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Original Article
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Evaluation of Factors Affecting the Prediction of Risk Factors for Obesity-Related Fatty Liver Disease in Children

Çelik and Kılıç Yıldırım. Risk Factors for Obesity-Related Fatty Liver Disease in Children

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ABSTRACT
Objectives: Childhood fatty liver disease (FLD) has become a major problem due to the dramatic increase in the incidence of obesity. In our country, studies on the factors affecting the risk for FLD are insufficient. In this single-center, retrospective and cross-sectional study, we aimed to evaluate the role of parameters affecting the prediction of the risk of FLD in obese children.
Materials and Methods: Ninety-one obese children (48 males, 43 females) aged 12.19±2.88 years were included in the study. Body weight (BW), height, left arm mid-circumference (LEMC), triceps skinfold thickness (TSF), waist circumference (WC), and hip circumference (HC) were measured. Body mass index (BMI), WC/HC ratio, and WC-to-height ratio were calculated. Obesity was defined as BMI at the 95th percentile and above according to age and gender. FLD was diagnosed using ultrasonography.
Results: FLD was present in 49.5% of obese children. In obese children with FLD, BW, height, BMI, TSF, TSF-standard deviation scores, WC, and HC measurements were found to be significantly higher than in obese children without FLD ($p<0.05$). In the logistic regression analysis, homeostasis model assessment of insulin resistance (HOMA-IR) score, TSF, and gender were determined as independent variables for FLD, with p-values and confidence intervals identified as follows: for HOMA-IR score [p=0.001, B: 1.927, 95% confidence interval (CI): 1.323-2.807], for TSF (p=0.010, B: 1.090, 95% CI: 1.021-1.163), and for gender (p=0.008, B: 0.215, 95% CI: 0.070-0.666).
Conclusion: According to the results of our study, HOMA-IR was identified as the most important factor playing a role in the development and progression of FLD. Male sex is a risk factor for steatosis. Although BMI and WC are the most commonly used measurements, TSF can also be easy indicator for detecting the presence of obesity-related FLD in children.
Keywords: Obesity, Nonalcoholic, Fatty Liver, Child, Sex Factors, Insulin Resistance, Skinfold Thickness

INTRODUCTION
Mandatory school closures and protective restrictions during the Coronavirus Disease 2019 (COVID-19) pandemic resulted in a considerable drop in physical activity, as well as changes in nutrition and sleep patterns, which raised the rate of obesity in children. Childhood fatty liver disease (FLD), a component of obesity-associated metabolic syndrome, is the most common liver disease characterized by fat accumulation in hepatocytes.[1] The prevalence of FLD was found to be 7.8% in the general population and 34.2% in obese

individuals in meta-analysis.[2] In our country, it has been reported that the prevalence of FLD is 23-62% in obese children.[3,4] Although FLD has a benign prognosis, approximately 3-5% of patients develop nonalcoholic steatohepatitis, which progresses to end-stage liver disease or hepatocellular carcinoma. Therefore, early diagnosis of FLD is crucial for prompt intervention, especially in obese children. Abdominal ultrasonography (USG) and liver function tests are recommended to determine the presence of FLD for all obese children over the age of three.[5] The results of the studies highlighted that some anthropometric indices can be used to predict FLD. However, this issue is still controversial. In this single-center, retrospective, and cross-sectional study, we aimed to evaluate the role of parameters affecting the prediction of the risk of FLD in obese children.

MATERIALS AND METHODS

A total of 91 children aged 7-18 years who applied to Eskişehir Osmangazi University Faculty of Medicine, Child Nutrition and Metabolism Polyclinic between January 2020 and February 2021 with complaints of overweight participated in our study. Exogenous obese patients with body mass index (BMI) at or above the 95th percentile according to age and gender were included in the study. Those with known systemic or metabolic problems, those using medications that could affect body weight (BW), those with genetic syndromes, and those for whom archive information could not be accessed were excluded from the study. Clinical, anthropometric and biochemical parameters, and hepatobiliary USG data of the patients were recorded retrospectively from the hospital registration system.

