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EDITORIAL

정상 Alanine Aminotransferase의 기준수치는 고정된 것인가? 변동하는 것인가?

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Standard Value of Serum Alanine Aminotransferase: Is It Fixed or Varied?

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Article: Detailed Distribution of Liver Enzymes according to Gender, Age, and Body Mass Index in Health Check-up Subjects **(Korean J Gastroenterol 2014;64:213-223)**

Serum ALT has been used as a surrogate marker of liver disease. It also occurs in small amounts in cardiac muscle, skeletal muscle and the kidney, but is quite specific to the liver. Although the interpretation of ALT activity may differ across various kinds of liver diseases, it is a explicitly sensitive test to detect a clinically significant liver disease even without specific symptoms. More importantly, for ALT as a measure of overall health and mortality risk, it is evident that abnormal ALT levels and subsequent mortality from liver disease are closely correlated.[1] ALT is also considered as a good indicator of diseases associated with obesity, cardiovascular disease, and other metabolic diseases. A population-based study revealed that the men with ALT ≥40 U/L had 1.7 times of death risk from cardiovascular causes and 2.2 times of all cause mortality compared to those with ALT <20 U/L.[2] A study[3] based on a community-wide database showed that the standardized mortality ratio (SMR) of ALT ≥2×upper limit of normal (ULN) was 1.51 and ALT < ULN was associated with lower SMR (0.61).

What is a universally acknowledged value as the normal ALT?

Unfortunately, the standard value of ALT used for setting ULN (around 40 IU/L) is based on a research from presumed healthy subjects who may have hepatitis C virus or fatty liver disease or obesity.[4,5]

Several factors need to be correctly construed for the determination of standard value of ALT. There is a significant diurnal variation of ALT activity with up to 45% change of range in a given day. In addition, day to day variation of ALT activity reaches 10% to 30%.[6,7] Furthermore, there is a wide variability in ULN of ALT across different laboratories where different instruments with variable reference ranges are used.[8] Of those laboratories having their own data to determine ULN of ALT, only 50% excluded patients with hepatitis B or C, and only 12% excluded overweight persons. Apart from liver disease, serum ALT may be affected by gender, with higher level in men than in women.[9] Age and smoking have a negative correlation with ALT level, whereas BMI and serum cholesterol level

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Table 1. Ninety-five Percentile of Upper Level of ALT and AST Value according to BMI

	BMI (kg/m^2)								
	≤23.5			≤25			≤30		
	Total	Male	Female	Total	Male	Female	Total	Male	Female
ALT (IU/L)	42	50	34	46	55	36	56	66	39
AST (IU/L)	35	38	32	36	39	33	40	43	34

Data from the article of Choi, et al. (Korean J Gastroenterol 2014;64:213-223).[12]

have a positive correlation with ALT activity.[10] In fact, prospective cohort studies revealed that the risk for mortality from liver disease began to increase even at lower ALT level (20-29 IU/L) than at the level that would be expected.[2]

Is the revised normal limit for ALT value truly applicable?

Lowering the ULN of ALT has been proposed by Prati et al.[9] Healthy ALT value was determined to 30 IU/L for men and 19 IU/L for women, excluding subjects with hepatitis B or C, BMI ≥24.9, drug history, abnormal cholesterol or glucose level. This new definition of the ULN of ALT increased sensitivity for hepatitis C virus infected blood donors from 40% to 60%. However, this would increase the number of abnormal values without definite evidence of risk reduction. When the proposed normal limit for ALT value was taken, a significant increase in the prevalence of fatty liver and significant hepatic fibrosis was detected in subjects with elevated ALT levels. However, the diagnostic utility for ALT to identify nonalcoholic steatohepatitis was not improved. In addition, adoption of this definition would increase the use of medical resources dramatically.[11]

In the current issue, Choi et al.[12] provided the knowledge about variability of liver enzyme according to gender, age, and BMI. This study from a large population in health check-up center, excluding the subjects with hepatitis B and C, showed that ALT, AST, and GGT were significantly increased with BMI, and also quantified the change of liver enzymes in proportion to increase of BMI along with stratified age and sex. Even though subjects who may have fatty liver, a history of significant alcohol consumption or drug were included, at any rate, 95 percentile of upper level of ALT and AST value according to BMI was drawn in this data (Table 1). As reported in the study by Lee et al.,[13] increased ALT level in subjects with high BMI or cholesterol does not necessarily indicate hepatocellular injury. Therefore, a careful interpretation of ALT level is needed before making a decision to initiate treatment in patients with high BMI or old age.

What is the best approach to determine standard value of ALT?

Between the two ways to establish ULN of ALT, outcome-based reference value with excluding the patients with any clinical or pathological liver disease seems to be more dependable than population-based reference value resulting from apparently healthy people.[9,13,14] This approach to determine ULN using outcome studies based on incidence of disease manifestations, is most appropriate in circumstances where liver disease is quite prevalent in study population or asymptomatic over long-term follow-up period.

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