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*Artículo:*




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Original Article

# Frequency of increased aminotransferases levels and associated metabolic abnormalities in obese and overweight children of an elementary school in Mexico City

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## Abstract

**Background:** Elevated ALT is an indirect marker of NAFLD in patients with non-alcohol abuse and without other known causes of chronic hepatitis. Obesity, type 2 diabetes and some dyslipidemias are associated to this condition. The purpose of this study was to determine the frequency of increased aminotransferases and associated metabolic anomalies among overweight and obese children. **Methods:** Children from an elementary school with obesity or overweight were included. Medical history and anthropometrics measurements were recorded and serum liver function tests, lipid profile, glucose and insulin levels, and HOMA index were determined. NAFLD diagnosis was considered in those children with ALT > 40 U/L and AST/ALT ratio < 1 after exclusion of other causes of chronic hepatitis. **Results:** Increase ALT levels (> 40 U/L) were found in 34/80 (42%) obese and overweight children; mean age was  $9.5 \pm 1.1$  years and mean BMI of  $25.8 \pm 3$ . The metabolic abnormalities in the study group were similar, there were no differences in insulin concentration, insulin resistance determined by HOMA-IR Index, serum lipid profile and serum glucose between children with or without increased ALT. **Conclusions:** The frequency (42%) of elevated ALT levels in children with excess

body weight in this study was greater to those reported in other pediatric populations. There were no differences among the metabolic alterations with or without increased ALT; these findings support that the principal pathogenic factor involved in the development of the hepatic injury may be located in the liver.

**Key words:** Non-alcoholic fatty liver disease, insulin resistance, obesity, childhood.

## Introduction

Non alcoholic fatty liver disease (NAFLD) is a common cause of elevated aminotransferases levels, although this entity seems to be a benign disorder, steatosis with fibrosis or cirrhosis has been reported in liver biopsy from adults and children.<sup>1,2</sup> In 650 hepatic biopsies performed in children due to different causes, fatty liver was found in 10.6% and steato-hepatitis in 2%.<sup>3</sup>

The natural history of NAFLD in children is unknown due to the lack of longitudinal studies. Some reports showed that liver histological changes of progression can be observed during infancy, steatosis with fibrosis and cirrhosis has been noted in different studies.<sup>4,5</sup>

NAFLD prevalence determined by ALT elevation in obese children has been reported from 9.5% to 25.5%,<sup>4,6-9</sup> and frequency seems to be higher in those children with hyperlipidemia and type 2 Diabetes.<sup>2,5</sup> Clinically, is a diagnosis of exclusion that should be suspected as cause of chronic hepatitis in patients who deny alcohol consumption and have serologic tests negative for infection and other congenital and acquired causes of liver disease. In most cases diagnosis is done during routine laboratory testing; increased alanine aminotransferase (ALT) and AST/ALT ratio <1 are the predominant laboratory abnormalities.<sup>10</sup>

In Mexico the prevalence of obesity increased in the past decade. According to the national nutritional report of the year 2000, obesity in children was found on 27.2%, in our Country no data is available in relation to NAFLD in obese children.<sup>11</sup>

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The aim of this study was to describe the frequency of elevated ALT levels and associated metabolic abnormalities in overweight and obese children from an elementary school.

## Methods

Children from an elementary school, located in a middle income area of Mexico City were invited to participate. Study design was approved by the Ethics and Investigation Review Board of the Pediatric Hospital, National Medical Center SXXI. Subjects that accepted to participate, informed consent was signed from both, children and their parents or guardians.

Evaluation was done between 8 am to 10 am; a questionnaire was used to obtain information on demographic and medical history. Anthropometric measurements were obtained in 833 children dressed only in light underwear and no shoes. Body weight was measured on a 140-kg capacity floor scale and height was obtained using the floor scale's stadiometer, with the child standing in the center of the scale. Height was measured to the nearest 0.5 cm and body weight to the nearest 0.1 kg. Body mass index (BMI) was calculated as weight (kg) divided by height (m<sup>2</sup>).<sup>12</sup> Abdominal circumference was measured to the nearest 0.1 cm at the level of the greatest frontal extension of the abdomen between the bottom of the rib cage and the top of the iliac crest. The equipments were regularly calibrated using reference samples provided by the manufacturer.

