Alanine aminotransferase as marker of cardiometabolic risk in overweight adolescents

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Abstract

Background: Alanine aminotransferase is a marker present in cases of liver damage, such as non-alcoholic fatty liver disease.

Objective: To identify the relationship between serum alanine aminotransferase values and cardiovascular risk markers in overweight adolescents.

Methods: In this cross-sectional study, were recruited 120 overweight adolescents aged 10-19 years. Height, weight and waist circumference were evaluated and used to calculate the body mass index. Taper index and arterial pressure were measured. Biomarkers lipid and glycemic profiles, triglycerides, high-density lipoprotein, alanine aminotransferase and aspartate aminotransferase values were measured and the triglyceride/high-density lipoprotein ratio was calculated. Statistical analysis was performed using Pearson's correlation coefficient and Fisher's exact test.

Results: Boys showed significantly increased values of alanine aminotransferase ($p < 0.050$), aspartate aminotransferase ($p < 0.010$) and taper index ($p < 0.010$), while girls had higher levels of fasting insulin ($p < 0.010$). In boys, alanine aminotransferase was positively correlated with fasting insulin ($p < 0.050$), triglycerides ($p < 0.050$) and systolic blood pressure ($p < 0.050$), whereas in girls, alanine aminotransferase was correlated with waist circumference ($p < 0.050$), taper index ($p < 0.050$), mass index body ($p < 0.010$), fasting insulin levels ($p < 0.010$), homeostatic model assessment of insulin resistance ($p < 0.010$) and high-density lipoprotein ($p < 0.010$).

Conclusion: Important correlations were identified between serum alanine aminotransferase values and cardiovascular risk markers in overweight adolescents.

Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is one of the leading causes of liver damage worldwide and has been growing all over the world mainly in obese populations, including young people. Steatosis is the initial spectrum of NAFLD, and it is characterized by excess liver fat (over 5% of its total weight) [1–3]. NAFLD can strike children and adolescents and is associated with insulin resistance (IR), obesity (especially visceral), and dyslipidemia (characterized by high triglyceride (TG) levels and low high-density lipoprotein (HDL)) [4, 5].

An imbalance between the input and output of fat cells in the hepatic tissue mediates excess liver fat accumulation, which is worsened by IR [6]; IR increases the amount of available free fatty acids in hepatic tissue as well as hepatic lipogenesis by inhibiting lipolysis in the adipocytes and lowering muscle glucose uptake. Additionally, decreased adiponectin production reduces triglycerides' use due to lower β-oxidation and very-low-density lipoprotein (VLDL) production, triggering the intra-hepatic accumulation of fat and disease progression [5, 1, 7]

One of the ways to track NAFLD is by determining serum levels of hepatic function biomarkers [1]. Studies have identified a relationship between increases in alanine aminotransferase (ALT) and metabolic changes such as IR, dyslipidemia, hypertension and obesity in adolescents [8, 9]. Parameters such as waist circumference (WC) and conicity index has been used to improve the tracking of NAFLD due to their association with visceral obesity [10–12]. Unfavorable lipid profiles can often be observed in patients with NAFLD. Thus, the TG/HDL ratio has been used as a predictor of NAFLD as well as IR-induced atherogenicity [13]

Even though previous literature has shown the efficacy of these markers as predictors of NAFLD in diagnosed pediatric populations, no studies have shown their efficacy in a population of undiagnosed Brazilian youth. This comprehension is especially relevant due to the substantial increase in NAFLD cases and associated comorbidities in this population and the feasibility of these measurements in clinical practice. Thus, our study's objective was to assess the relationship between serum levels of hepatic transaminases and cardiometabolic risk in a population of Brazilian overweight adolescents.

