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EDITORIAL

Alanine aminotransferase predicts incident steatotic liver disease of metabolic etiology: Long life to the old biomarker!

Amedeo Lonardo

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Amedeo Lonardo, Department of Internal Medicine, Azienda Ospedaliero-Universitaria of Modena (2023), Modena 41126, Italy

Corresponding author: Amedeo Lonardo, MD, Academic Research, Doctor, Professor, Senior Lecturer, Department of Internal Medicine, Azienda Ospedaliero-Universitaria of Modena (2023), Ospedale Civile di Baggiovara, Modena 41126, Italy. a.lonardo@libero.it

Abstract

Alanine aminotransferase (ALT) serum levels increase because of hepatocellular damage. Metabolic dysfunction-associated fatty liver disease (MAFLD), which identifies steatotic liver disease (SLD) associated with ≥ 2 metabolic abnormalities, has prominent sexual differences. The Metabolic Syndrome defines a cluster comprising abdominal obesity, altered glucose metabolism, dyslipidemia, and hypertension. Male sex, body mass index, glucose, lipids, ferritin, hypertension, and age independently predict ALT levels among blood donors. Over the last few decades, the reference range of ALT levels has been animatedly debated owing to attempts to update sex-specific reference ranges. With this backset, Chen *et al* have recently published a study which has two main findings. First, > 80% of individuals with MAFLD had normal ALT levels. Second, there was a linear increasing trend in the association between cumulative excess high-normal ALT levels and the rate of incident MAFLD. This study has biologically credible findings. However, it inaccurately considered sex differences in the MAFLD arena. Therefore, future studies on SLD owing to metabolic dysfunction should adopt locally determined and prospectively validated reference ranges of ALT and carefully consider sex differences in liver enzymes and MAFLD pathobiology.

Key Words: Alanine aminotransferase; Biomarker; History of medicine; Metabolic dysfunction-associated fatty liver disease; Metabolism; Nonalcoholic fatty liver disease; Reference range; Sex differences; Steatotic liver disease

Core Tip: The recent paper published by Chen *et al* has two main findings. First, > 80% of individuals with metabolic dysfunction-associated fatty liver disease (MAFLD) had normal alanine aminotransferase (ALT) levels. Second, there was a linear increasing trend in the association between cumulative excess high-normal ALT levels and the rate of incident MAFLD. Future studies on steatotic liver disease owing to metabolic dysfunction should adopt locally determined and prospectively validated reference ranges of ALT and carefully consider sex differences in liver enzymes and the pathobiology of MAFLD.

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INTRODUCTION

Aim

This editorial comments on the study by Chen *et al*[1]. To put this original contribution into a wider perspective, definitions are provided to illustrate both the aminotransferases and metabolic dysfunction-associated fatty liver disease (MAFLD). Moreover, the history and biology of transaminases are discussed. Next, biological features and reference range of transaminases are summarized. The study by Chen is then outlined, illustrating its points of strength and weakness. Finally, a research agenda is defined.

Definitions

Alanine aminotransferase (ALT) (also named alanine transaminase) is a cytosolic enzyme, involved in metabolism of amino acids, which catalyzes the transfer of the alpha-amino group from alanine to alpha-ketoglutaric acid[2]. ALT serum levels increase because of hepatocellular damage[3], *i.e.* "cytolysis" and are not necessarily associated with inflammation or steatosis[4]. Conversely, by definition, 5% of healthy individuals have abnormal ALT serum levels.

Nonalcoholic fatty liver disease (NAFLD) and MAFLD are two types of steatotic liver disease (SLD), with remarkable differences occurring between the two[5]. NAFLD is a diagnosis of exclusion: *i.e.*, it defines SLD in the absence of any secondary causes of steatosis (notably including significant alcohol consumption, viral hepatitis, and others)[6]. Instead, MAFLD identifies SLD associated with ≥ 2 metabolic abnormalities (among enlarged waist circumference, arterial hypertension, dyslipidemia, prediabetes, insulin resistance, and subclinical inflammatory state) MAFLD does not require the exclusion of competing causes of steatosis (such as alcohol and viral hepatitis)[6]. Stated otherwise, the MAFLD nomenclature allows assessing the interaction between alcohol consumption and metabolic dysfunction which, by definition, is not permitted by the NAFLD nomenclature[7].