Being overweight was defined as a BMI > 85th percentile and obesity was considered when BMI was > 95th percentile, according to the tables from the Center for Disease Control for children of the same age and gender.<sup>13</sup>

From those children with overweight or obesity who accepted to participate in the study, a 5 ml blood sample was drawn after 9 to 12 hour fasting; serum glucose, AST, ALT, Cholesterol (Ch), and High-density lipoprotein cholesterol (HDL-C) levels were assessed in a chemical analyzer (Ciba Corning Diagnostics, East Walpole, MA). Serum glucose was measured immediately by the Glucose Oxidase Method (Stanbio Laboratory Inc., Boerne, Tx) and cholesterol by the Trinder Method (cholesterol esterase and cholesterol oxidase). For HDL-C, measurement was carried on with Enzymatic Colorimetric Assay after precipitating very low and low-density lipoproteins (VLDL and LDL) with phosphotungstic acid in presence of magnesium. Reference values for lipids were taken from the NCEP.<sup>14</sup>

Plasma insulin concentrations were determined by a Double-antibody RIA Technique (Cis Bio International, Gif-sur-Yvette, France). The intraassay and interassay coefficients of variations were < 5% and 9% respectively. Insulin resistance was calculated using the homeostasis model assessment (HOMA) method. HOMA-IR estimate insulin resistance using both plasmatic insulin and glucose calcu-

lated as follows: (Fasting serum insulin [ $\mu$ U/dL]) (fasting serum glucose [mmol/dL])/22.5. Normal HOMA-IR range was considered when index was < 2.5.<sup>15,16</sup>

NAFLD diagnosis in those obese and overweight children was determined when ALT was > 40 U/L,<sup>3</sup> and AST/ALT ratio < 1; in all obese and overweight cases with or without elevated ALT other causes of chronic hepatitis were excluded by the determination of Viral Hepatitis panel: anti-HCV (ORTHO HCV 3.0, Elisa Test), HBsAg (Hepanostika HBsAg Uni-Form II Lab Biomerieux); autoimmune test for autoantibodies against cell nuclei (ANA), anti-smooth muscle anti body and antimitochondrial antibody by indirect immunofluorescence test (EU-ROIMMUN) and serum ceruloplasmin by immunochemical reaction (N Antisera to human ceruloplasmin, Normal range: 0.2-0.6 g/L Dade Behring). History of use of medication known to precipitate steatosis, alcohol abuse, total parenteral nutrition (TPN) administration, abdominal surgery and Diabetes history data were investigated.

Statistical Analysis. Data was expressed as mean values  $\pm$  Standard Deviation (SD), Mann Whitney U test was used to compare children with and without abnormal ALT, p value < 0.05 was considered statistically significant. The analysis was done using the SPSS program version 10 for Windows (SPSS Inc. Chicago Il).

## Results

From 833 children, aged 6 to 12 years screened by BMI, 125 children were found to be overweight and obese and 87 accepted to participate in the study. Elevated ALT (> 40 U/L) and AST/ALT ratio < 1 was found in 41/87 cases; TPN administration, surgery, both drug and alcohol abuse history were negative in all cases. Serum ceruloplasmin levels were normal, autoimmune markers negative and Anti-HCV negative in 87 cases. Hepatitis Virus B infection was found by positive HBsAg on 7/87 children who were excluded from the study.

Eighty children were included with and without elevated ALT, 64 (80%) were obese and 16 (20%) overweight, the mean age was  $9.5 \pm 1.15$  years, 44 (55%) were male, mean BMI was  $25.8 \pm 3$ . Type 2 Diabetes family history was positive in 19/34 (55%) in the group of children with altered ALT versus 35/46 (76%) in those without abnormal ALT. Increase ALT levels were found in 34/80 (42%), all were asymptomatic; there was no difference in age, gender, height and abdominal circumference between those with normal and abnormal ALT. Weight and BMI measurements were significantly higher in those with ALT > 40 U/dL (*Table I*).

Increased insulin concentrations and high HOMA-IR scores were found in 79/80 (98%) overweight and obese children, hypercholesterolemia (> 180 mg/dL) and hypertriglyceridemia (> 80 mg/dL) were detected in 46% (37/80) and 73% (59/80) of cases respectively and fasting hyperglycemia (> 100 mg/dL) in 4 (4.5%).

**Table I.** Demographic and clinical features of 80 obese and overweight children.

Parameter	ALT > 40 U/L n = 34	ALT < 40 U/L n=46
Mean age (yrs)	9.6 ± 0.9	9.4 ± 1.2
Gender (male/female)	22/12	22/24
Weight (kg)*	52.1 ± 1	48.2 ± 2
Height (cm)	140.4 ± 9	139 ± 9
BMI (kg/m <sup>2</sup> )*	26.2 ± 4	24.6 ± 3
Abdominal circumference (cm)	85.6 ± 9	81.5 ± 8

Data are presented as mean ± standard deviation

\* p &lt; 0.05 (Mann Whitney U Test)

