

## A COMPREHENSIVE REVIEW ON DIAGNOSTIC APPLICATIONS OF THE ENZYME ALANINE AMINO-TRANSFERASE

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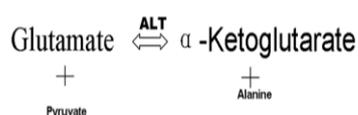
### ABSTRACT

Alanine aminotransferase is major enzyme present in living organisms. This enzyme is responsible for transfer amino group from alanine to  $\alpha$ -ketoglutarate. Activity of that enzyme depends on pyridoxal phosphate enzyme. In both males and females specific concentration of this enzyme is present. Alteration of this enzyme concentration in body cells suggests some kind of liver injuries, so this enzyme acts as diagnostic biomarker for liver injuries. In laboratory testing, the method which is easy to use for the determination of the level of alanine aminotransferase (ALT) is blood. ALT activity in the body determines the performance of the liver function and its diseases and gives an indication for the health of the person. However ALT activity in the body is changed by different factors such as age, hepatitis due to virus, alcohol intake, and medicines which are used. Alanine Aminotransferase (ALT) is present in blood serum and also in different body tissues. Liver disease, diabetes and some other diseases are due to the increased concentration of ALT in the body. For type 2 diabetes,  $\beta$ -sitosterol and hyperoside are taken as a ligand in molecular docking. Crystallography technique gives the molecular structure of Alanine transeminase enzyme and it is also present in the PDB data in the form of 31HJ which is also used in Schrodinger equipment for docking analysis. Alanine transminase and their ligand  $\beta$ -sitosterol and hyperoside describes that they were the better molecules with docks and their targets to associated with diabetics. After the blunt abdominal trauma the highly damaged organ is the liver. Persons with small indication of blunt abdominal trauma are difficult to find the liver damage in such persons.

**KEYWORDS:** Alanine aminotransferase.

### INTRODUCTION

Alanine aminotransferase discribed as ALT. ALT has also other set of names such as alanine transaminase, serum glutamic pyruvic transaminase or alanine aminotransferase represented by ALAT (Liu *et al.*, 2014). The enzyme commission of ALT is 2.6.1.2. that enzyme displaces amino group by alanine to  $\alpha$ -ketoglutarate.

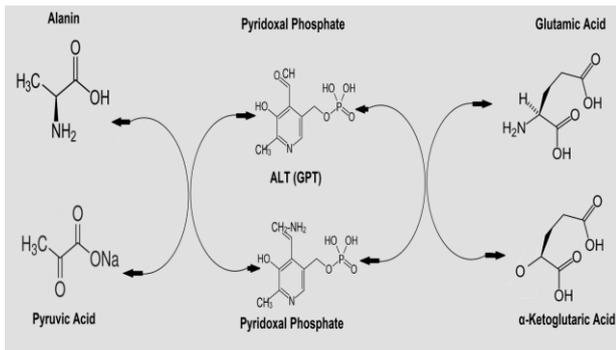


In women and man its value as follows: 5–38 IU/L, 10–50 IU/L. high concentration of that indicates different abnormal conditions in the body such as liver abnormality, heart malfunctioning etc. ALT help as to find liver necrosis or diseases. It is act as indicator for hepatic abnormality as it is found at cytosol of hepatocyte (Makheswari *et al.*, 2013). ALT is routinely

used in laboratory. The ALT concentration can be high in some diseases like muscles problem and hepatitis infection.

### Structure of Alanine Aminotransferase

ALT found in the cytosol of liver cell. It has four hundred ninety six amino acids, half life 47hrs. The portion of the DNA which is also called gene which formed ALT is found on chromosome number eight. This enzyme used in tricarboxylic acid cycle and that enzyme transfer amino group from L-alanine to  $\alpha$ -ketoglutarate and produces L-glutamate and pyruvic acid. Pyridoxal phosphate is used in that reaction (Makheswari *et al.*, 2013).



Mainly ALT is present in hepatocytic cells and in serum its very low concentration is present. And the activity of this enzyme is 3000 times higher in hepatocytes as compare to serum ALT. when any injury to liver cells occurs it is being released into serum and increases the ALT activity in serum, which can be actually used as marker for diagnosis of hepatocytes injury.