Various operational definitions of the Metabolic Syndrome (MetS) have been proposed between 1998 and 2009[8]. Conceptually, all maintain that the MetS is a cluster of cardio-metabolic factors. MetS is often triggered by an expanded and dysfunctional visceral adiposity, which is eventually conducive to insulin resistance–with or without impaired glucose metabolism and type 2 diabetes (T2D)–atherogenic dyslipidemia, and arterial hypertension among a substantial proportion of individuals[9]. Of concern, the individual features of the MetS tend to aggregate as time passes. Therefore, the presence of each of these constituents tends to predict the future incidence of additional components of the syndrome over time[9]. Initially believed to be "*the hepatic manifestation of the MetS*", NAFLD should now be more appropriately defined as both the cause and the effect of the MetS. Indeed, NAFLD and the MetS form a mutual and bi-directional relationship[10]. Therefore, several studies support the logical expectation that biomarkers allowing the identification of NAFLD will also be able to capture the MetS.

Based on analysis of approximately 200000 individuals in China, Zhou *et al*[11], found a significantly higher prevalence of MAFLD in men than in women (54.37% *vs* 20.88%). Additionally, fewer than 20% of men conducted a healthy lifestyle pattern as opposed to more than 90% of women[11]. This study confirms that NAFLD is more common among men than in pre-menopausal women and that, after menopause, women lose this "protection" from developing NAFLD[12]. Alarmingly, although seemingly spared by NAFLD, women exhibit a higher risk of disease progression towards more advanced forms of fibrosing liver disease[13]. Collectively, these sex differences support the notion that investigators designing and running research in this field should accurately consider sex differences in the NAFLD arena[14]. The same holds true for MAFLD.

Pathobiology, and modifiers of transaminase levels

Both the ALT and aspartate aminotransferase (AST) are released from damaged hepatocytes into the blood after hepatocellular injury or death[3]. Although this enzyme is found in other organs, particularly elevated levels of ALT are found in the liver[3]. Accordingly, ALT is deemed to be a more specific index of liver diseases than AST, which is found in both cytosol and mitochondria of several non-hepatic tissues including heart, skeletal muscle, and blood[3,15].

In the pre-hepatitis C virus era, serum levels of ALT were widely used to screen blood donors for the so called "non-A, non-B hepatitis" (NANBH). At that time, the odds of developing NANBH were higher in recipients of blood products from donors with ALT levels ≥ 60 international units (IU) per milliliter compared to those with ALT values < 29 IU/mL,

(45% *vs* 6%, respectively)[16]. Currently, measurement of serum ALT levels is the most frequently used test to identify patients with liver disease of different severity and etiology[2].

ALT values < 300 U/L are considered nonspecific. However, more marked elevations, *i.e.* ALT ≥ 500 U/L are compatible with viral hepatitis, is chemic hepatitis (shock liver), and toxin-induced liver damage, all conditions that primarily affect hepatocytes. The absolute level of the ALT elevation does not necessarily correlate with the extent of liver cell damage and has, therefore, limited prognostic significance[15]. Nevertheless, greatly elevated ALT levels are associated with hepatocellular diseases[15].

A large survey conducted in Italy among 21296 apparently healthy blood donors aged 18 years to 65 years found that the independent predictors of ALT were: male sex, body mass index (BMI), glucose, lipids, ferritin, hypertension, and younger age[17].

HISTORY OF TRANSAMINASES AND REFERENCE RANGE

In 1957, three distinguished Italian Researchers, Professors De Ritis *et al*[18] (whom, as a medical student and young fellow in gastroenterology, I had the privilege to know personally), published in *Clinica Chimica Acta* an original study. Their manuscript followed two previous reports from the same group published in 1955 on the same topic (in Italian). It was destined to change the history of hepatology by introducing the first (and still universally used) sensitive and specific non-invasive biomarker of liver disease. In their report, these eminent authors, based on a patient population comprising *"55 cases of acute viral hepatitis, 20 cases of convalescent viral hepatitis, 10 cases of bacterial hepatocholangitis, 13 cases of obstructive icterus, 13 cases of liver cirrhosis and 10 cases of congestive heart failure with hepatic enlargement"*, observe *"a remarkable increase in the transaminase activities"*, with an inversion in their AST/ALT ratio[18].

