CLINICAL RESEARCH ARTICLE

Pediatric obesity-related non-alcoholic fatty liver disease: waist-to-height ratio best anthropometrical predictor

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BACKGROUND: Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disorder in pediatric obesity. Our study aims to identify a predictive anthropometrical measure for NAFLD in obese children.

METHODS: We retrospectively enrolled children and adolescents with obesity. Physical, biochemical, and ultrasound assessments were available. ROC curve tests were performed to identify the best predictor of NAFLD among waist-to-height ratio (WHR), BMI z-score, and triponderal mass index (TMI, an anthropometric index recently associated with increased adiposity in children). Subsequently, a cut-off value was identified.

RESULTS: In total, 1900 children and adolescents (1011 with NAFLD) were included. WHR (AUC 0.62, 95% CI 0.59–0.64) was the best predictor of NAFLD compared to BMI z-score (AUC 0.58, 95% CI 0.55–0.60) and TMI (AUC 0.58, 95% CI 0.55–0.61). WHR ≥ 0.53 in boys and 0.63 in girls displayed the best sensitivity and specificity for NAFLD presence. In addition, children with high WHR showed a significantly higher risk of NAFLD (boys: OR 2.43, 95% CI 1.61–3.68, $p < 0.0001$; girls: OR 1.92, 95% CI 1.58–2.34, $p < 0.0001$) and elevated ALT (OR 5.71, 95% CI 2.09–15.56, $p = 0.0007$; girls: OR 2.16, 95% CI 1.70–2.74, $p < 0.0001$) independent of covariates.

CONCLUSIONS: WHR might represent a good anthropometric tool to candidate children and adolescents to NAFLD screening. WHR cut-off differs according to sex, being lower in boys than girls.

IMPACT:

- Waist-to-height ratio is a better predictor of non-alcoholic fatty liver disease risk compared to other anthropometric measures in obese children and adolescents.
- The predictive cut-off of waist-to-height ratio differs between boys and girls, being lower in boys than girls.
- The use of waist-to-height ratio measurement and its cut-off in clinical practice might help clinician in identifying obese children and adolescents at risk of non-alcoholic fatty liver disease.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) constitutes the most common chronic liver disease in childhood.[1,2] Estimates reported that about 7% of general pediatric population is affected by NAFLD, with higher rates among children and adolescents with obesity.[3] Paralleling pediatric obesity epidemic, NAFLD has reached worrying proportion over time. Moreover, children with severe obesity are more prone to have a more severe liver disease.[4] In addition, fatty liver disease has been associated with cardiovascular, metabolic, and renal comorbidities in adults and children.[5–8] Currently, NAFLD screening is recommended for all obese children aged 9–11 years and earlier for severely obese children.[9] Alanine aminotransferase (ALT) is used as a biochemical marker of NAFLD for screening, but it has some limitations. A twofold serum ALT level above the normal upper limit has 57% sensitivity and 71% specificity for NAFLD.[10] Ultrasound is performed for children with elevated ALT serum levels.[9]

Fat deposition in liver depends on both genetic and environmental factors.[11–14] The high prevalence of NAFLD in subjects with obesity highlights the role of adiposity excess in disease pathogenesis and progression. Of note, several studies have reported that not adiposity per se but visceral adiposity plays a pivotal role in obesity-related inflammation, insulin-resistance, and hepatic fat deposition.[15–18] Waist-to-height ratio (WHR) has been shown to be an indirect marker of visceral adiposity and a predictor of metabolic syndrome in children and adolescents with overweight and obesity.[19,20] In addition, recently, a new anthropometric index, the triponderal mass index (TMI), has been reported to be a better predictor of total adiposity compared to body mass index (BMI) in children and adolescents.[21] However, the ability of TMI in obesity-related comorbidities prediction needs to be further investigated.[22,23]

In this context, the aim of this study is to investigate whether anthropometric indexes like BMI z-score, TMI, and WHR can predict fatty liver disease in children and adolescents with obesity.

