Do we need to adjust upper normal limit of ALT?

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The upper limit of normal (ULN) for serum alanine aminotransferase (ALT) has long been considered to be 40 IU/L regardless of sex or body mass index (BMI). However, this concentration was determined principally from studies before the introduction of anti-hepatitis C virus (HCV) testing, and prior to development of the concept of nonalcoholic fatty liver disease (NAFLD). Several recent studies have demonstrated that the normal range of serum ALT concentration is significantly lower than the previously accepted thresholds if we consider the influence of NAFLD on serum ALT levels.

For the purpose of this review, I will briefly summarize factors affecting serum ALT levels, and then discuss why we should adjust the ULN for serum ALT. For convenience of explanation, the roles of serum ALT testing in clinical practice will be divided into three parts: ALT as a screening test for liver disease, ALT as a monitoring tool for liver disease, and ALT as a measure of overall health.

Factors Influencing Serum ALT Levels

ALT is found abundantly in the cytosol of hepatocytes and its activity in the liver is about 3,000 times that of serum activity. Traditionally, elevated serum ALT activities have been thought to be caused by release of ALT from damaged hepatocytes...
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However, several recent studies raise a question about this viewpoint. ALT activity varies day to day, and there is also a significant diurnal variation (higher in the afternoon). High caloric diet in healthy subjects can induce rapid elevation of serum ALT within the first week before the development of hepatic steatosis. In a mouse model of NAFLD, methionine-choline deficient diet could increase serum ALT activity approximately four-folds without increase in liver cell apoptosis or necrosis. Increased hepatic expression of ALT was the major determinant of serum ALT elevation. All these findings suggest that serum ALT activity can be controlled metabolically at least in part. In addition to physiological variability, wide variability in ALT ULN across different labs was reported resulting from variable reference intervals of different chemical analyzers.

**Definition of Healthy Normal Populations for Calculating Normal Range of Serum ALT Levels**

The definition of normal healthy populations is somewhat different from study to study. Prati et al and Piton et al defined ULN for healthy ALT level as the 95th percentile, since they thought that persons having low 2.5th percentile of ALT level are not in fact in disease states. In contrast, Lee et al set the ULN for healthy ALT levels at the 97.5th percentile. The AGA technical review on the evaluation of liver chemistry tests recommended to set the ULN at the 97.5th percentile, since, by definition, 5% of normal patients will have abnormalities of any given test (2.5% are above and 2.5% are below the 2nd standard deviation level). The study conducted by Prati et al had another problem in defining ULN for healthy ALT level, since they excluded persons with ALT levels >40 IU/L (for men) or 30 IU/L (for women) before analysis no matter whether they truly had liver disease or not. These differences can partly explain the lower values for the ULN for ALT levels in the study of Prati et al (30 IU/L for men, 19 IU/L for women) than those in the study of Lee et al (33 IU/L for men, 25 IU/L for women).

Another unresolved problem in defining normal healthy population is whether we should exclude persons with or at risk of NAFLD. Piton et al suggested that ALT levels should be interpreted with respect to BMI considering the positive association between ALT levels and BMI. This concept was questioned by Prati et al since NAFLD itself is not necessarily a benign liver disease without clinical significance. Recent studies have demonstrated that persons with NAFLD may have higher overall and liver-related mortality compared to general population. Therefore, persons with NAFLD should be excluded in defining normal healthy population. However, it can be controversial whether persons at high risk of NAFLD but without overt NAFLD should be excluded or not. Prati et al excluded not persons with NAFLD themselves but those at high risk of NAFLD, since it was practically difficult to exclude persons with NAFLD from those with normal or slightly high ALT levels without liver biopsy. In the study of Lee et al, healthy persons with higher BMI had higher serum ALT level compared to those with normal BMI, even though both of them had normal liver histology. In fact, evidences are still lacking whether persons without NAFLD but with risk factors for NAFLD have higher overall or liver-related mortality. In addition, a recent study showed a U-shaped association between BMI and overall mortality in Asians, and the lowest risk of death was seen among persons with a BMI in the range of 22.6 to 27.5 kg/m². The previous BMI cutoff point for Asians was 23 kg/m².

A third unresolved problem is related to the age of studied population. Since both voluntary blood donors and living liver
donors are usually young, it is difficult to get normal data from middle-aged or aged persons. In the study of Lee et al, serum ALT level correlated with age, but another study reported an inverted U-shaped association between age and ALT levels with a peak value between 40 and 55 years. Therefore, it is not still clear whether the ULN for serum ALT levels obtained from young populations can be used for middle-aged or aged persons.

**ALT as a Screening Test for Liver Disease**

The ULN for serum ALT activity is defined as the 97.5 percentile of ALT values among healthy normal populations, as discussed above. In fact, for the definition of normal range, it is not taken into consideration what proportions of patients with liver diseases may have ALT values within normal range. In other words, ALT values within normal range do not necessarily exclude the possibility that the tested individuals may have ongoing liver disease.

