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Upper Limits of Normal Aminotransferases in Children of Southern Iran

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Background: Alanine aminotransferase (ALT) level is the most common diagnostic test used for detection of liver damage; however in the past few years some studies have questioned the normal aminotransferase range in adults and have suggested its revision.
Objectives: In this study, we assessed the upper limit of ALT and aspartate transaminase (AST) in a healthy population of Iranian children.
Patients and Methods: A total of 500 apparently healthy children, aged 1 - 15 years, were enrolled in the study. Each patient's serum AST, ALT, triglyceride, cholesterol, and fasting blood sugar were checked. Participants with low or high body mass indexes as well as abnormal lipid profiles and fasting blood sugars were excluded from the study.
Results: A total of 340 subjects with a mean age of 9.2 ± 3.5 years were included in the study. According to our study we reported the 95th percentile of ALT values, corresponding to the upper limit of normal in healthy individuals, as 21 U/L for children. Furthermore, the 95th percentile of AST values, corresponding to the upper limit of normal range in healthy children, was 29 U/L.
Conclusions: A clearly lower cutoff of normality for liver enzyme values in children of our population was demonstrated in this study. However, age and gender were not found to be determining factors for upper limit of normal range for ALT in children.

Keywords: Aminotransferases; Normal; Children

1. Background

Liver is a vital organ with more than 500 different functions, the most important of which are metabolism, detoxification, protein synthesis, and production of biochemicals required for digestion (1). Hepatocytes have crucial roles in carrying out these functions. State of a patient's liver can be evaluated by a group of biochemical laboratory blood assays, known as liver function tests (LFT). Some of these tests determine the mass function of the liver (e.g. albumin), some are associated with the cellular integrity (e.g. transaminase), and others are related to the biliary tract (e.g. alkaline phosphatase) (1).

Alanine aminotransferase (ALT) and aspartate transaminase (AST) are enzymes present in the hepatocytes, which leak into the blood following an acute damage to liver cells. Considering the fact that AST is also present in red blood cells as well as cardiac and skeletal muscle, it is therefore not specific for liver damage (2). Clearance of aminotransferase is carried out within the liver by sinusoidal cells. Half-lives of ALT and AST in the circulation are about 47 and 17 hours, respectively. The magnitude of aminotransferase elevation can be classified as mild (< 5 times more than the upper limit of normal range), moderate (5 - 10 times more than the upper limit of normal range) or marked (> 10 times more than the upper limit of normal range). This classification is somewhat optional since no uniform definition exists and various studies use different cutoff points (3, 4).

In order to interpret the abnormalities in an LFT, it is necessary to know the normal reference ranges and upper limits of normal (5). It is well known that the aminotransferase levels can vary according to age and sex (2). In the past few years, some studies have questioned the normal aminotransferase ranges in adults and have suggested revision of the upper limits of normal (6, 7).

2. Objectives

In this study, we assessed the normal range and upper limits of ALT and AST in a healthy population of children at low risk for chronic liver disease, residing in the city of Shiraz (Southern Iran).

3. Patients and Methods

3.1. Study Population

From January 2008 to April 2010, a total of 500 appar-

Implication for health policy/practice/research/medical education:
Determination of normal values of liver aminotransferases is very important for analysis of liver function tests as well as diagnosis of liver diseases.

ently healthy children, aged 1 - 15 years, referred for regular checkup to Gastroenterohepatology Research Center affiliated to Shiraz University of Medical Sciences, were enrolled in the study. A complete history was taken and careful physical examination was performed in all patients and ones with any signs and symptoms of viral infections were excluded from the study. After explaining the objectives of the study to the parents, a written consent was obtained. A data collection form, including the patient's demographic data, and medical history regarding positive history of any liver, pancreatic, renal, cardiac, pulmonary, and hematologic disorders, and also use of or exposure to any chemical substance or medication including prescription and over-the-counter medications as well as herbal therapies, was completed by a physician interviewer. In addition, body weights and heights of all subjects were measured and entered in the data sheet. Body mass index (BMI) was calculated by dividing the weight (kg) to the squared height (m^2). All subjects with BMIs of lower than 5th percentile and higher than 95th percentile for their age were excluded. This study was approved by the Local Ethics Committee of Shiraz University of Medical Sciences.