Patients' BW, height, left arm mid-circumference (LEMC), triceps skinfold thickness (TSF), waist circumference (WC), and hip circumference (HC) measurements were taken by the same pediatric nurse. With the BMI weight (kg)/height (m^2) formula, percentile and standard deviation scores (SDSs) of BMI and height were calculated according to national growth charts. LEMC was measured using a non-stretchable tape measure passing through the middle of the distance between the olecranon and acromion, while TSF was measured using a skinfold caliper at the midpoint of the left arm, through a double fold of skin. SDS values for LEMC and TSF were evaluated according to Centers for Disease Control and Prevention references.

The measurement of WC was carried out by marking the point where the lowest rib and midaxillary line intersect the iliac crest on the right side while the child was standing. WC percentile values were calculated according to the percentile values developed by Hatipoglu et al.[6] HC was measured at the widest part of the gluteal area. The WC-to-height ratio (WC/height) ratio was calculated by dividing WC by height. The cut-off point of the WC/height ratio was taken as 0.57. The cut-off point for the WC/HC ratio was determined as ≥0.90.[7] According to the USG results, the degrees of steatosis were grouped as none, grades 1, 2, and 3. Obese patients included in the study were grouped as those with steatosis detected in liver USG (FLD) and those without steatosis (non-FLD).

Patients' age, gender, BW, height, BW for height (BWH), BMI, serum glucose, insulin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), free T4 (fT4), thyroid stimulating hormone (TSH), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) levels, were recorded. The diagnosis of dyslipidemia was made according to the criteria of the TG, TC, and LDL-C levels being at or above the 95th percentile or HDL-C levels being below the 5th percentile, by comparing with reference values according to age and gender.[8] The formula for insulin resistance (IR) was calculated using the homeostasis model assessment of IR (HOMA-IR) score: glucose x insulin/405.

Demographic, anthropometric, clinical and biochemical parameters were analyzed and compared between the FLD and non-FLD groups.

Ethical Statements

The study was approved by Eskişehir Osmangazi University Faculty of Medicine Ethics Committee (approval number: 2018-54, dated: 21.09.2018). The study was performed in accordance with the ethical rules based on the principles of the Helsinki Declaration. Written informed consent forms were obtained from the parents and the children (when appropriate).

Statistical Analysis

IBM SPSS 21 package program was used for analysis of the data. The distribution of the data was analyzed with the Kolmogorov-Smirnov test. For normally distributed variables, differences between groups were compared using the Independent Samples t-test. The Mann-Whitney U test was used for those not showing normal distribution. Logistic regression models were used to predict the presence of FLD using anthropometric parameters. Sensitivity and specificity of anthropometric indices in the suspicion of FLD were calculated by receiver operating characteristic (ROC) curve analysis. Results obtained with $p<0.05$ were considered significant.

RESULTS: Of the 91 exogenously obese patients who participated in the study, 43 were females and 48 were males. The mean age of the patients was 12.19±2.88 years (12.81±3.06 in females; 11.63±2.62 in males). According to hepatobiliary USG results, 49.5% of the children were found to have FLD (58.3% of the males and 39.5% of the females) (Table 1). The difference between the two genders was not significant (p=0.075). Of those with FLD, 35 had grade I, 9 had grade II, and 1 had grade III hepatosteatosis. In children with FLD, BW, height, BMI, TSF, TSF-SDS, WC, and HC measurements were statistically significantly higher than in children without

FLD (Table 1). WC was above the 97th percentile in 88 children and between the 95th and 97th percentiles in three. The WC/height ratio was ≥0.5 in all children, and the WC/HC ratio was ≥0.9 in 52 children. No significant difference was found between those with and without FLD in terms of WC/height ratio and WC/HC ratio (p>0.05).

Dyslipidemia was detected in 34.1% of all patients and in 18 of 45 patients with FLD. No statistically significant difference was found in terms of dyslipidemia between those with and without FLD (p=0.237). ALT, AST, insulin, TG, and HOMA-IR scores were found to be statistically significantly higher in patients with FLD (Table 2).

