

Clinically Important Enzymes and Diagnostic Applications



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Distribution and application of clinically important enzymes

Enzyme	Principle Sources of Enzyme in blood	Clinical applications
Alanine aminotransferase	Liver	Hepatic parenchymal diseases
Alkaline phosphatase	Liver, bone, intestinal mucosa, placenta	Bone diseases, hepatobiliary diseases
Amylase	Salivary glands, pancreas	Pancreatic diseases
Aspartate aminotransferase	Liver, skeletal muscle, heart erythrocytes	Hepatic parenchymal disease, muscle disease
Cholinesterase	Liver	Organophosphorus insecticide poisoning, hepatic parenchymal disease
Creatine kinase	Skeletal muscle, heart	Muscle diseases(M.I.)
γ-glutamyl transferase	Liver	Hepatobiliary diseases, marker of alcohol abuse
Lactate dehydrogenase	Heart, liver, skeletal muscle, erythrocytes, platelets, lymph nodes	Hemolysis, hepatic parenchymal diseases, tumor marker
lipase	Pancreas	Pancreatic diseases
5'-nucleotidase	Liver	Hepatobiliary diseases
Trypsin	pancreas	Pancreatic diseases

Pancreatic enzymes:

Acute pancreatitis is an inflammatory process in which pancreatic enzymes are activated and cause autodigestion of the gland. It is a result of anatomical changes that arise from two events.

1. The first is the autodigestion of the acinar cells by inappropriate activation of the pancreatic enzymes (especially trypsinogen) within the cell.
2. The second is the cellular injury response that is mediated by proinflammatory cytokines.

There are some enzymes that are synthesized and stored as the active enzymes in the zymogen granules. These include **α -amylase**, **lipase**, colipase, RNase, and DNase.

1. **α -Amylase: (EC3.2.1.1; 1,4- α -D-glucan glucanohydrolase; AMY)** is an enzyme of the hydrolyase class that catalyzes the hydrolysis of 1,4- α -glycosidic linkages in polysaccharides. AMYs are calcium metalloenzymes, with the calcium absolutely required for functional integrity.

AMYs normally occurring in human plasma are small molecules with molecular weights varying from 54 to 62 kDa. The enzyme is thus small enough to pass the glomeruli of the kidneys and AMY is the only plasma enzyme physiologically found in urine. The AMY activity present in normal serum and urine is of pancreatic (P-AMY) and salivary gland (S-AMY) origin.

Clinical Significance

Normal values of amylase: 28-100 U/L = 0.48-1.7 μ kat/L

CAUSES OF RAISED PLASMA AMYLASE ACTIVITY

- Marked increase (five to 10 times the upper reference limit):
 - acute pancreatitis:
 - severe glomerular impairment:
 - perforated peptic ulcer especially if there is perforation into the lesser sac.

Pancreatic pseudocyst. If the plasma amylase activity fails to fall after an attack of acute pancreatitis there may be leakage of pancreatic fluid into the lesser sac (a pancreatic pseudocyst). Urinary amylase levels are high, differentiating it from macroamylasaemia. This is one of the few indications for estimating urinary amylase activity, which is inappropriately low relative to the plasma activity if there is glomerular impairment or macroamylasaemia

Macroamylasaemia. In some patients a high plasma amylase activity is due to a low renal excretion of the enzyme, despite normal glomerular function. The condition is symptomless; it is thought that either the enzyme is bound to a high molecular weight plasma component such as protein, or that the amylase molecules form large polymers that cannot pass through the glomerular membrane. This harmless condition may be confused with other causes of hyperamylasaemia

2. **Lipase: (EC 3.1.1.3; triacylglycerol acylhydrolase; LPS)**.is a single – chain glycoprotein with molecular weight of 48 kDa. For full catalytic activity and greatest specificity the presence of bile salts and a cofactor called colipase, which is secreted by the pancreas, is required. LPS is a small molecule and is filtered through the glomerulus. It is totally reabsorbed by the renal tubules, and it is not normally detected in urine.

Clinical Significance

Normal values: 40-200 U/L

Plasma lipase levels are elevated in acute pancreatitis and carcinoma of the pancreas.

Note: serum amylase is increased in mumps, pancreatic disease or due to some other cause, where as lipase is increased only in pancreatitis. Therefore, the determination of both amylase and lipase together helps in the diagnosis of acute pancreatitis.

Liver enzymes:

The assay of serum enzymes is very useful for the differential diagnosis and monitoring of various hepatobiliary disorders.