3.2. Data Collection

Patients were instructed to remain fasting for at least 8 hours prior to the examination. A blood volume of 5 mL was taken from each patient, allowed to clot in the room temperature and further centrifuged. Serum AST and ALT levels were checked from the collected serum using Selectra XL analyzer (XLab Solutions, Romania). Biochemistry tests including; triglyceride, serum cholesterol, and fasting blood sugar were also taken. All procedures were performed during a few hours of blood sampling at the Gastroenterohepatology Research Center, affiliated to Shiraz University of Medical Sciences, Shiraz, Iran. Upper reference limits for serum biochemistry analyses were as follows: total cholesterol level: 200 mg/dL; triglyceride level: 150 mg/dL; fasting blood glucose level: 100 mg/dL.

3.3. Statistical Analysis

At first, Lilliefors test for normality was applied in order to confirm the normality of the observed data. The results found no evidence against the normality. Moreover, according to the central limit theorem (CLT), without knowing the distribution for the individual data, the mean of the data will follow the normal distribution if the number of observations exceeds 30. Obviously, in the case of a larger number of observations, the accuracy of the obtained results will be better than the case with limited observations. The normality test was checked overall and also separately for each group. Afterwards, the sample size could be determined according to the following formula;

$$n = 4 \times (S/e)^2$$

Where; 4 is a constant number for a 95% confidence interval, S indicates the standard deviation for sample, and e indicates the margin of error which is determined based on the difference between the mean of samples and the population. In this paper, according to this formula, 340 observations were incorporated through the statistical analysis.

4. Results

Forty participants were excluded because of high BMI (> 95th percentile), 98 due to low BMI (< 5th percentile), and 22 due to abnormal lipid profiles and fasting blood sugars. Therefore, a total of 340 subjects with a mean age of 9.2 ± 3.5 years and a male to female ratio of 1.2 were included in the study. There were 188 (55.3%) males and 152 (44.7%) females. None of the subjects had any positive medical history of chronic diseases or specific drug consumption. Therefore, our cases were assumed as a population of children at low risk for liver diseases.

Tables 1 and 2 show the sex-specific 95th percentiles for AST and ALT levels. The calculated range for ALT levels were 1 - 32 U/L in males and 1 - 36 U/L in females with 95th percentiles of 21.2 U/L and 21 U/L for males and females, respectively, and 21 U/L for all subjects. According to our study, we reported the 95th percentile of ALT values, corresponding to the upper limit of normal in healthy individuals as 21 U/L. The calculated range for AST levels were 1 - 39 U/L in males and 2 - 40 U/L in females with 95th percentile of 28.8 U/L for males and 29.6 U/L for females and 29 U/L for all subjects. Hence, the 95th percentile of AST value, corresponding to the upper limit of normal in healthy individuals, was 29 U/L. According to our analysis, there was no significant difference between the ALT and AST levels in males and females.

Table 1. Gender-Specific Normal Values for ALT Levels (U/L) in Children

	Males, n = 188	Females, n = 152	Overall, n = 340
Minimum	1	1	1
Maximum	32	36	36
95th percentile	21.2	21	21

Table 2. Gender-Specific Normal Values for AST Levels (U/L) in Children

	Males, n = 188	Females, n = 152	Overall, n = 340
Minimum	1	2	1
Maximum	39	40	40
95th percentile	28.8	29.6	29

Further, we categorized each gender into three age groups: 1 - 5, 5 - 10, and 10 - 15 years, and calculated a separate reference range for each group. Tables 3 and 4 show the 95th percentile values for AST and ALT levels, in respect to each age group. Our results demonstrated no significant relationship between the levels of liver enzymes and age in any of the two sexes, although the values of ALT slightly increased with age in females and AST values slightly increased with age in both sexes.

5. Discussion

Elevated liver enzyme levels may indicate liver damage or alteration in the bile flow. Liver enzyme elevation might be either the associated biochemical abnormality in a patient with signs and symptoms of liver disease, or an isolated, unexpected finding in a patient who has undergone a wide range of laboratory tests for a nonliver disease or for minor, nonspecific complaints. The latter condition is a common clinical scenario today because LFT is routinely added in automated blood chemistry panels. Isolated liver enzyme elevation in a seemingly healthy patient often represents a challenge even for the experienced clinicians (8).

