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Non-alcoholic fatty liver disease and metabolic syndrome in overweight adolescents

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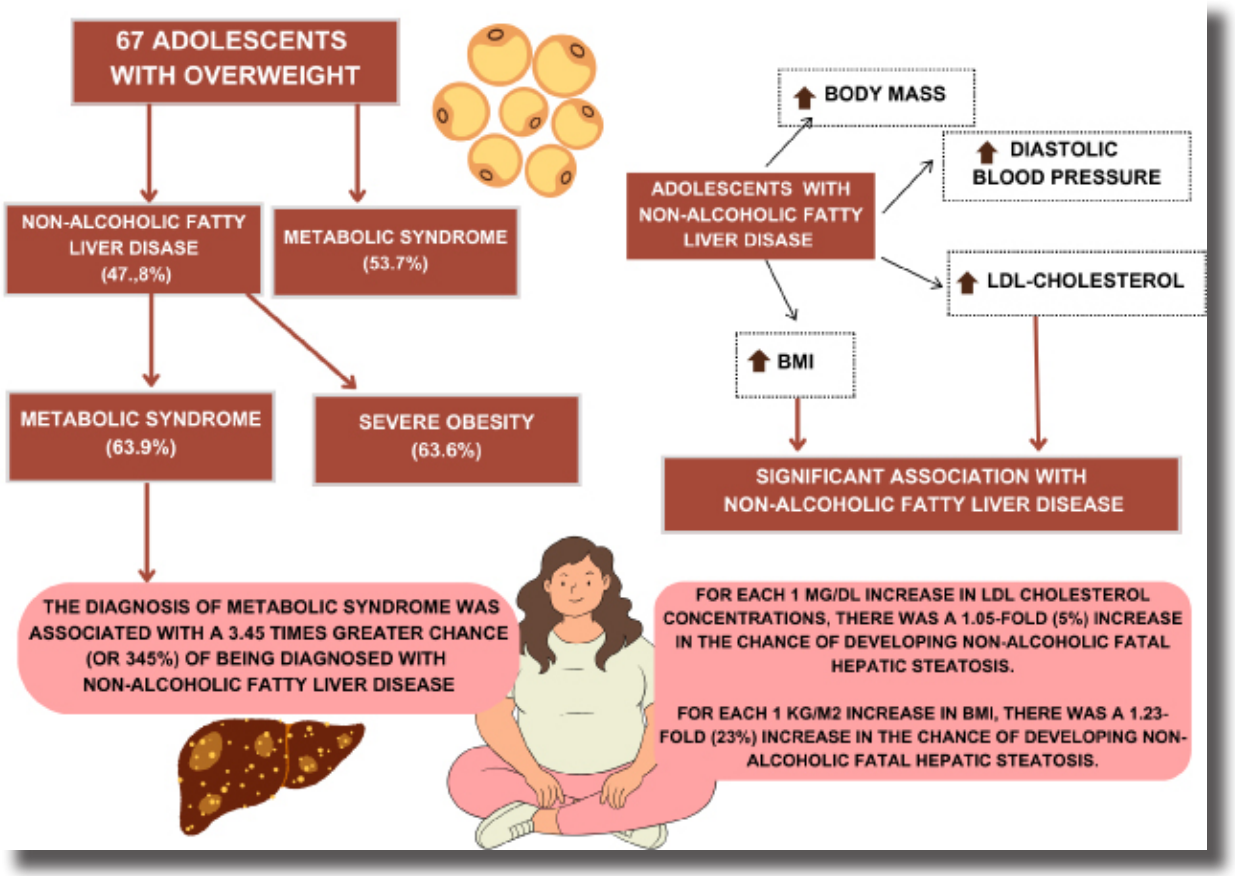
Graphical Abstract



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Abstract

Non-Alcoholic Fatty Liver Disease (NAFLD) is characterized by the accumulation of fat in the liver and may be associated with metabolic syndrome (MS). Metabolic syndrome is considered a cluster of metabolic alterations, including lipid, glycemic, and blood pressure disturbances, along with excess abdominal adiposity. The coexistence of these two conditions may predispose individuals to increased cardiovascular risk and mortality. The relevance of this study stands out in the Brazilian context, where the rising cases of NAFLD and MS in adolescents reflect a global trend but lack sufficient investigation into their interconnections within the national scenario. The objective of this study was to investigate the prevalence and relationship between NAFLD and MS in overweight adolescents, as well as to explore the magnitude of their association and the risk factors involved. A cross-sectional study with observational data analysis was conducted at a State Pediatric Hospital in São Paulo. The sample consisted of 67 adolescents aged 10 to 19 years, diagnosed as overweight. All participants underwent anthropometric evaluation, and biochemical and NAFLD data were collected from electronic medical records. For the diagnosis of metabolic syndrome (MS), the International Diabetes Federation criteria were used as a reference. In the total sample, the prevalence of NAFLD and MS was 47.8% and 53.1%, respectively. A significant association was observed between the presence of NAFLD and MS, with NAFLD being more prevalent in the group of adolescents with MS (63.9%) compared to the group without MS (39.1%). The presence of MS was associated with a 3.45 times higher likelihood of a NAFLD diagnosis. Adolescents with NAFLD had significantly higher values of weight, BMI, LDL cholesterol concentrations, and diastolic blood pressure compared to the group without NAFLD. Among the metabolic parameters, LDL cholesterol concentrations and BMI were associated with an increased likelihood of NAFLD. The findings of this study indicate a high prevalence of NAFLD and MS in overweight adolescents, as well as a significant association between these conditions, with particular emphasis on LDL cholesterol concentrations and BMI. Considering MS as a platform for the development of non-communicable chronic diseases and its association with hepatic steatosis, these findings serve as a warning for the adoption of preventive measures starting from the pediatric stage.