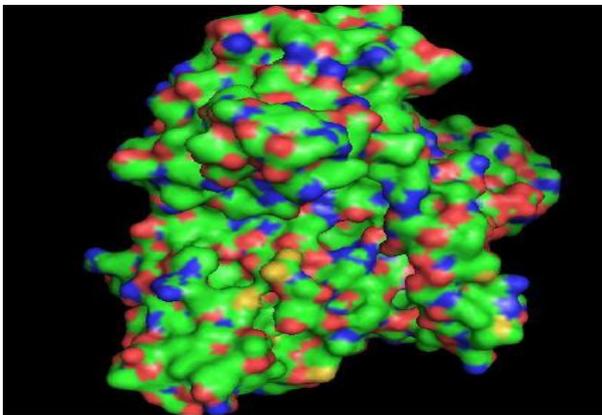


Figure 1: 3D structure of alanine aminotransferase.

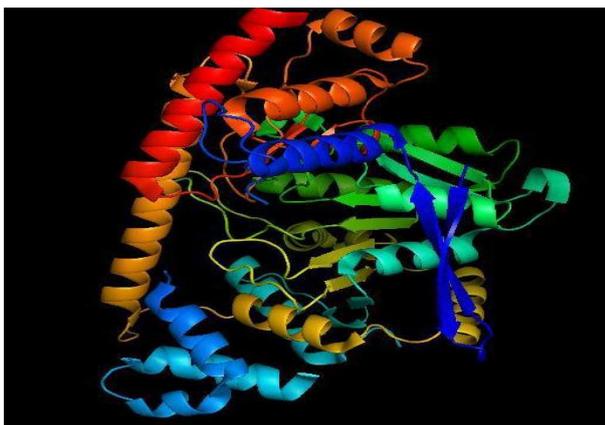


Figure 2: Structure of Alanine transaminase.

#### Chemical Formation and Physiology of ALT

ALT can be found in the cytoplasm of liver cell (Sherman *et al.*, 1991). ALT has four hundred ninety six amino acids, half-life of  $47 \pm 10$  hrs (Ishiguro *et al.*, 1991), and formed by ALT gene, that is present at chromosome eight (Sohocki *et al.*, 1997). Functionally, that enzyme transfer amino group from L-alanine towards alpha-ketoglutarate and the end gives L-glutamate and pyruvic acid (Figure 3).

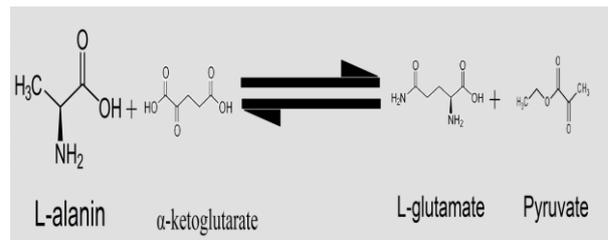


Figure 3: shows the conversion of L-alanine and Alpha-ketoglutarate into pyruvate and L-glutamate.

The transamination reaction completed with ALT has important in TCA. For that pyridoxal phosphate is necessary (Sherman *et al.*, 1991). ALT activity in liver has rounded about three thousand times greater as compared to ALT activity in blood (Sherman *et al.*, 1991). Whenever liver shows abnormality, ALT is discharged by hepatocyte and shows increase blood serum ALT activity. ALT found in muscle adipose tissues and brain. (Yanai *et al.*, 2005), the amount of ALT at such organ was very low as compared to liver (Weibrecht *et al.*, 2010).

