

Association of Serum Alanine Aminotransferase Levels with Cardiometabolic Risk Factors in Normal-Weight and Overweight Children

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Abstract

Objective: This study aimed to determine the prevalence of increased alanine aminotransferase (ALT), defined by a gender-specific cutoff value, among normal weight and overweight children; and to assess the relationship of increasing ALT levels with cardiometabolic risk factors.

Methods: This cross-sectional study was conducted among school students, aged 6-18 years in Isfahan, Iran. Based on the body mass index (BMI) percentiles, a group of normal-weight was compared with a group of overweight and obese students. Gender differences were considered for increased levels of ALT, i.e. 19U/L and 30U/L for girls and boys respectively.

Findings: The study participants consisted of 1172 students (56.2% girls), with a mean (SD) age of 12.57 (3.3) years. Among overweight/obese students the mean triglycerides (TG) and diastolic blood pressure was significantly higher in those with increased ALT than in those with normal ALT levels. The logistic regression analysis showed that among overweight/obese boys, for each 1 unit increase in ALT, the odds ratio (OR) of TG, total cholesterol and systolic blood pressure increased significantly. After adjusting for age, these associations remained significant, and the OR of high density lipoprotein cholesterol (HDL-c) decreased significantly. In the model adjusting for age and BMI, the ORs of TG and HDL-c remained significant. After adjusting for age and waist circumference, HDL-c was the only parameter with significant OR. Among overweight/obese girls, in all models applied, the OR was significant for TG and total cholesterol. A significant independent association was documented for waist circumference and increase in ALT after adjustment for BMI.

Conclusion: This study documented significant relationship of increased ALT levels, defined by a gender-specific cutoff point, with cardiometabolic risk factors and hypertriglyceridemic-waist phenotype in Iranian children and adolescents.

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Key Words: Cardiometabolic Risk Factors; Fatty Liver; Children; Prevention

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Introduction

Childhood obesity is increasing in developed and developing countries [1-3]. It is not only a public health problem, but also a clinical problem by its complications on different body organs.

Metabolic syndrome (MetS) and non- alcoholic fatty liver disease (NAFLD) are some of these health consequences [4,5]. MetS is a clustering of risk factors associated with chronic inflammation, insulin resistance, endothelial dysfunction, and cardiovascular diseases [6,7]. There is a growing body of evidence about the correlation of MetS with NAFLD [8-10].

It is suggested that fat accumulation in liver can predispose one to metabolic disorders and dyslipidemia [11]. Considering the long-term effects of NAFLD [12-15], the prevention, screening and controlling NAFLD from early life should be underscored [16]. Although liver biopsy is the gold standard diagnostic method for fatty liver [17], but given that it is an invasive method, imaging procedures and elevation of liver enzymes are usually used to detect NAFLD in population-based studies [18,19].

A study found serum triglycerides (TG) and alanine aminotransferase (ALT) are appropriate screening markers for suspected NAFLD in obese children and adolescents [20]. Usually in clinical setting, ALT level of 40 IU/L is often deemed as upper limit of the normal range in children. Some studies suggested lower cutoff values of ALT in children than in adults [21,22]. Some researchers also suggested gender differences for these levels, i.e. 19U/L and 30U/L for girls and boys respectively [4,23,24].

This study aimed to determine the prevalence of increased ALT, defined by a gender-specific cutoff value, among normal weight children and adolescents in comparison to their overweight/obese counterparts. The other objective of this study was to assess the relationship of increasing ALT levels with cardiometabolic risk factors.

Subjects and Methods

We have previously described the methods in details [25], herein we present it in brief. In the first

step of this survey, weight and height of 7554 randomly selected students, aged 6-18 years, were measured in Isfahan, Iran.

Their body mass index (BMI) was calculated as weight (Kg) divided by height squared (m^2), then they were categorized into three groups of normal weight, overweight and obese based on the BMI charts of the US centers for disease control and prevention [26]. A random sample was selected from each BMI group, and students were included in the study after obtaining written informed consents from parents and oral assents from students.

In addition to physical examination, fasting blood glucose, serum lipid profile and liver enzymes were determined among 1107 students.