**Table II.** Metabolic parameters in 80 obese and overweight children.

Parameter	ALT > 40 U/L n = 34	ALT < 40 U/L n = 46
Insulin (μU/dL)	49.5 ± 28.5	42.1 ± 23.4
Glucose (mg/dL)	77.9 ± 12.2	81.2 ± 11.5
HOMA-IR	9.51 ± 5.6	8.6 ± 5.0
Cholesterol (mg/dL)	176.5 ± 39	184.2 ± 28
Triglycerides (mg/dL)	141.5 ± 74	128.0 ± 75
HDL-C/(mg/dL)	43.1 ± 7.6	43.1 ± 6.9
LDL-C (mg/dL)	104.1 ± 36	115.4 ± 33
VLDL-C (mg/dL)	28.3 ± 14	25.6 ± 15
AST (U/L)	52.5 ± 31	31.2 ± 5
ALT (U/L)*	57.0 ± 16	33.3 ± 4

Data are presented as mean ± standard deviation

\* p &lt; 0.05 (Mann Whitney U test)

There were no significant differences in the metabolic parameters studied between children with and without elevated ALT. Insulin concentrations 49.5 ± 28 μU/dL vs 42.1 ± 23.4 μU/dL, high HOMA index scores 9.5 ± 5.6 vs 8.6 ± 5.0, total cholesterol 176.5 ± 39 mg/dL vs 184.2 ± 28 mg/dL, HDL-C 43.1 ± 7.6 mg/dL vs 43.1 ± 6.9 mg/dL and triglycerides 141.5 ± 74 mg/dL vs 128.0 ± 75 mg/dL, mean values were similar in both groups (p > 0.05) (Table II).

## Discussion

The frequency of 42% elevated aminotransferases in obese and overweight children found in this study is major from those reported with prevalence from 9.5% to 25.5%,<sup>4,6-9</sup> these differences could be explained by the use of diverse criteria and methods for the diagnosis. Non invasive imaging techniques had been used to estimate prevalence of hepatic steatosis;<sup>8,17,18</sup> using ultrasound among 810 children, fatty liver was found to be 2.6% on those with normal weight increasing up to 22.5% in those with obesity.<sup>6</sup> Steatosis also has been evaluated by MRI; in 22 children with obesity and hepatomegaly, elevated ALT (99 ± 46 U/L) was found in 92%.<sup>17</sup> These radiological modalities are useful to detect fatty liver and increased ALT level could discriminate simple liver steatosis from steatohepatitis. Beside these methods, abnormal

ALT levels have been used to estimate prevalence of NAFLD in the majority of the reports, the most frequently noted is a two to threefold elevation on serum levels of ALT;<sup>1,19</sup> normal values has been established between 10 U/L to 40 U/L in most laboratories.<sup>20</sup> We used this cutoff value, where abnormal range was determined when ALT was > 40 U/L.<sup>3,20</sup> Our results showed a high frequency of obese and overweight children with elevated ALT levels (34/80), due to the cutoff value that was used, the majority of these children, 28/34 cases had elevated ALT levels between 40 to 60 U/L reflecting mild liver inflammation and only 6/34 cases showed more active inflammation (ALT > 60 U/L). It has been reported that values > 2 fold from normal value are found in those with more liver damage; in 17 children with NAFLD biopsy-proven, 53% had fibrosis and cirrhosis, the ALT level was found from 2.2 to 16 times up from the normal range, except in one who had mild elevated ALT (1.6 times up from normal value),<sup>2</sup> this suggested that ALT level > 2 x could help to identify those cases that could have more severe liver damage.

Liver biopsy has not been used by routine to diagnose NAFLD in children, although in case reports studies in which biopsies were performed, a wide spectrum of histopathology abnormalities had been found from mild steatohepatitis to cirrhosis; among 299 obese children, Kinugasha et al, found 36 cases (13%) with elevated ALT and diagnosed steatohepatitis in 11/36 cases who underwent liver biopsy;<sup>4</sup> Rashid et al, studied 36 children with unexplained elevation of aminotransferases, obesity was identified in 83%, liver biopsy was performed in 24 cases showing inflammation in 88% and fibrosis-cirrhosis in 75%.<sup>5</sup> These biopsy findings showed that liver changes with fibrosis could be in up to 50% of the cases without or with few clinical manifestations and challenges like obesity could aware the clinician to suspect NAFLD.

The identification of those cases in risk to develop a major liver damage and evaluate the necessity of liver biopsy has been reported in adults; major age, obesity, type 2 diabetes, insulin resistance, ALT more than twice normal, and AST/ALT ratio > 2<sup>1,21</sup> are potential predictors of NAFLD; in children these associated features and its impact in the development of progressive NAFLD has been examined poorly in the context of histological findings, it seems that high ALT and insulin levels correlates with the presence of fibrosis; recently 43 cases of children with NAFLD biopsy-proven were studied retrospectively to determine the correlation of liver changes and clinical or biochemical variables, steatohepatitis and fibrosis were strongly related to hyperinsulinemia (49 ± 9 μU/mL) and elevated ALT (103 ± 71 U/L).<sup>22</sup>

