASH, fibrosis, and cirrhosis. Currently, NAFLD is the leading cause of chronic liver diseases globally [14]. The overall global incidence of NAFLD is around 25%, ranging from 13%, 23%, and 27.4% in Africa, Europe and Asia respectively [15].

The two-hit hypothesis of pathogenesis of NAFLD has now been surpassed by a multi-hit model incorporating multiple interlocking processes such as lipotoxicity, innate immune activation, and microbiome on a background of genetic and environmental factors [16]. Most of the NAFLD subjects are always obese with association with pathogenic conditions [17]. Adoption of a sedentary lifestyle, less physical activity, availability of excess food calories is leading to the increasing prevalence of obesity. A higher risk of NAFLD is seen in children who gain weight during their school years than the weight gain in late adulthood [18].

It is reported that around 15-21% of Asian patients with NAFLD are non-obese ranging from 17% (Taiwan) to 75% (India). Moreover, the proportion of non-obesity can be high as 45% in adolescents with NAFLD [19] [20]. Lean NAFLD is associated with the heterogeneous spectrum of diseases resulting from various etiologies including dual alcoholic and non-alcoholic fatty liver disease, congenital and acquired lipodystrophy, genetic factors, congenital defect of metabolism, endocrine disorders, jejunoileal bypass, starvation or the receipt of total parental nutrition [21][22]. Metabolic disorders (Cystic fibrosis, Wilson's disease, α -1 antitrypsin deficiency, galactosemia, hereditary fructose intolerance), celiac disease, hepatitis C, diabetes mellitus, drug toxicity are less common causes of the steatosis [23]. Also, maternal overnutrition, gestational diabetes mellitus, intrauterine growth retardation and antibiotic use during pregnancy and infancy may be associated with an increased risk of NAFLD in children [24].

The diagnosis of NAFLD involves the identification of steatosis in the absence of a secondary cause followed by risk stratification for the presence of NASH and significant fibrosis [25]. For the diagnosis of 'Steatosis', Ultrasound is modality of choice and serological markers such as Fatty Liver Index (FLI), NAFLD Fat Score (NAFLD FS), and Hepatic Steatosis Index (HIS) can also be used [26] [27]. For diagnosis of 'Fibrosis', Fibroscan can be done along with scores like FIB-4 score, NFS (NAFLD Fibrosis Score), etc [28].

Goyal P. et al conducted study in 2018 at Punjab to study correlation of NAFLD with BMI and biochemical markers. Goyal P. et al concluded that Z-BMI, mid arm circumference, waist circumference and ALT, AST, GGT, Triglycerides

(TG), fasting blood glucose, HSCRP and uric acid were significantly higher in NAFLD and HDL-c was lower. They stated that the most significant associated risk factors with NAFLD were TG and Z-BMI. An early lifestyle interventional approach for the treatment of NAFLD can prevent NASH [29].

Anderson et al performed a systemic review and meta-analysis to estimate the prevalence of NAFLD in young people and to determine whether this varies by BMI category, gender, age. Anderson et al found that prevalence was generally higher in males compared with females and increased incrementally with greater BMI [30].

Alavian SM et al. performed a study on 966 children aged 7-18 years in Iran to investigate the prevalence of NAFLD in Iranian school-aged children and adolescents and to study association of NAFLD with biochemical and anthropometric measures. Alavian SM et al concluded that NAFLD was significantly associated with increasing age, waist circumference, ALT, fasting insulin and increased total cholesterol, LDL cholesterol and triglycerides [31].

Management of NAFLD consists of Life style modification, weight loss (if BMI>25 kg/m²), decreased consumption of fats/ oils, daily exercise and controlled glycaemic levels (if diabetic) [32] [33].

3. Material & Methods

This observational cross-sectional study was conducted at MGM Medical College & Hospital, Kamothe, Navi Mumbai and MGM School, Nerul from July 2020 to October 2021 after Institutional Ethical & Scientific committee approval. Adolescents between age group of 12 to 19 years were taken into study after taking written informed consent from parents of children. Children with a previous history of chronic liver disease, having medication that can cause steatosis or altered liver function and other conditions that may affect the liver function such as pregnancy and substance abuse were excluded from the study.