ALT levels higher than 19U/L and 30U/L were considered as abnormal for girls and boys, respectively [4,23,24]. The pediatric metabolic syndrome was defined based on the modified criteria of the Adult Treatment Panel III consisting of 1) fasting TG >100 mg/dL; 2) HDL-C <50 mg/dL (except in boys aged 15-18 y, in whom the cut-off was <45 mg/dL); 3) waist circumference >75th percentile for age and gender in the population studied; 4) systolic/diastolic blood pressure >90th percentile for gender, age and height; and 5) fasting blood glucose (FBG) >100 mg/dL [27,28].

Statistical analysis: Data were analyzed by SPSS statistical software version 17.0 (SPSS Inc, Chicago, IL., USA) using Analysis of variance (ANOVA) and logistic regression analyses. In the latter analysis, each 1 unit increase in ALT was considered as an independent factor and other variables as dependent ones. Four models were applied: the first model was unadjusted; the second was adjusted for age, the third for age and BMI, and the fourth was adjusted for age and waist circumference (WC).

Findings

The study participants consisted of 1172 students (56.2% girls), without significant difference in the mean age of girls and boys (12.6 ± 3.3 vs. 12.3 ± 3.1 years, respectively).

Overall, 38.3% of boys were normal weight and 61.7% were overweight and obese; the

Table 1: Characteristics of study population (n=1172) according to weight status

Parameters	Boys (43.8 %)		Girls (56.2%)	
	Normal weight (38.3%)	Overweight & obese (61.7%)	Normal weight (41.1%)	Overweight & obese (58.9%)
Age (years)	12.7 (3.3)	12.7 (2.9)*	12.2 (3.5)	12.9 (3.1)*
Body mass index(kg/m ²)	16.4 (2.5)	25.36.8 (4.1)*	16.9 (3.0)	24.8 (3.0)*
Waist circumference(cm)	65.4 (8.3)	88.4 (11.7)*	67.8 (9.3)	86.5 (10.5)*
Systolic blood pressure (mmHg)	97.8 (12.3)	109.0 (15.7)*	97.8 (13.9)	105.5 (13.6)*
Diastolic blood pressure (mmHg)	60.2 (9.1)	66.0 (10.7)*	61.8 (9.1)	65.2 (10.5)*
Fasting blood glucose (mg/dl)	82.7 (8.8)	82.7 (8.8)	81.2 (8.2)	82.7 (11.2)
Triglycerides(mg/dl)	93.0 (37.5)	126.1 (66.4)*	154.7 (87.8)	105.3 (45.7)*
Total cholesterol(mg/dl)	82.7 (8.8)	175.0 (33.5)*	164.4 (27.2)	174.9 (31.1)*
HDL-cholesterol(mg/dl)	48.6 (11.7)	43.4 (9.8)*	47.7 (10.7)	44.6 (10.1)*
LDL-cholesterol(mg/dl)	90.4 (21.6)	107.3 (27.9)*	96.7 (24.4)	106.2 (26.7)*
Alanine aminotransferase (U/l)	16.2 (6.7)	24.5 (11.4)*	15.7 (8.4)	19.65 (10.1)*

ALT: Alanine Aminotransferase (U/L) / HDL-C: High Density Lipoprotein Cholesterol / LDL-C: Low Density Lipoprotein Cholesterol

*P. value <0.05

corresponding figure for girls was 41.1% and 58.9%, respectively. Except FBG, all other variables studied were significantly higher in overweight and obese group than in their normal-weight counterparts.

Table 2 presents the mean values of variables studied in normal- and overweight/obese groups with normal or increased values of ALT [4,23,24]. Among overweight/obese students, the mean BMI, WC, TG and diastolic blood pressure was

Table 2: Anthropometric and metabolic data in boys and girls according to serum levels of alanine aminotransferase