Methods

This cross-sectional study was performed from October 2016 to August 2019. The project was approved by the Research Ethics Board of the Onofre Lopes University Hospital (HUOL) of the Federal University of Rio Grande do Norte, Natal, Brazil (reference number: 56763716.7.0000.5292). Consent forms were adequate with the regional language, age range and objective of the study. Throughout the project, all methods followed the relevant ethical guidelines and regulations.

We estimated our sample size considering a Spearman's or Pearson's correlation of 0.26, $\alpha = 0.05$ and statistical power of 80% [14]. Thus, our final sample consisted of 120 adolescents of both sexes aged 10–19 years. Participants had their first medical appointment at the pediatric endocrinology clinic of the HUOL, Natal, Brazil, and were diagnosed with overweight and obesity according to the criteria established by the World Health Organization (WHO) [15], Mass Index Body (BMI) for age.

Inclusion criteria were: (1) being 10 to 19 years old and diagnosed with overweight or obesity. Exclusion criteria were: (1) having impaired physical or cognitive function; (2) being pregnant or lactating; (3) taking vitamin or mineral supplements; (4) being diagnosed with diabetes; (5) using medication to treat insulin resistance or type 2 diabetes mellitus; (6) having genetic syndromes associated with obesity or other diseases; (7) having any chronic or acute diseases (i.e.: heart and/or kidney failure, cancer).

Anthropometrical assessments were performed using height and weight, which were obtained according to the procedures described in the Anthropometric Standardization Reference Manual [16] and WHO recommendations [17]. After calculating the BMI, we identified participants as being overweight or obese. The classification was performed following the sex and age-specific BMI cutoffs of the WHO. Participants were classified as overweight or obese in the presence of a BMI Z-score equal or greater to + 1 and + 2, respectively. The conicity index (CI) was obtained using the following equation: CI = waist circumference

(m)/0,019 x √body weight (kg)/height (m). Blood pressure values and pubertal stages were obtained from the endocrinologist's medical records at the consultation day.

Participants were asked to provide blood samples after fasting for 10 to 12 hours to assess biochemical biomarkers. The blood was fractionated and destined for measurements of fasting blood glucose levels, oral glucose tolerance test (OGTT), insulin levels, cholesterol, HDL cholesterol, triglyceride, TG/HDL and ALT and AST activities. Biochemical determinations were performed with kits Wiener (Wiener Laboratories, Rosario, Argentina) following the manufacturer's instructions and using the CMD-800 biochemical analyzer (Wiener Laboratories, Rosario, Argentina).

IR was assessed using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), calculated using the following equation: IR = fasting blood glucose (mg/dL) x 0,05551. A value of > 3 was considered as testing positive for IR, following the 2019–2020 guidelines of the Brazilian Diabetes Society [18]. The cutoff points for ALT are 22 mg / dl for girls and 26 mg / dl for boys (3). To assess the presence of dyslipidemia, were used the cutoff points suggested by the guideline for dyslipidemia and prevention of atherosclerosis [19]. All analyses were performed by the Clinical Analysis Laboratory of the HUOL.

Data were analyzed using version 17.0 of the SPSS software. We used central tendency and dispersion measures (mean, median, and standard deviation) for continuous variables. Proportion measures were used for categorical variables. Differences between mean values were tested using a two-sample t-test, while the chi-squared test was used for differences between prevalence. Correlations were estimated using Pearson's correlation coefficient, and associations were determined using Fisher's exact test. We performed simple linear regressions using the ALT concentrations as the dependent variable. All statistical analyses were considered significant when the p-value was lower than 5%.

Results

This study was performed with 120 overweight and/or obese adolescents. Boys represented 52,5% of the studied adolescents. 89% of the studied girls were in the pubertal stage. Boys showed higher values for ALT ($p < 0.050$), AST ($p < 0.010$) and conicity index ($p < 0.010$), while girls showed higher fasting insulin levels ($p < 0.010$). ALT over the maximum limit was present in 20.6% of the studied boys and 29.8% of the girls. Table I shows the biochemical and anthropometric data of the participants.