Data collection was done by interviewing the mother/ father/ attending guardian using a case record which contained demographic variables and anthropometry. The demographic variables included were name, age, gender, address. Anthropometry included height, weight, waist circumference and hip circumference were measured using standard guidelines [34][35]. Further, BMI (Body Mass Index) and WHR (Waist-Hip Ratio) were calculated using this data. Based on the World health organisation (WHO) charts for 'BMI for age', children were classified as obese (BMI for age > +1 SD) and underweight (BMI for age < -1 to -2 SD) respectively.

Adolescents who were malnourished (obese, underweight) were selected with the help of purposive sampling technique by taking into consideration of their BMI. The sample size of 60 (30 obese and 30 underweight) was calculated by taking

overall 10 % prevalence of malnutrition, 95% confidence level and 10 % margin of error.

Ultrasonography of Abdomen of all 60 patients was done. Five-point ultrasonographic criteria of diagnosis of fatty liver disease recommended by Dasharty's was used to diagnose NAFLD: (1) Increased hepatic brightness (hyper-echogenicity), (2) posterior attenuation of the right lobe, (3) increased contrast between the right kidney and liver, (4) loss of visualization of the right diaphragm and (5) diminished visibility of the intra hepatic vessels [36]. Also, fasting venous blood samples were obtained from all 60 patients and used for the assessment of SGOT, SGPT, Lipid profile (total cholesterol, LDL, HDL, TG), FBSL (Fasting blood sugar levels) and HbA1c.

Statistical Analysis

Data were analysed using Stat V 13 software. Continuous variables were shown in Mean ± SD whereas, categorical variables were presented in percentage and frequency. The odds ratio was assessed to find the association between the exposure and outcome. The p-value is less than or equal to 5% considered as significant.

4. Results

Table 1: Distribution of subjects according to age

Age (Years)	Frequency (n)	Percentage (%)
17	11	18.3
18	12	20
19	37	61.7

Table 2: Frequency distribution of gender

Gender	Frequency (n)	Percentage (%)
Male	28	46.7
Female	32	53.3

Total 60 adolescents were included in our study.

From table no. 1, The average age of the children was 18.43±0.78 years ranged from 17 years to 19 years. From table no. 2, among the included subjects, 53.3% (n=32) were female and 46.7% (n=28) were male.

Table 3: BMI diagnosis of subjects

BMI diagnosis	Frequency (n)	Percentage (%)
Obese	30	50
Underweight	30	50

Table 4: Age wise distribution of BMI percentile

BMI Percentile	Age(Years)					
	17(n)		18(n)		19(n)	
	Obese	Underweight	Obese	Underweight	Obese	Underweight
<5 th	0	8	0	2	0	12
<95 th	2	0	6	0	12	0
>5 th	0	0	0	1	0	2
85 th – 95 th	0	0	2	0	8	0
5 th –10 th	0	1	0	1	0	3
Total	2	9	8	4	20	17

Table 5: WHR (Waist Hip Ratio) diagnosis of subjects

WHR diagnosis	Frequency (n)	Percentage (%)
Normal	31	51.7
Obese	16	26.7
Overweight	13	21.6

According to BMI for age, 50% (n=30) of subjects were obese and 50% (n=30) were underweight (Table No. 3). Most of 17-year-old participants were under weight (n=9) whereas, in 18 and 19-year-old subjects majority were obese (n=8, n=20) (Table No. 4).

According to WHR (Waist Hip Ratio), 51.7% (n=31) of subjects were normal whereas, 26.7% (n=16) and 21.7% (n=13) were obese and overweight respectively (Table No. 5).

Table 6: Distribution of BMI categories according to USG abdomen findings

USG abdomen findings	Obese group, n (%)	Underweight group, n (%)
Mild hepatomegaly with grade1 fatty liver	5 (16.7)	1 (3.3)
Mild hepatomegaly with grade2 fatty liver	1 (3.3)	0
No abnormality	24 (80)	29 (96.7)