Multiple factors are acknowledged to affect ALT determinations, including age, sex, ethnicity, physical activity, muscle disease, medications, and metabolic disorders[2]. Ethnic differences in ALT values between Caucasians and Hispanics as well as between Blacks and Hispanics; Hispanics *vs* Caucasians and Blacks have been reported in children and adults by various authors[19]. However, findings are sometimes conflicting. An old study conducted among 7,495 white and 1,842 black participants without diabetes in the Atherosclerosis Risk in Communities Study found median ALT levels to be significantly higher in white participants than in black participants[20]. Conversely, a more recent study conducted among 6719 individuals found that African Americans had significantly lower ALT serum values than non-African Americans, irrespective of BMI levels[21]. Therefore, all the above listed modifiers cannot be neglected when establishing local reference ranges of ALT.

The reference range for ALT level, first established in the years spanning from the 1950s to the 1980s, has changed little since then[15]. Similarly, to other clinical laboratory tests, the normal range was the mean of values from a "healthy group of individuals" ± 2 SD. Serum levels of ALT normally are low such as 10 to 40 U/L in most laboratories; however, normal values may vary greatly among laboratories[15].

It should be noted that the "healthy reference populations" used at those times included men and women, often medical students, blood donors, and laboratory technicians[3]. This raises the question whether previously established normal ALT range are really accurate[3]. Another Italian group, led by Prati *et al*[22], addressed the notion that those-called "reference" populations were likely to include many individuals with NAFLD, probably underestimating the true prevalence of chronic liver disease. Those lifestyle habits predisposing to NAFLD are widespread in many countries. Therefore, these investigators thought that a critical revision of ALT limits would require the definition of "healthy ranges" rather than a generic update of "normal ranges". To this end, a population with negligible risk of liver disease was identified, by assembling donors who had normal BMI, serum levels of cholesterol, triglyceride, and glucose, and no use of medication. With this strategy, Prati *et al*[22] defined healthy serum ALT values at < 30 U/L for men and < 19 U/L for women. In 2010, Lee *et al*[23] used Prati's criteria [modified by the BMI cutoff points for Asians (< 23 kg/m^2)] in their cohort of 1,105 potential liver donors (643 men and 462 women) with histologically normal livers. These authors found that the healthy ALT values were 33 IU/L for men and 25 IU/L for women[23]. Another study, conducted among 7,403 Koreans (average age: 48 years, 49.9% were male) reported that the upper limit of the healthy range of the serum ALT level was 31 IU/L for males and 23 IU/L for females[21]. Interestingly, this study also found that *"An unhealthy normal ALT level"*, [defined as patients with serum ALT level of 31–40 IU/L (males) or 23–40 IU/L (females)], was associated with a higher prevalence of the MetS and insulin resistance[24].

A recent systematic review concluded that the normal range of ALT should indeed be redefined; however, this redefinition should be done according to localized data, keeping into account regional differences, methods used in ALT measurements, and the upper limit of normality[25].

SUMMARY OF AND COMMENTS ON THE STUDY PUBLISHED IN *WORLD JOURNAL OF GASTROENTEROLOGY*

In this issue of *World Journal of Gastroenterology*, to investigate the associations between repeated high-normal ALT measurements and the risk of new-onset MAFLD prospectively, Chen *et al*[1] followed a cohort of 3553 individuals (1741 men and 1812 women) for four consecutive health examinations over a 4 year period. The study has two main findings. Firstly, the large majority (> 80% of participants) of MAFLD patients had normal ALT levels. Secondly, there was a linear increasing trend in the association between cumulative excess high-normal ALT levels and the rate of incident MAFLD.

