The Turkish Journal of Pediatrics 2019; 61: 714-722
DOI: 10.24953/turkjped.2019.05.010

Original

Cardiometabolic risk factors in Turkish children with hepatosteatosis

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Received: 29th June 2018, Accepted: 1st September 2018

SUMMARY: Aslan A, Erdemli S, Durukan Günaydın G, Aslan M, Yazar RÖ, Kabaalioğlu A, Ağırbaşlı MA. Cardiometabolic risk factors in Turkish children with hepatosteatosis. Turk J Pediatr 2019; 61: 714-722.

We aimed to investigate the prevalence of cardiometabolic (CM) risk factors (impaired fasting glucose (>100 mg/dL), high blood pressure, overweight or obesity, high serum triglycerides (TG) and low serum high-density lipoprotein cholesterol levels) in children with hepatosteatosis detected by abdominal ultrasound. Children whom ultrasound examination revealed hepatic steatosis were included in the study. Medical records, anthropometric and biochemical parameters were reviewed for the presence of the CM risk factors. Presence of ≥3 risk factors was defined as metabolic syndrome (MS).

One hundred and forty-eight children and adolescents (67 boys, 81girls, and mean age 12.1±2.7 years) with hepatosteatosis were included. Sonographic hepatosteatosis grades of 1, 2 and 3 were observed in 111 (75%), 33 (22.3%), and 4 (2.7%) subjects, respectively. MS was observed in 36 patients (24.3%). The number of CM risk factors and degree of hepatic steatosis were correlated (r=0.183, p=0.026). Serum TG levels in girls and age in boys were significantly associated with the presence of medium to severe hepatosteatosis (grades 2 or 3) (R^2=.342, =.040 and R^2=.538, p=.001, respectively). CM risk factors and MS are common in children with hepatosteatosis. The presence and grade of hepatosteatosis on ultrasound can be used as surrogate markers of MS and CM risk in children.

Key words: pediatric, ultrasonography, hepatosteatosis, cardiometabolic risk factors.

Longitudinal studies confirm that cardiometabolic (CM) risk factors such as insulin resistance, glucose intolerance, diabetes mellitus (DM), obesity, hepatosteatosis, hypertension, and dyslipidemia increase the incidence of cardiovascular disease (CVD).[1-8] The clustering of CM risk factors in obese children portends the future risk of CVD and DM in adulthood, but prospective tracking studies remain limited in developing countries.[1-4] Primordial prevention of CVD during childhood and adolescence is particularly important since it can prevent subsequent development of complex diseases such as atherosclerosis, hypertension, and DM.

Evaluation of CM risk in children comes with its challenges, as the threshold values for standard risk variables are population specific and change with age and physiological growth during the pubertal development. For instance, the International Diabetes Federation (IDF) definition of abdominal obesity considers waist circumference > 90th percentile of the local population.[8] Yet, waist circumference percentiles or anthropometric measures are affected by the ethnicity and socioeconomic status of the population. Furthermore, adequate percentile information for developing countries is not readily available and temporal changes occur.[9] Therefore, challenges remain ahead of the definition of metabolic syndrome

(MS) and CM risk in children and adolescents in developing countries and alternative morphological criteria are needed.

Fatty infiltration of hepatocytes (hepatosteatosis) is commonly observed in obese children and adolescents.[10,11] Liver biopsy is the reference test for assessing the severity of hepatosteatosis but it is not feasible as a screening test of CM risk in the pediatric population. On the other hand, ultrasonography is a cheap, easy to use, widely available diagnostic tool which can be used to determine the fatty infiltration of hepatocytes noninvasively.[12-15] In this study, we aimed to introduce the role of ultrasonography as a screening test for CM risk factors of impaired fasting glucose, high blood pressure (BP), obesity, high serum triglycerides (TG) and low serum high-density lipoprotein cholesterol (HDL-C) levels in children and adolescents.

Material and Methods

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by Institutional Ethics Committee (Decision number 2017/313).

Parent, guardian or next of kin consent was not required for the minors because the study was designed as a retrospective study.