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Moreover, the most appropriate cut-off value for these anthropometric parameters as a clinical screening tool in NAFLD diagnosis was identified.

METHODS

The cohort and clinical evaluation

We retrospectively and consecutively collected data from children and adolescents with obesity (BMI ≥ 95th percentile for age and sex according to Italian reference charts), who have attended the obesity outpatient clinic of the Department of Pediatrics of the University of Campania Luigi Vanvitelli of Naples from January 2008 to January 2019. The ethical committee approved the study and written informed consent was obtained before any procedure. Patients with secondary forms of obesity and taking alcohol or medications potentially affecting liver function or determining fatty liver were excluded. Additionally, we excluded patients affected by metabolic hepatopathy, viral hepatitis, autoimmune hepatitis, celiac disease, endocrine hepatopathy, muscular diseases, and alpha-1-antitrypsin deficiency.

Patients underwent physical and anthropometrical examination. Body weight was measured by a balance beam scale, the child being undressed. Height was measured by a Harpenden stadiometer. BMI was calculated by dividing the weight for the height square. BMI z-score was calculated according to the lamba–mu–sigma method[24] according to reference charts.[25] TMI was calculated as the ratio between weight and height cubed (kg/m^3).[22] Waist circumference was measured with a flexible tape measure after normal expiration, at the midpoint between the lowest rib and the iliac crest while the subjects were standing and were in under-clothes. The average value of two waist measurements was obtained and, as indirect measure of the amount of abdominal fat, the ratio between waist and height, both measured in centimeters, was calculated. Pubertal stage according to Tanner criteria was assessed.

Biochemical and ultrasound assessment

Baseline fasting blood samples were obtained to assess serum alanine transaminase (ALT) and aspartate transaminase (AST). ALT > 40 IU/L was classified as elevated. In patients with elevated liver enzymes, metabolic hepatopathy, viral hepatitis, autoimmune hepatitis, celiac disease, endocrine hepatopathy, muscular diseases, alpha-1-antitrypsin deficiency, and hepatitis B and C were excluded.

Fatty liver was assessed as present or absent according to ultrasonography at the initial clinical evaluation. It was determined based on abnormally intense, high-level echoes arising from the hepatic parenchyma and liver kidney differences in echo amplitude. Two experienced radiologists with good agreement (Cohen's $\tilde{k} = 0.85$, $p < 0.0001$) performed the ultrasound for hepatic steatosis detection.

Statistical analysis

Continuous variables were tested for normality according to Kolmogorov–Smirnov test. Patients were divided in two groups: NAFLD and non-NAFLD group. Differences for continuous variables were investigated by Student's t-test and Mann–Whitney U test for independent samples as appropriate. Differences in categorical variables were evaluated with Chi square and Fisher exact tests. Predictive power of BMI z-score, TMI, and WHR for NAFLD were determined with receiver operating characteristic (ROC) curve tests. Moreover, we compared the areas under the curve (AUC) for BMI z-score, TMI, and WHR to identify the best predictor. Best predictor cut-off value was obtained using the Youden index (maximum (sensitivity + specificity − 1))[26]. Univariate logistic regression analyses were performed to assess the risk of presenting NAFLD and elevated ALT according to cut-off group. Multiple logistic regression analysis was performed with age, BMI z-score, and pubertal stage as covariates.

SAS$^®$ University Edition (SAS Institute Inc., Cary, NC) was used for all analyses. Data are expressed as mean ± standard deviations (SD). P values <0.05 were considered statistically significant.

RESULTS

The cohort included a total of 1900 children and adolescents with a mean age of 10.50 ± 2.89 years and a mean BMI z-score 2.84 ± 0.69 (Table 1). NAFLD prevalence in our study population was 53.21% (Table 1). Age and pubertal stage distribution did not significantly differ between the NAFLD and non-NAFLD groups (Table 2). Children and adolescents with NAFLD showed significantly higher BMI, BMI z-score, TMI, waist circumference, WHR, liver enzymes, and prevalence of male sex (all $p < 0.0001$, Table 2).

