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Association of elevated serum alanine aminotransferase with metabolic factors in obese children: sex-related analysis

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Abstract

Alanine aminotransferase (ALT) elevations are considered a surrogate marker of nonalcoholic liver disease and predict later development of diabetes and metabolic syndrome in adults. The aim of the present study is to evaluate the prevalence of high ALT levels in obese children using updated and sex-related cutoff ALT value (ALT >30 IU/L for boys and >19 IU/L for girls). We also analyzed the association between ALT levels and metabolic factors in the 2 sexes. Three-hundred fifty-eight obese children (168 boys and 190 girls; age range, 6-16 years) were studied. Inclusion criteria were as follows: *obesity*, defined by an individual body mass index (BMI) greater than or equal to the 95th percentile for age and sex; negativity of markers for viral hepatitis; and no alcohol consumption. Two hundred six nonobese children (92 boys and 114 girls; age range, 6-16 years) served as a control group for ALT levels. The percentage of obese children with elevated ALT was 36% in boys and 55% in girls. Obese boys with ALT greater than 30 IU/L showed higher mother's BMI ($P < .025$), BMI, waist circumference, insulin resistance evaluated with homeostasis model assessment (HOMA-IR) index ($P < .0001$, for all), and systolic and diastolic blood pressure ($P < .025$, for both) compared with those with ALT not exceeding 30 IU/L. The ALT levels correlated positively with mother's BMI, BMI, waist circumference, HOMA-IR, triglycerides, and blood pressure. In linear regression analysis, waist circumference was the only independent factor associated with ALT level ($\beta = 0.370$, $t = 3{,}905$, $P < .0001$). Obese girls with ALT greater than 19 IU/L exhibited lower age ($P < .025$) and higher triglycerides ($P < .0001$) than girls with ALT not exceeding 19 IU/L. The ALT levels correlated positively with triglycerides and HOMA-IR and negatively with age and Tanner stage. In linear regression analysis, ALT levels were independently associated only with triglycerides ($\beta = 0.330$, $t = 4.588$, $P < .0001$). Our study shows that a high proportion of obese children present elevated ALT levels. This abnormality is associated in boys, more than in girls, with preclinical traits of the metabolic syndrome. The adoption of sex-related cutoff of ALT levels is desirable also for the pediatric population.

1. Introduction

In the absence of other causes of liver disease, an unexplained elevation in alanine aminotransferase (ALT) is commonly considered a surrogate marker of nonalcoholic fatty liver disease (NAFLD). Nonalcoholic fatty liver disease is characterized by fat infiltration of the liver that can evolve into steatohepatitis, fibrosis, and eventually cirrhosis [1]. Several studies have shown that NAFLD is strongly associated with obesity, type 2 diabetes mellitus, and the metabolic syndrome; therefore, it is now viewed as an insulin resistance–related liver disease [1-4].

The worldwide epidemic of childhood obesity has raised interest in NAFLD in the pediatric population [5,6]. A postmortem examination performed in children aged 2 to 19 years reported a 10% prevalence of fatty liver, which dramatically increases to 38% in obese children [7]. Recent studies have shown that obese children with modest elevations of ALT present several metabolic abnormalities, such as deterioration in insulin sensitivity and glucose tolerance, hypertriglyceridemia, and hypoadiponectinemia [8,9]. In addition, ALT elevation is associated with increased

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intrahepatic fat accumulation measured by magnetic resonance imaging [9]. Most of the available studies have used a cutoff of greater than 40 IU/L to define high ALT level regardless of sex [10,11]. However, adopting the same normal limits for both sexes may not be adequate because, in the general population, the levels of liver enzymes are higher in males than in females. On this basis, recent studies have proposed different upper limits of ALT for the 2 sexes in the adult population, that is, 30 IU/L for men [12,13] and 19 IU/L for women [12]. The question of analyzing ALT elevation by sex has important clinical implication given the significance of ALT elevation not only as a marker of liver injury but also as a predictor of metabolic diseases [14,15]. In the present study, we examined the prevalence of elevated ALT in a large cohort of obese children using updated upper limits of ALT levels. In addition, the metabolic characteristics associated with ALT elevation in the 2 sexes were evaluated.

2. Population and methods

2.1. Participants

The study population included 358 obese children—168 boys and 190 girls, with an age range of 6 to 16 years—consecutively observed among subjects attending the Outpatient Unit of the Pediatric Department of Pozzuoli Hospital in the period 2003-2007. Inclusion criteria were as follows: *obesity*, defined by an individual body mass index (BMI) greater than or equal to the 95th percentile for age and sex [16]; negativity of markers for viral hepatitis; and no alcohol consumption.