Table I. Demographical, anthropometrical and biochemical characteristics of the study population according to sex.			
	Total (n = 120)		
	Boys (n = 63)	Girls (n = 57)	p-value
Age (years)	11.29 ± 1.44	11.53 ± 1.60	0.3887
Sexual Maturation (%)	30 (70)	31 (89)	0.0454*
BMI (kg/m^2)	26.21 ± 3.51	26.78 ± 3.71	0.3842
Waist Circumference (cm)	89.17 ± 10.40	85.72 ± 9.64	0.0625
Conicity Index	1.29 ± 0.06	1.24 ± 0.08	0.0000**
Fasting Glucose (mg/dL)	94.59 ± 7.92	93.10 ± 7.20	0.2875
Fasting Insulin (uU/mL)	10.01 ± 4.79	13.69 ± 8.57	0.0043**
HOMA-IR	2.84 ± 3.83	3.16 ± 2.06	0.5769
Total Cholesterol (mg/dL)	168.05 ± 40.11	171.23 ± 30.08	0.6293
HDL-c (mg/dL)	39.25 ± 7.70	39.75 ± 7.63	0.7217
Triglycerides (mg/dL)	122.49 ± 86.86	125.05 ± 61.49	0.8559
TG/HDL	3.38 ± 2.80	3.36 ± 2.06	0.9691
ALT (U/L)	25.82 ± 20.38	19.63 ± 11.79	0.0477*
AST (U/L)	25.61 ± 7.39	22.36 ± 5.28	0.0079**
SBP (mm/Hg)	115.26 ± 11.68	113.32 ± 12.10	0.4086
DBP (mm/Hg)	73.02 ± 8.23	70.44 ± 10.26	0.1615

ALT: alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HOMA-IR, homeostatic model assessment-insulin resistance; TG, triglycerides; HDL-c, high density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure. Data shown as mean ± standard deviation and as frequency. The t-test was used to compare mean values. [a]The chi-squared test was used to compare proportions. *p < 0.050, **p < 0.010.

In boys, it has been observed that as ALT concentrations rise, fasting insulin, triglycerides and systolic blood pressure increase concomitantly (p < 0.050). Whereas in girls, ALT increases along with waist circumference and taper index (p < 0.050), as well as BMI, fasting insulin and HOMA-IR (p < 0.010) and decreases with HDL cholesterol (p < 0.010) (Table II).

Table II. Correlations between ALT, anthropometrical and biochemical markers according to sex.				
Variables	Boys (n = 63)		Girls (n = 57)	
	Pearson R	p-value	Pearson R	p-value
Age (years)	0.078	0.552	-0.168	0.212
BMI (kg/m^2)	0.151	0.246	0.351	0.007†
Waist circumference (cm)	0.148	0.256	0.330	0.012*
Conicity index	0.083	0.524	0.296	0.025*
Fasting glucose (mg/dL)	0.070	0.592	-0.067	0.620
Fasting insulin (mg/dL)	0.299	0.020*	0.417	0.001†
HOMA-IR	0.002	0.988	0.387	0.003†
Total cholesterol (mg/dL)	0.211	0.102	-0.213	0.114
HDL-c (mg/dL)	-0.111	0.393	-0.373	0.004†
Triglycerides (mg/dL)	0.262	0.045*	0.085	0.532
TG/HDL-c	0.247	0.060	0.199	0.142
SBP (mm/Hg)	0.320	0.022*	0.197	0.171
DBP (mm/Hg)	0.262	0.063	0.052	0.722

ALT, alanine aminotransferase; BMI, body mass index; HOMA-IR, homeostatic model assessment-insulin resistance; TC, total cholesterol; TG, triglycerides; HDL-c, high density lipoprotein; TG/HDL-c, TG to HDL ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Correlations were estimated using the Pearson correlation coefficient.