There are three types of enzymes:

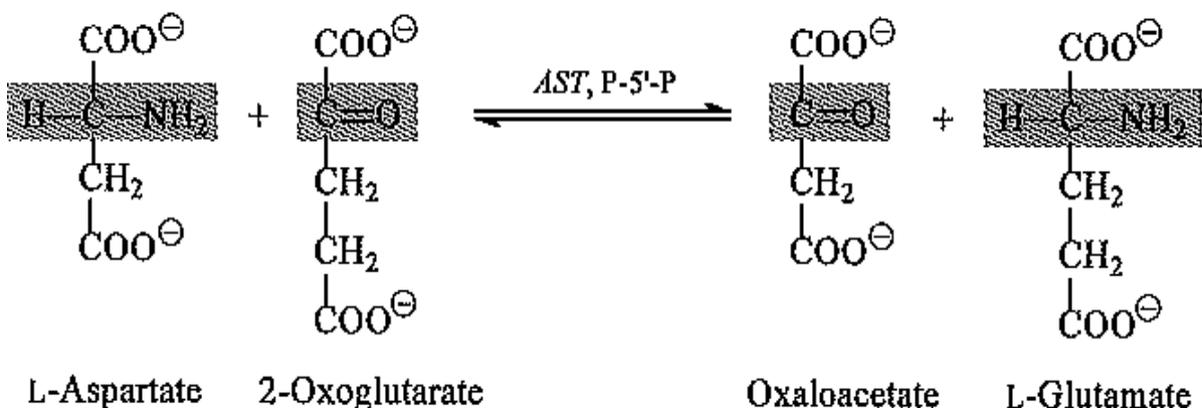
1. Enzymes which are normally present inside the hepatocytes released into the blood when there is a hepatocellular damage= **markers of hepatocellular damage.**
2. Enzymes which are primary membrane bound (plasma membrane or side of hepatocytes) = **markers of cholestasis.**
3. Enzymes which are synthesized in the hepatocyte= **indicates disturbances in the hepatocellular synthesis.**

1. Markers of hepatocellular damage.

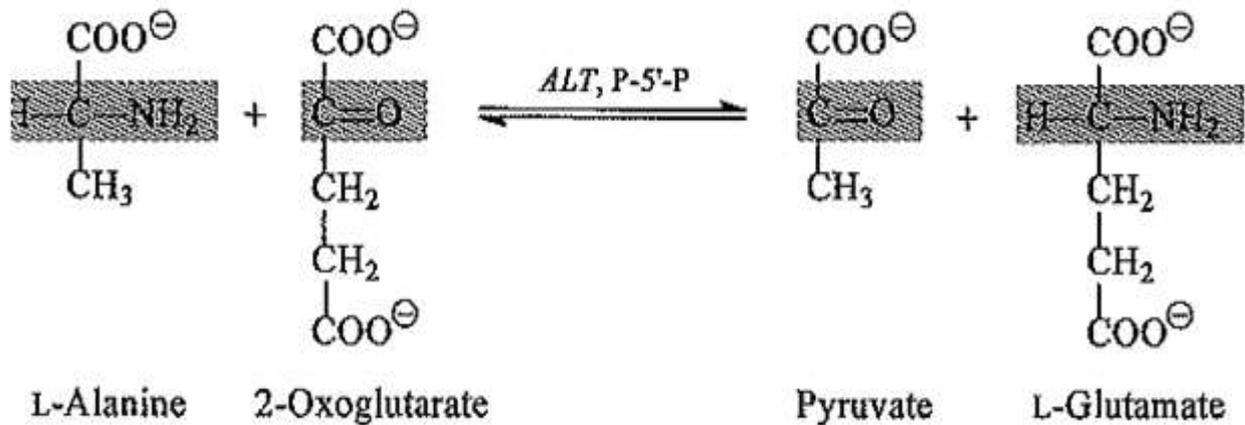
1. Aminotransaminases

The transaminases are enzymes involved in the transfer of an amino group from a 2-amino- to a 2-oxoacid: they need the cofactor, pyridoxal phosphate for optimal activity. They are widely distributed in the body.

The 2-oxoglutarate/L-glutamate couple serves as one amino group acceptor and donor pair in all amino-transfer reactions; the specificity of the individual enzymes derives from the particular amino acid that serves as the other donor of an amino group. Thus AST catalyzes the reaction:



ALT catalyzes the analogous reaction:



The reactions are reversible, but the equilibrium of AST and ALT reactions favor formation of aspartate and alanine respectively.

- Location:
 - AST present in cytosol and mitochondria
 - ALT located in cytosol of liver
- In the liver, the concentration of ALT per unit weight of the tissue is more than AST.
- These enzymes are more important in assessing and monitoring the degree of liver cell inflammation and necrosis.
- The highest activities of ALT are found in hepatocytes and muscle cells.
- Hepatocytes have very high activity of ALT, therefore elevations in serum ALT are considered to be relatively specific for liver disease.
- AST may be elevated in other forms of tissue damage, such as myocardial infarction, muscle necrosis and renal disorders.
- In liver disease, the ALT level is increased markedly compared to AST.
- In acute viral hepatitis there is a 100-1000 times increase in both ALT and AST but ALT level is increased more than that of AST

Table: Aminotransferase activities in human tissues, relative to serum as unity

	AST	ALT
Heart	7800	450
Liver	7100	2850
Skeletal muscle	5000	300
Kidneys	4500	1200
Pancreas	1400	130
Spleen	700	80
Lungs	500	45
Erythrocytes	15	7
Serum	1	1

From King J. *Practical clinical enzymology*. London: D Van Nostrand Co, Ltd, 1965.

a. Aspartate Transaminase (EC 2.6.1.1; L-aspartate:2-oxoglutarate aminotransferase; AST)

Clinical Significance

Normal values of AST: male: <35 U/L = <0.60 μ kat/L
 Female: <31 U/L = <0.53 μ kat/L

AST (glutamate oxaloacetate transaminase. GOT) is present in high concentrations in cells of cardiac and skeletal muscle, liver, kidney and erythrocytes. Damage to any of these tissues may increase plasma AST levels. Half- life = 17 hours.