ALT level is the most common diagnostic test for liver damage detection; however, sometimes patients with minimal liver diseases have normal ranges of ALT, questioning the reference ranges capabilities for differentiation of hepatic injuries. When establishing the laboratory parameters, it is common to define the normal range as the mean value within ± 2 standard deviations observed in the reference, which is the normal population. Accordingly, 2.5% of the normal population has abnormal liver enzymes levels. In a large, national, population-based study in United States, elevated ALT levels were found in 2.8% of the population. The authors reported younger age, male sex, higher BMI, waist-to-hip circumference ratio, fasting serum leptin, triglyceride, insulin, and glucose concentrations as factors associated with elevated ALT levels (9).

Table 3. The 95th Percentile Values for ALT Levels (U/L) by Age in Males and Females

Age Groups	Males	Females
1 - 5, n = 29	12.9	13.2
5 – 10, n = 146	17.6	16.6
10 – 15, n = 165	16.5	18.4

Table 4. 95th Percentile Values for AST Levels (U/L) by Age in Males and Females

Age Groups	Males	Females
1 – 5, n = 29	25.5	24
5 – 10, n = 146	26.8	24.9
10 – 15, n = 165	28.9	27

Consequently in the recent years, many studies have stated revisions in the upper limits of normal ranges for liver enzyme levels in adults of various populations worldwide (6, 7, 10-12). Studies regarding this fact in the pediatric age groups are still limited. Since the 1950s, there have been only minimal alterations in the mean level of ALT which had been set at 40 U/L for healthy adults (10). In 2002, American Society of Internal Medicine conducted a study on healthy blood donors and reported the updated upper limits of ALT as 30 U/L for males and 19 U/L for females (6). A similar study, carried out in 2003 on healthy Iranian blood donors, stated the upper limit of normal for nonoverweight females and males as 34 U/L and 40 U/L, respectively (5). Lee et al. also found the ALT thresholds to be lower than previously-accepted levels in healthy individuals (values were reported 33 U/L for males and 25 U/L for females) (11).

Regarding the current pediatric ALT reference ranges, a research performed in London in 2009 showed the 95th percentile value of ALT in < 18 months of age as 60 U/L for males and 55 U/L for females, decreasing to 40 U/L for males and 35 U/L for females by the age of 18 months (12). The SAFETY study performed in 2010 in the pediatric population of the United States with the aim of determining an appropriate ALT threshold value for diagnosis of chronic liver diseases in children, estimated the 95th percentile level of ALT as 25.8 U/L for males and 22.1 U/L for females (13).

In this study, we reported the upper limit of normal for ALT in healthy Iranian children to be 21 U/L in both sexes. A previous cohort study performed on school children of Tehran, Iran, between 7 - 18 years, demonstrated the 95th percentile for ALT in males and females as 30 U/L and 21 U/L, respectively. This study also showed a linear relationship between age and ALT in females, but not in males (14). In other studies, aminotransferase levels were reported to vary according to age and sex, and the authors recommended being aware when using age- and sex-appropriate reference limits (2, 15). However, in our study we demonstrated no age-related difference in liver enzyme levels.

This study had limitation since we did not investigate the subjects for metabolic diseases as well as viral hepatitis B and C and according to their history and previous clinical examinations considered them free of liver problems.

We demonstrated a clearly lower cutoff of normal liver enzyme values in children of our population than previously available. However, in this study, age and gender were not found to be determining factors for upper limits of normal ALT. Although further investigations in various geographic regions are required to re-examine the normal levels of liver enzymes in children, at the present time we suggest the values derived from this study to be used as the reference for identifying children with possible liver diseases in our area.

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Authors' Contribution

Seyed Mohsen Dehghani, Mahmood Haghighat, Mohammad Hadi Imanieh, and Asma Erjaee contributed to the study concept and design, drafting of the manuscript, critical revision of the manuscript, and study supervision; Seyed Mohsen Dehghani, Asma Erjaee, and Razieh Ahmadi were in charge of acquisition of data, analysis and interpretation of data, and drafting of the manuscript.

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