#### Clinical Factors Associated with Serum ALT Level Hepatic causes

Viral hepatitis (mostly hepatitis B and C virus) are the important reasons in increasing alanin-aminotransferase level throughout the world (Pendino *et al.*, 2005). person infected with chronic and acute hepatitis ALT activity has a sign of liver damage (Rehermann *et al.*, 2005). Increase in ALT level mostly seen in catalytic acute stage and after that in effective HBV removal (Liaw *et al.*, 2007) told the change in ALT activity by HBV infection ALT activity is a important sign for the treatment selected in person suffering from HBV (Liaw *et al.*, 2007). however that in debatable and (Lai *et al.*, 2007) show fibroses and inflammation at 37 persons suffering from HBV also has normal ALT level (Lai *et al.*, 2007). in contrast to HBV infection, the ALT level as not much important in HCV diagnosis and treatment, most person suffering with SCV lead to chronic hepatitis permanent lever cell injure (Rehermann *et al.*, 2005). more than 6 out of 10 in SCV carrier have normal ALT concentration or few increase in ALT concentration  $< 2$  time the higher range of normal [ULN] with oftenly liver histologic lesion verified with liver biopsy (Alter *et al.*, 1981). changes in the ULN of ALT level (29 IU/L in men and 22 IU/L in women) is the suited way for identification of HCV infections in US population has a greater ratio of HCV infection (Ruhl *et al.*, 2013). However, HCV-RNA titer is strongly associated with ALT elevation, researchers described about 68% patient with +ve HCV-RNA concentration has ALT increase with asymptomatic blood donor which examined +ve with antibodies to HCV(anti-HCV).

#### Alcohol Consumption

Over alcohol consumption is a major reason of ALT elevation in peoples. In Italy 45.6% results of the liver test is contributed to over alcohol consumption ( $\geq 28$

g/day) (Pendino *et al.*, 2005). However at US peoples survey over alcohol consumption (>1 time/day) is major reason in ALT increase after that HCV infection (Clark *et al.*, 2003), ALT activity had directly linked to duration of alcohol consumption and quantity of it. For some duration and low quantity of alcohol intake did not increase the ALT level by a considerable amount in young's (Gunji *et al.*, 2010). However few differences are present in the results because of the biological results of alcohol misuse. A survey was conducted in UK in which alcohol abusers from the different countries is included the result of that shown that people from south Asia are more likely to be liver damage by alcohol abuse (Wickramasinghe *et al.*, 1995). Short consumption of alcohol does not affect majorly the ALT elevation because it also had effect on insulin sensitivity improvement (Alatalo *et al.*, 2008).

### Autoimmune hepatitis

Autoimmune hepatitis is not commonly a liver disease, and the phenomenon by which autoimmune hepatitis develops is not well known. For the detection of autoimmune hepatitis ALT elevation is available as an instrument. ALT activity gives the indication of the survival of the patient who has undergone immunosuppressive treatment with autoimmune hepatitis. In a survey which is conducted on 84 peoples of Japan which are suffering from autoimmune hepatitis a constantly low level of ALT ( $\leq 40$  U/l) is considered the minimum level with improve prognosis (Miyake *et al.*, 2005). Another survey results shows that a link of constant ALT increase and low survival in 69 autoimmune hepatitis patients (Miyake *et al.*, 2006). ALT assumed an important non invasive marker of inflammation in persons suffering from autoimmune hepatitis (Fabbri *et al.*, 2013).

### Non-hepatic cause

Metabolic problems for example hepatitis due to virus, alcohol consumption and few medicines, all these are called the causes of ALT elevation which is not explainable are contributed to Mets (Liangpunsakul *et al.*, 2005). These results are same to pandemic of obesity (James *et al.*, 2004), Mets show a regular abnormalities such as glucose intolerance, obesity, dyslipidaemia and high blood pressure creates concern throughout the world in recent few years. If we compare the major cause of ALT elevation with Mets the former factor is ignored when compared with major factor. In a survey, ALT levels measured in Mets patients as give as the standered by the National Cholesterol Education Programmed Adult Treatment Panel III (NCEP-ATP-III) criteria, is about thirty percent more as compared participants not having Mets in a male population of south china (Liu *et al.*, 2012). Effect of Mets on ALT increase was progressive and additive with linear trend (Yun *et al.*, 2010; Cotler *et al.*, 2010). Although the ULN values that lies within the limit and that is not considered the impact of Mets was greater as compared to the upgrade values, the dominance of Mets is linked with the increasing