CAUSES OF RAISED PLASMA AST ACTIVITIES

- Artefactual.

Due to in vitro release from erythrocytes if there is haemolysis or if separation of plasma from cells is delayed.

- Physiological.

During the neonatal period (about 1.5 times the upper adult reference limit).

- Marked increase (10 to 100 times the upper adult reference limit):

Circulatory failure with 'shock' and hypoxia:

Myocardial infarction

Acute viral or toxic hepatitis.

b. Alanine Transaminase (EC 2.6.1.2; L-alanine:2-oxoglutarate aminotransferase; ALT)

Clinical Significance

Normal values of ALT: male: <45 U/L = <0.77 μ kat/L
 Female: <34 U/L = <0.58 μ kat/L

ALT (glutamate pyruvate transaminase. GPT) is present in high concentrations in liver and to a lesser extent, in skeletal muscle, kidney and heart. Half- life = 47 hours
In liver damage, both enzymes are increased but ALT increases more. In myocardial infarction AST is increased with little or no increase in ALT.

CAUSES OF RAISED PLASMA ALT ACTIVITIES

- Marked increase (10 to 100 times the upper limit of the adult reference range)
circulatory failure with 'shock' and hypoxia:
 Acute viral or toxic hepatitis.
- Moderate increase:
 Cirrhosis (may be normal or up to twice the upper adult reference limit): infectious mononucleosis (due to liver involvement):
 Liver congestion secondary to congestive cardiac failure:
 cholestatic jaundice (up to 10 times the upper reference limit in adults); surgery or extensive trauma and skeletal muscle disease (much less affected than AST)

2. Markers of cholestasis

1. **Alkaline phosphatase (EC 3.1.3.1; orthophosphoric-monoester phosphohydrolase [alkaline optimum]; ALP). Half-life= 10 days**

Clinical Significance

The alkaline phosphatases are a group of enzymes that hydrolyse organic phosphates at high pH. They are present in most tissues but are in particularly high concentration in the osteoblasts of bone and the cells of the hepatobiliary tract, intestinal wall, renal tubules and placenta. The exact metabolic function of ALP is unknown but it is probably important for calcification of bone.

In adults plasma ALP is derived mainly from bone and liver in approximately equal proportions: the proportion due to the bone fraction is increased when there is increased osteoblastic activity that may be physiological

Causes of raised Plasma ALP activity

- *Physiological: There is a gradual increase in the proportion of liver ALP with age: in the elderly the plasma bone isoenzyme activity may increase slightly.*
- *Bone disease*
rickets and osteomalacia
secondary hyperparathyroidism .
- *Liverdisease-.*
- *Malignancy.*
bone or liver involvement or direct tumor production.

POSSIBLE CAUSES OF LOW PLASMA ALP ACTIVITY

- *Arrested bone growth*
- *Hypophosphatasia: an autosomal recessive disorder, associated with rickets or osteomalacia.*

Table: reference intervals for alkaline phosphatase activities inn serum

Sex	Age (years)	Reference Interval (U/L)
Male/Female	4-15	54-369
Males	20-50	53-128
	≥60	56-119
Females	20-50	42-98
	≥60	53-141

ISOENZYMES OF ALKALINE PHOSPHATASE

Bone disease with increased osteoblastic activity, or liver disease with involvement of the biliary tracts, are the commonest causes of an increased total alkaline phosphatase activity.

Assays for ALP isoenzymes are needed when:

- I. The source of an elevated ALP in serum is not obvious and should be clarified.*
- II. The main clinical question is concerned with detecting the presence of liver or bone involvement*
- III. In the case of metabolic bone disorders, to ascertain any modifications in the activity of osteblastes to monitor the disease activity and the effect of appropriate therapies.*

2. **Gamma-glutamyl-transferase (EC 2.3.2.21; γ -glutamyl-peptide: amino acid γ -glutamyltransferase; GGT):** catalyzes the transference of the γ – glutamyl group from peptides and compounds that contain it to an acceptor

Gamma-glutamyltransferase occurs mainly in the cells of liver, kidneys, pancreas and prostate. Plasma GGT activity is higher in men than in women.

Clinical Significance

Normal values for GGT male: <55 U/L = <0.94 μ kat/L
 Female: <38 U/L = <0.65 μ kat/L

Causes of raised plasma GGT activity

- Induction of enzyme synthesis, without cell damage, by drugs or alcohol.
- Hepatocellular damage, such as that due to infectious hepatitis:

A patient should never be labeled an alcoholic because of a high plasma GGT activity alone.