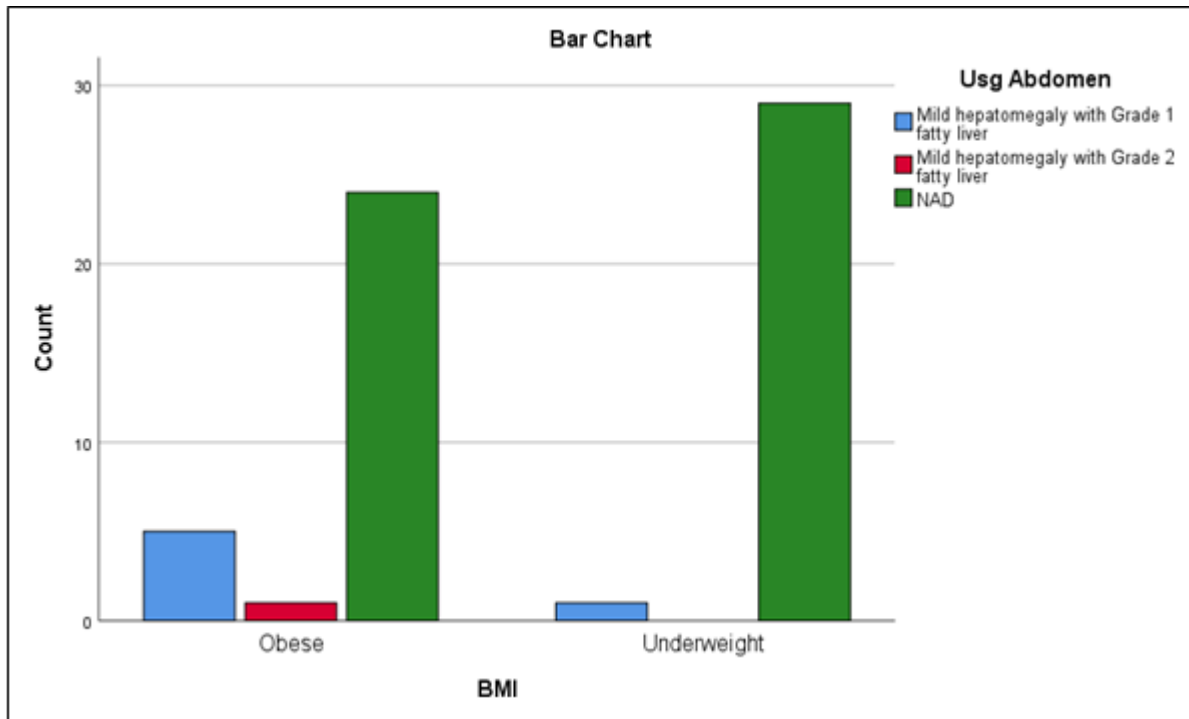


Figure 1: Distribution of BMI categories according to USG abdomen findings

Table 7: Distribution of WHR categories according to USG abdomen findings

USG abdomen Findings	Normal, n (%)	Obese, n (%)	Overweight, n (%)
Mild hepatomegaly with grade 1 fatty liver	1 (3.2)	1 (6.3)	4 (30.8)
Mild hepatomegaly with grade 2 fatty liver	0	1 (6.3)	0
No abnormality	30 (96.8)	14 (87.5)	9 (69.2)

