Section A -Research paper

Hepatic Transaminase and Other Prognostic Lab in ACS

Kamel Hassan Ghazal, Nader Talaat Kandeel, Mohamed Abdelaziz Abdelgawad Ali , Ahmed Said Eldamanhory

Department of Cardiology, Faculty of Medicine, Zagazig University, Egypt

***Corresponding author:** Mohamed Abdelaziz Abdelgawad Ali
Email: Melsaba138@gmail.com

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Abstract:

Elevations of hepatic transaminase (serum alanine transaminase [ALT] and serum aspartate aminotransferase [AST]) levels in patients with acute coronary syndrome (ACS), although transient, may result in exclusions from clinical efficacy trials due to suspected liver disease.

Key words: Hepatic**,** ALP**,** GGT

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Introduction:

The four liver enzymes alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), ALT and (AST) are commonly measured in clinical context to determine liver disease, as they are released into the blood stream after liver injury **(1)**

Because AST has a relatively short half-life compared with ALT (18hours vs 36hours), ALT increases more than AST soon after liver injury and, thus, the AST over ALT ratio (referred as 'De Ritis ratio') represents the time course and aggressiveness of disease in most circumstances**(2).**

Because assays for these enzymes are inexpensive and routinely applied in clinical laboratory tests, they may be useful for the rapid identification of individuals at high risk for certain diseases. Indeed, a growing body of epidemiological evidence indicates that blood levels of liver enzymes are associated with liver injuries and with a wider range of disease outcomes, including type 2 diabetes mellitus, non-alcoholic fatty liver disease and cardiovascular diseases (CVD), as well as with all-cause and cause-specific mortality **(2)**

However, previous prospective studies have predominantly focused on GGT and its associations with incident CVD and all-cause mortality, whereas ALP and the two transaminases have received less attention **(2)**

As far as we are aware, no prospective study has been conducted to comprehensively evaluate the associations of ALT with risks of the most common cancer entities lung, prostate and breast, and no study so far has examined the associations of ALP and AST with any organspecific cancer entities. In addition, the AST/ALT ratio (De Ritis ratio) has been studied as a prognostic tool in patients with various diseases, but less so as a risk factor for mortality and not at all in relation to incident chronic diseases in general, including CVD **(3)**

Elevated activities of the two serum transaminases; ALT and AST maybe associated with liver disease. Elevation of

the levels of any of the two enzymes has been found in 7.9% of the general population, whereas the prevalence of high ALT levels may reach 20% in diabetics **(4)**

Elevation of these enzymes is strongly related to obesity, diabetes and dyslipidemia, and their measurement may act as a surrogate marker of NAFLD presence. Of the two enzymes, ALT appears to have a role in gluconeogenesis, and seems to be more related to liver fat accumulation than AST. Some authors have suggested that minor elevation of this enzyme's level may be a good predictor of mortality from liver disease **(5)**.

A study of the association of serum ALT activity and ten-years' risk of CVD in participants of the Third National Health and Nutrition Examination Survey (NHANES-III) had reported that those with elevated ALT levels had a higher calculated CVD risk than those with normal ALT activity, if viral hepatitis or excessive alcohol consumption were excluded. **(6)**

AST structure, function and circulating levels

AST structure is similar across various species. In humans, AST exists as two genetically and immunologically distinct isoenzymes: cytoplasmic AST (cAST or GOT1) and mitochondrial AST (mAST or GOT2), **(7)**

Both isoenzymes catalyze the same reaction albeit with different kinetics, share a sequence homology of ~45% and are thought to have evolved from a common ancestral gene (via gene duplication). The enzyme consists of two identical dimers where each dimer consists of a large and a small domain **(8)**

Each monomer of cytoplasmic AST represents a polypeptide chain of 413 amino acid residues with a secondary structure consisting of α-helices and β-strands and a molecular weight of approximately 45 kD**(7)**.

Each dimer has an identical binding site for pyridoxal 5'-phosphate which is located in the dimer interface (Figure 1). Pyridoxal-5'-phosphate is stabilized by a number of surrounding amino acid residues. The human mitochondrial pre-AST contains 430 amino acid residues (deduced from nucleotide sequence analysis of cDNAs) including N-terminal 29-amino acid sequence which is required for enzyme entry in mitochondria **(9)**

Cytoplasmic AST is more acidic (isoelectric point ~5.5) compared with mitochondrial AST (isoelectric point >8). While mitochondrial AST exists as a single form, cytoplasmic AST exists in 3 to 5 isoforms detected by isoelectric focusing. In the liver, 80% of AST activity is found in mitochondria and 20% in cytoplasm **(7)**