Other enzymes

Glutamate dehydrogenase (EC 1.4.1.3; L-glutamate: NAD(P)⁺ oxidoreductase, deaminating; GLD) is a mitochondrial enzyme found mainly in the:

- a. liver
- b. heart muscle
- c. kidneys

but small amounts occur in other tissue, including

- d. brain
- e. skeletal muscle tissue
- f. leukocytes

Clinical significance

GLD is increased in serum of patients with hepatocellular damage offering differential diagnostic potential in the investigation of liver disease, particularly when interpreted in conjunction with other enzyme test results. The key to this differential diagnostic potential is to be found in the intraorgan and intracellular distribution of the enzyme. As an exclusively mitochondrial enzyme, GLD is released from necrotic cells and is of value in estimation of the severity of liver cell damage. GLD activity in serum is stable at 4°C for 48 hours and at -20°C for several weeks. The GLD upper reference limits are 6U/L (women) and 8U/L (men), when a method optimized at 37°C is used.

Clinical Cases:

Case1: A healthy 43- year old male, on no medication, had the following results of tests performed during a private healthcare screening program.

Plasma

Bilirubin 43 μ mol/L (< 20)

Unconjugated bilirubin 36 μ mol/L (< 5)

Alanine aminotransferase 21 U/L (< 42)

Alakaline phosphatase 126 U/L (< 250)

Albumin 40 g/L (35-45)

Gamma-glutamyltransferase 42 U/L (< 55)

Urinary bilirubin negative

Normal full blood count, reticulocytes and blood film.

Discussion

The raised concentration of the plasma bilirubin is predominant ly unconjugated. There is no evidence of haemolysis and the other liver function tests are normal. A likely diagnosis is of Gilbert's syndrome. This is a common condition and its diagnosis is based on the exclusion of liver disease and heamolisis in the presence of a modest concentration of unconjugated hyper bilirubineamia.

Case2: A 50-year old known alcoholic make attended the general medical clinic because of ascites and the following abnormal liver test results

Plasma:

Bilirubin 52 μ mol/L (< 20)

Alanine amino transferase 76 U/L (< 42)

Alakaline phosphatase 271 U/L (< 250)

Albumin 18 g/L (35-45)

Gamma-glutamyltransferase 324 U/L (< 55)

Urinary bilirubin and protin normal.

Discussion

The abnormal liver test and hypoalbuminaemia together with ascites supported the diagnosis of cirrhosis, secondary to his alcohol problem. Hypoalbumineamia may be due to many disorders, such as gross protienuria, but in the presence of hepatic disease suggests a reduction in hepatic synthetic typical of cirrhosis.

Serum Patterns in different liver diseases

Ref: Schmidt E, Schmidt FW. "Brief guide to practical enzyme diagnosis", Houston, 1977, Boehringer Mann-heim Diagnostics.