Keywords: Metabolic Syndrome. Hepatic Steatosis. Adolescent.

INTRODUCTION

Obesity is a multifactorial disease characterized by excessive accumulation of body fat, influenced by various factors such as sedentary behavior, poor eating habits, and genetic and psychological conditions[1]. Childhood obesity has been increasing alarmingly both globally and in Brazil[2,3]. According to the National School Health Survey (*Pesquisa Nacional de Saúde do Escolar* - PENSE), Brazilian adolescents showed a prevalence of overweight at 23.7% and obesity at 7.8%, with nearly one-third of this age group classified as having excess weight[2]. The significant rise in obesity within the pediatric population has become a public health issue and a growing concern globally and nationally due to the numerous harmful health consequences of excess weight, including the development of non-communicable chronic diseases[3].

Visceral adipose tissue is considered an endocrine organ, and under conditions of excessive adiposity, it is directly associated with a subclinical and chronic inflammatory process. This process is characterized by the elevation of pro-inflammatory adipokines such as tumor necrosis factor-alpha (TNF-alpha), leptin, interleukin 6 (IL-6), and angiotensinogen, and the reduction of anti-inflammatory adipokines such as adiponectin. The inflammatory process resulting from excessive abdominal adiposity is involved in the pathophysiology of metabolic alterations associated with obesity, particularly insulin resistance, lipid profile disturbances, and the development of metabolic syndrome (MS)[4].

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MS consists of a cluster of metabolic dysregulations, including hyperglycemia, elevated blood pressure levels, hypertriglyceridemia, low levels of high-density lipoproteins (HDL), and central obesity—factors that increase the long-term risk of cardiovascular diseases[5]. One of the complications associated with obesity is Non-Alcoholic Fatty Liver Disease (NAFLD), a condition characterized by the accumulation of fat in the liver which, if untreated, can progress to more severe liver diseases such as fibrosis, cirrhosis, and, in extreme cases, cancer. Recently, the term "metabolic-associated fatty liver disease" (MAFLD) has been proposed to describe NAFLD related to metabolic dysfunctions, a condition that already affects approximately 25% of the global population[6].

Among adolescents with obesity, NAFLD is a growing concern due to its potential progression to more severe liver diseases and the lack of symptoms, which hinders early diagnosis[7]. The relationship between MS and NAFLD involves complex pathophysiological mechanisms, including insulin resistance, chronic systemic inflammation, and lipid profile alterations, which are common conditions in adolescents with obesity[8]. Insulin resistance occurs when insulin-dependent cells fail to respond adequately to insulin, resulting in hyperglycemia, hyperinsulinemia, the development of type 2 diabetes mellitus, elevated triglycerides, and LDL cholesterol particles. These factors contribute to fat deposition in liver tissue. Furthermore, increased lipolysis in visceral adipose tissue leads to a greater influx of free fatty acids to the liver, increasing the likelihood of local fat deposition. Dysregulation in lipoprotein metabolism, sedentary lifestyles, and poor dietary patterns are commonly associated causes of NAFLD[8,9].

Several clinical studies have investigated childhood obesity and its metabolic and hepatic complications in adolescents, including the presence of NAFLD and MS[10-12]. Some international studies conducted with adolescents have highlighted the association between MS and NAFLD, emphasizing the pathophysiological mechanisms related to excessive visceral adipose tissue, insulin resistance, subclinical chronic inflammation, and lipid profile alterations[10,13,14]. Despite the relevance of NAFLD and MS to public health, studies exploring these conditions in the pediatric population are scarcer in Brazil. Most have been conducted with small sample sizes and have been limited to analyzing either the prevalence of MS or NAFLD and their associated factors in isolation[15-18]. The study by Resende *et al.* (2014)[15], conducted with 34 adolescents from Uberlândia, Minas Gerais, found that half of the sample had MS, and 82.3% of those with MS also presented with NAFLD. Another study conducted with 129 overweight or obese children and adolescents in Campina Grande, Paraíba, reported that approximately 49.6% had MS, 44.2% had insulin resistance, and 28.7% had NAFLD[16]. Similarly, the study by Duarte et al. (2011)[17] evaluated 77 children and adolescents aged 2 to 13 years in Recife, Pernambuco, and found a prevalence of NAFLD in 42.9% and MS in 27.3% of the sample, with 47.6% of those with MS also presenting with NAFLD.

Adolescence represents a critical phase for health interventions, as habits and health conditions established during this period tend to persist into adulthood[19]. Thus, this study aimed to investigate the prevalence and relationship between NAFLD and MS in overweight adolescents, as well as to explore the magnitude of their association and the risk factors involved. Identifying these interconnections in Brazilian adolescents can provide a foundation for developing health promotion and treatment strategies, particularly those focused on lifestyle and public policies addressing childhood obesity. Moreover, by examining the relationship between NAFLD and MS in this group, the study seeks to contribute to understanding the pathophysiological bases of these conditions and to strengthen research in the national context.