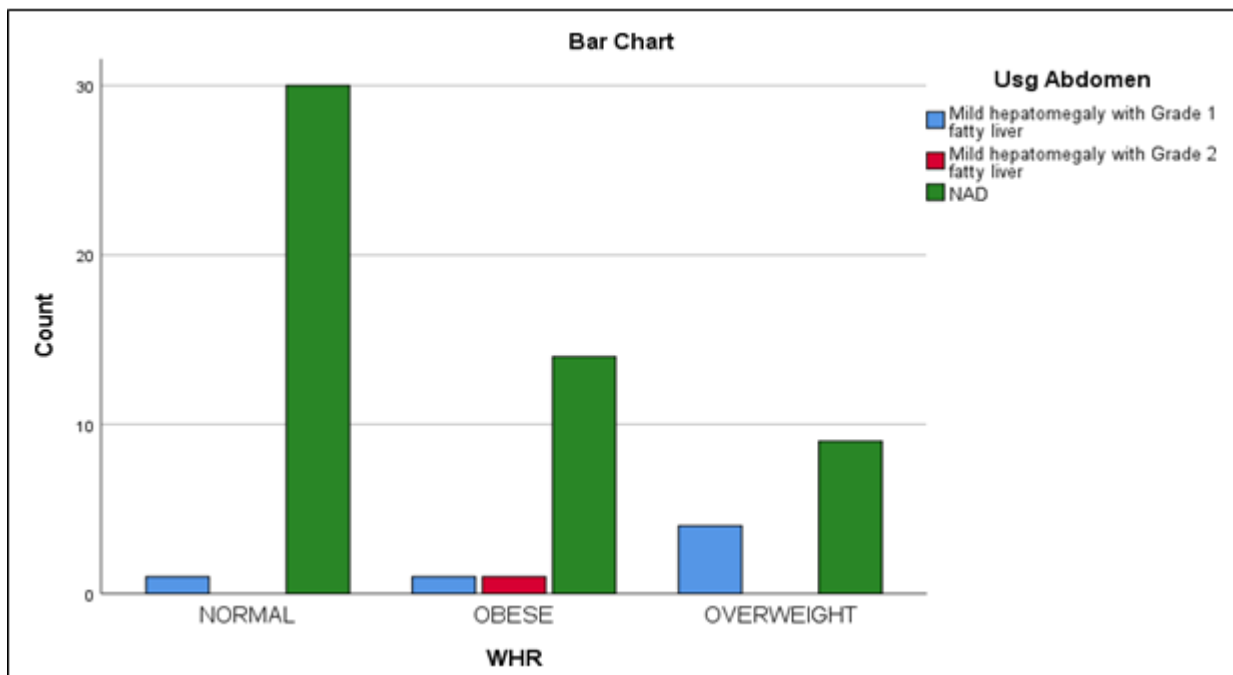


Figure 2: Distribution of WHR categories according to USG abdomen findings

From table no. 6, USG abdomen assessment in obese participants showed mild hepatomegaly with grade 1 fatty liver in 5 subjects (16.7%) and hepatomegaly with grade 2

fatty liver in 1 subject (3.3%), whereas, in 24 subjects (80%) no abnormality was detected. In overweight patients, USG abdomen suggested mild hepatomegaly with grade 1 fatty

liver in 1 subject (3.3%). No abnormality was detected in 29 subjects (96.7%). Obesity and underweight were insignificantly associated with the USG abdomen findings (p=0.12).

From table no. 7, Participants who were categorized according to WHR as normal, obese, and overweight, the USG abdomen findings showed mild hepatomegaly with grade 1 fatty liver in 1 (3.2%), 1 (6.3%), and 4 (30.8%) subjects respectively. A significant association was found between WHR categories and USG findings (p=0.02).

Table 7: Distribution of BMI categories according to SGOT

SGOT	Obese group, n (%)	Underweight group, n (%)
Normal	24 (80)	29 (96.7)
Abnormal	6 (20)	1 (3.3)

Table 8: Distribution of BMI categories according to SGPT

SGPT	Obese group, n (%)	Underweight group, n (%)
Normal	24 (80)	29 (96.7)
Abnormal	6 (20)	1 (3.3)

In patients categorized according to BMI as an obese and underweight group, SGOT levels were abnormal in 6 (20%) and 1 (3.3%) patients respectively (Table no. 7). There is significant association observed between SGOT levels and patients who were obese and underweight (p=0.044). Whereas, the SGPT levels were normal in 24 (80%) and abnormal in 29 (96.7%) patients (Table no.8). There is significant association of obesity and underweight with SGPT levels (p=0.044).

Table 9: Distribution of WHR categories according to SGOT findings

WHR	SGOT	
	Normal, n (%)	Abnormal, n (%)
Normal	30(96.8)	1(3.2)
Obese	14(87.5)	2(12.5)
Overweight	9(69.2)	4(30.8)

Table 10: Distribution of WHR categories according to SGPT findings

WHR	SGPT	
	Normal, n (%)	Abnormal, n (%)
Normal	30 (96.8)	1 (3.2)
Obese	14 (87.5)	2 (12.5)
Overweight	9 (69.2)	4 (30.8)

For participants who were categorized according to WHR as normal, obese, and overweight, the SGOT was abnormal in 1 (3.2%), 2 (12.5%), and 4 (30.8%) subjects (Table no. 9), whereas SGPT was abnormal in 1 (3.2%), 2 (15.5%), and 4 (30.8%) subjects respectively (Table no. 10). There is significant association of WHR with SGOT (P=0.034) and SGPT (P=0.034).