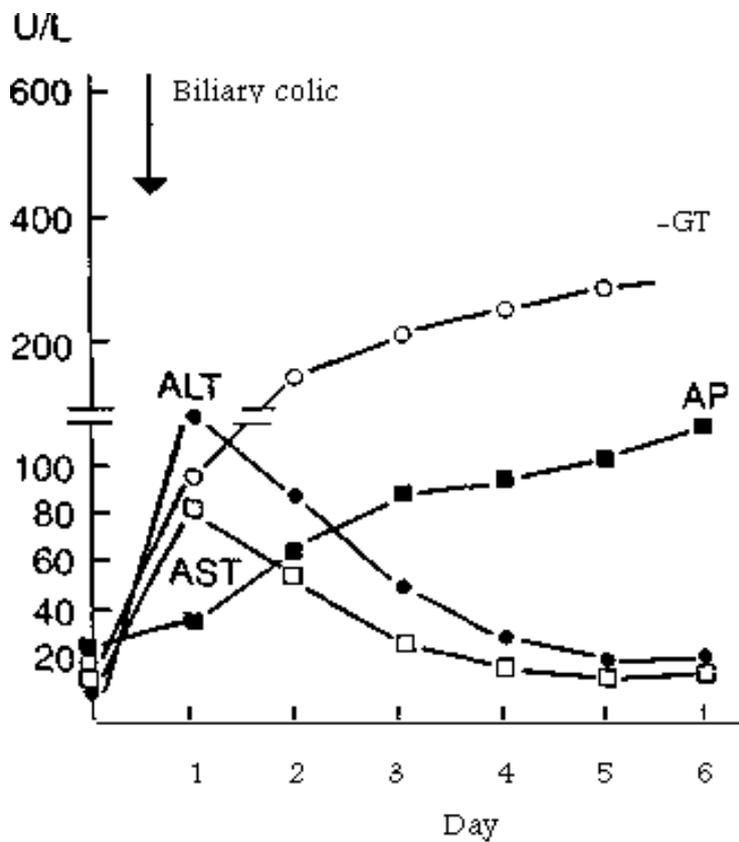


Fig. Course of serum enzyme activities in obstructive jaundice

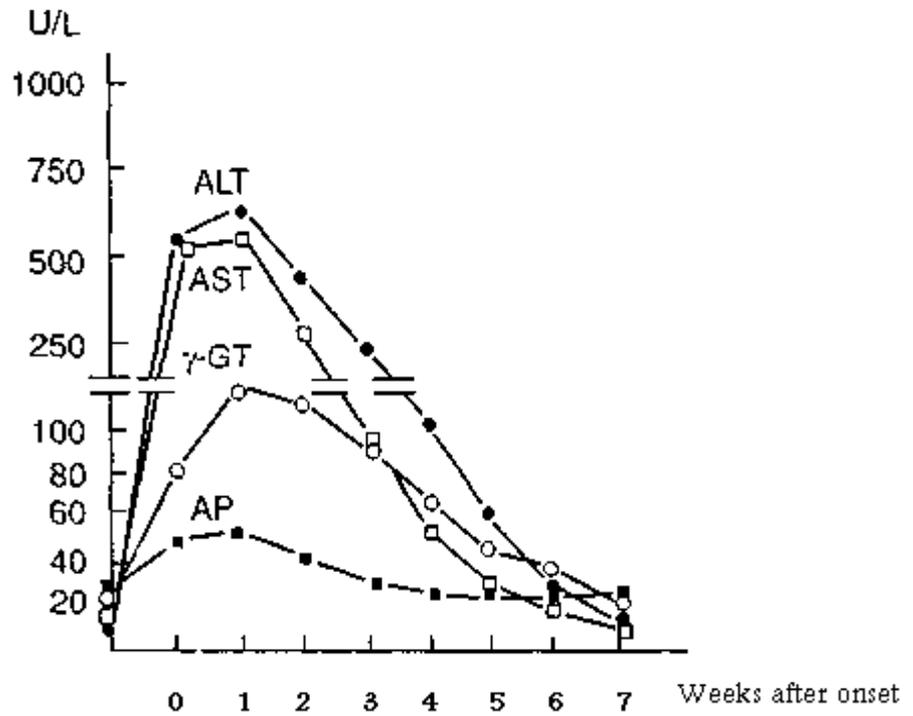


Fig 2. Course of serum enzyme activities in acute viral hepatic

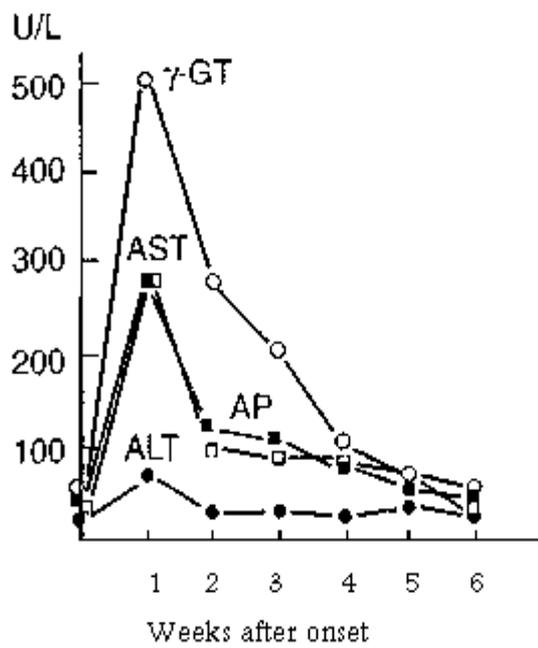
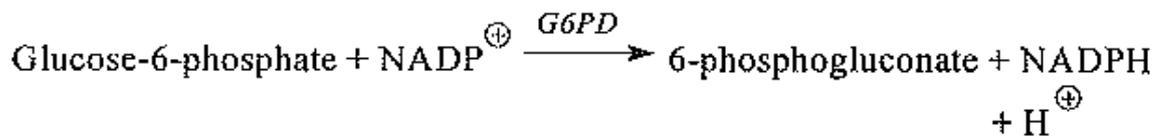
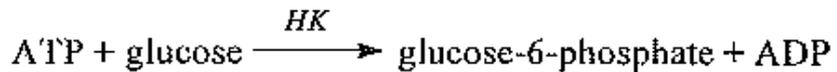
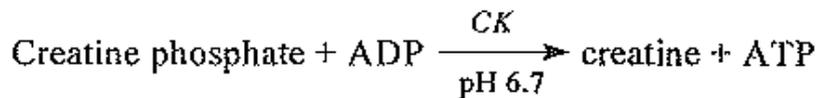