Parameters	Normal weight (n=448)				Overweight and obese (n=673)			
	Boys (n=183)		Girls (n=255)		Boys (n=303)		Girls (n=370)	
	ALT ≤30 (n=177)	ALT >30 (n=9)	ALT ≤19 (n=203)	ALT >19 (n=52)	ALT ≤30 (n=236)	ALT >30 (n=67)	ALT ≤19 (n=214)	ALT >19 (n=156)
Age (y)	11.6 (3.3)	13.0 (2.9)	12.2 (3.5)	12.1 (3.4)	12.7 (3.0)	12.7 (2.6)	13.2 (3.1)	12.5 (3.07)
Body Mass Index (kg/m ²)	16.3 (2.3)	18.0 (2.5)*	16.8 (3.1)	17.1 (2.8)	12.9 (3.9)	27.1 (4.4)*	24.2 (3.9)	25.6 (3.8)*
Waist circumference (cm)	64.9 (7.7)	71.5 (8.2)*	67.4 (9.4)	68.8 (9.2)	87.0 (11.1)	93.1 (12.5)*	87.1 (10.3)	88.5 (10.5)*
Systolic Blood Pressure (mmHg)	97.6 (12.4)	97.1 (11.1)	98.1 (14.3)	97.0 (11.9)	107.8 (15.8)	112.7 (15.3)	105.9 (14.2)	105.0 (12.8)
Diastolic Blood Pressure (mmHg)	60.2 (9.2)	60.0 (7.6)	62.1 (9.07)	60.6 (9.2)	65.1 (10.0)	68.7 (12.3)*	66.0 (11.1)	64.2 (9.6)
Fasting Blood Glucose (mg/dl)	82.3 (8.6)	88.1 (12.2)	81.3 (8.3)	80.7 (7.9)	83.2 (8.4)	85.0 (8.27)	82.1 (12.5)	83.6 (9.1)
Cholesterol (mg/dl)	156.4 (25.0)	159.4 (21.6)	163.9 (27.1)	167.6 (27.9)	172.2 (34.1)	184.9 (30.22)	172.1 (32.5)	178.9 (29.0)*
HDL-C (mg/dl)	89.8 (21.8)	12.5 (88.4)	95.8 (24.2)	101.6 (24.2)	106.1 (28.5)	111.4 (25.72)	104.1 (27.4)	109.3 (25.6)
LDL-C (mg/dl)	48.9 (11.5)	46.1 (16.9)	48.6 (11.2)	44.3 (8.3)*	43.1 (9.8)	44.3 (9.9)	44.8 (9.5)	44.2 (10.9)
Triglycerides (mg/dl)	92.6 (37.5)	97.0 (43.6)	97.8 (40.1)	104.8 (46.1)	120.6 (63.2)	145.7 (67.7)*	117.5 (65.9)	133.7 (63.3)*

ALT: alanine aminotransferase (U/L) / HDL-C: High Density Lipoprotein Cholesterol / LDL-C: Low Density Lipoprotein Cholesterol

*P. value <0.05

Table 3: Logistic Regression analysis for each 1 unit increase in alanine aminotransferase in overweight and obese boys and girls

	Model I			Model II			Model III			Model IV		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Boys												
TG (mg/dl)	1.04	1.02-1.07	<0.001	1.04	1.02-1.07	<0.001	1.03	1.01-1.06	0.01	1.03	1.01-1.06	0.1
HDL (mg/dl)	0.98	0.96-1.01	0.07	0.98	0.95-1.00	0.04	0.97	0.95-1.00	0.02	0.97	0.95-0.99	0.02
LDL (mg/dl)	0.96	0.88-1.04	0.3	0.95	0.87-1.04	0.3	0.95	0.86-1.04	0.3	0.95	0.86-1.04	0.3
T.Chol (mg/dl)	1.02	1.00-1.05	0.02	1.03	1.00-1.05	0.02	1.02	1.00-1.04	0.1	1.02	1.00-1.04	0.1
FBG (mg/dl)	0.99	0.94-1.05	0.8	0.99	0.94-1.05	0.8	0.99	0.93-1.05	0.7	0.99	0.93-1.05	0.7
SBP (mmHg)	1.04	1.01-1.07	0.01	1.04	1.01-1.07	0.01	1.02	0.99-1.05	0.2	1.01	0.98-1.05	0.4
DBP (mmHg)	1.03	0.98-1.09	0.2	1.04	0.98-1.10	0.2	1.03	0.96-1.09	0.4	1.03	0.97-1.10	0.3
WC (cm)	1.03	0.98-1.07	0.3	1.03	0.98-1.08	0.2	0.97	0.93-1.03	0.3	0.96	0.90-1.02	0.2
Girls												
TG (mg/dl)	1.04	1.02-1.07	<0.001	1.04	1.02-1.07	0.002	1.03	1.01-1.06	0.009	1.03	1.01-1.06	0.009
HDL (mg/dl)	1.01	0.99-1.05	0.3	1.01	0.99-1.04	0.3	1.01	0.99-1.04	0.5	1.01	0.98-1.04	0.4
LDL (mg/dl)	0.96	0.88-1.06	0.5	0.97	0.88-1.06	0.5	0.95	0.85-1.05	0.3	0.95	0.86-1.06	0.4
T.Chol (mg/dl)	1.03	1.01-1.05	0.01	1.03	1.01-1.05	0.01	1.02	1.00-1.05	0.05	1.02	1.00-1.05	0.04
FBG (mg/dl)	1.02	0.99-1.07	0.2	1.03	0.99-1.07	0.2	1.62	0.98-1.07	0.3	1.02	0.98-1.07	0.3
SBP (mmHg)	1.01	0.96-1.05	0.8	1.00	0.96-1.05	0.8	0.99	0.99-1.05	0.8	0.99	0.95-1.05	0.9
DBP (mmHg)	0.98	0.91-1.07	0.7	0.99	0.91-1.07	0.7	0.93	0.81-1.07	0.3	0.97	0.87-1.08	0.5
WC (cm)	1.00	0.95-1.05	0.9	1.00	0.95-1.04	0.8	0.95	0.90-0.99	0.02	0.92	0.85-0.99	0.02