With the logistic regression model, HOMA-IR score, TSF, and gender were determined as independent variables for FLD (Table 3). For the detection of FLD, the threshold values determined for TG, TSF, and HOMA-IR were 126 mg/dL, 26.5 mm and 3.35, respectively. HOMA-IR had the highest diagnostic accuracy with 64.4% sensitivity and 65.2% specificity. For TSF and TG, 62.2% sensitivity and 63% specificity were found (Table 4, Figure 1).

DISCUSSION

In our study, the rate of FLD was found to be 49.5% (58.3% of males and 39.5% of females). In various studies, the prevalence of FLD among obese children was found to be 12-80%.[9,10] In the study of Özhan et al.,[11] FLD was detected in 60.8% of 332 obese children, while Kirel et al.[3] found it to be 40%.

There are not enough data examining the place of anthropometric measurements in determining the risk factors for FLD in children and adolescents in our country. Commonly used, BMI and WC are strongly associated with FLD in both children and adults. The WC/height ratio has been proposed as an alternative measure that accounts for both longitudinal growth and central adiposity.[7,12] Skinfold thickness measurement, especially TSF, is frequently used to evaluate subcutaneous fat tissue, one of the most important storage areas of body fat.

In our study, BW, height, BMI, TSF, TSF-SDS, WC, and HC measurements were significantly higher in obese children with FLD compared to obese children without FLD. Various studies suggest the use of parameters such as WC, WC/HC ratio, WC/height ratio, and IR to identify obese children at high risk of FLD.[13] Maffeis et al.[14] suggested that the WC/height ratio is an important parameter in predicting FLD. Lin et al.,[15] on the other hand, emphasized the importance of WC in predicting FLD in obese children.

In a study conducted in China with 7229 students, WC/height ratio was reported to be a significant independent risk factor for FLD.[16] In our study, consistent with the literature, WC was above the 97th percentile in 96.7% of children and between the 95th-97th percentile in 3.3% of children. The WC/height ratio was found to be 0.5 and above in all children, and the WC/HC ratio was found to be 0.9 and above in 57.1% of the children. Contrary to the literature, no significant difference was found between those with and without FLD in terms of WC/height ratio and WC/HC ratio. On the other hand, HOMA-IR score, TSF, and gender were determined as independent variables for FLD with the logistic regression model. IR is an important component of the metabolic syndrome and contributes to the pathophysiology of FLD. In our patients with FLD, the HOMA-IR score was statistically significantly higher, and the threshold value determined by the ROC curve was 3.35. Accordingly, the IR rate was 50.54%. Insulin resistance was identified as the most important factor in the development and progression of FLD, with an odds raito (OR) of 1.927 and a 95% confidence interval (CI) of 1.323-2.807. TSF was found to be the second most significant factor and an independent predictor of the presence of FLD, (p=0.010, OR= 0.090, 95% CI: 1.1021-1.163). The threshold value for the detection of FLD was determined as 26.5 mm (for TSF). TSF>26.5 mm was detected in 52.45% of our patients. It has been observed that subcutaneous fat accumulation in the extremity regions of the body is as important as central fat accumulation.

In our study, dyslipidemia was detected in 34.1% of all patients and in 40% of 45 patients with FLD. However, no significant difference was found in terms of dyslipidemia between those with and without FLD. Hypertriglyceridemia is a well-known risk factor for FLD. In our study, only TG levels among lipid parameters were found to be significantly higher in patients with FLD. Another independent risk factor for FLD was found to be sex. Özhan et al.[11] found the prevalence of FLD to be significantly higher in pubertal children, with a prevalence of 67.8% in males compared to 55.0% in females. In our study, similar to the literature, FLD was detected in 58.3% of males and 39.5% of females.

The use of hepatic USG to assess hepatosteatosis is not the most reliable method. The proton density fat fraction, measured by magnetic resonance imaging (MRI-PDFF), provides an accurate, validated marker of hepatic steatosis. The lack of MRI-PDFF measurements is one of the most important limitations of our study. Another limitation of our study is the number of patients. Further studies are needed to increase the power by including more patients in the study.