concentration of ALT in the peoples. The community which is based on Korean peoples, the Ors in Mets is the greatest quintiles with ALT was 7.1 times greater as compared to standard quintiles in males while 2.1 times greater in females (Jeong *et al.*, 2004). Whole participants are selected within the ULN values (ULN value 30U/l in men while 19U/l in women) (Jeong *et al.*, 2004). Another Korean national study describe the elevation of Mets fragments as give standard by NCEP-ATP-3 criteria, within the subgroup which has more ALT levels (Suh *et al.*, 2009). Regarding to lipoprotein, ALT is strongly associated by intermediate density lipoprotein (IDL) or apo-lipoprotein B (Apo-B) after which adjust different variables with separate model (Lorenzo *et al.*, 2013). That links are contributed to stable affects in insulin resistance or liver disease with fats in patients has increased ALT level (Gunji *et al.*, 2010). Effect of Mets parts to ALT function is somewhat vary. Effect of separate Mets parts on ALT elevation is disproportionation (Liu *et al.*, 2012). Body mass index (BMI) and waist circumference (WC), give obesity component of Mets that are strongly associated with ALT elevation (Ioannou *et al.*, 2006; Piton *et al.*, 1998). However the exact mechanism is still unknown. Probably mechanism lies in that phenomena of obesity is abdomen fat is potentially associated in visceral organs in which there is accumulation of fats in adipose tissues which are the major factor in causing hepatotoxic fatty acids (Falck *et al.*, 2001). In US population survey (Ruhl *et al.*, 2003). BMI losses its importance while determining the link between obesity or ALT anomalies after that when there is adjustment for leptin, insulin or triglyceride concentration instead of WC that are representation of visceral adipose accumulation giving a sign of BMI that is associated with obesity or ALT anomalies. Other important point is the obesity – ALT increase linked to change by insulin resistance (IR). A survey is based upon Korean adults by national health show that the prevalence of IR was strongly linked to status of obesity (Park *et al.*, 2012). ALT elevation which is induced by OR of obesity is considerably reduced when adjust the homeostasis model (HOMA-IR) is a index of IR level (Matthews *et al.*, 1985). The central obesity is the major Mets part which affects ALT level in population.

### Hemochromatosis

Hemochromatosis a disease which is mostly occurred in peoples of Nordic descent is not the major cause of ALT elevation. Mutation in HFE gene is the main reason of hemochromatosis; while iron over use is the major reason of liver injury. For the diagnosis of hemochromatosis HFE mutation test, blood serum ferritin and total iron binding ability should be measured (Powell *et al.*, 1998). Liver biopsy is done in that patient for the detection of hemochromatosis and liver injury due to iron load and the other test are not so much supportive in such cases.

### Occurrence of Alanine Aminotransferase

Liver is a vital organ of the body and plays very important roles in body like formation of proteins, blood clotting factors, synthesis of triglycerides, glycogen, cholesterol and production of bile. Liver is the largest internal organ of body present in right side of belly. (Wedro *et al.*, 2016) Liver is also involved in metabolization of toxins. Use of alcohols can be too much harmful for liver diseases. Many enzymes are necessary for proper functioning of liver and these enzymes include Alanine-aminotransferase, Aspartate transaminase, Alkaline phosphatase, Gamma-glutamyl transferase. Our main focus of study will be alanine aminotransferase enzyme. This enzyme is produced by hepatocytes in liver. This enzyme is specific diagnostic marker of hepatocellular injury or infection. This enzyme is very specific as compare to other enzymes as this enzyme is abundant in liver tissues and present in very lower concentration in other tissues. The level of this enzyme changes during different situations in body. Level of ALT in body increases when certain drugs are used or strenuous exercises are performed as this enzyme is also involved in production of energy in liver cells. (Wedro *et al.*, 2016).

### ALT as Diagnostic Marker for Liver Diseases

Different diseases can occur in body which includes hepatitis, liver scarring, cancers and harmful effects of toxins or medications on liver. Some of major symptoms of liver diseases are jaundice, pain and swelling of abdomen, bleeding and fatigue etc. Few enzymes of the liver are sensitive to the abnormality that occurs in liver. So, these enzymes are used as diagnostic biomarkers of liver dysfunction. Alanine aminotransferase is one of excellent diagnostic biomarker for detection of liver diseases.

ALT enzyme occurs in kidney, heart, muscles but its high concentration is present in liver. This enzyme is mainly present in cytoplasm and carries out transamination reactions. Normal serum level of ALT is 7–56 U/L. injury to liver cells increases the ALT levels. Level of ALT up to 300 U/L is nonspecific. ALT level equals to 500 U/L or greater than this are observed in different liver diseases like viral hepatitis, liver shock and liver damage caused by toxins. ALT level elevates in case of viral hepatitis like A, B, C, D and E.