Model I: unadjusted; Model II: adjusted by age; Model III: adjusted by BMI and age; Model IV: adjusted by waist and age

OR: Odds Ratio / CI: Confidence Interval / P: P value / SBP: Systolic Blood Pressure / DBP: Diastolic Blood Pressure / TG: Triglyceride/ T.Chol: Total Cholesterol/ HDL: High Density Lipoprotein/ LDL: Low Density Lipoprotein / FBG: Fasting Blood Glucose / WC: Waist Circumference

significantly higher in the overweight/obese group with increased ALT than in those with normal ALT levels.

In overweight/obese boys, the mean BMI, WC and TG increased significantly across the quartiles of ALT; among girls, this increase was also significant for FBG, total cholesterol and low density lipoprotein cholesterol (LDL-c) (Fig. 1).

Table 3 demonstrates the results of the logistic regression analysis for each 1 unit increase in ALT as an independent factor and others as dependent variables. Among normal-weight students, the only significant association was documented for WC in girls in the model adjusted for age and BMI. Among overweight/obese boys, for each 1unit

increase in ALT, the ORs of TG, total cholesterol and systolic blood pressure increased significantly.

After adjusting for age, these associations remained significant, and the OR of high density lipoprotein cholesterol (HDL-c) decreased significantly. In the model adjusting for age and BMI, the ORs of TG and HDL remained significant. After adjusting for age and WC, HDL was the only parameter with significant OR. Among overweight/obese girls, in all models applied, the OR was significant for TG and total cholesterol. A significant independent association was documented for WC and increase in ALT after adjustment for BMI.

