Serum Transaminases: Quo Vadis

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Introduction

Serum transaminases (also called aminotransferases) are basically enzymes in the human body which help in catalyzing reactions involving transfer of the α-amino groups. Alanine transaminase (ALT) helps in conversion of alanine into pyruvate and Aspartate transaminase (AST) helps in formation of α-ketoglutarate from aspartate [1]. Both AST and ALT are sensitive markers of acute hepatocellular injury and are routinely used to identify liver disease since 1955 [2]. Both are readily available, inexpensive, and routinely assayed in clinical practice [3]. AST which was formerly known as serum glutamic oxaloacetic transaminase (SGOT), is found in both cytosol and mitochondria in several organs such as the liver, cardiac muscle, skeletal muscle, kidney, brain, pancreas, lung, leukocytes, and erythrocytes but the concentration is highest in the hepatic parenchyma. On the contrary, ALT (formerly serum glutamic pyruvic transaminase or SGPT) is a cytosolic enzyme which is predominantly present in the liver. Hence ALT is a more specific indicator of liver injury than AST. Serum levels of these enzymes reflect injury of the concerned organs especially the liver. However, the degree of elevation of the serum transaminases may not correlate with the extent of liver injury [4].

Defining Normalcy for Transaminases

The normal values for aminotransferases in serum vary considerably among laboratories. The normal range is usually defined as the mean of the reference population plus 2 standard deviations which represents the serum values of approximately 95% of a normally distributed population. Hence each laboratory has its own reference range for the serum transaminases depending on the mean and standard deviation of the resident population of the region. Several studies in the past, based on blood donors (after exclusion of people with viral hepatitis) had suggested an upper limit of normal for the ALT level between 40 to 50 IU/L [5-7]. Later on, due to increasing prevalence of patients with metabolic disorders like metabolic syndrome and non-alcoholic fatty liver disease, there has been a debate on revision of upper limit of normal for serum aminotransferases. Prati et al. [8] in 2002 came forth with the idea that subjects with metabolic abnormalities must be excluded while evaluating the upper limit of normal for serum ALT level. Subsequently many authors have re-evaluated the upper limit of normal of ALT values in specific populations, including adults and adolescents and observed similar results [9-13] (Table 1). However, there is concern regarding the cost effectiveness and unclear benefits of implementing lower value of upper limit of normal [14]. Lowering the upper limit of normal [ULN] for ALT will lead to larger number of patients with abnormal values necessitating further work up for transaminitis and treatment. This may impose a high financial burden in resource constrained countries.

Implications of Change in ULN for Serum Transaminases in Various Diseases

Implications in Non-alcoholic fatty liver disease (NAFLD)

NAFLD encompasses a wide histopathological spectrum, which ranges from simple benign fatty liver to non-alcoholic steatohepatitis (NASH), NASH related liver cirrhosis, portal hypertension and ultimately hepatocellular carcinoma [15,16]. Population based prevalence of NAFLD is found in 30-40% in men and 15-20% in women [17]. Higher prevalence has been observed in people with type 2 diabetes mellitus (T2DM) i.e., up to 70% [18]. In a study conducted in coastal eastern India, one fourth of the general population had fatty liver on routine ultrasonographic screening [19]. NAFLD is considered as a hepatic manifestation of the metabolic syndrome [20,21]. In fact, some studies have even stressed its importance as an independent predictor of metabolic syndrome and insulin resistance [22,23]. Patients with NAFLD often have raised serum ALT levels [24-26]; NAFLD is the commonest cause of unexplained mild ALT elevation [27,28]. Despite the fact that mild ALT elevation is attributed to NAFLD, the correlation between the degree of ALT elevation and the histologic severity of NAFLD is non-linear [29,30]. Further, serum transaminases are also integral part of several clinical scoring systems which were proposed to identify advanced fibrosis in patients with NAFLD and other liver diseases. The scoring systems include the aspartate aminotransferase (AST)-to-platelet ratio index (APRI) [31], the aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio [32] the BARD score [33] and the BAAT score [34]. These scoring systems had used the upper limit of 40 IU/L for serum transaminases. Change in the cutoff to a lower value could affect the sensitivity and

| Authors (year) [Reference] | Number of participants enrolled | Male Female ratio | Mean age (± SD) | Statistical Methods used | ULN of ALT value (IU) |
|----------------------------|---------------------------------|------------------|----------------|-------------------------|----------------------|
| Ruhl et al. 2012 [10]      | 3747                            | 0.75             | 42.0 ± 16.9    | 95th percentile one sided | 24 for men |
|                            |                                 |                  |                |                         | 18 for women         |
| Lee et al. 2010 [11]       | 1105                            | 1.39             | 29.1 ± 9.0     | 97.5th percentile one sided | 35 for men |
|                            |                                 |                  |                |                         | 26 for women         |
| Schwimmer et al. 2010 [12] | 982                             | 1.26             | 14.5 ± 1.8     | 95th percentile one sided | 25.8 for boys |
|                            |                                 |                  | 15.1 ± 1.8     |                         | 22.1 for girls       |
| Kang et al. 2011 [13]      | 1745                            | 0.68             | 41.8 ± 12.5    | 95th percentile one sided | 28 for all |
|                            |                                 |                  |                |                         | 31 for men |
|                            |                                 |                  |                |                         | 23 for women         |
| Wu et al. 2012 [14]        | 2894                            | 0.75             | 52.4 ± 13.1    | 95th percentile one sided | 21 for men |
|                            |                                 |                  |                |                         | 17 for women         |

Table 1: Comparison of updated upper limits of normal serum alanine transaminase various recent studies.