Patients

Patients were selected from children and adolescents who were referred to Radiology Department of a tertiary center, for abdominal ultrasonography. Abdominal ultrasonography reports of children and adolescents in radiology information system of our institution were searched for the terms of "hepatosteatosis, fatty liver, hyperechogenic liver" between the dates from September 2016 to February 2017. On the radiology information system, abdominal ultrasonography reports of 501 patients with sonographic hepatosteatosis were identified. The medical records, anthropometric and biochemical parameters of the patients were reviewed to investigate the presence of CM risk factors on hospital information system, retrospectively. Among 501 patients, 34 patients with chronic diseases, 28 patients with syndromic obesity and 291 patients with incomplete test results were excluded. Eventually, 148 patients diagnosed with hepatosteatosis by ultrasonography constituted the final study group. Patients who had a history of chronic illness, active infection, alcohol consumption, psychiatric illness, renal insufficiency, malignancy, and DM were excluded. Data related to age (year), body mass index (BMI), blood pressure, lipid profile, and fasting blood glucose were recorded, and the correlations between risk parameters and sonographic hepatosteatosis grades were analyzed. BMI was obtained by dividing weight (in kilograms) to the square of height (in meters) (kg/m^2). The overweight or obesity status of the patients was assessed by age- and sex-specific cut-off points of BMI.[16]

Ultrasound Imaging

Abdominal ultrasonography was performed by three radiologists using a PVT-375BT+6C1 convex transducer (Aplio™ 300 and 500; Toshiba Medical Systems Corporation, Otawara, Japan). The liver diameter was measured on midclavicular axis from upper margin to the lower margin of liver and noted as millimeter (mm). Sonographic assessment of hepatosteatosis grades of 1 to 3 was based on a comparison of the echogenicity of the liver and the kidney and absence of echogenic walls of intrahepatic vessels (Fig. 1).[17]

Definition of Hepatosteatosis and Grades on Ultrasonography Examination

Grade 1 hepatosteatosis: There is a mild fatty infiltration of liver parenchyma. The parenchymal echogenicity is slightly increased when compared to the kidney and intrahepatic vessels and diaphragm are visualized.

Grade 2 hepatosteatosis: The echogenicity of liver parenchyma is increased with a slight deterioration in the visualization of the diaphragm and intrahepatic vessels.

Grade 3 hepatosteatosis: There is a moderate to severe fatty liver change seen in this state. The increased liver parenchymal echogenicity causes poor or non-visualization of the borders of the diaphragm and intrahepatic vessels.[17]

For further analysis; patients were classified into two groups by sonographic evaluation as