Two hundred six nonobese children comparable for age and sex distribution to the obese group served as a control group for ALT levels. These children were enrolled from subjects referred to the Outpatient Unit of the Pediatric Department for allergy-related problems. None of them had a history of hepatic or gastrointestinal disease. The study was approved by the Local Ethics Committee, and informed consent was obtained from the parents of all participants.

2.2. Measurements

Weight was determined to the nearest 0.1 kg on a medical balance; height was measured to the nearest 0.1 cm with a wall-mounted stadiometer. Parental BMI was determined by recall from both parents of obese children. Waist circumference was measured using a flexible tape at the high point of the iliac crest at minimal respiration when the participant was in a standing position [17]. *Sexual maturation* was defined according to Tanner stage for pubic hair (I-V) [18]. *Late puberty status* was defined by Tanner stage IV and V. Blood pressure was measured according to standard criteria [19] at the right arm in the supine position after a 5-minute rest using a clinical sphygmomanometer with an appropriately sized cuff, and a stethoscope placed over the brachial artery pulse; 3 readings were taken 2 minutes apart, and the average value was used in the analyses. *Metabolic syndrome* was defined according to the International Diabetes Federation criteria in subjects older than 10 years [20].

Fasting blood sample was drawn from all participants for determination of biochemical parameters in the centralized laboratory of Pozzuoli Hospital.

Alanine aminotransferase, aspartate aminotransferase (AST), fasting plasma glucose, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and insulin were determined according to standard procedures using a ROCHE analyzer (Modular Analytics Serum Work Area, 68298 Mannheim, Germany). Insulin sensitivity was evaluated by homeostasis model assessment (HOMA-IR) index using a standard formula: fasting insulin (in microunits per liter) × fasting glucose (in millimoles per liter) divided by 22.5.

2.3. Data analysis

Data are expressed as mean ± SD or number (percentage). Given the skewed distribution of plasma insulin, HOMA-IR, triglycerides, ALT, and AST, the statistical analysis of these variables was applied after log transformation. Means were compared by unpaired Student *t* test. χ^2 or Fisher exact test, as appropriate, was used to compare proportions. Pearson correlation was used to evaluate the relation between ALT and clinical and biochemical variables. A linear regression analysis was performed to evaluate which variables were independently associated with ALT levels separately in the 2 sexes. A P value less than .05, 2-sided, was considered statistically significant. Statistical analysis was performed with SPSS for Windows version 13.0 (SPSS, Chicago, IL).

3. Results

The main features of the study samples are reported in Table 1. The obese and control groups were similar for age, sex, and Tanner stage distribution. In the control group, the 95th percentile of ALT levels was 24 IU/L in boys and 19 IU/L in girls (Table 1). Obese children showed higher levels of both ALT ($P < .0001$) and ALT ($P < .001$) compared with nonobese children.

Obese boys showed a lower percentage of subjects in late puberty ($P < .025$); higher values of ALT ($P < .0001$), AST ($P < .0001$), and diastolic blood pressure ($P < .01$); and lower fasting insulin ($P < .025$) and HOMA-IR ($P < .025$) compared with obese girls. No difference was found between the 2 groups with respect to age, BMI, waist circumference, and other metabolic parameters. The percentage of subjects with ALT levels greater than the upper limit was 36% and 55% in obese boys and girls, respectively.

The metabolic characteristics of boys and girls categorized by high and low ALT levels are summarized in Table 2. In the absence of specific cutoff for children, we used the values obtained in adult population—30 IU/L in boys and 19 IU/L in girls—to define the categories of high ALT levels.

Table 1
Features of the control and obese group

	Control group	Obese group	Obese boys	Obese girls
n	206	358	168	190
Male (%)	92 (45)	168 (47)	–	–
Age (y)	10 ± 3	10 ± 3	10 ± 3	10 ± 3
Late puberty (%)	24 (12)	57 (16)	18 (11)	39 (20)*
ALT (IU/L)	15 ± 4	27 ± 16‡	32 ± 19	23 ± 11‡
AST (IU/L)	24 ± 6	26 ± 8†	28 ± 8	23 ± 7‡
BMI (kg/m^2)	17 ± 3	28 ± 5‡	28 ± 5	28 ± 4
Waist circumference (cm)		89 ± 11	90 ± 12	89 ± 11
Mother's BMI (kg/m^2)		27 ± 5	27 ± 5	28 ± 5
Father's BMI (kg/m^2)		28 ± 3	28 ± 3	29 ± 3
Fasting plasma glucose (mg/dL)		86 ± 7	86 ± 7	85 ± 8
Fasting plasma insulin (mU/L)		15 ± 10	14 ± 8	17 ± 12*
HOMA-IR		3.3 ± 2.4	2.9 ± 1.8	3.5 ± 2.7*
Cholesterol (mg/dL)		162 ± 30	161 ± 32	163 ± 29
HDL cholesterol (mg/dL)		51 ± 12	50 ± 11	51 ± 12
Triglycerides (mg/dL)		90 ± 45	88 ± 44	92 ± 46
Systolic blood pressure (mm Hg)		105 ± 11	106 ± 11	105 ± 11
Diastolic blood pressure (mm Hg)		63 ± 10	64 ± 10	62 ± 10†

* $P < .025$.
† $P < .01$.
‡ $P < .0001$.