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METHODS

Study Design and Sample

This study employed a cross-sectional design with an observational approach to the data and utilized a convenience sample comprising overweight adolescents, based on the classification proposed by the World Health Organization (WHO)[20] and recommended by the Brazilian Ministry of Health[21]. The use of a convenience sample was chosen due to the accessibility and availability of participants for this research, consisting of patients who routinely attended the pediatric endocrinology outpatient clinic at a Estadual Children's Hospital in São Paulo, Brazil, where the study was conducted. This approach facilitated the recruitment of overweight adolescents and allowed data collection under specific conditions that naturally met the inclusion criteria. Adolescents aged 10 to 19 years with a Body Mass Index (BMI)-for-age greater than 1 standard deviation for age[21] were included in the study.

Exclusion criteria were defined to minimize factors that could interfere with the metabolic and hepatic outcomes analyzed. Adolescents with autoimmune diseases, corticosteroid use, and neurological conditions (such as autism spectrum disorder and Down syndrome) were excluded, as these factors affect metabolism and may be associated with hormonal and inflammatory alterations. Temporary or permanent intellectual disabilities were considered exclusion criteria to ensure sample homogeneity, as these factors can influence eating behavior and adherence to study protocols. Food allergies and conditions such as type 1 diabetes mellitus were excluded because they require specific dietary and therapeutic interventions that could impact the studied variables. Pregnant adolescents were excluded due to the metabolic and hormonal changes characteristic of pregnancy, which could distort the results. Lastly, a history of alcohol abuse was an exclusion criterion due to its direct impact on liver function, including alterations in liver transaminases and fat accumulation in the liver. These exclusion criteria were carefully selected to ensure the reliability of the results and to focus on the associations between obesity, MS, and NAFLD.

The selection of participants from a single location and with specific health characteristics may introduce biases and limit the representativeness of the results. Consequently, the findings may not be generalizable to the broader pediatric population. These limitations indicate that the results should be interpreted within the specific context of this study and suggest the need for future research with larger and more representative samples to confirm the external validity of the findings and assess their applicability to more diverse populations.

Data Collection

Data collection was conducted between August 2022 and April 2023 at a pediatric endocrinology outpatient clinic of a Estadual Children's Hospital located in São Paulo, Brazil.

Anthropometric Assessment

Participants underwent anthropometric assessment, including measurements of height, weight, and waist circumference, following the standardization provided by the Ministry of Health[21]. To minimize bias, researchers were trained prior to the start of data collection to ensure standardized procedures for all anthropometric measurements. A Toledo® electronic scale, calibrated with a precision of 0.01 kg, was used. All participants were instructed to remove shoes and jackets before stepping on the scale. Height was measured using a wall-mounted stadiometer, Tonelli® brand, with a precision of 0.01 m. Participants wearing caps or hair ties were instructed to remove them to ensure accurate measurements[21]. Waist circumference was measured using a non-elastic

measuring tape placed directly on the skin, with the participant in a supine position during exhalation. The measurement was taken at the midpoint between the costal arch and the iliac crest. Measurements of height and waist circumference were taken three times, and the average of the three values was used for analysis[21].

Blood Pressure Assessment, Diagnosis of Metabolic Syndrome, and Non-Alcoholic Steatohepatitis

All researchers underwent training for blood pressure measurement. Blood pressure was measured using the Vita(i) 120 device after a five-minute rest period. For standardization, measurements were taken on the right arm with the participant in a seated position, legs uncrossed, and arm extended on the examination table. Long-sleeved shirts were removed to avoid interference.

Fasting glucose, fasting insulin, lipid profile (total cholesterol, cholesterol fractions, and triglycerides), and liver enzymes—glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), and gamma-glutamyl transferase (GGT)—were collected from the patients' medical records. To ensure up-to-date information, only test results from the three months preceding the start of data collection were considered current. Data extraction from medical records was conducted by two researchers to ensure data consistency and minimize potential errors. Additionally, the insulin resistance index was calculated using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) formula: fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5[22]. All tests were conducted in the same laboratory of the hospital where the data collection took place.

The diagnosis of MS was made based on the criteria of the International Diabetes Federation[5], which considers an altered waist circumference (above the 90th percentile) associated with two other altered parameters:

a) HDL cholesterol: less than 40 mg/dL
b) Triglycerides: greater than 150 mg/dL
c) Glucose: above 100 mg/dL
d) Systolic blood pressure: greater than 130 mmHg
e) Diastolic blood pressure: greater than 85 mmHg

The diagnosis of NAFLD was obtained from the participants' medical records and based on the results of total abdominal ultrasound, which was also performed within the hospital by the same evaluator, a specialist in diagnostic imaging, who had no access to or knowledge of this study. Ultrasound is widely used in clinical settings due to its accessibility and cost-effectiveness, as well as being a non-invasive and radiation-free procedure. However, ultrasound has limitations, particularly in detecting mild steatosis, and may underestimate fat accumulation compared to more sensitive methods[23]. Other imaging methods, such as hepatic elastography and magnetic resonance imaging, are recognized as more sensitive for quantifying liver fat and can provide more precise assessments. Nonetheless, due to their high cost, these methods were not available in the context of this research[24,25]. Thus, biomarkers for hepatic steatosis, such as liver enzyme levels, were used to complement our analyses.