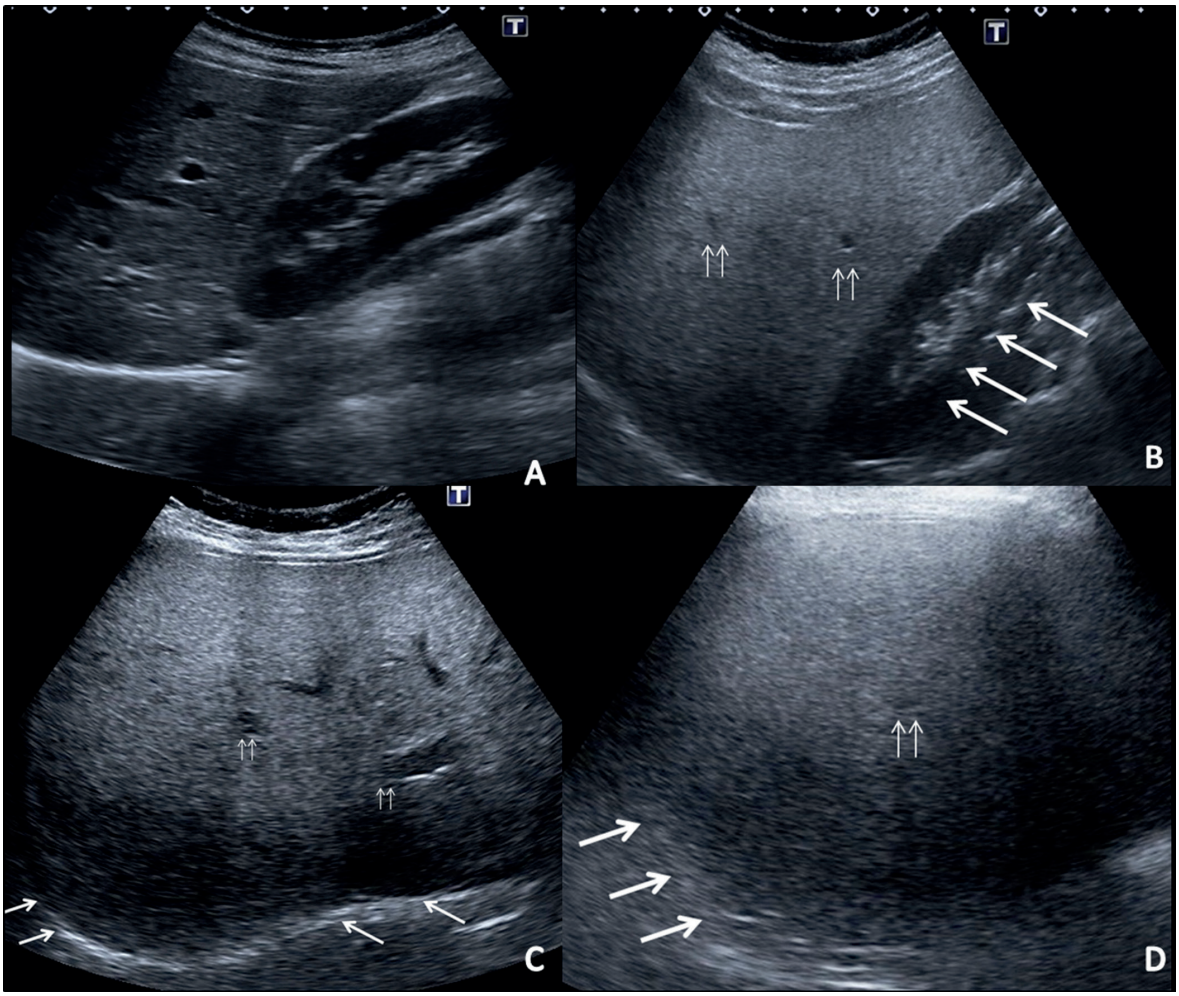

Fig. 1. Assessment of hepatosteatosis on ultrasonography. **A.** Ultrasonographic appearance of a healthy liver. The borders of liver and vascular structures are clearly seen. **B.** 10-year-old boy with grade 1 hepatosteatosis. The echogenicity of the liver is higher than that of the right kidney cortex (thick arrows). Note that intrahepatic vessels can be seen (thin arrows). **C.** Grade 2 hepatosteatosis. The liver is diffusely hyperechogenic, but diaphragm (thick arrows) and intrahepatic vessels (thin arrows) are still seen. Hyperechogenic portal vein wall is obscured due to increased fatty infiltration (thin arrows). **D.** Grade 3 hepatosteatosis. The echogenicity of the liver is increased due to diffuse fatty infiltration that hindered the visualization of the diaphragm (thick arrows) and intrahepatic vessels (thin arrows) by attenuating ultrasound waves.

medium hepatosteatosis (sonographic grade 1 hepatosteatosis) and severe hepatosteatosis (sonographic grade 2 and 3 hepatosteatoses) (Fig. 1).

Cardiometabolic Risk Factors

Medical records, anthropometric and biochemical parameters were reviewed to investigate the presence of CM risk factors. CM risk criteria include overweight/obesity, impaired fasting glucose (IFG), increased TG and decreased HDL-C serum levels, and high BP. IFG is defined as fasting serum glucose level greater than 100 mg/dL.[18] The growth curve designed for healthy Turkish children was used to obtain the age-specific height percentile level for each case.[19] The Task Force Report on High Blood Pressure in Children and Adolescents was used to determine children and adolescents with high BP (≥95th percentile).[20] We used the National Heart Lung and Blood Institute Growth and Health Study (NGHS) as the reference population as

age- and sex-specific lipid percentiles were not available in Turkish children.[21]

Definition of Metabolic Syndrome

MS criteria in children and adolescents were modified from those of the National Cholesterol Education Program (NCEP) Adult Treatment Panel.[6] A serum TG level of at least the 90th percentile or a serum HDL-C level not exceeding the 10th percentile was considered as a risk determinant of MS.