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specificity of the scoring systems. Further, a reduced upper limit of normal could render a large number of NAFLD patients eligible for liver biopsy, which could be a huge burden for the hepatologists, besides being of doubtful or unproven utility.

Implications in chronic hepatitis B

Viral hepatitis infection is one of the leading cause of serum transaminase elevation worldwide [24-26]. Serum ALT activity is an indicator of liver injury in patients with both acute and chronic viral hepatitis [35]. Chronic HBV infection is usually asymptomatic and is sometimes discovered because of an elevated AST or ALT level detected on routine blood testing. In HBV infection, elevation in serum levels of transaminases (especially ALT) is observed in two processes, such as during cytolysis immune response (acute phase) and after ineffective HBV clearance (chronic phase) [36]. Among chronic hepatitis B patients, elevated levels of ALT is associated with progression of liver disease. The cumulative risk of development of liver related complications appears to be highest among the patients with ALT values at least 1 to 2 times above the upper limits of normal [37]. However, there is some controversy. A study by Lai et al. [38] had reported that significant fibrosis and necro-inflammation were observed in 37% of patients infected with HBV with persistently normal ALT levels. On the contrary, among the chronic hepatitis B infected patients who are hepatitis B e antigen (HBeAg) positive, serum ALT is also a predictive marker of the likelihood of HBeAg serocconversion [39]. Besides, ALT activity is also a crucial reference indicator in treatment selection and the evaluation of prognosis in patients infected with HBV [36,40,41]. Thus, in HBV infected patients, ALT is useful not only in determining the presence of significant liver disease and need for antiviral treatment but also in predicting the future course in the natural history. All the international guidelines for treatment for chronic hepatitis B patients are based on upper limit of normal of ALT. Revision of the same to a lower value would lead to a larger fraction of patients becoming eligible for antiviral treatment. This may result in a large fiscal burden on the individual patients and the exchequer of the developing nations too.

Implications in chronic hepatitis C

Patients with Chronic HCV infection are often asymptomatic. However, serum ALT levels fluctuate in HCV infected individuals and values may not uncommonly fall into the normal range [42]. Being an asymptomatic infection, HCV is frequently diagnosed when ALT elevations are noted during routine blood testing. According to a study by Conry-Cantilena et al. [43] 69% of asymptomatic blood donors who tested positive for HCV antibody had elevated ALT activity [43]. In the same cohort, patients with severe liver damage on liver biopsy had at least one elevated ALT determination in their lifetime. Among the HCV infected patients who initially have normal ALT values, on follow up, most of them develop persistently elevated ALT levels [44]. Interestingly, female HCV patients are more likely to have normal ALT levels than males [45]. Chronic HCV patients who have persistently normal serum ALT levels tend to have lower necroinflammatary and fibrosis scores on liver histopathology than their counterparts with elevated serum ALT activities [46]. Unlike chronic HBV infection, the ALT level is less helpful in guiding antiviral treatment because as per recent guidelines, irrespective of ALT values, all treatment-naïve and -experienced patients with compensated chronic liver disease related to HCV who are willing to be treated, who do not have any contraindications to treatment, except those with limited life expectancy due to nonhepatic causes, should be considered for HCV antiviral therapy [47-49].

Implications in Drug Induced Liver Injury (DILI)

Drug Induced Liver Injury is defined as alteration in liver function tests which occur as an unintended response to exposed drug(s) at appropriate or recommended doses for treatment or prophylaxis of diseases [50,51]. As per the updated definition, DILI is defined as elevation in ALT or AST > 5 times of ULN (upper limit of normal) without symptoms, or rise in alkaline phosphatase > 2 times of ULN or rise in serum bilirubin > 2 times of ULN in bilirubin with any rise in AST and ALT elevation. Besides, AST or ALT > 2 times of ULN with symptoms also defines DILI [52]. Hence the decision regarding withholding a drug depends on the upper limit of normal. Bringing the same to a lower level will lead to earlier change of first line agents in various diseases a large number of patients. This is very important especially in tuberculosis where the first line drugs are most efficacious, cheap and with least side effects. A lower normal level might result in a large number of patients stopping first line anti-tubercular regimens prematurely and switching over to second line agents which would lead to longer duration of treatment, high incidence of toxic effects and compliance issues. The policy makers must consider these problems too before deciding on a new upper limit of normal.

Conclusion

Before deciding on redefining the upper limit of normal for transaminases, its protein ramifications have to be kept in mind, since all management guidelines for liver diseases and definitions of liver diseases are based on the earlier upper limit of normal of 40 IU/L. By lowering ULN for transaminases, more patients with NAFLD will qualify for liver biopsy and a large number of chronic hepatitis B patients who were earlier ineligible will become eligible for antiviral therapy. This may have a huge impact on the financial burden especially in developing and resource constrained nations in the absence of proper guidance. Hence any consensus recommendation on lowering the ULN for transaminases should be accompanied by a pragmatic and realistic guidance which should take into consideration not only these issues, but must also address and safeguard carrier opportunities and job security for those with minimal transaminase elevation, since a significant proportion of job seekers may be rendered ineligible or declared medically unfit on the basis of the new upper limit of normal for transaminases. Hence, we should be very careful in deciding the upper limit of normal for transaminases.

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