Table 11: Distribution of participants according to blood parameters

Variable-Median	Obese	Underweight
SGOT	78	82
SGPT	85.5	85
TOTAL CHOLESTEROL	185	179
HDL	50	38
LDL	119	113
TGL	139	140
RBS	176.5	157
HBA1C	5.2	4.4

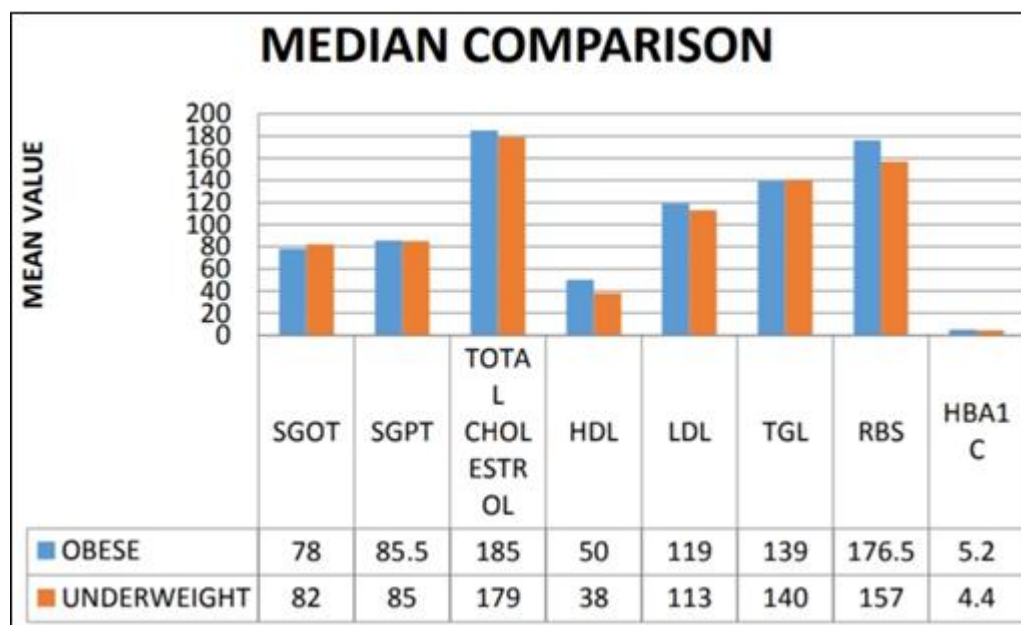


Figure 3: Distribution of participants according to blood parameters

In our study, SGPT, Total cholesterol, HDL, LDL, RBS and HbA1c levels were high in obese group whereas SGOT and Triglycerides were high in underweight group [Table no. 11 and Figure no. 3]

5. Discussion

Increased occurrence of NAFLD is associated with the global obesity pandemic. Prevalence of lean NAFLD or non-obese NAFLD is also increasing. NAFLD has a close association with obesity, CV disease, type 2 diabetes, and hepatocellular carcinoma which in turn causes increase in morbidity and mortality. The study was undertaken to assess the NAFLD in adolescents with malnutrition (obese and under nutrition). Total 60 adolescents were included in this study. The average age of study subjects was 18.43 ± 0.78 years ranged from 17 years to 19 years, among which 53.3% ($n=32$) were female and 46.7% ($n=28$) were male. Similar study was done by Lin MS et al in which average age of study subjects was 15.5 ± 2.8 years, ranged from 10 to 19 years, 50.1% being male [37].

Assessment of risk factors of fatty liver suggested that BMI is among the most common epidemiological indexes used in the assessment of obesity [38] [39] [40] [41]. The risk of fatty liver is 4.1 to 14 times more in subjects with higher BMI than normal BMI individuals [42] [43]. In our study, considering the International Obesity Task Force reference for BMI, subjects were divided into obese (≥ 25) and underweight (< 18) [44] [45]. According to age, most of 17-year-old participants had underweight ($n=9$) whereas, in 18 and 19-year-old subjects majority were obese ($n=8$, $n=20$). Despite being commonly used for the prediction of NAFLD, BMI has its limitations including population-specific reference or change in body composition with growth and development. These limitations are overcome by using the WHR (Waist Hip Ratio). In our study, according to WHR, 51.7% of subjects were normal whereas, 26.7% and 21.7% were obese and overweight respectively. Al-Attas OS et al also suggested that WHR is more strongly associated with obesity than BMI [46].