CONCLUSION

HOMA-IR was identified as the most important factor playing a role in the development and progression of FLD. Male gender is a risk factor for steatosis. Although BMI and WC are the most commonly used anthropometric measurements, TSF measurement can also be a simple and easy indicator for detecting the presence of obesity-related FLD in children. More studies are needed before it can be used in mass screening.

Ethics
Ethics Committee Approval: The study was approved by Eskişehir Osmangazi University Faculty of Medicine Ethics Committee (approval number: 2018-54, dated: 21.09.2018).
Informed Consent: Written informed consent forms were obtained from the parents and the children (when appropriate).

Footnotes
Authorship Contributions
Surgical and Medical Practices: G.K.Y., Concept: G.K.Y., Design: G.K.Y., Data Collection or Processing: G.K.Y., A.T.Ç., Analysis or Interpretation: G.K.Y., A.T.Ç., Literature Search: G.K.Y., A.T.Ç., Writing: G.K.Y.
Conflict of Interest: The authors have no conflicts of interest to declare.
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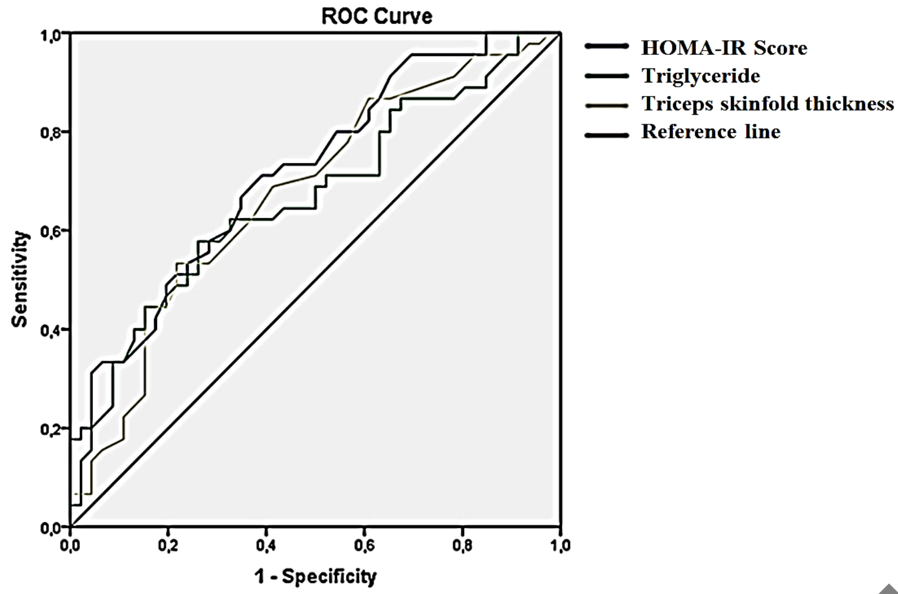

Figure 1. Receiver operating characteristic curve
HOMA-IR: Homeostasis model assessment of insulin resistance

Table 1. Baseline characteristics of children with and without FLD

Variables	Children with FLD	Children without FLD	p-value
Gender	17 female/28 male	26 female/20 male	0.075*
Weight (kg)	78.55±22.95	66.03±19.40	0.006*
Weight (SD score)	2.95±1.10	2.51±1.06	0.055*
Height (cm)	158.78±14.60	151.42±13.92	0.016*
Height (SD score)	0.94±1.04	0.68±1.34	0.30*
BMI (kg/m^2)	30.49±5.35	28.05±4.19	0.017*
BMI (SD score)	2.57±0.64	2.36±058	0.104*
Mid-upper arm circumference (cm)	32.24±5.16	30.47±4.23	0.078*
Mid-upper arm circumference (SD score)	1.34±0.51	3.21±1.32	0.946**
TSF (cm)	30.20±8.32	25.03±7.85	0.003*
TSF (SD score)	2.02±0.74	2.84±7.74	0.031**
WC	98.44±12.45	90.78±11.76	0.003*
HC	108.25±14.58	101.80±13.41	0.031*
WC/height	0.62±0.057	0.59±0.050	0.062*
WC-to-hip ratio	0.91±0.067	0.89±0.066	0.179*