Subjects with 3 or more of the following 5 criteria were considered to have MS:

1. Elevated systolic and/or diastolic blood pressure (≥ 95th percentile),
2. BMI level indicating overweight or obesity,
3. Elevated serum TG level (≥ 90th percentile level),
4. Low serum HDL-C level (≤ 10th percentile level),
5. Impaired serum fasting glucose level (≥ 100 mg/dL).[16,18,20,21]

Children and adolescents ≥3 criteria were considered to have metabolic syndrome.[6]

Statistical Analyses

Descriptive parameters are shown as means ± standard deviation. Shapiro-Wilk Test was used for assessing whether the continuous variables were normal or skewed distributed. Comparisons were made by Independent-samples T-Test and Mann-Whitney U Test. Categorical variables among the groups were compared by the X^2 test. Logistic regression analysis was used to present the predictors of MS. A value of $p<0.05$ on the 2-sided test was accepted as the significance level. Statistical analyses were performed by using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM (IBM Corp. Released 2013).

Results

One hundred and forty-eight patients (81 girls, 67 boys, mean age 12.1 ± 2.7 [range 8-17] years) were identified with sonographic hepatosteatosis. The mean BMI in the study population was 28.8±5.2 kg/m^2. The demographic data of the patients are presented in Table I. Girls displayed shorter height and higher serum HDL-C levels compared to boys (Table I). Sonographic hepatosteatosis grades of 1, 2 and 3 were observed in 111 (75%), 33 (22.3%), and 4 (2.7%) patients, respectively. Table II shows the distribution of gender,

Table I. Anthropometric and Metabolic Data from 148 Children and Adolescents.

	Girls (n = 81)	Boys (n = 67)	p[a]
Age (year)	12.0 ± 2.9	12.2 ± 2.5	0.735
Systolic blood pressure (mmHg)	111 ± 13	111 ± 12	0.794
Diastolic blood pressure (mmHg)	68 ± 9	69 ± 8	0.648
Weight (kg)	69 ± 20	74 ± 22	0.115
Height (cm)	153 ± 12	158 ± 14	0.024
Body mass index (kg/m^2)	28.7 ± 5.5	28.9 ± 5.1	0.761
Total cholesterol (mg/dl)	171 ± 38	174 ± 34	0.700
HDL-C (mg/dl)	47 ± 12	43 ± 7	0.024
LDL-C (mg/dl)	101 ± 28	104 ± 31	0.487
Triglycerides (mg/dl)	121 ± 62	136 ± 87	0.227
Fasting blood glucose (mg/dl)	93 ± 25	89 ± 8	0.271

[a]Student T-Test
kg; kilogram, cm; centimeter, mg/dl; milligrams per deciliter, HDL-C; high-density lipoprotein cholesterol, LDL-C; low-density lipoprotein cholesterol.

Table II. Distribution of Gender, Body Mass Index, and Liver Diameter Based on Sonographic Hepatosteatosis Grades.

Hepatosteatosis Grades	Gender		Age (year)	BMI (kg/m²)*	Liver size (mm)
	Girls	Boys			
Grade 1 (n=111)	44 (39.6%)	67 (60.4%)	11.67 ± 2.65	28.14 ± 5.2	131.81 ± 17.43
Grade 2 (n = 33)	21 (63.6%)	12 (36.4%)	13.06 ± 2.52	30.30 ± 5.3	149.55 ± 13.61
Grade 3 (n = 4)	2 (50%)	2 (50%)	15.25 ± 1.7	36.25 ± 3.3	163.33 ± 5.77
p value	0.047[a]		0.002[b]	0.002[b]	<0.001[b]

[a]Mann Whitney U test, [b]StudentT-Test
*BMI = body mass index

Table III. The Frequency of Cardiometabolic Risk Factors in Children with Hepatosteatosis.

Risk Determinant	N	%
Obesity	109	73.6
Overweight	33	22.3
Overweight or obesity	68	95.9
Diastolic blood pressure between 90-95th percentile	1	0.7
Diastolic blood pressure > 95th percentile	1	0.7
Systolic blood pressure between 90-95th percentile	4	2.6
Systolic blood pressure > 95th percentile	12	7.9
Systolic and/or diastolic blood pressure ≥ 90th percentile	16	10.6
HDL-C ≤ 10thpercentile	45	29.8
HDL-C ≤ 40 mg/dl	46	30.5
Triglycerides ≥ 90thpercentile	47	31.1
Triglycerides ≥ 110 mg/dl	70	46.4
HDL-C ≤10th percentile and/or triglycerides ≥90th percentile	72	47.6
Fasting glucose > 100 mg/dl	20	13.2

mg/dl; milligrams per deciliter, HDL-C; high-density lipoprotein cholesterol.