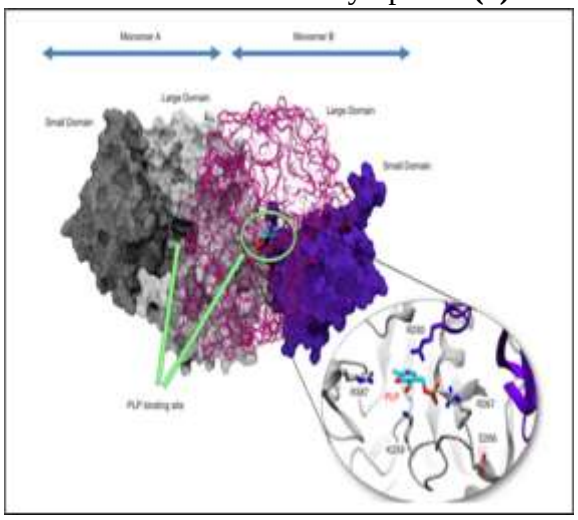

Figure 1: Structure of human cytoplasmic aspartate aminotransferase. Catalytically important amino acid residues are shown with one letter symbol and number. E, glutamic acid; K, lysine; R, arginine; PLP, pyridoxal-5'-phosphate.(9).

Roles of AST and ALT

Aminotransferases are chemicals that the liver uses to make glycogen. Glycogen is

the stored form of glucose, the sugar that the body uses for energy. Any glucose not immediately used will be changed into glycogen. It is then stored in cells for future use. Most will be stored in the liver. The leftover amount will be warehoused in the: Skeletal muscles, Glial of the brain, other organs **(10)**

AST: is found in a variety of tissues, including the liver, brain, pancreas, heart, kidneys, lungs, and skeletal muscles. If any of these tissues are damaged, AST will be released into the bloodstream. While increased AST levels are signs of a tissue injury, it doesn't always relate to the liver **(11).**

ALT: is found mainly in the liver. If your ALT level is high, this may be a sign of a liver injury. It could be minor or severe. Occasional increases in ALT may occur when you have a short-term infection or illness. Sustained increases are more serious. That's because this may mean there's an underlying disease and a greater chance of liver damage**(11)**

The risk factors that associated with Increased AST and ALT level.

Like ALT, AST is present in significant quantities in hepatocytes, Although ALT is present in the cytosol, AST is present in the mitochondria. Increased serum ALT reflects cell membrane damage and leakage; significant AST increases tend to reflect more serious hepatocyte damage because the mitochondria are not damaged as readily as is the cell membrane **(12)**

AST is, however, present in significant quantities in many other tissues, including muscle and RBCs; therefore, increased AST is not as specific for hepatic injury as is increased ALT. Exercise and intramuscular (IM) injections may increase serum AST **(12)**

The most common causes of increased AST include hepatic disease, muscle disease (inflammation or necrosis), or hemolysis (spontaneous or artifactual). Increased AST is an indication to measure serum ALT to determine whether the increased AST is from the liver (significant increases in both ALT and AST suggest that AST increases are of hepatic origin). One may also measure the hematocrit and observe the color of the plasma and serum on a centrifuged blood sample to check for hemolysis **(12)**.

Continuous AST (entered as natural logarithm of AST values) was not associated with all-cause or CVD mortality. However, an AST level >37 U/L was associated with the risk of all-cause and CVD mortality in the hepatitis B surface antigen negative subjects after adjustment for age, body mass index, smoking, alcohol consumption, education, physical activity, diabetes, total cholesterol, high-density lipoprotein, systolic and diastolic blood pressure and C-reactive protein **(13)**.

Adding AST in a multivariable model alongside baseline demographic and clinical variables did not improve discrimination power of the model for mortality at 35 or 20 years of follow-up. However, AST improved risk discrimination for mortality at 10 years of follow-up **(14)**

De ritis ratio

The ratio of serum AST and ALT was initially described by De Ritis and has been known as the De Ritis ratio. Over the past several decades, it has subsequently been shown to be a useful prognostic predictor in critical illness and malignant tumors, including acute myocardial infarction,

cardiovascular surgery, metastatic renal cell carcinoma, and upper tract urothelial carcinoma **(15)**.

Liver dysfunction is central in Secondary Hemophagocytic Lymphohistiocytosis (sHLH). Elevated liver enzymes, hepatomegaly, and coagulopathy are signs of liver involvement. In fact, the inclusion of increased transaminase levels was supported by the 2009 ASH guidelines for the diagnosis of sHLH from Professor **(16)**

Several observational studies indicated that patients with sHLH who had hepatic involvement had significantly worse overall survival than those patients without hepatic involvement. It is crucial for physicians to identify poor prognosis patients earlier after diagnosis and before treatment and to apply effective combination therapy. However, data identifying relevant hepatic prognostic factors for patients with sHLH are lacking **(12)**.