Chronic hepatitis can be identified if ALT elevated level remains for more than six month after that attack of acute hepatitis. Decreased insulin sensitivity, adiponectin, reduced glucose tolerance as well as elevated level of free fatty acids and triglycerides are also associated with increased ALT level. Metabolic syndromes risk in adults increases with increase in ALT level.

### Effect of Age on Alt Level

Level of ALT is fall down in both sexes i.e. male and female with increase in age. And this change in ALT level is independent of syndrome components, adiposity

signaling biomarkers etc. (Dong *et al.*, 2010). Effect of age on the ALT change is based on quantitative discrimination, and has the importance in diagnostic value for prediction of all factor and disease specific mortality. Recent authoritative review (Kim *et al.*, 2008) shown that high ALT level increases the death rate in general population, however that point is debate able in old persons. During the several survey on old peoples indicates the inverse relation between ALT activity and death rate (Elinav *et al.*, 2006), however that was verified by meta analysis (Liu *et al.*, 2014). ALT activity may be linked to increasing age of a person or fragility in older peoples (Dong *et al.*, 2010). The role in screening the liver physiology is independent. However age increasing factor has its own importance in a lot of covariate studies (Chen *et al.*, 2007), as in peoples low ALT level has a major role in death rate therefore clinicians must carefully describe the very low level of ALT as in case of older peoples.

### Upper Limit of Normal (ULN) For ALT as a Hot Scientific Topic

Formal ULNs for ALT level are given as standered in donor blood along with non-B, non- C hepatitis is between forty to fifty U/l (Aach *et al.*, 1981). That standered does not consider metabolism covariates that caused liver and low to high ALT elevation (Mathiesen *et al.*, 1999). Persons suffering from metabolic abnormalities are increasing therefore ALT values considered important aspect in this regard. Metabolic covariates are included when determining ULNs of ALT activity by a lot of scientist during the last few years. The idea of metabolic anomalies must exluded while determining ULN of ALT level is dangerous to the health of people given in an assignment by (prati *et al.*, 2002). Different scientist re determine the ULN of ALT in young and adult (Lee *et al.*, 2010). In detail ULNs of ALT levels has difference in a sense of ethnicity, either male or female and age distribution. The differences in definition called as healthy subject and method of statistic may also participate to change in ULNs. (Pacifico *et al.*, 2013) is summarized the results of blood serum ALT level and publish their study. The causes of ALT elevation are hepatitis due to virus, more alcohol intake, metabolic abnormalities and also liver disease due to fat (Pendino *et al.*, 2005). Factors listed above and their problem must be removed while determining ULTs of ALT value in that population. However, we re-determine the reports ULNs of ALT value from evaluating important exclusion data in different district as a additive and given the information with category (Table 1,).