Ethical Aspects and Data Confidentiality

The study was approved by the Ethics and Research Committee of the São Camilo University Center (No. 5.653.370). All guardians signed the informed consent form (ICF), and participants assented to participation through the Informed Assent Form (IAF). To ensure data confidentiality, each participant was registered with a numerical code, which was used in all records and data analyses to protect the identity of those involved in the data tabulation and analysis process. The data were handled and accessible only to the researchers of this study.

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Statistical Analysis

Statistical analysis was performed using JAMOVI software, and a significance level of $p<0.05$ was adopted, a commonly used threshold in biomedical research to reduce the probability of Type I errors, i.e., the chance of rejecting the null hypothesis. This value was chosen to balance statistical rigor with the feasibility of detecting meaningful associations among the investigated variables.

The Shapiro-Wilk normality test was applied to assess the distribution of variables and guide the selection of statistical tests based on Gaussian distribution. The descriptive profile of the sample was represented by mean and standard deviation for parametric variables and median (minimum and maximum) for non-parametric variables. To compare groups based on the presence or absence of NAFLD, the independent t-test was used for normally distributed data, while the Mann-Whitney test was applied for non-normally distributed data. Pearson and Spearman correlation tests were used to explore relationships between parametric and non-parametric numerical variables, respectively.

Categorical variables were described as percentages. The chi-square test was used to verify associations between categorical variables, such as the presence of NAFLD, the presence of MS, and other metabolic alterations. Additionally, two binary logistic regression models were performed to identify factors associated with the diagnosis of NAFLD, considered the dichotomous dependent variable (presence or absence of the condition). The models were designed to meet the essential prerequisites for this type of analysis. First, the independence of observations was ensured. To verify the absence of multicollinearity among independent variables, a Variance Inflation Factor (VIF) > 0.8 was considered acceptable. Model fit analysis was also conducted, evaluating McFadden's pseudo-R-squared, the overall accuracy rate of the model, specificity, and sensitivity. These methodological precautions aimed to ensure that the binary logistic regression models were robust, facilitating the accurate identification of factors associated with NAFLD.

RESULTS

A total of 67 participants were evaluated, with a prevalence of NAFLD observed in 47.8% (n=32) and MS in 53.7% (n=36) of the sample. In the chi-square tests (Table 1), significant associations were found between the presence of NAFLD and the diagnosis of MS x^2=8.11, p=0.004. The prevalence of MS was higher in the group of adolescents with NAFLD compared to those without the diagnosis (63.9% vs. 36.1%). It was also observed that elevated diastolic blood pressure (DBP) was associated with NAFLD x^2=4.19, p=0.041, with approximately 63.0% of adolescents with NAFLD presenting elevated DBP. Although no significant association was observed between NAFLD and nutritional status, it was evident that the prevalence of severe obesity was higher in the group with NAFLD (63.6%).

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Table 1 - Prevalence of metabolic syndrome, alterations in metabolic syndrome parameters, and nutritional status of adolescents with and without non-alcoholic fatty liver disease attended at an outpatient clinic. São Paulo, 2023.

	NAFLD Group (n=32)	No NAFLD Group (n=35)	P
Metabolic Syndrome (%)			**0.004**
Yes	63.9	36.1	
No	29.0	71.0	
Elevated Waist Circumference (%)			0.507
Yes	50	50	
No	37.5	62.5	
Elevated Glucose (%)			0.307
Yes	52.3	47.7	
No	39.1	60.9	
Elevated Triglycerides (%)			0.090
Yes	75.0	25.0	
No	43.1	56.9	
Reduced HDL (%)			0.128
Yes	53.8	46.2	
No	34.6	65.4	
Elevated Systolic Blood Pressure (%)			0.072
Yes	60.7	39.3	
No	38.5	61.5	
Elevated Diastolic Blood Pressure (%)			**0.041**
Yes	63.0	37.0	
No	37.5	62.5	
Nutritional Status (%)			0.094
Overweight	22.2	77.8	
Obesity	44.4	55.6	
Severe Obesity	63.6	36.4	

NAFLD, Non-Alcoholic Fatty Liver Disease; Chi-square association test; **p-value <0.05**.

Figure 1 illustrates the significant association observed between the number of altered metabolic parameters and the presence of NAFLD x^2=12.5, p=0.015. It is evident that participants without NAFLD showed fewer metabolic alterations, while those diagnosed with NAFLD exhibited a greater number of metabolic alterations.

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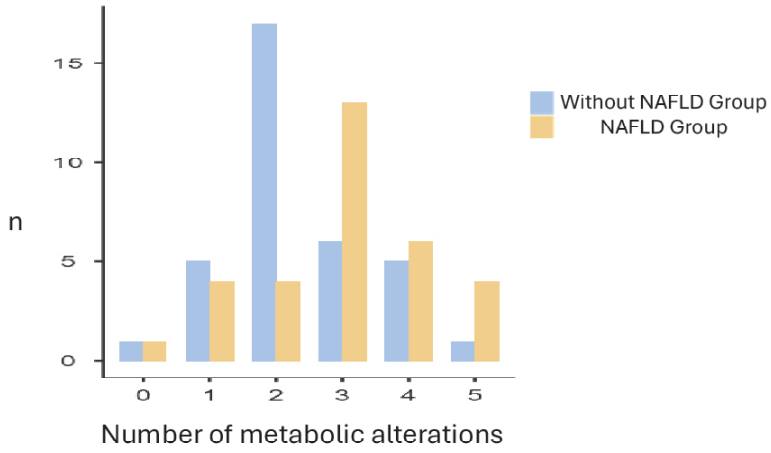

Figure 1 - Association Between the Number of Metabolic Alterations and the Presence of Non-Alcoholic Steatohepatitis (NAFLD) in Overweight Adolescents Attended at an Outpatient Clinic of a Estadual Hospital. São Paulo, 2023.

