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ORIGINAL ARTICLE

Non-alcoholic fatty liver disease (nafld) in pediatric patients with excess weight - retrospective single center study

Carolina Vitor Vidal[1], Paula Jordani Zaia[1], Miriam Hashimoto[1]

Keywords:
Non-alcoholic Fatty Liver Disease,
Obesity,
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Abstract

Objective: to assess the prevalence of non-alcoholic fatty liver disease (NAFLD) in a group of overweight/obese pediatric patients; to evaluate which clinical, anthropometric and laboratory parameters differ between patients with and without NAFLD and to associate the alterations with the presence of NAFLD. **Methods:** retrospective observational study between 2012-2017, involving overweight/obese children and adolescents in 2 groups: WITH-NAFLD and WITHOUT-NAFLD. The presence of hepatic steatosis on ultrasound was considered for diagnosis of NAFLD. Studied variables: age, sex, systolic (SBP) and diastolic (DBP) blood pressure, birth weight (BW), weight, height, body mass index (BMI), BMI Z-score, waist circumference (WC), fasting blood glucose, insulin, IR-HOMA, triglycerides, total cholesterol and fractions, transaminases (ALT and AST) and thyroid stimulating hormone (TSH). Statistical analysis using Chi-square and Mann-Whitney tests for comparison between two groups; multivariate logistic regression analysis for association with NAFLD; $p<0.05$. **Results:** 174 patients were evaluated, 35 WITH-NAFLD (20.1%). SBP>95th percentile (29 vs 14; p= 0.003), BMI (29.7 vs 27.5; p=0.010), BMI Z-score (3.2 vs 2.9; p=0.036), WC (93 vs 88.5; p=0.046), insulin (15.7 vs 12.8; p=0.028), IR-HOMA (3.2 vs 2.5; p=0.028) and ALT (39 vs 27, $p<0.001$) were significantly higher in WITH-DHGNA group. The others parameters did not differ. ALT was the only associated parameter with NAFLD (1.06; p=0.003) by multivariate logistic regression. **Conclusion:** one fifth of overweight/obese pediatric patients had NAFLD and had higher degrees of obesity, abdominal adiposity, insulin resistance and systolic pressure values. ALT was associated with NAFLD.

[1] UNESP, Pediatria - Botucatu - São Paulo - Brasil.

Correspondence to:
Carolina Vitor Vidal.
Universidade Estadual Paulista. Av. Prof. Mário Rubens Guimarães Montenegro, s/n - UNESP - Campus de Botucatu - Botucatu/SP - CEP 18618687. E-mail: vidal@yahoo.com.br

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in children and adolescents. Obesity, a growing disorder in this population, is the main risk factor and, therefore, the prevalence of NAFLD has increased significantly in recent years[1,2].

NAFLD is a liver disease resulting from the accumulation of fat in the liver unrelated to alcohol use and includes a variety of liver changes, from asymptomatic steatosis to evolution with inflammatory activity, necrosis, steatohepatitis, fibrosis, cirrhosis and even hepatocellular carcinoma[3] .

The importance of its diagnosis and treatment arises from NAFLD being considered the hepatic component of metabolic syndrome (MetS) and, therefore, being associated with a higher incidence of chronic non-communicable diseases in the pediatric population. Children with NAFLD often have many clinical findings that overlap with MetS, which consists of a set of risk factors for diseases related to metabolism and obesity, highlighting cardiovascular diseases, type 2 diabetes mellitus and systemic arterial hypertension[4].

In this panorama, there are currently some recommendations for screening tests. The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommends carrying out liver function tests and liver ultrasound in all children and adolescents with obesity[5]. The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) suggests measuring the liver enzyme, alanine transferase (ALT), in all pediatric patients over 9 years of age with obesity or overweight and some associated risk factor for NAFLD[6]. Therefore, investigation and early diagnosis of NAFLD are prioritized.

Regarding diagnosis using ultrasound, hepatic steatosis can be graded according to its severity. In general, there is a diffuse increase in hepatic echogenicity and progressive blurring of the visualization of intrahepatic vessels as the severity of the disease increases. As it is an operator-dependent exam, there may be limitations to the method[7].