Boys with ALT greater than 30 IU/L showed higher mother's BMI ($P < .025$); BMI, waist circumference, fasting insulin, and HOMA-IR ($P < .0001$, respectively); and systolic and diastolic blood pressure ($P < .025$, respectively) as compared with those with ALT not exceeding 30 IU/L. The correlation analysis between ALT and the main clinical variables is summarized in Table 3. Among boys, ALT correlated positively with mother's BMI, BMI, waist circumference, HOMA-IR, triglycerides, and blood pressure. Linear regression analysis was performed using ALT level as the dependent variable and all factors significantly associated with ALT by univariate analysis as independent variables. Waist circumference was the only factor independently associated with ALT level ($\beta = 0.370$, $t = 3{,}095$, $P < .001$).

Girls with ALT greater than 19 IU/L exhibited lower age ($P < .025$) and percentage of subjects in late puberty ($P < .05$), and higher triglycerides ($P < .0001$) than girls with ALT not exceeding 19 IU/L. The ALT levels correlated positively with triglycerides and HOMA-IR and negatively with age and Tanner stage (Table 3). In linear regression analysis, the ALT level was independently associated only with triglycerides ($\beta = 0.330$, $t = 4.588$, $P < .0001$).

Table 3
Correlation analysis between ALT levels and clinical variables in obese boys and girls

	All subjects	Boys	Girls
Age	−0.036	0.107	−0.162†
Tanner stage	−0.074	0.116	−0.185†
BMI	0.141‡	0.295‖	−0.036
Mother's BMI	0.101	0.305§	−0.065
Diastolic blood pressure	0.076	0.248§	−0.120
HOMA-IR	0.180§	0.285‖	0.167†
Systolic blood pressure	0.129†	0.255§	−0.047
Triglycerides	0.222‖	0.168*	0.353‖
Waist circumference	0.159‡	0.289‖	−0.012

* $P < .05$.
† $P < .025$.
‡ $P < .01$.
§ $P < .001$.
‖ $P < .0001$.

Table 2
Anthropometric and metabolic data in boys and girls according to ALT levels

ALT levels	Boys		Girls	
	≤30 IU/L	>30 IU/L	≤19 IU/L	>19 IU/L
n (%)	107 (64)	61 (36)	86 (45)	104 (55)
Age (y)	10 ± 2	11 ± 3	11 ± 3	10 ± 3†
Late puberty (%)	10 (9)	8 (13)	24 (23)	15 (18)*
BMI (kg/m^2)	27.0 ± 3.5	30.0 ± 5.8§	28.2 ± 4.0	28.1 ± 4.5
Waist circumference (cm)	87.8 ± 10.4	93.8 ± 12.8‡	89.1 ± 10.2	88.7 ± 11.3
Mother's BMI (kg/m^2)	26.2 ± 5.0	28.5 ± 5.9†	28.4 ± 5.9	27.0 ± 4.9
Father's BMI (kg/m^2)	27.6 ± 3.0	28.2 ± 3.2	28.6 ± 3.3	28.7 ± 3.6
Fasting plasma glucose (mg/dL)	86 ± 6	87 ± 7	85 ± 8	85 ± 8
Fasting plasma insulin (mU/L)	12 ± 6	17 ± 10§	16 ± 12	17 ± 12
HOMA-IR	2.5 ± 1.3	3.7 ± 2.3§	3.4 ± 2.9	3.6 ± 2.6
Cholesterol (mg/dL)	160 ± 31	164 ± 33	159 ± 25	167 ± 31
HDL cholesterol (mg/dL)	51 ± 10	48 ± 12	51 ± 12	52 ± 13
Triglycerides (mg/dL)	82 ± 38	97 ± 53	82 ± 38	101 ± 51†
Systolic blood pressure (mm Hg)	105 ± 11	109 ± 11†	105 ± 12	104 ± 11
Diastolic blood pressure (mm Hg)	63 ± 9	67 ± 10†	63 ± 11	62 ± 9
Metabolic syndrome (%)	2/60 (3)	1/40 (2)	1/54 (2)	3/57 (5)

* $P < .05$.
† $P < .025$.
‡ $P < .01$.
§ $P < .0001$.

4. Discussion

Our study examined the distribution of elevated ALT in obese boys and girls using sex-related cutoff of normality of ALT levels. We found that, in obese boys, ALT elevation is associated with several features of the metabolic syndrome, such as central adiposity, insulin resistance, and higher levels of blood pressure, whereas, in girls, elevated ALT level is mainly associated with triglycerides.