A comparison between BMI z-score, TMI, and WHR area under the ROC (AUROC) curves for NAFLD was performed (Fig. 1). BMI z-score showed a good prediction for NAFLD (AUC 0.58, 95% CI 0.55–0.60, $p < 0.0001$). Similarly, we observed a significant predictivity of NAFLD for TMI (AUC 0.58, 95% CI 0.55–0.61, $p < 0.0001$). However, WHR displayed a significantly higher AUROC (AUC 0.62, 95% CI 0.59–0.64) compared to both BMI z-score ($p = 0.0003$) and TMI ($p < 0.0001$) (Fig. 1). The optimal cut-off for WHR according to Youden test was 0.58. This cut-off value showed 60.6% sensitivity, 55.7% specificity, a positive predictive value of 60.9%, and a negative predictive value of 55.4%.

In addition, because boys are more prone to develop NAFLD, we investigated whether the WHR cut-off differed according to sex. We observed that in males a WHR ≥ 0.53 showed the best sensitivity (74%) and specificity (39%) for NAFLD presence according to Youden test (AUC 0.59, 95% CI 0.56–0.63, $p < 0.0001$). Conversely, in girls, the best WHR cut-off value was 0.63, with a sensitivity of 66% and a specificity of 53% (AUC 0.63, 95% CI 0.59–0.66, $p < 0.0001$).

The odds of showing NAFLD and elevated ALT according to WHR cut-off are reported in Table 3.

Among boys, children and adolescents with high WHR had a 2.43-fold higher risk (95% CI 1.61–3.68, $p < 0.0001$) of showing NAFLD, independent of the effect of age, pubertal stage, and BMI z-score ($p = 0.003$). Moreover, they had a significantly higher risk

Table 1.	Characteristics of the study population.	
Variable ($n = 1900$)	Mean	SD
Age (years)	10.50	2.89
Sex (M, %)	50.23	
Pubertal Stage (I/II/III, %)	61.07/22.52/16.41	
Weight (kg)	67.49	21.85
Height (m)	1.46	0.15
BMI (kg/m^2)	31.01	5.02
BMI z-score	2.84	0.69
TMI (kg/m^3)	21.43	3.08
Waist (cm)	89.13	21.46
WHR	0.61	0.06
AST (IU/dL)	24.63	10.24
ALT (IU/dL)	28.89	20.32
NAFLD (%)	53.21	

Data are expressed as mean ± SD for continuous variables and as frequency (%) for categorical variables.
ALT alanine aminotransferase, *AST* aspartate aminotransferase, *BMI* body mass index, *NAFLD* non-alcoholic fatty liver disease, *TMI* triponderal mass index, *WHR* waist-to-height ratio.

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Table 2. Anthropometric and biochemical differences between NAFLD and non-NAFLD groups.

Variable	NAFLD (n = 1011)	Non-NAFLD (n = 889)	p
Age (years)	10.63 ± 2.82	10.40 ± 2.94	0.08
Sex (M, %)	55.43	45.05	*
Pubertal Stage (I/II/III, %)	61.96/23.18/14.86	60.11/22.21/17.68	0.25
Weight (kg)	70.30 ± 22.59	64.80 ± 20.68	*
Height (m)	1.47 ± 0.15	1.44 ± 0.15	0.001
BMI (kg/m^2)	31.78 ± 5.13	30.25 ± 4.77	*
BMI z-score	3.01 ± 0.66	2.87 ± 0.70	*
TMI (kg/m^3)	21.79 ± 3.14	21.02 ± 2.96	*
Waist (cm)	91.82 ± 26.77	85.88 ± 10.76	*
WHR	0.62 ± 0.06	0.60 ± 0.06	*
AST (UI/dL)	26.03 ± 11.66	23.29 ± 8.42	*
ALT (UI/dL)	32.73 ± 23.48	24.94 ± 15.86	*

Data are expressed as mean ± SD for continuous variables and as frequency (%) for categorical variables.
ALT alanine aminotransferase, AST aspartate aminotransferase, BMI body mass index, NAFLD non-alcoholic fatty liver disease, TMI triponderal mass index, WHR waist-to-height ratio. *p < 0.0001.