*Chi-square Test with Fisher's Correction; **p<0.05**.

The anthropometric and biochemical profile of the sample, according to the presence or absence of NAFLD, is presented in Table 2. Using the independent t-test, it was observed that the group with NAFLD showed significantly higher values of weight (kg) [t(65) = -2.10; p = 0.040], BMI (kg/m²) [t(65) = -3.18; p = 0.002], LDL-c concentrations [t(59) = -2.35; p = 0.022], and diastolic blood pressure [u(65) = 388; p = 0.031] compared to the group without NAFLD.

Table 2 - Anthropometric and Metabolic Profile of Adolescents With and Without Non-Alcoholic Fatty Liver Disease (NAFLD) Attended in the Outpatient Clinic of a Estadual Hospital. São Paulo, 2023.

	NAFLD Group (n=32)	No NAFLD Group (n=35)	P
Anthropometric Profile			
Weight (kg)	85.4 ± 16.3	77.4 ± 14.98	**0.040**
Height (cm)	94.7 ± 78.6	107.1 ± 77.8	0.063
Waist circumference (cm)	100.8 ± 11.6	95.9 ± 9.5	0.059
BMI (kg/m²)	33.0 ± 4.9	29.4 ± 4.3	**0.002**
BMI z-score	3.0 (1.8 – 5.3)	2.5 (1.3 – 3.8)	0.349
Metabolic Profile			
Glucose (mg/dL)	93.5 (76 – 139)	90.0 (72 – 133)	0.174
Insulin (uU/mL)	15.7 (5.5 – 77.3)	16.1 (5.8 – 30.0)	0.200
HOMA-IR	3.41 (1.25 – 26.50)	3.62 (1.23 -5.92)	0.184
Triglycerides (mg/dL)	130.8±95.4	105.1 ± 93.8	0.243
Total cholesterol (mg/dL)	169 (101 – 251)	144 (93 – 342)	0.298
LDL-c (mg/dL)	98.6 ± 27.9	84.3 ± 18.9	**0.022**
HDL-c (mg/dL)	37.5 ± 9.6	40.5 ± 10.6	0.236
VLDL-c (mg/dL)	22 (9 -71)	16.5 (8 – 47)	0.267
Systolic Blood Pressure (mmHg)	130.3 ± 18.5	124.6 ± 13.8	0.153

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DOI: 10.15343/0104-7809.202448e16332024I

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Metabolic Profile	NAFLD Group (n=32)	No NAFLD Group (n=35)	P
Diastolic Blood Pressure (mmHg)	70 (45 – 92)	67 (21 – 86)	**0.031**
GOT (mg/dL)	24 (16 – 64)	23.5 (13 – 39)	0.087
GPT (mg/dL)	19 (9 – 131)	19 (7 – 49)	0.146
GGT (mg/dL)	22 (11 – 96)	19.5 (11 – 57)	0.251
Vitamin D	21 (10 – 42)	19.5 (12 – 35)	0.390

Parametric numerical variables are presented as mean ± standard deviation, and non-parametric variables as median (minimum–maximum); p-value refers to the independent t-test or Mann-Whitney test; p-value in **bold** <0.05; Homeostasis Model Assessment Insulin Resistance (HOMA-IR); Low-Density Lipoprotein (LDL-c); High-Density Lipoprotein (HDL-c); Very Low-Density Lipoprotein (VLDL); Systolic Blood Pressure (SBP); Diastolic Blood Pressure (DBP); Body Mass Index (BMI); Glutamic-oxaloacetic transaminase (GOT); Glutamic-pyruvic transaminase (GPT); Gamma-Glutamyl Transferase (GGT).

To confirm the associations found, logistic regression models were created to investigate the predictors of Non-Alcoholic Fatty Liver Disease (NAFLD) (Table 3). In Model 1, the diagnosis of Metabolic Syndrome (MS) was associated with a 3.45-fold higher chance (or 345%) of NAFLD diagnosis in overweight adolescents. In this test, accuracy was 68.2%, with a specificity of 66.7% and sensitivity of 69.6%. The pseudo-R-squared was 19.8%. The variables sex, HOMA-IR, and age did not show a significant association with the diagnosis of NAFLD.

In Model 2, the independent variables associated with the diagnosis of NAFLD were LDL-cholesterol concentrations and BMI. For each 1 mg/dL increase in LDL-cholesterol concentrations, there was a 1.05-fold (5%) increase in the likelihood of NAFLD. Regarding BMI, each 1 kg/m² unit increment was associated with a 1.23-fold (23%) increase in the likelihood of developing NAFLD. In this test, accuracy was 79.1%, with a specificity of 81% and sensitivity of 77.3%.

Table 3 - Logistic regression models.