BMI, and liver diameter based on sonographic hepatosteatosis grade groups. Children with higher grades of hepatosteatosis were older and displayed higher liver diameter and BMI (Table II).

The prevalence of CM risk factors among children with hepatosteatosis is shown in Table III. MS was observed in 36 patients (24.3%). There was a weak and positive correlation between the number of CM risk factors and sonographic *severity of steatosis* (r=0.183, p=0.026). Logistic regression analysis was performed to find the predictors of medium to severe hepatosteatosis (n=37, 25%) in study participants. Among the covariates of the 5 CM risk factors and age, serum TG levels in girls and age in boys were significantly associated with medium to severe hepatosteatosis grade (R^2=0.342, p=0.040, and R^2=0.538, p=0.001, respectively) (Tables IV and V). Serum TG/HDL-C ratio was significantly higher in patients with severe hepatosteatosis compared to medium hepatosteatosis. Median (interquartile range) levels are 2.3 (1.8) versus 3.1 (2.7), p=0.017 (Fig. 2).

Discussion

Primordial prevention of CVD can be achieved by early identification of CM risk factors in children and adolescents.[2] In this study, we investigated the frequency of CM risk factors

Table IV. Logistic Regression Analysis Model of Severe Hepatosteatosis (Grade 2 And 3) in Girls using the 5 Cardiometabolic Risk Variables.

	Beta Coefficient	p	Odds Ratio	95 % CI for OR	
				Lower	Upper
Age (year)	0.063	0.708	1.065	0.764	1.485
BMI (kg/m^2)	0.013	0.875	1.013	0.860	1.194
Systolic BP (mmHg)	0.025	0.587	1.025	0.937	1.121
Diastolic BP (mmHg)	0.025	0.730	1.025	0.891	1.178
FBG (mg/dl)	0.020	0.145	1.020	0.993	1.048
HDL-C (mg/dl)	-0.026	0.480	0.974	0.905	1.048
Triglycerides (mg/dl)	0.013	0.040	1.013	1.001	1.025
Constant	-9.855	0.020	<0.001		

CI; Confidence interval, OR; Odds ratio, BMI; body mass index, kg/m^2; kilogram per meter square, BP; blood pressure, mmHg; millimeters of mercury, FBG; fasting blood glucose, mg/dl; milligrams per deciliter, HDL-C; high-density lipoprotein cholesterol. Nagelkerke R Square: 0.342.

Table V. Logistic Regression Analysis Model of Severe Hepatosteatosis (Grade 2 And 3) in Boys using the 5 Cardiometabolic Risk Variables.

	Beta Coefficient	p	Odds Ratio	95 % CI for OR	
				Lower	Upper
Age (year)	0.723	0.001	2.061	1.335	3.181
BMI (kg/m^2)	-0.010	0.906	0.990	0.842	1.165
Systolic BP (mmHg)	0.028	0.534	1.028	0.942	1.123
Diastolic BP (mmHg)	-0.057	0.342	0.945	0.840	1.062
FBG (mg/dl)	-0.003	0.941	0.997	0.917	1.084
HDL-C (mg/dl)	-0.002	0.978	0.998	0.881	1.131
Triglycerides (mg/dl)	-0.005	0.318	0.995	0.985	1.005
Constant	-7.389	0.276	0.001		

CI; Confidence interval, OR; Odds ratio, BMI; body mass index, kg/m^2; kilogram per meter square, BP; blood pressure, mmHg; millimeters of mercury, FBG; fasting blood glucose, mg/dl; milligrams per deciliter, HDL-C; high-density lipoprotein cholesterol. Nagelkerke R Square:0.538.

and dyslipidemia in children and adolescents with non-alcoholic hepatosteatosis displayed by ultrasonography.

Identifying the surrogate markers for MS and CM risk in children and adolescents is crucial for the primordial prevention of CVD. The current study demonstrates that prevalence of MS in children with hepatosteatosis is nearly 10 fold higher than the prevalence of MS in healthy school children of Turkey.[22] Hepatosteatosis grade correlates with the number of CM risk factors. Hypertriglyceridemia is the most common CM risk factor in children with hepatosteatosis. Gender-specific associations exist and serum TG levels are significantly associated with medium to severe hepatosteatosis in girls.