Table 3. Odds ratio of showing NAFLD and elevated ALT according to WHR cut-off value group.

	OR	95% CI	p	Adj p
Boys				
NAFLD	2.43	1.61–3.68	*	0.003
Elevated ALT (>40 IU/L)	5.71	2.09–15.56	0.0007	0.006
Girls				
NAFLD	1.92	1.58–2.34	*	*
Elevated ALT (>40 IU/L)	2.16	1.70–2.74	*	*

ALT alanine aminotransferase, NAFLD non-alcoholic fatty liver disease. *p < 0.0001.

1.70–2.74, p < 0.0001), independent of confounding factors (p < 0.0001).

DISCUSSION

In the present study we have shown that high WHR is associated with an increased risk of NAFLD in a large cohort of children and adolescents with obesity. Moreover, WHR was a better predictor of NAFLD compared to BMI z-score and TMI, and we identified a WHR cut-off point for NAFLD screening. Interestingly, the cut-off differed according to sex, being lower in boys compared to girls.

Liver steatosis is often asymptomatic and accidentally identified during abdominal ultrasound or biochemical investigations performed for other indications. However, NAFLD diagnosis is important to be done as it might evolve in end-stage liver disease, especially for at risk children as those with obesity. To date, ALT serum levels and ultrasound are the screening tools available in practice. ALT measurement is widely available and minimally invasive. However, there is poor consensus on reference normal values. Ultrasound is indicated in children with elevated liver enzymes, but it is limited by low sensitivity and specificity particularly for less severe NAFLD degrees. Current guidelines recommend performing NAFLD screening in obese children aged 9–11 years.[10] Nevertheless, our results suggest that anthropometry might support the clinician in the decision making of performing NAFLD screening in obese children and adolescents.

Visceral fat, instead of total adiposity, is the main factor responsible for obesity-related comorbidities,[15,16,18] and WHR has been proposed as a feasible clinical tool for metabolic syndrome prediction in both children with overweight and obesity.[19–21] In our cohort, children with NAFLD showed significantly higher BMI, BMI z-score, waist circumference, WHR, TMI, liver enzymes, and male sex prevalence compared to children without NAFLD. These findings suggest that upper body fat distribution might be predictive of NAFLD. Similarly, previous studies reported a significant association between NAFLD risk and visceral adiposity in pediatric populations with obesity.[17,27,28] In a cohort of Turkish obese children and adolescents, a WHR cut-off of 0.62 was predictive of fatty liver.[29] Moreover, Li et al.[30] observed that WHR is significantly associated with the presence of fatty liver in both overweight and lean subjects in a cohort of Chinese children. The authors reported that a WHR of 0.50 in lean subjects and 0.53 in overweight children were predictive of NAFLD. In addition, a community-based cross-sectional study involving 1210 adolescents in Taiwan reported that a WHR of 0.47 was significantly associated with increased risk of hepatic steatosis.[31] Here we report that, overall, a WHR ≥ 0.58 might be a valid anthropometric marker of fatty liver in Italian children and adolescents with obesity. NAFLD development is highly influenced by ethnic background,[32] and Asian ethnic groups have a higher prevalence of fatty liver.[33] Therefore, we speculate that among Chinese
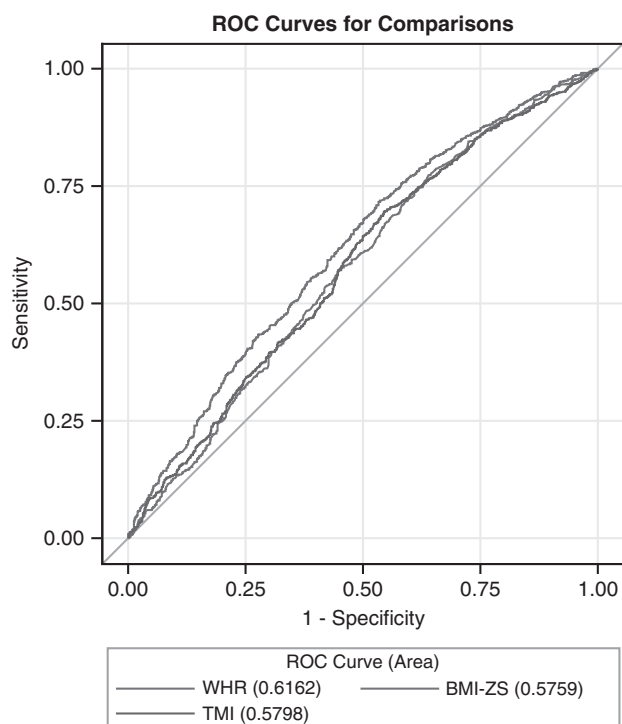