Model 1						Confidence Interval 95%	
Predictors	**Estimates**	**Standard Error**	**Z**	**P**	**Odds ratio**	**Lower Limit**	**Upper Limit**
Intercept	-3.705	2.503	-1.480	0.139	0.0246	1.820	3.320
Metabolic Syndrome							
- Yes – No	1.493	0.724	2.062	**0.039**	4.4511	1.076	18.410
Sex							
- Male – Female	0.900	0.701	1.283	0.199	2.4595	0.622	9.720
HOMA-IR	0.205	0.154	1.333	0.182	1.2275	0.908	1.660
Age	0.117	0.159	0.737	0.461	1.1241	0.823	1.530
Model 2						**Confidence Interval 95%**	
Predictors	**Estimates**	**Standard Error**	**Z**	**P**	**Odds ratio**	**Lower Limit**	**Upper Limit**
Intercept	-15.962	5.65428	-2.823	0.005	0.000	0.000	0.008

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DOI: 10.15343/0104-7809.202448e16332024I

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Model 2						Confidence Interval 95%	
Predictors	**Estimates**	**Standard Error**	**Z**	**P**	**Odds ratio**	**Lower Limit**	**Upper Limit**
Diastolic Blood Pressure	0.065	0.042	1.558	0.119	1.067	0.983	1.157
LDL-cholesterol	0.052	0.022	2.410	**0.016**	1.054	1.010	1.099
HOMA-IR	0.090	0.170	0.528	0.597	1.094	0.784	1.525
Triglycerides	0.012	0.008	1.608	0.108	1.012	0.997	1.027
Age	-0.091	0.177	-0.512	0.609	0.913	0.645	1.292
BMI	0.213	0.103	2.065	**0.039**	1.238	1.011	1.515

P- value <0,05.

In the correlation analyses presented in Table 4, a positive correlation was observed between triglycerides concentrations and insulin as well as HOMA-IR. Regarding LDL-cholesterol concentrations, a positive correlation was noted with total cholesterol, VLDL-c, triglycerides, and the liver enzymes TGO and TGP. Finally, a positive correlation was observed between GGT concentrations and the number of altered Metabolic Syndrome (MS) parameters.

Table 4 - Correlations Between Metabolic Profile and Liver Enzymes in Overweight Adolescents Attended in the Outpatient Clinic of a Municipal Hospital. São Paulo, 2023.

Triglycerides		
	r/rho	p
Insulin	0.317	0.034
HOMA-IR	0.342	0.023
LDL-C		
	r/rho	p
Total Cholesterol	0.887	<0.001
VLDL	0.280	0.032
TG	0.260	0.043
GOT	0.367	0.009
GPT	0.320	0.017
GGT		
	r/rho	p
Number of Altered MS Parameters	0.397	0.004

*Homeostasis Model Assessment Insulin Resistance (HOMA-IR); Low-Density Lipoprotein (LDL-c); Very Low-Density Lipoprotein (VLDL); Glutamic-oxaloacetic transaminase (GOT); Glutamic-pyruvic transaminase (GPT); Gamma-Glutamyl Transferase (GGT); Metabolic Syndrome (MS).

DISCUSSION

One of the main findings of this study concerns the high prevalence of NAFLD (47.8%) and MS (57.1%) in the sample of overweight adolescents, highlighting the significant association between these conditions confirmed by the chi-square test and logistic regression analysis. In the group with NAFLD, the prevalence of MS was even higher, around 63.9%. A systematic review and meta-analysis study investigating the prevalence of MS in 43,227 Brazilian adolescents indicated that 2.9% of boys and 2.4% of girls have the condition[26]. The prevalence of MS becomes even more concerning in adolescents with obesity. A previous study conducted with 195 adolescents diagnosed with obesity in São Paulo, Brazil, found a prevalence of MS in 25.16% of the total sample. The prevalence of NAFLD in this sample was 66.0% in adolescents with MS and 25.5% in those without MS, further reinforcing the relationship between these two conditions[27]. Another Brazilian study, conducted with 90 children and adolescents with overweight or obesity in Brasília, Brazil, also revealed the coexistence of these two conditions. Those diagnosed with NAFLDpresented a higher number of criteria for MS when compared to patients without NAFLD[28].

The high prevalence of Metabolic Syndrome (MS) in the pediatric population is considered a global concern. An important systematic review and modeling analysis study conducted by Noubiap *et al.(2022)*[29] provided global prevalence estimates of MS in children and adolescents up to 2020. A total of 169 studies were evaluated, comprising 550,405 participants from 44 countries. The global prevalence of MS was estimated at 2.8% for children and 4.8% for adolescents, totaling approximately 25.8 million children and 35.5 million adolescents affected by this condition. Prevalence rates varied according to income levels of countries and regions, with higher MS prevalence observed among children in Central Latin America (8.2%) and adolescents in high-income English-speaking countries (6.7%).

The occurrence of Non-Alcoholic Fatty Liver Disease (NAFLD) has also become a concern during the pediatric phase. Among children and adolescents, the prevalence of NAFLD has substantially increased worldwide over the past three decades, rising from 19.3 million to 29.5 million in 2017, representing an annual increase of 1.35%[30]. It is known that the data are even more alarming in overweight children and adolescents. The global prevalence of NAFLD is 13% in the general pediatric population and estimated at 47% among those diagnosed with obesity, being higher in boys than in girls[7]. A Brazilian study conducted with 83 adolescent students from a public school in São Paulo, Brazil, identified that among those evaluated with excess weight, the presence of NAFLD was 27.7%[18].

