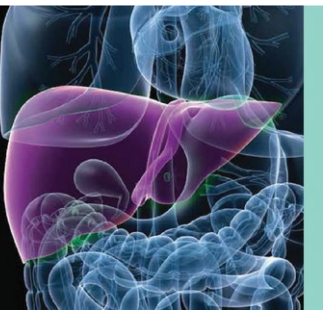

Misconception: You Can't Have Liver Disease With Normal Liver Chemistries

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The liver function tests (LFTs) are one of the more common tests ordered on patients, yet their name is a misnomer. The conventional laboratory LFT panel has biochemical measures of liver function and liver injury. When considering liver function, it is important to remember that the liver has synthetic and metabolic roles. For example, the Model for End-Stage Liver Disease uses international normalized ratio as a measure of synthetic function and total bilirubin as a measure of metabolic capacity when assessing the severity of liver dysfunction. Despite the liver's tremendous capacity for regeneration, chronic liver injury can result in fibrosis and eventually end-stage liver disease. Classically, aminotransferase elevation is interpreted as a marker of hepatocellular damage, and alkaline phosphatase elevation signifies cholestasis. There are two major fallacies that occur when using liver biochemistries as a means to identify patients with chronic liver disease. The first relates to how normal aminotransferase levels are defined. The second is the assumption that liver tests should be elevated in the setting of chronic liver disease. This review addresses both key issues. For simplicity, we focus on alanine aminotransferase (ALT) levels, which are a more specific marker of hepatocellular damage.

WHAT DEFINES A "NORMAL" ALT LEVEL?

A basic laboratory premise is the definition of clinically elevated values. To accomplish this aim, laboratories use selected populations to establish internal reference ranges with normal values defined as within two standard deviations of the mean.[1] For aminotransferases, these reference populations are often heterogeneous and may include patients with viral hepatitis, metabolic syndrome, polypharmacy, or substance abuse. For instance, some reference ranges were created before the identification of the hepatitis C virus. One study of 11 clinical laboratories involved in the Non-Alcoholic Steatohepatitis Clinical Research Network showed that all participating

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; AUC, area under the curve; LFT, liver function test; NAFLD, nonalcoholic fatty liver disease; ROC, receiver operating characteristic; ULN, upper limit of normal.

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Potential conflict of interest: Nothing to report.

Received May 20, 2018; accepted July 7, 2018

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laboratories excluded subjects with known medical conditions from the reference population, but none excluded overweight or obese subjects.[1] The reference populations themselves varied in size from 94 to 1354 subjects and sometimes were established decades prior. The upper limits of normal (ULNs) for ALT between laboratories varied from 35 to 79 U/L in men and 31 to 55 U/L in women. Thus, a patient with "normal" ALT when measured at one laboratory could have twice the ULN if measured at another. Similarly, in a French study with 1033 healthy blood donors, the ULN of ALT was 31 in women and 42 in men with a body mass index less than 23.[2] When donors with a body mass index greater than 23 were analyzed, the ULN for ALT was 44 in women and 66 in men.[2] A 2002 study of healthy blood donors without serological liver disease, medication use, substance abuse, or obesity forms the basis for the ULN of ALT in men and women used in the American Association for the Study of Liver Diseases (AASLD) Practice Guidelines for Treatment of Chronic Hepatitis B.[3] That study of 3927 donors at lowest risk for liver disease found median ALT values of 9 U/L in women and 13 U/L in men, with the 95th percentile at 19 U/L for women and 30 U/L for men.[3] More recent Chinese studies also advocate lower ULN cutoffs for ALT values, between 22 and 35 in men and 22 and 23 in women.[4,5]

HOW COMMON IS LIVER DISEASE IN PATIENTS WITH NORMAL LIVER CHEMISTRIES?

It is important to note that even after lowering the threshold for a normal ALT value, liver disease can still occur in patients with values within these more stringent reference ranges. One study found that patients with nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis and a normal ALT (mean values 26 and 29, respectively) had no significant difference in inflammation, ballooning, or fibrosis on liver biopsy when compared with patients with elevated ALT.[6] Another study in patients with chronic hepatitis B infection and persistently normal ALT, defined as less than 40 U/L, found histological disease activity in 14% to 40%, depending on e antigen status.[7] When updated ULNs for ALT cutoffs were used as advocated by AASLD guidelines,[8] a significant minority of these patients were still found to have histologically active disease. For identifying cirrhosis, elevated ALT and AST have poor specificities of 23% and 62%, respectively, with sensitivities of 78% and 88%.[9] Therefore, ALT is an imperfect biomarker for identifying histological inflammation and can be normal in patients with cirrhosis. This is reflected in hepatitis C screening guidelines that recommend testing all baby boomers irrespective of risk