The study aimed to evaluate the prevalence of NAFLD in overweight pediatric patients; verify whether clinical, anthropometric and laboratory parameters differ between patients with and without NAFLD and associate possible changes found with NAFLD.

METHODS

This is an observational and retrospective study based on data from patients followed at the childhood obesity outpatient clinic of a tertiary university hospital, between July 2012 and December 2017. Patients aged between 5-16 years with the diagnosis of overweight according to WHO criteria[8], classified as overweight when the body mass index (BMI) Z score for age is between >+1 and ≤+2; and as obesity when the BMI-for-age Z-score is >+2. Patients with incomplete data and those who did not undergo liver ultrasound (US) at the service were excluded. Two groups were compared: WITH-NAFLD and WITHOUT-NAFLD. NAFLD was considered by the presence of hepatic steatosis on ultrasound[9].

Measurement of body weight with a digital scale (in kilograms) and height with a fixed wall stadiometer (in centimeters) was carried out by the pediatric nursing team, using the same measuring instruments.

The ultrasound was performed at the service by more than one professional, supervised by the same Radiology team, and with the same ultrasound device. The diagnostic criterion for NAFLD was considered to be a diffuse increase in hepatic echogenicity, associated or not with blurred visualization of the intrahepatic vessels[7].

The study groups were compared according to clinical, anthropometric and laboratory variables. Clinical: age, sex, systolic blood pressure (SBP), diastolic blood pressure (DBP). Anthropometrics: birth weight (BW), weight, height, BMI, BMI Z score, waist circumference (WC). Laboratory: fasting blood glucose (GLuC), insulin (INS), Homeostatic Model Assessment (IR-HOMA), triglycerides (TG), total cholesterol (TC), low-density lipoproteins (LDL), high-density lipoproteins (HDL), thyroid stimulating hormone (TSH), aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

The Chi-Square and Mann-Whitney tests were used to compare groups and multivariate logistic regression analysis was used to verify the association with NAFLD, with results at $p<0.05$ being significant. Analysis carried out with SPSS 21.0. This study approved by the Research Ethics Committee (CAAE: 47186315.2.0000.5411).

RESULTS

With 341 patients followed at the outpatient clinic, 98 were excluded due to failure to perform liver US and 69 due to incomplete study data. Of the 174 evaluated, 35 were from the WITH-NAFLD group and 139 WITHOUT NAFLD, with a NAFLD prevalence of 20.1% (figure 1).

There was no difference between the groups in clinical variables; however, when analyzing BP values > 95th percentile for age and sex, there was a higher occurrence of SBP in patients WITH-NAFLD (29% vs 14%; p=0.03) and without difference in DBP (26% vs 18%; p=0.30). There was also no difference regarding sex in the occurrence of NAFLD (males 43% vs females 53%; p=0.27). The anthropometric variables studied, weight, BMI, BMI Z score and WC measurement were significantly higher in the with NAFLD group, with all patients in this group being obese or severely obese (Z score > two). In comparison, 10% of the w/out NAFLD group were overweight. When WC measurements above the 90th percentile were evaluated, high values were found in both groups without a significant difference (91% vs 88%; p=0.54). Regarding laboratory variables, fasting insulin, IR-HOMA and ALT values differed between groups, being higher in the with NAFLD group (table