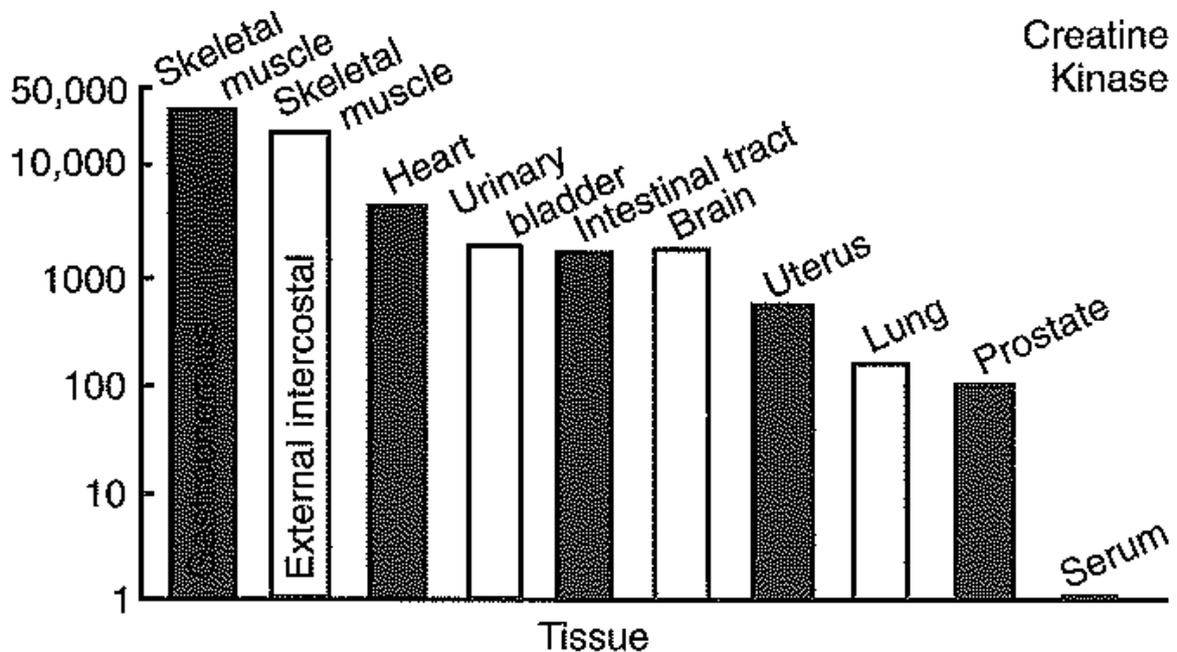
Fig 3. Course of serum enzyme activities in acute alcoholic hepatitis

Muscle enzymes:

1. *Creatine Kinase (EC 2.7.3.2; adenosine triphosphate: creatine N-phosphotransferase CK)*



CK is most abundant in cells of cardiac and skeletal muscle and in brain, but also occurs in other tissues such as smooth muscle.



The concentration gradients between some human tissues and serum for creatine kinase. The concentration gradient is logarithmic

CK-MB accounts for about 35 per cent of the total CK activity in cardiac muscle and less than five per cent in skeletal muscle: its plasma activity is always high after myocardial infarction. It may be detectable in the plasma of patients with a variety of other disorders in whom the total CK activity is raised, but this accounts for less than six per cent of the total.

CK-BB is present in high concentrations in the brain and in the smooth muscle of the gastrointestinal and genital tracts. Although they have also been reported after brain damage and in association with malignant tumours of the bronchus, prostate and breast, measurement is not of proven value for diagnosing these conditions. In malignant disease plasma total CK activity is usually normal.

Approximate concentrations of tissue CK activity (expressed as multiple activity concentrations in serum and cytoplasmic isoenzyme composition

Tissue	Relative CK Activity	ISOENZYMES, %		
		CK-BB	CK-MB	CK-MM
Skeletal muscle(red fibers)	50,000	<1	3	97
Skeletal muscle(white fibers)	50,000	<1	1	99
Heart	10,000	<1	22	78
Brain	5,000	100	0	0
Smooth muscle				
Gastrointestinal tract	5,000	96	1	3
Urinary bladder	4,000	92	6	2

2. Lactate Dehydrogenase (EC 1.1.1.27; L-lactate: NAD⁺

oxidoreductase; LD) catalyses the reversible interconversion of lactate and pyruvate. The enzyme is widely distributed in the body, with high concentrations in cells of cardiac and skeletal muscle, liver, kidney, brain and erythrocytes: measurement of plasma total LD activity is therefore a non-specific marker of cell damage.

LD has a molecular weight of 134 kDa and is composed of four peptide chains of two types: M (or A)

H (or B)

Each under separate genetic control

The subunit compositions of the five isoenzymes are listed below in order of their decreasing anodal mobility in an alkaline medium.

LD-1 (HHHH; H₄) = migrates fastest towards the anode

LD-2 (HHHM; H₃M)

LD-3 (HHMM; H₂M₂)

LD-4 (HMMM; HM₃)

LD-5 (MMMM; M₄)

Clinical significance

Normal range of total LDH: 180-360 U/L = 3.1-6.1 μ kat/L

It is increased in plasma in M.I., acute leukemias, generalized carcinomatosis and in acute hepatitis. Estimation of its isoenzymes is more useful in clinching diagnosis between hepatic disease and M.I.