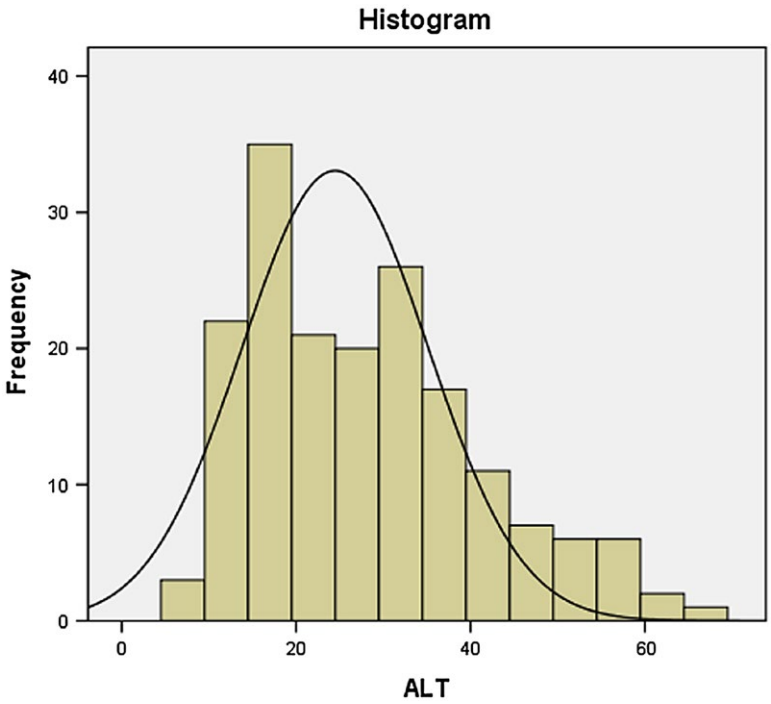

FIG 1 ALT values in 177 overweight patients undergoing bariatric surgery. Mean = 28.16; standard deviation = 13.091.

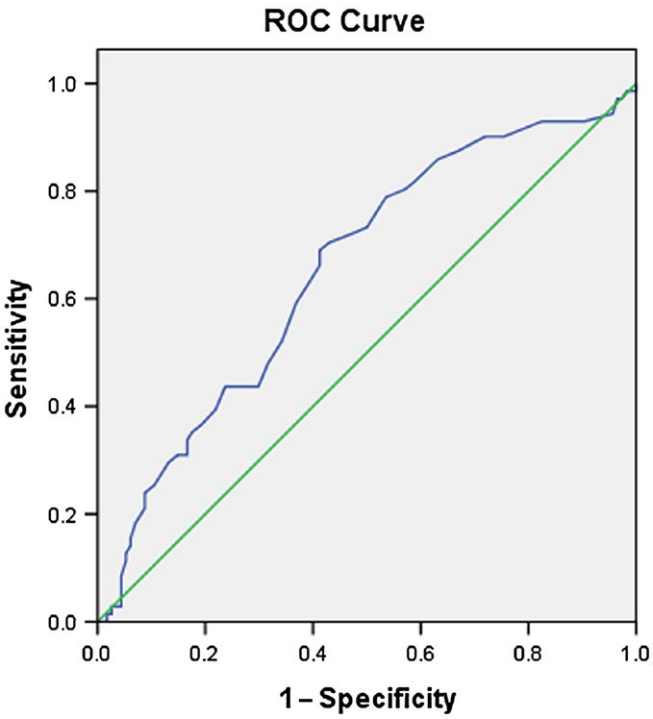

FIG 2 ROC curve for ALT in discriminating the presence of nonalcoholic steatohepatitis in patients undergoing bariatric surgery (AUC = 0.653). Diagonal segments are produced by ties.

factors or ALT levels. Similarly, in the most recent AASLD guidance document on fatty liver disease, patients with NAFLD with metabolic syndrome or with potential fibrosis based on noninvasive tests are recommended to be considered for liver biopsy.[10] ALT levels are *not* advocated as a means to risk-stratify the severity of liver disease in NAFLD.

Another example is included to highlight this concept. Patients undergoing bariatric surgery are almost universally affected by NAFLD. However, only a portion will experience steatohepatitis and progressive fibrosis. An elevated ALT is one potential marker of steatohepatitis. Fig. 1 is a histogram of ALT values in a group of patients undergoing bariatric surgery. The mean ALT in this group was 28 U/L, and the 95 percentile value was 54 U/L. These patients underwent routine surgical liver biopsy and were classified as having bland fat alone or steatohepatitis. Fig. 2 shows a receiver operating characteristic (ROC) curve plotting the true-positive fraction (sensitivity) versus the false-positive fraction (1 – specificity) at differing ALT values in identifying steatohepatitis. The area under the curve (AUC) for ALT in discriminating bariatric patients with steatohepatitis versus bland fat was 0.65, whereas the ideal clinical test would have an AUC close to 1.0. Therefore, patients with steatohepatitis have a greater *probability* of having higher ALT levels compared with those without steatohepatitis; however, many bariatric surgery patients with steatohepatitis will have normal ALT values.

CONCLUSION

Although elevated ALT levels often signify ongoing hepatic inflammation, many patients with chronic liver disease and progressive fibrosis may have normal values. Thus, a "normal" aminotransferase value does not exist in clinical medicine. Although lowering the ULN of ALT may improve the detection of liver disease, some patients may still have chronic liver disease and even cirrhosis despite ALT values within more stringent reference ranges. Simply stated, liver chemistries need to be interpreted in the appropriate clinical context and should not be used as absolute markers for the detection or exclusion of liver disease.

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