NAFLD is a silent disease associated with various health consequences, becoming a concern due to its severe long-term impacts, including impaired liver function, steatohepatitis, higher risk of fibrosis, cirrhosis, and hepatocellular carcinoma[7,31]. An important cohort study that followed 8,919 adults and elderly individuals over a 16-year period revealed that NAFLD associated with metabolic alterations was an independent predictor of overall mortality and cardiovascular disease. These results were not observed when only the presence of NAFLD was analyzed[32].

Currently, the term Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) has been suggested to describe the association between metabolic dysfunctions and Non-Alcoholic Fatty Liver Disease (NAFLD), better characterizing its pathophysiology and the factors involved in the onset or progression of the disease. Among the metabolic risk factors, abdominal adiposity identified by waist circumference, blood pressure alterations, triglycerides, HDL, and glycemic metabolism disorders stand out.

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Individuals with these combined alterations present higher risks for the progression to more advanced forms of liver diseases and cardiovascular mortality[6]. Although the isolated identification of MS and NAFLD is important in clinical practice, it is increasingly recognized that the joint identification of these two conditions and their early treatment can mitigate the synergistic effects of health damages caused by MAFLD[6]. In our study, the diagnosis of MS increased the likelihood of NAFLD occurrence by 345%.

The relationship between metabolic disorders and hepatic fat accumulation can be explained by pathophysiological mechanisms related to excess fat in the abdominal region. Visceral adipose tissue, which is responsible for secreting pro-inflammatory cytokines such as IL-6, TNF-alpha, and resistin, induces chronic inflammation, insulin resistance, and oxidative stress in individuals with obesity. Together, these mechanisms contribute to metabolic disturbances such as hyperinsulinemia, hyperglycemia, hypertriglyceridemia, and hypercholesterolemia, all of which are linked to fat deposition in hepatic tissue. Elevated lipolysis rates in visceral adipose tissue are associated with a greater influx of free fatty acids into systemic circulation and the liver, exacerbating fat accumulation within hepatocytes and accelerating the progression of both conditions[4,8-9]. In a study conducted with a sample of adolescents diagnosed with obesity, it was noted that each 1 cm increase in visceral fat was associated with a 1.97-fold higher risk in boys and a 2.08-fold higher risk in girls of developing NAFLD[10].

The relationship between waist circumference and the presence of NAFLD was evaluated in a study that analyzed 247 adolescents with obesity in São Paulo, Brazil. NAFLD was identified in 60% of participants, with those in the third and fourth quartiles of waist circumference showing a higher prevalence of NAFLD compared to those in the first quartile. Adolescents diagnosed with NAFLD had significantly higher values for body weight, BMI, BMI z-score, total body fat, waist circumference, visceral fat, insulin, Homeostasis Model Assessment Insulin Resistance (HOMA-IR), and liver enzymes AST and ALT when compared to adolescents without NAFLD. Thus, it is important to highlight the clinical relevance of monitoring this anthropometric measure, as it demonstrates an increased risk of steatosis, with fat deposition in specific regions appearing to be more significant than overall excess body fat[33].

In our study sample, adolescents with NAFLD showed a higher prevalence of severe obesity (63%) compared to the group without NAFLD (36.4%). Furthermore, they exhibited significantly higher values for weight, BMI, diastolic blood pressure, and LDL-c concentrations. Similar results were observed in the U.S. study National Health and Nutrition Examination Survey (NHANES) 2017-2018, which identified that children with NAFLD were more likely to have higher BMI z-scores, a higher prevalence of hypertension, and metabolic alterations[34].

The diagnostic criteria traditionally used to identify NAFLD include imaging exams, biochemical markers, and liver histology, alongside the absence of significant alcohol consumption or diagnoses of liver diseases or conditions leading to fat accumulation in hepatocytes (such as viruses, drugs, and autoimmune diseases). The liver transaminases AST, ALT, and GGT are considered biomarkers used to monitor liver injury, but they have recently been associated with metabolic alterations. A recent systematic review that analyzed over 70 studies and 275,000 individuals demonstrated that AST, ALT, and GGT concentrations were higher in individuals diagnosed with MS[35]. A study conducted in Rio de Janeiro with 144 adults with obesity, which examined the relationship between NAFLD and MS, revealed significantly higher mean levels of liver injury markers ALT and GGT in individuals with MS[36]. Similarly, in adolescents with obesity, GGT, AST, and ALT levels were significantly higher in partici-

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pants with MS. Additionally, a positive correlation was found between liver enzymes and waist circumference[27].

Among liver enzymes, GGT has emerged as a marker for cardiovascular diseases. Elevated GGT concentrations may be associated with increased oxidative stress and inflammation, mechanisms involved in the pathophysiology of MS, NAFLD, and cardiovascular diseases. Oxidative stress is intensified by elevated GGT levels, as this enzyme is involved in the catabolism of reduced glutathione, an essential antioxidant for iron metabolism, promoting greater release of free radicals. These alterations are directly related to insulin resistance, inflammation, and hepatic fat deposition[37]. In our study, we observed a significant positive correlation between the concentrations of liver enzymes ALT and AST and the lipid profile measured by LDL-c. We also observed a positive correlation between GGT and the number of altered parameters of Metabolic Syndrome.

In a cohort study conducted with a sample of 1,504 adults, elevated GGT concentrations were positively associated with a higher risk of cardiovascular diseases, such as stroke and combined recurrent vascular events[38]. Furthermore, GGT was identified as a predictor of mortality in various non-liver-related pathologies, including metabolic risk, cardiovascular diseases, chronic kidney disease, and neoplasms[37].