ISOENZYMES OF LD

LD₁ fraction predominates in cells of cardiac muscle, erythrocytes and kidneys.

LD₅ is the most abundant form in the liver and in skeletal muscle. Whereas in many conditions there is an increase in all fractions, the finding of certain patterns is of diagnostic value.

- Predominant elevation of LD₁ and LD₅. (LD₁ greater than LD₅ occurs after myocardial infarction, in megaloblastic anaemia and after renal infarction.
- Predominant elevation of LD₂ and LD₃ occurs in acute leukaemia: LD₃ is the main isoenzyme elevated due to malignancy of many tissues.
- Elevation of LD₅ occurs after damage to the liver or skeletal muscle.

Other clinically important enzymes

1. Acid Phosphatase (EC 3.1.3.2; orthophosphoric acid-monoester phosphohydrolase [acid optimum]; ACP)

Acid phosphatase is present in lysosomes, which are organelles present in all cells with the possible exception of erythrocytes. Extralysosomal ACPs are also present in many cells:

- a. prostate,
- b. bone (osteoclasts),
- c. spleen
- d. platelets
- e. erythrocytes.

The lysosomal and prostatic enzymes are strongly inhibited by d-tartrate ions (tartrate-labile ACP), whereas the erythrocyte and bone isoenzymes are not (TR-ACP)

Normal range of TR-ACP: 1.5-4.5 U/L= 0.03-0.08 μ kat/L

Elevated TR-ACP

- a. Paget disease*
- b. Hyperparathyroidism with skeletal involvement*
- c. Presence of malignant invasion of bones by cancers*

The only nonbone condition in which elevated activities of TR-ACP are found in serum is Gaucher disease of the spleen, a lysosome storage disease.

The main indications for estimation are to help diagnose prostatic carcinoma and to monitor its treatment. The estimation is gradually being replaced by the measurement of plasma prostate specific antigen (PSA) a protein derived from the prostate. This test is more specific and sensitive for diagnosis and monitoring treatment. However, it may be raised in similar circumstances to those affecting prostatic ACP and is more expensive to estimate. ACP is more useful for monitoring the treatment of a known case of disseminated prostatic carcinoma than for making the diagnosis.

- 2. Glucose -6-phosphate Dehydrogenase (EC 1.1.1.49); D-Glucose -6-phosphate: NADP⁺ oxidoreductase; G6PD** *is expressed in all cells and catalyzes the first step in the hexose monophosphate pathway, the conversion of glucose-6-phosphate to 6-phosphogluconate, generating NADPH. G6PD deficiency is the most common enzymeopathy , affecting 400 million people worldwide. More than 400 different types of G6PD variants have been described, leading to different enzyme activities associated with a wide range of biochemical and clinical phenotypes.*

The majority of G6PD –deficient individuals develop hemolysis only when oxidative stress occurs, as with infections and after ingestion of certain drugs or fava beans.

Outside these periods, they are usually asymptomatic; however, G6PD deficiency also leads to mild to severe chronic hemolysis, exacerbated by oxidative stress.

The reference interval for G6PD on erythrocytes is 8-14U/g Hb. Values >18 U/g Hb are often encountered in any condition associated with younger than normal RBCs but are of no clinical significance.

Plasma enzyme patterns in diseases

Muscle Disease

In the muscular dystrophies plasma levels of the muscle enzymes. CK and the transaminases, are increased, probably because of leakage from the diseased cells. Results of plasma CK estimation are the more specific.

Although plasma enzyme activities are usually normal in neurogenic muscular atrophy; the number of false positives makes such tests unreliable in differentiating these conditions from primary muscle disease.

Hematological Disorders

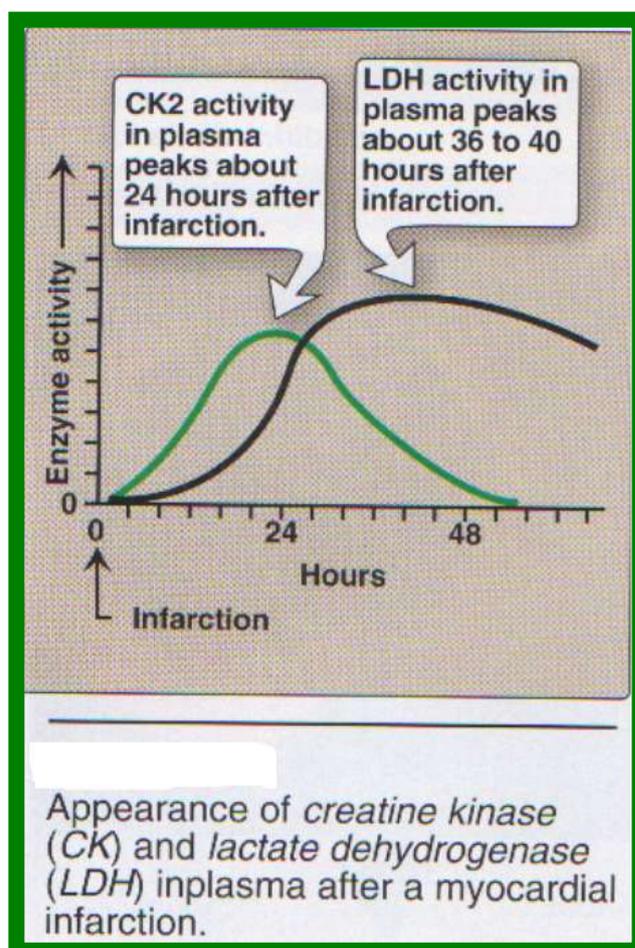
Very high activities of LD (HBD) may be found in megaloblastic anaemias and leukemias and in other conditions in which bone marrow activity is abnormal. Typically there is much less change in the plasma AST than in the LD (HBD) activities.