The impact of updating the normal definition of ALT on the screening for liver disease is largely unknown. One study from Korea showed a positive association between ALT levels even within the normal range by conventional criteria and liver-related mortality. Men with ALT values in the range of 30-39 IU/L had 6.9 times higher mortality from diseases of digestive system, in which liver diseases accounted for 89%, than those with ALT values of less than 20 IU/L. These data strongly suggest that we should lower the ULN for serum ALT levels, especially when only serum ALT is used for the screening of liver diseases. In the study by Kim et al, serum HBsAg and/or anti-HCV antibody levels were not tested, and the presence of underlying liver cirrhosis or history of alcohol abuse was excluded only by a self-reported questionnaire. Given that Korea was an area with endemic chronic HBV infection and high rates of alcohol abuse, the increased number of liver-related deaths might be caused by unreported or unrecognized chronic HBV infection and/or alcohol-related cirrhosis. However, this study was conducted about 20 years ago and the disease pattern has been changing rapidly. These days, the commonest cause of mild ALT elevation is NAFLD in Korea. And also, the prevalence of chronic HBV infection or alcohol abuse is steadily declining. Therefore, it is not certain whether these results are reproducible these days. A recent population-based cohort study in United States, where chronic HBV infection is not endemic, showed that persons with NAFLD, whose ALT levels were higher than 30 IU/L for men and 19 IU/L for women, had about 4-fold higher mortality from liver diseases compared to normal population. This result also supports the rationale of adjusting the ULN for serum ALT, despite the recent changing disease pattern in Korea. However, a recent population-based study performed in the United States showed that about 40% of the general population would have abnormal ALT levels using the updated Prati definition, suggesting that application of these new definitions could result in a dramatic increase in the use of medical resources. And also, it is not clear which one is more cost-effective in identifying persons at risk, updating the ULN of serum ALT activity or an addition of serum HBsAg testing in an HBV-endemic area.

Another problem that can be induced by the updated definition(s) is wasting of blood donors. The differences between the conventional and updated criteria mostly resulted from NAFLD or obesity, which are not transmittable diseases. Since tests for blood donation include tests for serum HBsAg or anti-HCV antibodies in Korea, adjustment of normal range of serum ALT activities is not indicated for this purpose.
ALT as a Monitoring Tool for Liver Disease

It is well known that HCV-infected patients with persistently normal ALT levels may have significant liver disease. Likewise, Asian chronic hepatitis B patients with ALT levels between 0.5 and 1 x ULN by conventional criteria developed cirrhotic complications more frequently than those with ALT levels below 0.5 x ULN. Furthermore, the ULN for ALT in patients who successfully cleared the HCV by treatment was approximately 30% lower than the threshold chosen to identify the chronic hepatitis C patients with ‘persistent normal ALT level’ (ALT levels \( \leq 30 \) IU/L). All these findings suggest that we should revise the ALT criteria in order to identify more chronic hepatitis patients with active inflammation. However, this approach would doubtless result in the unnecessary use of antiviral agents, in that an elevated ALT level might be a consequence of patient age, BMI, total cholesterol level, or any/all of these combined with NAFLD. Therefore, careful interpretation of clinical parameters or a liver biopsy would be necessary before initiating treatment with antiviral agents, especially in older patients, those with high BMI or serum total cholesterol, and/or those with NAFLD.

As for NAFLD, ALT levels within the conventional criteria clearly correlated with the prevalence of NAFLD in Korean populations, though this study was not a community-based one. Therefore, we can detect more patients with NAFLD by the revised ALT criteria. However, current treatment of NAFLD is mostly based on weight reduction, diet control, and exercise. The ALT level per se cannot be used as a surrogate marker for active necroinflammation and development of end-stage liver diseases in future in NAFLD patients. Therefore, the treatment policy will not be changed whether we use the conventional criteria or updated criteria of ALT in patients with NAFLD.

ALT as a Measure of Overall Health

Several studies have investigated the relationship of abnormal ALT with overall mortality. Some studies showed that higher ALT was associated with mortality from all causes, but others did not. In the study of Kim and their colleagues, men with higher ALT had an increased risk of death not only from liver diseases but also from cardiovascular diseases (CVD). And, these findings could be observed even in men with ALT levels between 20 and 39 IU/L compared to those with ALT levels <20 IU/L. Another study from Korea also showed that elevated ALT levels are independently associated with increased CVD- or diabetes-related mortality, although this was not a community-based study. Subjects with the highest quartile of ALT levels (\( \geq 31 \) IU/L) had 2.28-fold higher CVD- or diabetes-related mortality compared to those with the lowest quartile (\( \leq 15 \) IU/L). The long-term follow-up study of the community-based Framingham Heart Study sample also showed that higher ALT levels were associated with increased odds of the development of metabolic syndrome and diabetes, even within the normal range. In contrast, another population-based study reported that ALT was associated only with liver disease mortality but not with deaths from CVD, diabetes, or neoplasm. In this study, ALT elevation was associated with more than 3 times the risk of diabetes mortality after adjusting for age. However, in a model adjusting for multiple factors, the increased risk was not statistically significant. These results were consistent whether the cut-off levels were set at 40 IU/L for men and 31 IU/L for women or at 30 IU/L for men and 19 IU/L for women. As for CVD risk, despite the positive association between serum ALT and CVD mortality in two Korean studies, as previously described, the risk was absent or weak in population-based study performed in the United States. Some authors questioned the proposed linear relationship between ALT and incident CVD, since ALT may
in fact exhibit a U-shaped association with total mortality. Therefore, the association between serum ALT and CVD risk is still debatable.

Conclusions

Several studies have shown that adjustment of the ULN for serum ALT activities can identify more patients at high risk for mortality not only from liver disease but also from metabolic syndromes. Therefore, current evidences suggest that we should adjust the ULN for serum ALT activities. However, a careful interpretation is essential in clinical practice, since several factors other than hepatic necroinflammation can influence the ALT levels in individual patients.

References