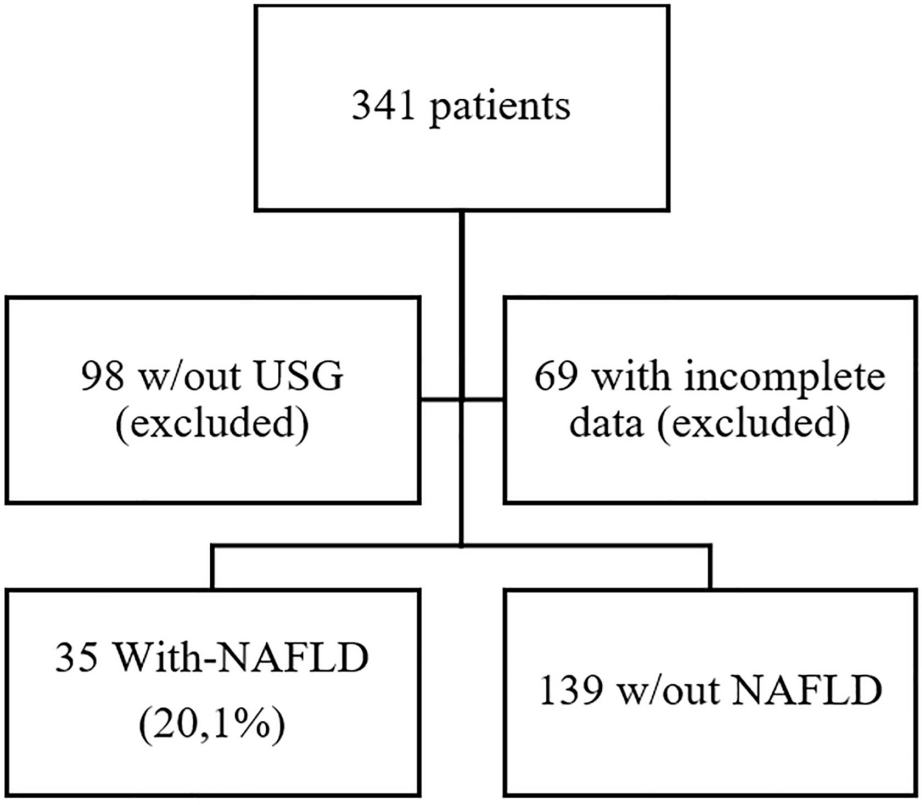


Figure 1. Flowchart of patients included in the study.

Table 1. Comparison of variables between the WITH-NAFLD and WITHOUT-NAFLD groups.

	COM-DHGNA (n=35)	SEM-DHGNA (n=139)	p
BW (g)	3.010 (1.490 – 4.500)	3.300 (960 – 4.900)	0.220
Age (years)	10 (5 – 15)	10 (5 – 16)	0.568
Weight (kg)	66.3 (38.2 – 118.6)	62.1 (26.8 – 144.6)	0.237
Height (cm)	146 (120.8 – 180)	148.5 (113.5 – 180)	0.632
BMI (kg/m2)	29.7 (22.7 – 47.7)	27.5 (19.8 – 59.8)	0.010
BMI Z score	3.2 (2.3 – 9.1)	2.9 (1.6 – 5.9)	0.036
WC (cm)	93 (72.5 – 144)	88.5 (54.5 – 144)	0.046
SBP (mmHg)	110 (90 – 150)	110 (80 – 160)	0.353
DBP (mmHg)	70 (50 – 90)	70 (50 – 100)	0.989
INS (µU/mL)	15.7 (5.4 – 42.4)	12.8 (2 – 53.9)	0.028
GLUC (mg/dL)	90 (69 – 105)	89 (71 – 109)	0.451
IR-HOMA	3.2 (0.9 – 8.8)	2.5 (0.4 – 8.9)	0.028
TC (mg/dL)	158 (101 – 218)	156 (94 – 240)	0.477
HDL (mg/dL)	39 (22 – 65)	42 (22 – 78)	0.453
TG (mg/dL)	87 (46 – 441)	97 (36 – 317)	0.629
LDL (mg/dL)	97.6 (52 – 150)	90 (32.4 – 157.6)	0.437
AST (mg/dL)	30 (15 – 94)	27 (15 – 75)	0.079
ALT (mg/dL)	39 (13 – 158)	27 (8 – 128)	<0.001
TSH (UI/mL)	2.6 (0.4 – 7.3)	2.5 (0.8 – 8.7)	0.659

Table 2. Multivariate logistic regression analysis.