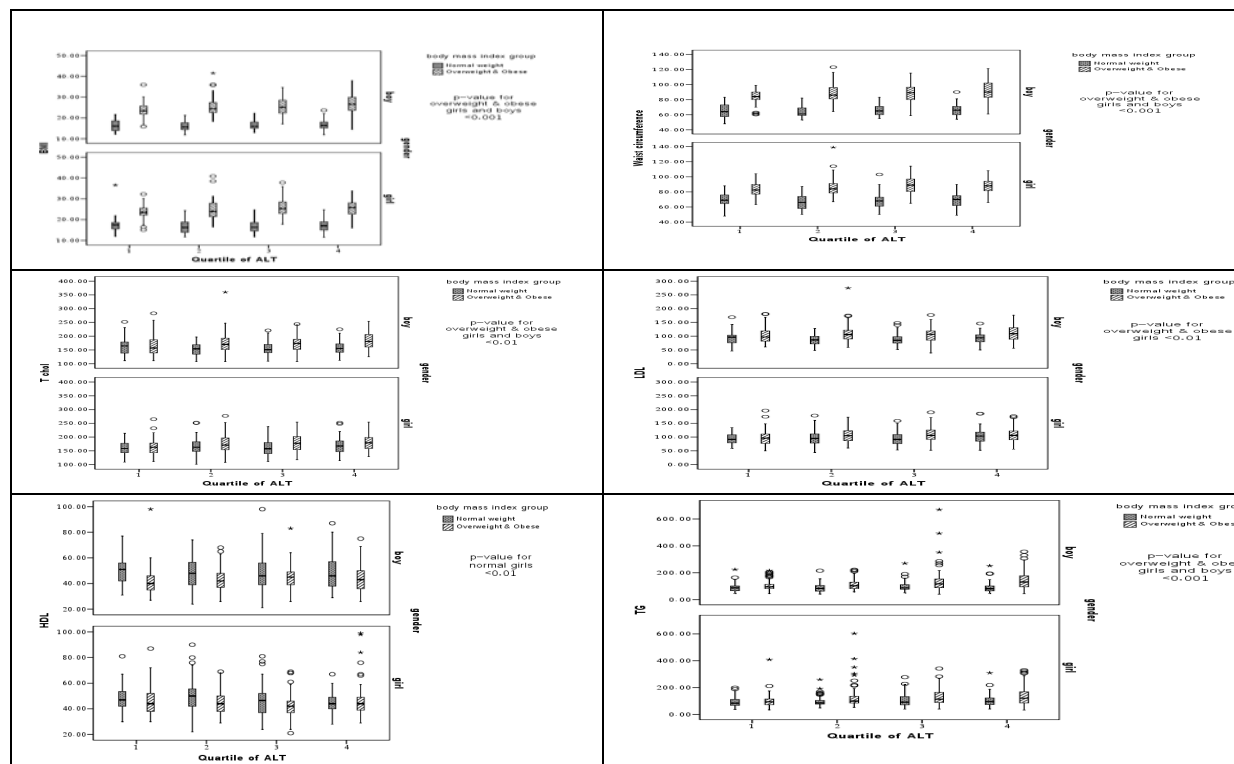


Fig. 1: Comparison of variables studied in normal-weight vs. overweight and obese girls and boys according to alanine aminotransferase quartiles

Discussion

This study confirmed significant association of ALT levels to cardiometabolic risk factors in children and adolescents.

Although the cutoff values used to determine the increased ALT levels were different in our study with a study conducted among Korean teenagers [15], but the findings of the two studies are consistent with each other. Both studies showed significant association of increased ALT with abdominal obesity, high TG and low HDL-C; i.e. the components of the metabolic syndrome.

By using same cutoff values for ALT in a study conducted among Italian children [23], we found similar associations of increased ALT levels with the components of the metabolic syndrome.

A study among Brazilian children documented ALT as a predictive factor for the metabolic syndrome, with increasing ALT levels correlated

with gradual increase in the components of the metabolic syndrome among overweight children [20].

Similar association is documented for increase in ALT and insulin resistance among Korean obese children [29].

These studies conducted in the pediatric age group are in line with studies among adult population. A study in Scottish men showed an association between the increase in ALT levels and the components of the metabolic syndrome.

Moreover, this study revealed that the diabetes risk was 3.38 times higher in men at highest ALT quartile in comparison with those at the lowest quartile [12].

The current findings might be confirmatory evidence for previous studies about the epidemiologic and clinical implication of the hypertriglyceridemic-waist phenotype in children and adolescents [30,31]. Després et al proposed that this phenotype might represent "an altered, dysfunctional, and highly lipolytic adipose tissue that is a major culprit abnormality behind the metabolic syndrome and associated

cardiometabolic risk, independently from classical cardiovascular disease risk factors such as age, sex, and plasma low density lipoprotein (LDL) cholesterol levels"^[32].

Given the association of overweight and lifestyle behaviors with fatty liver^[33,34] and the considerably high prevalence of overweight in our community, even among young children^[35], lifestyle change ^[36]for prevention and control of weight disorders and related complications, as fatty liver, should be underscored.

Study limitations and strengths: The main limitation of this study is its cross-sectional nature. However its strength is its population-based design and its novelty in using gender-specific cutoff values for increased ALT in Iranian children.

Conclusion

This study documented significant relationship of increased ALT levels, defined by a new and gender-specific cutoff point, with cardiometabolic risk factors in Iranian children and adolescents. It underscored the association of hypertriglyceridemic-waist phenotype with increased ALT, as a surrogate marker of fatty liver. These findings should be confirmed in future longitudinal studies.

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Conflict of Interest: None to declare

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