Assessment of the CM risk in children comes with difficulties.[2,22,23] It is important to initiate effective and timely screening and prevention strategies. Ethnic differences in anthropometric indices present challenges in the identification and prediction of CM risk criteria prevalence in children. Furthermore, anthropometric indices change during pubertal development.[23,24] The population's ethnicity can alter the prevalence of CM risk factors.[23-25] For instance, in Turkish children, the prevalence of overweight and

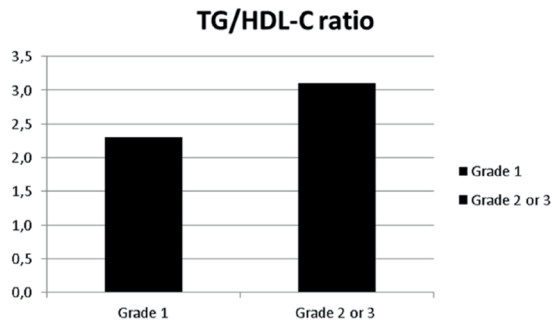

Fig. 2. TG/HDL-C ratio is significantly higher in subjects with Grade 2 or 3 compared to Grade 1 hepatosteatosis. Median (interquartile range) levels are 2.3 (1.8) versus 3.1 (2.7), p=0.017.

obesity has increased significantly over the last 2 decades. Similarly, temporal trends exist in blood pressure, BMI, lipids and fasting glucose among Turkish children and adolescents.[9,26] Therefore, alternative and readily available risk assessment tools for CM risk in children are needed. Study findings suggest that ultrasonography is a valuable tool in screening hepatosteatosis and identifying high CM risk factors in children and adolescents. The carotid intima-media thickness (CIMT) is increased in children with hepatosteatosis when compared with healthy controls and obese children without hepatosteatosis which is an early atherosclerosis maker.[27] CIMT correlates with the grade of steatosis and indicates that hepatosteatosis and CIMT are valuable parameters in predicting the risk of early atherosclerosis in children and adolescents.

We examined a representative sample of overweight and obese children with hepatosteatosis from Istanbul. Each country should establish its own reference values for determination of obesity and metabolic disturbances. Anthropometric indices vary among socioeconomic classes and regional differences exist. In a previous study from Ankara[28], Turkey, among obese children and adolescents with dyslipidemia, 63% had hepatosteatosis and 22% had grade 2-3 hepatosteatosis. Dyslipidemia and insulin resistance in obese children enhance lipid intake and production in the liver as a potential pathophysiologic pathway leading to the development of hepatosteatosis. In prior studies[26], dyslipidemia in children was defined as serum total cholesterol > 200 mg/dL, TG levels > 150 mg/dL, LDL-C levels > 130 mg/dL, or HDL-C < 40 mg/dL. However, serum lipid levels change with puberty, gender, and ethnicity and adequate percentile information are needed to assess the hyperlipidemia in children. Our study findings explore dyslipidemia in hepatosteatosis by investigating the gender and age-specific serum TG and HDL-C percentile levels and display that prevalence of hypertriglyceridemia in children with hepatosteatosis is much more common (nearly half of the cases) than previously reported.[26] Similar to our findings, a prior study from Korea[28] indicates that serum TG to HDL-C ratio (cut-off 2.63) showed the highest predictability for CM risk factor clustering. We display that the median TG to HDL-C ratio for the group with Grade 2 or 3 hepatosteatosis is 3.1, confirming their findings. Therefore, age and gender-specific percentile information and evaluation of the median serum TG to HDL-C ratio are needed to assess dyslipidemia in children.

This chart review and cross-sectional study of hepatosteatosis in children come with several limitations. Socioeconomic status, diet, physical activity statuses are not available which can all affect CM risk factors in children. Puberty and serum sex hormone levels can alter the CM risk factors which are not assessed in the context of this study.[29] Our study group consisted of patients who applied to public hospitals in large cities; therefore, most of the participants are assumed to be from middle to lower socioeconomic level and may not exemplify all children and adolescents in Turkey. We need future prospective studies to confirm the study findings. Although histopathology is a reference test, we used ultrasonography for verification of the diagnosis of hepatosteatosis in the study group.

Hepatosteatosis and CM risk factors are prevalent in obese children. Reliable surrogate markers of dyslipidemia and CM risk in children will facilitate identification of children and adolescents with high risk. Abdominal ultrasonography is readily available, and our study findings suggest that ultrasonography can provide a useful assessment of CM risk in children and adolescents.

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