In addition to elevated insulin levels, another metabolic factor that has been associated with increased ALT levels in obese children is abnormal lipid profile; hypercholesterolemia has been reported close to 25% and hy-

pertriglyceridemia in 50%;<sup>2,3,5,23</sup> in our total group of cases independently of the ALT levels, 73% showed altered lipid concentration. Due to the frequent asymptomatic character of NAFLD, and the probability of progression, monitoring is recommended, specialty in those cases with ALT > 2 fold upper the normal limit, AST/ALT ratio > 1, obesity and metabolic associated risk factors.<sup>19,21</sup>

AST/ALT ratios > 1 suggest an advanced form of NAFLD or might be related with alcohol-induced steatohepatitis.<sup>1</sup> In adults AST/ALT ratio has been identified as a risk factor for fibrotic liver disease,<sup>1,24</sup> in children AST/ALT ratio > 1 has been reported in 30%, reflecting a severe liver injury,<sup>9</sup> in contrast with our cases where AST/ALT ratio was < 1 probably due to a minor liver inflammation.

Type 2 diabetes has also been related to NAFLD and reported in 28 to 55% in adult population,<sup>1</sup> in children is not so common, from 0 to 11%.<sup>5,7,25</sup> however the probabilities for the affected obese child to develop latter type 2 diabetes is high, especially when there is a positive family history,<sup>26,27</sup> in this study 66% of the overweight and obese children had relatives with type 2 diabetes. Hyperglycemia was found in 4 of our cases (4.5%), none of them had previous history of impaired glucose tolerance; ALT was not elevated in two of these obese children; whether when or which child with these metabolic risk factor is going to developed NAFLD is difficult to predict until more longitudinal epidemiological studies be available.

Actually NAFLD is considered part of the Metabolic Syndrome,<sup>28</sup> however the mechanism involved in the development of liver injury is not clear. In this study insulin resistance determined by HOMA-IR was found in the majority of the overweight and obese children with or without hepatic inflammation. In a similar way in 67 obese children insulin resistance was demonstrated in all and 12 of them (17.9%) had raised ALT levels.<sup>29</sup> Insulin resistance is an important factor in the accumulation of hepatocellular fat, whereas excess intracellular fatty acids, oxidant stress, adenosine triphosphate depletion and mitochondrial dysfunction may be important causes of hepatocellular injury in the steatotic liver, it is still to be defined the role of insulin resistance in steatohepatitis and determine if other metabolic abnormalities in a subject with a predisposing genetic environment cause the development of liver disease and progression to cirrhosis.<sup>24,28,30</sup> Although the detection or not of elevated ALT in an obese child, metabolic consequences are multiple and begin in childhood; the risk of developing obesity in adulthood is 80% in those who were obese children; we found a portion of obese children with insulin resistance without biochemical evidence of liver disease, the early recognition and treatment of this problem may lower the risks of complications in infant obesity including NAFLD.<sup>18,31,32</sup> Management with weight reducing diets and physical activity had demonstrated the normaliza-

tion of serum ALT.<sup>5,7,23</sup> Treatment with AUDC and Vitamin E reported in children, showed to be ineffective in obese children to normalized elevated ALT.<sup>25,33</sup> Clearly these reports did not support a long term benefit and weight control treatment and physical activity program continue to be the first choice, in all of our children a gradual weight loss and exercise program was indicated. Closely monitoring metabolic risk factors and liver function test in these children, will permit to select those for liver biopsy and treatment with new promising medication that reduce insulin resistance.<sup>34</sup>

The diagnosis of NAFLD required clinically a high index of suspicion because the majority of patients are asymptomatic or elevated transaminases are noted incidentally during blood test, clinical features such as obesity could help to detect those in risk. Although NAFLD can occur in children with weights appropriated for their age in most of the reports weight is characteristically above the 85th percentile,<sup>4-9</sup> in our study in order to identify those children with major risk to develop NAFLD we decided to evaluate those with overweight and obesity and ruled out other frequent causes of chronic hepatitis; with this evaluation 7 children were excluded from the study because they were found to have positive HBsAg, these cases underwent further evaluation for Hepatitis B management as per the current recommendations guidelines.<sup>35</sup>

In this study the frequency of altered liver function test in children with excessive body weight was elevated to that observed in others populations. The metabolic alterations in obese children with and without elevated ALT were similar. The presence of obesity and hyperinsulinemia, associated with elevated aminotransferases, may help to identify cases on risk to develop progressive liver disease.<sup>22</sup> It is known that hyperinsulinemia favors retention of triglyceride in hepatocytes especially in obese subjects, however steatosis by itself can exist without progressive fibrosis;<sup>30</sup> thus it is possible that unknown intrahepatic mechanisms may cause the hepatocellular necrosis and inflammation. Further studies are needed to enhance our understanding of the pathogenesis and natural history of this condition in order to give an effective medical therapy.

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