Epidemiological evidence for an association between AST, ALT and CVD and mortality

The activity of ALT in the hepatocytes is 7000-fold greater than in the serum, and this abundance is the reason for using it as a marker for non-alcoholic fatty liver disease (NAFLD) in many epidemiological studies. Clark et al. proposed that elevated AST or ALT levels are predictive of the presence of NAFLD if two basic criteria are met: 1) exclusion of alternative chronic liver diseases, e.g., alcoholic liver disease, hepatitis B or C infection, and hemochromatosis; and 2) presence of features of the metabolic syndrome **(17).**

Although AST activity is higher in myocardium compared with ALT or GGT, AST has drawn less epidemiological interest with respect to the association with CVD compared with other enzymes. In this narrative review, the existing epidemiological evidence will be assessed without time or type of the study restriction. AST was mostly investigated in the setting of the association of liver enzymes with CVD. As a consequence, evidence on the association between AST and CVD remains limited**(18).**

Following the first report of increased AST activity in patients with acute myocardial infarction, measurement of serum AST was routinely used for the diagnosis of this disease. Numerous studies over the subsequent 2 decades investigated the AST value for the diagnosis, quantification of ischemic damage (necrosis) and risk stratification of patients with acute myocardial infarction. **(19)**

In acute myocardial infarction, AST start raising 6 to 8 hours after the symptom onset, reaches the peak level at 24 to 36 hours and returns to normal in 3 to 7 days. Reperfusion by thrombolysis or balloon angioplasty shortens the time to AST peak value **(20)**

The widespread distribution of AST across human tissues (particularly in liver and skeletal muscle) and relatively late increase in serum activity following coronary occlusion are disadvantages of this test with respect to the diagnosis of myocardial infarction. Since more sensitive biomarkers of myocardial ischemia/necrosis became available, AST is no longer used for the diagnosis of acute myocardial infarction **(21).**

Mechanisms of association of AST, ALT with CVD.

The underlying mechanisms of the association between AST and the risk for CVD or mortality are mostly hypothetical. It is

important to note that there is no conclusive evidence that AST activity in serum parallels AST activity within the cells **(7)**

Although, transamination is a fundamental reaction in the metabolism, a direct link between metabolic derangement associated with high or low AST levels and CVD remains largely unexplored. Furthermore, there are no known specific physiological function of AST in circulation outside the function as constituent of plasma proteins **(7)**

Thus, in order to explain the risk associated with AST, attention should be focused on underlying morbid conditions that are associated with high or low AST levels. For ease of presentation, putative mechanisms linking high and low AST levels with CVD or mortality are analyzed separately. An association between elevated AST level and the risk for CVD may be explained by at least four mechanisms **(17)**

First, the most common cause of AST elevation in circulation is liver disease. The most relevant liver disease with respect to the association with CVD is NAFLD. NAFLD is a progressive liver disease occurring in the absence of excessive alcohol consumption that is characterized by intrahepatic triglyceride accumulation and inflammation and hepatocyte injury progressing gradually to liver fibrosis, cirrhosis and hepatocellular carcinoma **(22)**

Second, an elevated AST level is associated with cardiovascular risk factors, particularly, metabolic syndrome, abdominal obesity, insulin resistance and diabetes. In the Framingham Heart Study, elevated liver enzymes (ALT and AST) were associated with increased risk for arterial hypertension, diabetes, metabolic syndrome, impaired fasting glucose and insulin resistance estimated by HOMAIR. The associations between liver enzymes and metabolic disorders persisted after adjustment for visceral fat and insulin resistance. However, the association was stronger for ALT than AST **(23)**

Third, elevated AST may reflect chronic alcoholism. A thorough discussion of cardiovascular effects of alcohol is outside the scope of this review.

Although it has been repeatedly reported that moderate alcohol consumption may have salutary effects on coronary arteries (and consequently on the risk for coronary artery disease) any amount of alcohol is toxic to myocardium. Chronic alcohol consumption is associated with increased oxidative stress, lipid peroxidation, acetaldehyde toxicity and increased local (hepatic and myocardial) and systemic inflammation (particularly increased expression of tumor-necrosis factor alpha, and inflammatory cytokines),**(24)**

Fourth, elevated AST level may be a marker of structural CVD. Release of AST from myocardium in conditions of increased stress (such as stress imposed by cardiovascular risk factors) or acute ischemia/necrosis (acute coronary syndromes) or reperfusion-related injury may also explain the increased cardiovascular risk associated with higher AST levels. Historically, AST was the first biochemical test used for diagnosis of acute myocardial infarction and the biomarker was used in clinical setting for diagnosis of this condition until substituted by more sensitive tests **(25)**

Finally, if AST and ALT share common factors underlying their low activities as recently suggested, then putative factors underlying low ALT levels may also underlie low AST levels and association with CVD. Concluding remarks This narrative review summarized the existing knowledge on the association between AST and CVD. AST activity in serum is routinely assayed and used for the assessment of liver disease. In addition, AST is a reliable marker of general health and high and low levels of this biomarker have clinical meaning.

In this regard, abnormal values of AST activity in serum not occurring in the setting of clinically overt inflammatory liver disease may be a harbinger of health problems that need to be investigated. An elevated AST level (outside inflammatory liver disease) may indicate an increased CVD risk **(26)**.

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