Monitoring serum concentrations of liver transaminases such as AST, ALT, and GGT plays an important role in the evaluation and management of patients with NAFLD and MS. These markers can provide significant insights into liver and metabolic alterations. However, it is important to note their limitations as indicators of NAFLD. While sensitive, they are not specific, do not differentiate degrees of steatosis, do not indicate the presence of steatohepatitis or fibrosis, and are not capable of identifying early disease progression. Moreover, they can be influenced by other conditions such as excessive alcohol consumption, other liver diseases, and hepatotoxic medications[31,35]. In our study, no significant differences in liver transaminases were observed between those with and without NAFLD. Thus, while these liver enzymes may be helpful, an integrated approach that includes imaging exams is essential for accurate diagnosis and effective disease management. The diagnosis of NAFLD should be confirmed with more precise tests, such as transient hepatic elastography, a non-invasive marker of fibrosis with greater specificity[25]. Additionally, magnetic resonance imaging with liver fat mapping allows for more precise quantification of liver fat content, enabling monitoring of NAFLD progression without the need for biopsy[24].

The rise in cases of NAFLD and MS aligns with lifestyle changes experienced by modern society. The high consumption of ultra-processed foods, sweetened beverages, and sedentary behavior have contributed to the increase in adolescents with obesity, MS, and NAFLD. Diets rich in refined carbohydrates and trans fats are associated with insulin resistance, dyslipidemia, and hepatic fat accumulation in adolescents. Consistently consuming high-calorie diets promotes the metabolization of fatty acids into triacylglycerol, leading to fat accumulation within hepatocytes and in other metabolism-related tissues such as muscle, adipose tissue, blood vessels, and the pancreas[39].

In this context, several studies in the literature indicate the effectiveness of nutritional interventions and physical exercise in improving obesity, MS, and NAFLD in children and adolescents with obesity[39,40]. A recent systematic review with meta-analysis, which included 11 studies with a total of 493,682 participants, showed that higher vegetable (OR = 0.78, 95% CI = 0.67-0.91) and fruit consumption reduced the risk of NAFLD[41]. Weight loss interventions demonstrated significant effects on parameters related to NAFLD and MS, such as reductions in blood glucose, insulin, HOMA-IR, weight, BMI, BMI z-score, waist circumference, triglyceride levels, and liver enzymes[42].

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The findings of this study have significant clinical implications, especially for overweight adolescents, emphasizing the importance of therapeutic actions and public policies aimed at addressing childhood obesity. These include programs for food and nutrition education, promotion of regular physical exercise, and psychosocial support within family and school contexts, as recommended by the World Health Organization[43]. These interventions should focus not only on reducing body weight but also on modulating metabolic risk factors, contributing to the prevention of future hepatic and cardiovascular complications[40,43].

Given that this study uses clinical and laboratory information from medical records, future research employing artificial intelligence or big data analysis is suggested as a promising avenue. These approaches could enable the analysis of large volumes of clinical and laboratory data from electronic medical records in a multicenter manner, expanding the understanding of the relationship between obesity, MS, and NAFLD, as well as facilitating early diagnosis and risk stratification of patients. Thus, the importance of outpatient follow-up is highlighted for requesting diagnostic tests, monitoring, and recording health information to optimize intervention capabilities in at-risk populations and strengthen future research efforts.

Our study has limitations, such as its cross-sectional design, which does not allow for the establishment of causal relationships. The small and convenience-based sample limits the generalizability of our findings to the general population, underscoring the need for larger studies with broader samples. The potential variability in data collection from medical records may introduce biases, especially regarding standardization. Another limitation is related to the clinical setting, which restricts the sample to adolescents already being monitored for specific conditions such as overweight, potentially not fully reflecting the general population.

The use of abdominal ultrasonography as an imaging exam for diagnosis also has limitations, as its sensitivity and specificity may vary, particularly in cases of mild or moderate steatosis. Factors such as the evaluator's experience and individual patient characteristics, such as severe obesity, may affect image quality. More advanced imaging methods, such as transient hepatic elastography and magnetic resonance imaging, could provide a more accurate assessment of the presence and severity of NAFLD. Acknowledging these limitations is essential to contextualize the findings and emphasize the need for future studies with more representative samples, more precise diagnostic tests, and additional strategies to minimize variations in data collection. To overcome these limitations, future studies with larger and more representative samples and longitudinal designs are recommended to track the progression of NAFLD and MS concurrently in adolescents over time. Nevertheless, the present study provides valuable findings for understanding the associations between MS and NAFLD in overweight adolescents within the national context.

CONCLUSION

A positive association between Non-Alcoholic Steatohepatitis (NAFLD) and Metabolic Syndrome (MS) was observed in overweight adolescents, indicating a direct relationship between metabolic disorders and the substantial increase in hepatic fat accumulation. Although the results did not show an association between NAFLD and nutritional status, severe obesity was more prevalent in the group with NAFLD.

Given the increase in obesity cases observed in recent decades, the importance of investigating the presence of NAFLD and MS in the pediatric population is emphasized. It is concluded that further studies on the relationship between metabolic alterations and NAFLD in overweight adolescents are essential, as well as reinforcing the comprehensive approach to patients for the prevention, intervention, and treatment of these diseases.

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