$p<0.05$ is statistically significant. *: Independent Samples t-test, **: Mann-Whitney U test, WC/height: Waist circumference to height ratio, FLD: Fatty liver disease, SD: Standard deviation, BMI: Body mass index, TSF: Triceps skinfold thickness, WC: Waist circumference, HC: Hip circumference

Table 2. Laboratory values of children with and without FLD

	Total (n=91)	Children with FLD (n=45)	Children without FLD (n=46)	
Serum levels	Mean ± SD	Mean ± SD/Median (IQR)	Mean ± SD/Median (IQR)	p-value
Glucose (mg/dL)	83.7±6.55	83.64±7.00	83.76±6.16	0.722*
Insulin (uIU/mL)	19.86±13.73	21.10 (15.70)	13.75 (8.75)	0.00**
ALT (U/L)	23.49±13.91	23.0 (21.5)	16.5 (9.0)	0.002**
AST (U/L)	22.39±8.76	23.0 (8.5)	18.5 (6.5)	0.029**
TC (mg/dl)	161.83±34.11	164.28±33.50	159.43±34.89	0.5*
LDL Cholesterol (mg/dL)	105.23±32.13	106.3±30.65	104.18±33.82	0.756*
HDL Cholesterol (mg/dL)	44.83±10.29	43.06±8.78	46.46±11.41	0.106*
TG (mg/dL)	138.87±77.662	161.89±87.05	116.36±60.04	0.005*
TSH (uIU/mL)	7.15±37.8	2.63 (1.71)	2.54 (1.16)	0.301**
fT4 (ng/dL)	2.89±15.49	1.17 (0.26)	1.26 (0.27)	0.316**
HOMA-IR Score	4.14±3.29	4.1 (3.1)	2.8 (1.58)	0.00**

$p<0.05$ is statistically significant. *: Independent Samples t-test, **: Mann-Whitney U test, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TC: Total cholesterol, LDL: Low-density lipoproteins, HDL: High-density lipoproteins, TG: Triglyceride, TSH: Thyroid stimulating hormone, HOMA-IR: Homeostasis model assessment-estimated insulin resistance, FLD: Fatty liver disease, SD: Standard deviation, IQR: Interquartile range, fT4: Free T4

Table 3. Independent variables in logistic regression analysis

Variables	B parameter equation	Standard error	p-value	Exp. (B) OR (95% CI lower-upper)
Gender	-1.536	0.576	0.008*	0.215 (0,070-0,666)
TSF	0.086	0.033	0.010*	1.090 (1.1021-1.163)
HOMA-IR score	0.656	0.192	0.001*	1.927 (1.323-2.807)
Constant	-4.113	1.183	0.001*	0.016

p<0.05 is statistically significant. *: Logistic regression, OR: Odds ratio, Exp.: Exponentiated, TSF: Triceps skinfold thickness, HOMA-IR: Homeostasis model assessment of insulin resistance, CI: Confidence interval

Table 4. Factors effective in estimating FLD with ROC curve

Risk factors	AUC (OR 95%)	Cut-off	Sensitivity (%)	Specificity (%)	p-value
TG	0.665 (0.553-0.777)	126	62.22	63	0.007
TSF	0.675 (0.564-0.786)	26.5	62.2	63	0.004
HOMA-IR score	0.719 (0.616-0.822)	3.35	64.4	65.2	0.000

p<0.05 is statistically significant. ROC: Receiver operating characteristic, FLD: Fatty liver disease, AUC: Area under the curve, OR: Odds ratio, TG: Triglyceride, TSF: Triceps skinfold thickness, HOMA-IR: Homeostasis model assessment-estimated insulin resistance