Severe in vivo haemolysis produces changes in both AST and LD (HBD) activities which mimic those of myocardial infarction.

Myocardial Infarction

All plasma enzyme activities (including that of CK-MB) may be normal until at least four hours after the onset of chest pain due to a myocardial infarction; blood should not be taken for enzyme assay until this time has elapsed. The simultaneous measurement of plasma CK-MB activity, which is shown to exceed six per cent of the total CK activity, may occasionally help in the early diagnosis: a raised plasma CK-MB activity or concentration alone is not diagnostic of an infarction.

Most of the CK released after a myocardial infarction is the MM isoenzyme, which is found in both skeletal and myocardial muscle and has a longer half-life than the MB fraction. After about 24 hours the finding of a high MM and undetectable MB does



not exclude myocardial damage as a cause of high total CK activities: by this time the plasma HBD activity is usually raised. In most cases of suspected myocardial infarction measurement of plasma total CK and LD₁ (HBD) activities, together with the clinical and ECG findings, are adequate to make a diagnosis. Plasma total CK activity alone can be very misleading.

A raised plasma total CK activity, due entirely to the MM isoenzyme, may follow recent intramuscular injection, exercise or surgery, this is more likely if associated with normal plasma LD₁ (HBD) or AST activity.

Newer markers for myocardial infarctions: troponin T and troponin I are regulatory proteins involved in myocardial contractility. both being evaluated as an early and specific marker of acute myocardial infarction. Elevated serum troponins are more predictive of adverse outcomes in unstable angina or myocardial infarction than the conventional assay of CK2.

Enzymes in Malignancy

Plasma total enzyme activities may be raised or an abnormal isoenzyme detected, in several neoplastic disorders.

- Serum prostatic (tartrate-labile) acid phosphatase activity rises in some cases of malignancy of the prostate gland.*
- Any malignancy may be associated with a non-specific increase in plasma LD₁ (HBD) and, occasionally, transaminase activity.*
- Plasma transaminase and alkaline phosphatase estimations may be of value to monitor treatment of malignant disease. Raised levels may indicate secondary deposits in liver or of alkaline phosphatase, in bone. Liver deposits may also cause an increase in plasma LD or GGT.*
- Tumors occasionally produce a number of enzymes, such as the 'Regan' ALP isoenzyme.' LD (HBD) or CK-BB. assays of which may be used as an aid to diagnosis or for monitoring treatment.*

Other Clinical correlations

1. **Niemann-Pick disease: Acid Sphingomyelinase Deficiency**

- **Sphingomyelin**, a ubiquitous component of cell membranes, especially neuronal membranes, is normally degraded within lysosomes by the enzyme **sphingomyelinase**.
- In patients with **Niemann-Pick disease**, inherited deficiency of this enzyme causes sphingomyelin to **accumulate in lysosomes** of the brain, bone marrow, and other organs.
- Enlargement of the lysosomes interferes with their normal function, leading to cell death and consequent **neuropathy**.
- Symptoms include **failure to thrive** and **death** in early childhood as well as **learning disorders** in those who survive the postnatal period.

2. **Homocysteinuria: Cystathionine β -synthase Deficiency**

1. **Cystathionine β -synthase** catalyzes conversion of homocysteine to cystathionine, a critical **precursor of cysteine**.
2. Deficiency of this enzyme leads to the most common form of **homocystinuria**, a pediatric disorder characterized by **accumulation of homocysteine** and reduced activity of several sulfotransferase reactions that require this compound or its derivatives as substrate.
3. **Accumulation of homocysteine and reduced transsulfation** of various compounds leads to abnormalities in connective tissue structures that cause altered blood vessel wall structure, loss of skeletal bone density (**osteoporosis**), **dislocated optic lens (ectopia lentis)**, and increased risk of **blood clots**.

3. **Enzyme Replacement Therapy for Inborn Errors of Metabolism**

- **Lysosomal enzyme deficiencies**, which frequently result in disease due to **accumulation of the substrate** for the missing enzyme, are suitable targets for **enzyme replacement therapy (ERT)**.
- In ERT, **intravenously administered enzymes** are taken up directly by the affected cells through a receptor-mediated mechanism.
- ERT provides temporary relief of symptoms but must be given repeatedly and is not a permanent cure.