Variable	OR	CI 95%	p
Z score BMI	1.00	0.57-1.73	0.986
WC	1.01	0.97-1.04	0.732
SBP>P95	2.70	0.92-7.87	0.069
INS	0.92	0.77-1.10	0.378
IR-HOMA	1.72	0.71-4.13	0.228
ALT	1.06	1.02-1.10	**0.003**

1). When evaluating ALT values above 40 IU/L, considered as a cutoff point by many authors, there was a 48.5% occurrence in the with-NAFLD group.

Using multivariate logistic regression, the variables that differed between the groups were analyzed and the likelihood of developing NAFLD is 1.06 times higher in patients with higher ALT values (table 2).

DISCUSSION:

Although NAFLD is the most common liver disease in childhood and adolescence, its prevalence is not yet well defined in the literature. In the present study, there was a 20.1% prevalence of NAFLD, a value below studies that evaluated only patients with obesity, such as the systematic review and meta-analysis by Anderson et al[10] with 36.1% and the review carried out by Schwimmer et al[11] with a 38% prevalence of NAFLD. The prevalence was similar to the recent study by Yu et al[12], with 26% in obese children and adolescents aged between 9 and 17 years.

In the study carried out, BP > 95th percentile occurred in 29% of the with-NAFLD group, a finding similar to that of Schwimmer et al[11], of 35.8%, which correlated the presence of systemic arterial hypertension (SAH) with the greater severity of liver disease. In the study by Pacifico et al[13], 61% of patients with NAFLD had high blood pressure, but they were obese adolescents with a higher average age.

Some biochemical data that demonstrate insulin resistance (IR), such as fasting hyperinsulinemia and IR-HOMA, as well as greater adiposity verified by anthropometric measurements (BMI and WC), occurred at a greater proportion among children and adolescents with NAFLD, similar findings in different studies[14,15,16]. Hyperinsulinemia and IR, accompanied by adiposity, would lead to increased uptake of free fatty acids and consequent buildup of fat in hepatocytes, with increased lipid peroxidation. Visceral adiposity appears to have an important role in the pathogenesis of NAFLD through the production of many inflammatory adipokines, such as tumor necrosis factor-α, adiponectin and resistin, which are involved in the induction of IR and the inflammatory process in the liver[14].

Multivariate logistic regression indicated that ALT was an independent risk factor for NAFLD. Similarly, Khusial et al[17] also demonstrated higher levels of ALT in patients with NAFLD, with this change being present in 24% of these patients (24 vs 19, p<0.001). Noureddin et al[18] described that around 50% of patients with NAFLD may have normal ALT levels, which is why it is neither reliable nor accurate to use this test alone for the screening and diagnosis of NAFLD. This proportion was similar in the study carried out, in which 51.5% of patients in the with-NAFLD group had ALT below the value considered high. Therefore, although elevated ALT is associated with NAFLD, association with other methods for diagnosing NAFLD is recommended[3]. In another study, using ALT dosage and ultrasound to detect hepatic steatosis, Draijer et al found that ALT and liver ultrasound evaluated separately presented moderate diagnostic accuracy and the strategy of combining ALT and US did not improve accuracy[19].

This study obtained complete liver ultrasound data and anthropometric, clinical and laboratory variables from all 174 patients analyzed. Thus, it was possible to carry out the statistical analysis without prejudice to the lack of information when comparing the groups. Furthermore, it was carried out on overweight children and adolescents from a single follow-up clinic, enabling data to be obtained in a careful and homogeneous way.

The main limitation of the study was the diagnosis of NAFLD by liver US, which may have underestimated the prevalence in relation to mild cases of NAFLD. Liver biopsy, considered the gold standard for diagnosing NAFLD, would not be indicated for most patients, as it is an invasive diagnostic method.

CONCLUSION:

The prevalence of NAFLD was 20.1% among children and adolescents followed at the childhood obesity clinic of a university center. The with-NAFLD group showed a higher degree of adiposity, blood pressure values, ALT and RI indices. Only ALT has been associated with NAFLD.

NAFLD is a liver disease with increasing prevalence in the pediatric population in a context of childhood obesity epidemic. This panorama could justify the implementation of a routine screening exam in target populations, with the aim of early diagnosis and treatment, avoiding progression and possible complications.

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