Regarding the first finding, a British study conducted among 436 MAFLD patients, 288 of whom submitted to liver biopsy, found that applying a lower upper normal limit (UNL) in aminotransferases would make the fraction of individuals with either advanced fibrosis or biopsy-proven metabolic dysfunction-associated steatohepatitis and normal biochemistry to fall substantially[26]. This study provides clear rationale for revising current UNL although it must be acknowledged that reducing the ALT normal range might lead to an increase in unnecessary second-line investigations in clinical practice.

This investigation follows an "ambispective" (or ambidirectional) study design. In other words, it uses preexisting data (*i.e.*, the exposure has already occurred, before the study), but an outcome has yet to materialize and therefore needs prospective monitoring. This type of study design is believed to be especially useful in assessing events/phenomena that take time to occur, and exposures that could trigger multiple outcomes of interest[27]. Additionally, this is a "cohort" study. "Cohort" literally means a fraction (of soldiers of an ancient Roman Legion) and cohort studies are ideally suited for studying exposures of low occurrence (*e.g.*, environmental disasters)[27], which is not the case of MAFLD, a common disorder worldwide.

As a hybrid model (namely combining retrospective and prospective features), ambispective cohort studies, compared to prospective and retrospective designs, have both advantages and disadvantages. This type of cohort study is useful for analyzing exposures that may have both short- and long-term outcomes, or more than one outcome; it may be useful for analyzing outbreaks, epidemics, or other unexpected and unpredictable events, for which data must necessarily be collected retrospectively[27]. Conversely, lifestyle habits may vary over time while a study is being conducted, particularly among those individuals who have been enrolled in clinical studies[28]. Additionally, the incidence rate of MAFLD in China, based on a recent study conducted among 6873 individuals, followed for 4.6 years, was 27.0% (95%CI: 25.5%-28.4%)[7]. These data imply that MAFLD is not a rare disorder and, indeed, it will develop in more than one in four individuals during a time frame < 5 years in China.

Another point to consider in the study by Chen is the range of ALT which has been considered normal of ≤ 40, irrespective of sex[1]. As, illustrated above, this option may be amenable to criticism given that it fails to adopt both the "updated" reference range and to consider sex differences related to this range[22].

Not with standing these methodological limitations, which prevent accurate analysis of sex differences, it is noteworthy that the study by Chen conceptually agrees with a previous study by Chang *et al*[29]. These authors found that, inapparently healthy, nondiabetic Korean men, increased ALT concentration, even within the reference interval, was an independent predictor of incident NAFLD[29].

Finally, when discussing the recommended range of ALT for assessing SLD, it is important to consider that lowering the ALT cut-off improves the diagnosis of MASLD with advanced fibrosis in primary care[30].

CONCLUSION

Many decades have elapsed since pioneering studies supporting the use of ALT in clinical practice were published. However, although more accurate methods to ascertain liver disorders and hepatic fibrosis have since become available, ALT remains the most widely used biomarker of liver damage globally[17]. ALT still maintains its diagnostic value in the MAFLD arena. Unexpectedly if compared to the quite restricted patient population in which it was first validated[18], the determination of ALT has been extended to predict outcomes other than viral hepatitis. High ALT values though in the normal range predict incident diabetes[31] and are associated with the MetS[32]. Moreover, a strong network interaction links NAFLD/MAFLD with cardiovascular risk, explaining why serum ALT within the normal range may be considered as a novel factor of cardiometabolic risk[33].

Future, prospective, population studies on SLD owing to metabolic dysfunction should rigorously adopt updated (and possibly locally determined and accurately validated) reference ranges. Moreover, sex differences should carefully be considered across the whole spectrum from hepatic enzymology to pathobiology of SLD due to metabolic dysfunction. Finally, the need for adopting updated and more restrictive reference ranges of ALT should always be balanced with the risks of losing diagnostic specificity, which would overload local Health Systems with a heavy burden of false positives.

FOOTNOTES

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Country of origin: Italy

ORCID number: Amedeo Lonardo 0000-0001-9886-0698.

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