*$p < 0.050$, $^{\dagger}p < 0.010$

Discussion

To the best of our knowledge, this is the first study to investigate the association between ALT levels and anthropometrical and biochemical characteristics of adolescents from northeast Brazilian. In boys, ALT was correlated with fasting insulin, triglycerides and systolic blood pressure (SBP). In girls, ALT was correlated with BMI, WC, conicity index, fasting insulin and HDL-c. Thus, we identified a relationship between ALT levels and the diagnostic criteria for MS.

Conicity index, ALT and AST levels were higher in boys when compared to girls. These sex-specific differences are in agreement with previous studies [4, 20]. Girls showed higher stages of sexual maturation and fasting insulin values. In this context, there is a consensus that higher insulin levels are

related to body fat distribution. Higher accumulation of fat in central areas, referred to as visceral body fat, triggers a decrease in insulin action and, consequently, hyperinsulinemia. Thus, in addition to excess weight, the pubertal stage can also lead to metabolic changes [21–24].

The percentage of boys and girls with ALT over the maximum limit was 20.6% and 29.8%, respectively. There is conflicting literature on the proportion of individuals with increased ALT activity, which can be attributed to different cutoff points for this age group [25, 26]. The cutoffs for ALT of 22 mg/dl for girls and 26 mg/dl for boys, used in this study have been recommended due to being more accurate and sex-specific and were determined and validated using a representative and diverse sample.[4] A study assessing obese Japanese adolescents' hepatic enzymes found alteration in 16.3% of the studied boys and 5.3% of the girls [10].

It is well established that the accumulation of liver fat is intimately related to diagnostic criteria for MS, along with elevated of transaminases values (especially ALT) [4, 27]. This fact was confirmed by our findings, where it was observed that, in boys, higher levels of ALT were related to increases in fasting insulin, triglycerides, and SBP. In line with this, other researchers also found positive correlations between higher ALT quartiles and biochemical and anthropometric variables in boys. The same compensatory mechanism can explain higher insulin values and the accumulation of intrahepatic fat: insulin resistance, mediated especially by the accumulation of visceral fat. When in excess, this tissue leads to chronic, low-grade inflammation due to higher macrophage infiltration, which produces pro-inflammatory cytokines such as TNF-α. These cytokines then decrease insulin action on that tissue [3, 28].

We found that, in both sexes, fasting insulin was correlated with ALT. In girls, there was also a correlation between HOMA-IR and ALT, which indicates the close relationship between IR and NAFLD. It is established that increases in visceral fat decrease adiponectin production, which has anti-inflammatory properties and is crucial to maintaining energetic homeostasis. Low levels of this adipokine and high TNF-α lead to lower insulin sensitivity, creating a state of hyperinsulinemia and IR. When combined with decreased adiponectin, IR contributes to NAFLD development, where the accumulation of liver fat leads to an increase in serum ALT values [3].

Another finding in our study was that, in boys, ALT was correlated with PAS and triglycerides. It was found that high SBP is a possible marker of NAFLD [29, 30]. Increases in SBP are independently associated with an increased risk of NAFLD, and this relationship is more evident in individuals with hypertriglyceridemia. Still, studies show the relationship between increased waist circumference and high blood pressure, aligning the results [31]. Thus, it is recommended that the assessment and control of SBP be included in the monitoring of overweight adolescents [32].

In patients with NAFLD, dyslipidemia is often present as a combination of increased triglycerides and decreased HDL-c. In the male participants of our study, we found a correlation between triglycerides and ALT. In girls, ALT was negatively correlated with HDL-c. Studies that investigated the relationship between

undesirable lipid profiles and NAFLD in overweight children and adolescents have also presented similar findings [14, 33].