The impact of sex on the levels of liver enzymes has been analyzed in adolescents in the National Health and Nutrition Examination Survey III survey [21], but has been little explored in childhood obesity [10,22,23]. A study performed on a school-based sample of obese adolescents reported a higher prevalence of abnormal ALT in boys (44%) than in girls (7%), using a cutoff of 40 IU/L for both sexes [10]. In our study, the prevalence of elevated ALT was 36% in boys and 55% in girls, values quite different from those reported by Schwimmer et al [10]. The discrepancy may be due to the fact that Schwimmer et al used the same cutoff for both sexes. Moreover, the limit of 40 IU/L was derived from a so-called normal population that may have included subjects with NAFLD, with the consequence that the threshold of normality was falsely elevated. More recent studies performed in adult populations have differentiated the normal limit of ALT by sex, setting upper limits for ALT levels at 30 IU/L for men [12,13] and at 19 IU/L for women [12]. To date, normal limits of ALT for the pediatric population have not been established. In the absence of normal values for children, in the present study, we used the cutoff proposed for the adults (reported above). On the other hand, it is worth noting that these values are very close to those of the 95th percentile of our control boys and girls.

Similarly to adulthood obesity, ALT elevation in obese children is associated with features of the metabolic syndrome [10,24]. However, given the lack of sex-related data, it is not known whether the metabolic profile associated with ALT elevation is different in the 2 sexes. To the best of our knowledge, our study is the first one to analyze the impact of sex on the relation between ALT levels and the main factors of the metabolic syndrome. We found that ALT elevation is closely associated with central adiposity, insulin resistance, and blood pressure in obese boys, whereas, in obese girls, ALT elevation is mainly associated with triglycerides.

The reasons behind this different pattern are not immediately clear. A possible explanation can be envisaged in the greater accumulation of central fat in obese boys. This interpretation is supported by the results of the linear regression analysis showing that waist circumference is an independent predictor of ALT levels in boys. In addition, a post hoc analysis showed that boys with ALT greater than 30 IU/L had significantly higher waist circumference ($P < .01$) than girls with ALT greater than 19 IU/L (data not shown). Interestingly, this group also presented higher systolic ($P < .025$) and diastolic ($P < .01$) blood pressure, thus displaying some typical traits that predate the metabolic syndrome. On the other hand, it is well known that central adiposity clusters with factors of the metabolic syndrome in both adults and children [25,26]. In addition, it should be kept in mind that, in boys, regardless of age and pubertal status, adiponectin levels are lower than those in girls [27] and that low adiponectin is associated with higher waist circumference, particularly in boys [28]. This could contribute to explain the stronger association of elevated ALT with components of the metabolic syndrome in boys than in girls. This association appears to be independent of age and pubertal status.

The finding of a close relation between ALT levels and maternal BMI observed in boys deserves a comment. This is in line with the study of Kazumi et al [29] showing that, in young men aged 18 to 20 years, BMI, waist circumference, insulin resistance, and liver enzymes were positively related with the mother's BMI but not the father's. The authors interpreted this finding as a result of the fact that mitochondrial DNA, which regulates energy expenditure, is maternally inherited. Associations of the mother's BMI with the son's liver enzymes may be compatible with the fact that aminotransferase reactions are associated with the citric acid cycle, which takes place in the mitochondria.

Seven children of our cohort (3.3%) met the criteria recently proposed by the International Diabetes Federation for the definition of the metabolic syndrome in children older than 10 years. This low prevalence did not allow us to quantify the risk of the metabolic syndrome related to ALT elevation. However, because in childhood obesity elevated ALT is linked to subclinical manifestations of the metabolic syndrome, particularly in boys, the suggestion is that ALT levels greater than the cutoff levels be viewed as a warning signal prompting intervention to reduce excess weight.

A potential limitation of the present study is the cross-sectional design of the study that does not allow us to evaluate the potential impact of ALT levels on the progression of the metabolic abnormalities. Longitudinal monitoring of these children will clarify this issue. Another limitation is that only pubic hair was used for Tanner staging, which may reduce the accuracy of sexual development staging in obese subjects where premature adrenarche is more common. Finally, our control group came from a population of children with allergy-related problems; however, all of them had a negative history of liver disease.

In conclusion, using updated and sex-related ALT cutoff values, we found that a high proportion of obese children present elevated ALT levels. This abnormality is associated, in boys more than in girls, with some preclinical traits of the metabolic syndrome, thus underscoring the need for early preventive strategies against obesity in children. Like in adults, it is advisable to introduce sex-related cutoff of ALT levels also for children. Prospective studies will verify the predictive power of these limits.

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