**Table 1: Updated Upper Limit of Normal Serum Alanine Aminotransferase Value in Reported Studies.**

Authors, country, year [reference]	Number of enrolled participants' (M/F)	Age of enrolled participants [years, mean $\pm$ SD or mean (age range)]	Exclusion of viral hepatitis $\checkmark$ / $\times$	Exclusion of excessive alcohol consumption $\checkmark$ / $\times$	Exclusion of medication $\checkmark$ / $\times$	Exclusion of metabolic abnormality $\checkmark$ / $\times$	Exclusion of fatty liver disease by imaging tools $\checkmark$ / $\times$	Liver biopsy $\checkmark$ / $\times$	Statistical methods
Piton, et al, France, 1998,[84]	487/546	30 $\pm$ 0.36	$\checkmark$	$\times$	$\times$	$\times$	$\times$	$\times$	95 <sup>th</sup> percentile on sided
Prati et al, Italy, 2002,[107]	3865/2970	29.8 $\pm$ 9.5	$\checkmark$	$\times$	$\checkmark$	$\checkmark$	$\times$	$\times$	95 <sup>th</sup> percentile on sided
Kariv R et al, Israel, 2006,[109]	6124/11374	31.91 $\pm$ 17.07	$\checkmark$	$\times$	$\checkmark$	$\checkmark$	$\times$	$\times$	95 <sup>th</sup> percentile on sided
Poorten et al, Australia, 2007,[110]	206/0	16.8 $\pm$ 1.4	$\checkmark$	$\checkmark$	$\checkmark$	$\checkmark$	$\times$	$\times$	95 <sup>th</sup> percentile on sided
Jamali et al, Iran, 2008,[111]	628/1300	40.7 $\pm$ 14.7	$\checkmark$	$\checkmark$	$\times$	$\times$	$\times$	$\times$	95 <sup>th</sup> percentile on sided
Kibaya et al, Kenya, 2008,[112]	1020/521	30(18-55)	$\times$	$\times$	$\times$	$\times$	$\times$	$\times$	97.5 <sup>th</sup> percentile on sided
Lee et al, Korea, 2010,[108]	643/462 for pathological normality 346/313 met for prati criteria	29.1 $\pm$ 9.0 for all 27.2 $\pm$ 8.4 for men 31.6 $\pm$ 9.3 for	$\checkmark$	$\checkmark$	$\times$	$\checkmark$	$\times$	$\checkmark$	97.5 <sup>th</sup> percentile on sided

It is given in Figure 2, the ULNs of ALT levels in survey removing the subject by metabolic abnormalities was more that without (41.0 $\pm$ 10.8 vs. 27.1 $\pm$ 7.0 U/l). Almost one third lower upon ULN of ALT define when removing the factors that of metabolic disturbances. The adoption of an updated ULN of ALT activity in after studying increased the sensitivity of the diagnosis of strong hepatic disorder with acceptable specific decreased (Wu *et al.*, 2012).

#### Role of Alanine Aminotransferase in Plants

ALT activity has depended on pyridoxal phosphate and that enzyme found in every plant and different parts of plant. The activity of ALT is measured in different region of plant such as leave, flower, root and endosperm. This enzyme has vital role in plant metabolism.

Pyruvate and glutamate are reacted to form alanine and oxaloglutarate by the action of this enzyme. Therefore this enzyme is involved in the formation of various amino acid in the body by metabolizing the carbon compounds. When plants are encountered with less oxygen condition like flooding then that enzyme has important role. When oxygen level available to plants

diminished then activity of this enzyme enhances, therefore accumulation of alanine in plants also enhances. Accumulation of alanine in response to tention condition does not harm plant, but it remains glycolytic flux and maintains carbon and nitrogen stocks in the cell.

#### *Arabidopsis*AlaATI knock-out mutant (*alaat1-1*)

studies demonstrated that ALT not only plays important role in plants during tention stage but also in recovery phase when stress situation is being ended. These enzymes carry out fast conversion of alanine into glutamate again during recovery phase.

#### CONCLUSION

In this article it has been discussed that the blood-serum-ALT activity and the different factors such as age, medication and liver function are studied and show how the activity of ALT is changed with these factors. The level of ALT gives an indication of the liver functions and also helpful in determining the disease of liver. ALT activity and its level are altered in such circumstances such as autoimmune disorder, viral hepatitis, alcohol intake, hemochromatosis thus altering the functions of liver. Obesity also has a significant effect on metabolic abnormalities. The normal values of ALT are mostly

dependent on different district. The association of metabolism and demography factor on ALT activity is studied in various surveys. Low level of ALT may progress to the process of aging; frailty is also increased in young's due to activity of ALT. The first choice of drug docking with Alanine transaminase enzyme in the treatment of diabetes is Metformin. Therefore,  $\beta$ -sitosterol and hyperoside are assumed that these are the developing drugs in the treatment of diabetes. Blood test for the liver function was link with the age and death rate in the older peoples. It has been shown that non alcoholic fatty liver disease (NAFLD) after two obesity are link to increase in mortality and morbidity now a days it can be seen that older people the chances of obesity and weight are more common as compared to young's due to the activity of alanine transaminase activity. A survey is arranged to find out the importance of hepatic transaminases to find out the liver damage and their severity after the blunt abdominal trauma. In that survey all such patients are involved which have undergone treatment in our institutes from January 2008 and December 2010. The degree of liver damage is confirmed by CT scans and surgical findings.

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