We did not find correlations between TG/HDL and ALT in either sex. In boys, however, the correlation was close to the significance margin. Other authors [34] found that individuals with NAFLD presented higher TG/HDL values, which was also directly related to ALT, cholesterol, insulin and HOMA-IR. Again, IR can be observed as the primary mediator of this process, promoting an increased secretion of larger VLDL particles rich in triglycerides, which lowers HDL-c concentrations [35]. The decrease in adiponectin due to an accumulation of visceral tissue lowers HDL-c and increases circulating triglycerides, which increases the TG/HDL ratio [36].

In girls, we found a correlation between ALT levels and all anthropometric parameters assessed in this study. BMI showed the strongest correlation. BMI is considered an important risk factor for NAFLD in adolescents, with excess body fat being highly relevant for the progression of this disease [37]. A study performed on a cohort of Danish children and adolescents found that, across all age ranges, those who were overweight or obese showed elevated ALT [38]. As we previously mentioned, there is an evident relationship between the accumulation and distribution of body fat – mainly in central areas – and NAFLD. Waist circumference (WC) has been used as a tool in NAFLD screening, as increases in WC can predict the risk of this disease in obese adolescents, especially in values above 99 cm [11].

Another group of researchers [39] also found that, in obese adolescents, an increase of 1 cm in WC was associated with a twofold increase in NAFLD risk. We also found a positive correlation between ALT and conicity index, which is obtained from WC, weight and height. Previous studies have found a relationship between conicity index, IR and obesity, which highlights the efficacy of this measure as a predictor of NAFLD [12]. Anthropometric measurements are low-cost and easily applicable in clinical settings. Thus, they can be implemented in the clinical screening of populations at risk of cardiovascular diseases, especially those who are obese.

Our study presents some limitations, such as the fact that the cross-sectional design does not identify a cause-and-effect relationship between ALT and the studied anthropometric and metabolic variables. We also did not use imaging tests to screen for NAFLD, which is considered the most accurate. However, even though it is an indirect measure of hepatic injury, we highlight that ALT is an accessible and practical way to track the progression of NAFLD, being one of the most widely used methods in clinical practice. Our study found that using BMI, waist circumference, and conicity index measurements can be reliable techniques to estimate increases in ALT, a risk factor for developing hepatic steatosis in overweight and obese adolescents, especially girls.

Conclusions

Important correlations between serum ALT values and cardiovascular risk markers were identified in overweight adolescents, suggesting a possible low-cost application to assess the risk of

developing NAFLD. Identifying new measures that can identify and/or suggest NAFLD in this population is crucial to preventing this disease and improving patients' prognostics.

Abbreviations

NAFLD - Non-Alcoholic Fatty Liver Disease

IR- Insulin Resistance

TG - Triglyceride

HDL - High-density lipoprotein

VLDL - Very-low-density lipoprotein

ALT - Alanine Aminotransferase

WC - Waist Circumference

HUOL - Onofre Lopes University Hospital

WHO - World Health Organization

BMI - Mass Index Body

CI - Conicity Index

OGTT - Oral Glucose Tolerance Test

HOMA-IR - Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)

AST - Aspartate Aminotransferase

SBP - Systolic Blood Pressure

Declarations

Ethics approval and consent to participate

The project was approved by the Research Ethics Board of the Onofre Lopes University Hospital (HUOL) of the Federal University of Rio Grande do Norte, Natal, Brazil (reference number: 56763716.7.0000.5292).

Consent for publication

Consent forms were adequate with the regional language, age range and objective of the study. Informed consent was provided by the participants and their parents and/or guardians.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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Authors' contributions

SCVC Lima, worked on research design, text design, data analysis and final writing. MEB Silva participated in the collection, analysis and interpretation of data and article writing . JB Pimentel assisted in data collection and final review. ABR Pinheiro worked on data collection and article writing. EPS Araújo and AA Rezende participated in the research design and data collection. PRM Azevedo participated in the analysis and interpretation of the data. MMGD Lopes and BLL Maciel Collaborated in the text conception, critical review and final draft. RF Arrais cooperated in data collection. All authors read and approved the final manuscript.

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