In our study, we found that 'BMI for age' have no significant correlation with USG abdomen findings to diagnose NAFLD ($p=0.12$). These findings suggested that BMI is not a dependable modality in the assessment of NAFLD in adolescents.

On the other hand, significant association was found between WHR categories and USG findings ($p=0.02$). Similar results were concluded by the study of Ge W, Parvez F et al [47].

In patients' categorized according to BMI', a significant association was seen between SGOT and patients who were obese and underweight ($p=0.044$). Similar results were concluded by Piton A. et al [48] and Kim WR et al [49]. Also, significant association was seen between SGPT and patients who were obese and underweight ($p=0.044$). Similar results were concluded by Tunsaringkarn T et al [50]. The SGPT is a more specific and quite sensitive biomarker for liver disease, which had exhibited its association with the prediction of

mortality in patients with liver disease as demonstrated in the underweight subjects [51] [52] [53] [54]. Moreover, Ramalh et al and Pulzi et al. suggested that greater the BMI, greater the degree of liver damage [55] [56]. In contrast with these findings the study of Das AK et al. suggested no association between BMI categories and liver enzymes level [57]. The difference in the results may be due to the variation in gender, age, and dietary habits, etc.

In patients 'categorized according to WHR', a significant association was seen between SGOT and patients who were normal, obese, and overweight ($p=0.02$). WHR categories also have significant association with SGPT levels ($p=0.034$). Kelishadi R et al also concluded similar results [58].

In our study SGPT, Total cholesterol, HDL, LDL, RBS and HbA1c levels were high in obese group, whereas SGOT and Triglycerides were high in underweight group. Similar results were concluded by Mansour-Ghanaei R et al [59]. Our study found that inpatients categorized according to BMI as an obese and underweight group, the SGOT and SGPT levels were significantly associated, whereas USG abdomen findings were not significantly associated. Similarly, in patients categorized according to WHR as normal, obese, and overweight, had a significant association with SGOT, SGPT levels and USG abdomen findings.

6. Conclusion

BMI categories were significantly associated with the SGOT, SGPT levels, but not with USG abdomen scans. WHR (Waist Hip Ratio) categories were significantly associated with the SGOT, SGPT and USG abdomen scans. BMI and WHR along with biochemical parameters can be used to predict the risk of NAFLD in adolescents in resource-poor setup.

7. Future Scope

The strength of the current study was the adequate sample size and uniform application of the protocol. The limitations of the study were the investigator was not blinded and the study was single centered, altogether could have led to some bias. Various other serological variables were not evaluated in this study. Moreover, intervention to reverse the risk factors of NAFLD was not included in the scope of the present study. Further, a well-designed study of a large sample size including all variables with intervention to reverse the risk factors could provide further evidence to confirm the present study findings.

Conflicts of Interest

The authors have no conflicts of interest.

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Author Profile



Dr. Pawan M. Nimbhorkar, M.B.B.S. (Government Medical College, Nagpur, Maharashtra) 2018. M.D. Family Medicine (MGM Medical College & Hospital, Navi Mumbai, 3rd year Junior Resident). E-mail ID: pawannimbhorkar95@gmail.com. Contact No: 9561944606 / 8830908210. Correspondence Address: Dr. Pawan M. Nimbhorkar, Department of Family Medicine, MGM Medical College, Kamothe, Navi Mumbai – 410209 Maharashtra, India.

Dr. Rakesh Thamke, M.B.B.S., M.D. Pediatrics, Currently working as Associate Professor & Head, Department of Family Medicine, MGM Medical College & Hospital, Navi Mumbai. E-mail ID: rthamke@yahoo.com

Dr. Vijay Kamale, M.B.B.S., M.D. Pediatrics. Currently working as Professor & Head, Department of Pediatrics, MGM Medical College & Hospital, Navi Mumbai. E-mail ID: drvijaykamale@gmail.com

Dr. Akshai B., M.B.B.S., M.D. Pediatrics. Currently working as Senior resident, Department of Pediatrics, MGM Medical College & Hospital, Navi Mumbai. E-mail ID: akshaifreat@gmail.com