Fig. 1 Receiving operating characteristic (ROC) curves for non-alcoholic fatty liver disease comparison. Blue line indicates waist-to-height ratio area under the ROC curve. Red line refers to BMI z-score area under the ROC curve. Green line indicates TMI area under the ROC curve.

The figure title reads "ROC Curves for Comparisons" with axes Sensitivity (y-axis) and 1 - Specificity (x-axis). Legend: ROC Curve (Area) — WHR (0.6162), BMI-ZS (0.5759), TMI (0.5798).

of elevated ALT (OR 5.71, 95% CI 2.09–15.56, p = 0.0007), independent of covariates (p = 0.006).

Among girls, the OR for NAFLD was 1.92 for those with high WHR (95% CI 1.58–2.34, p < 0.0001), independent of confounders (p < 0.0001) and the OR for elevated ALT was 2.16 (95% CI

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children a lower amount of visceral fat might be more detrimental for hepatic steatosis than in Caucasian children. Moreover, NAFLD occurrence is influenced by sex[3] as males display higher risk for NAFLD development and progression.[34] It has been suggested that this sex dimorphism of NAFLD might be explained by both endocrine factors, namely estrogens protective action and different metabolic pathways, such as de novo lipogenesis[35] and adipose tissue browning.[36] In light of this knowledge, we investigated whether the WHR cut-off changed according to sex. We observed that our cohort boys showed a lower WHR cut-off point compared to girls (0.53 versus 0.63). Interestingly, the WHR cut-off for NAFLD in our cohort is lower than that described for metabolic syndrome (0.60).[20] This finding might suggest that hepatic fat accumulation could precede metabolic syndrome occurrence in children and adolescents with obesity.

In addition, in our population, the groups with high WHR showed significantly higher risk for elevated ALT, independently of the effect of confounding factors.

We acknowledge that the lack of biopsy proven NAFLD and the retrospective design are limitations of this study. Moreover, as NAFLD and body fat distribution are influenced by genetic background, our results should be limited to Caucasian children and the WHR cut-off might change in other ethnic groups. Therefore, we suggest to perform NAFLD screening in Caucasian patients with WHR above the cut-off. Nevertheless, the retrospective design of the study might limit the strength of the recommendation. However, it is the first study to measure anthropomorphic measures as predictors of NAFLD in a large cohort of Caucasian children and adolescents with obesity and a prospective case–control study would be of interest in validating this observation.

In conclusion, we showed that WHR is a better predictor of pediatric NAFLD compared to other anthropometric indexes in children and adolescents with obesity, and that a cut-off value of 0.53 in boys and 0.63 in girls might represent a good anthropometric screening tool in order to identify children and adolescents with elevated risk of fatty liver disease. In addition, it could be hypothesized that it would gain in utility when combined with biochemical markers of NAFLD.

AUTHOR CONTRIBUTIONS

ADDITIONAL INFORMATION

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