

Biochemical markers in diagnosis and follow up of disease

Foundation Block

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biochemical markers

- What is a biomarker?
- Enzymatic diagnosis and prognosis of a disease
- Enzymes as markers of disease:
Amylase, ALT, AST
- Plasma proteins as markers of disease: **Albumin**
- Tumor markers: **α -fetoprotein, PSA**

what is a biomarker?

- A biological molecule found in blood, other body fluids, or tissues that indicates a normal or abnormal process such as a disease or a condition
- A biomarker is measured to diagnose a disease, follow up a disease or treatment.

diagnosis and prognosis

Diagnosis:

- Identification of a disease from its signs and symptoms

Prognosis:

- The future outcome of a disease





enzymatic diagnosis and prognosis of disease

Enzymes are used clinically in three ways:

1. As indicators of enzyme activity or concentration in body fluids (e.g. serum, urine) in the diagnosis/prognosis of a disease
2. As analytical reagents in measuring activity of other enzymes or compounds in body fluids
3. As therapeutic agents



- Most common body fluids: serum and plasma

Enzymes are:

- Plasma-specific

Or

- Tissue-specific

Plasma-specific enzymes



- Normally present in plasma
- Perform their functions in blood
- High level of activity in plasma than in tissue cells
- Examples: blood clotting enzymes (thrombin), cholinesterase, etc.



Tissue-specific enzymes

- Present inside the cell
- Concentration is lower in plasma
- Released into the body fluids in high concentration due to:
 - cell damage
 - defective cell membrane



- Intracellular enzymes are present only in their cells of origin
- Some are secretory enzymes that are secreted by salivary glands, gastric mucosa and pancreas
- In disease, plasma levels of secretory enzymes increase when their cells are damaged
- The diagnosis of organ disease is done by measurement of enzymes of that tissue

factors affecting serum enzyme levels

- Cell damage
- Rate of enzyme synthesis and clearance
- Enzyme inhibitors
- Glucose deficiency
- Localized hypoxia (less oxygen)
- Ischemia (obstruction of blood vessels)
- Necrosis
- Tissue infarction due to ischemic necrosis (e.g. Myocardial infarction)

qualities of a good biomarker assay

- Ability to accurately diagnose a disease
- Ability to accurately predict prognosis of a disease
- Complies with treatment follow up
- Sample should be easily obtained (blood, urine, etc.)

qualities of a good biomarker assay

- Rapid test to deliver results faster
- Sensitive
 - Ability of an assay to detect small quantities of a marker
- Specific
 - Ability of an assay to detect only the marker of interest



enzymatic markers (some examples)

- Amylase
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)



amylase in acute pancreatitis

- Acute pancreatitis is the inflammation of pancreas caused by:
 - Obstruction of the pancreatic duct
 - Gallstones
 - Alcohol abuse

- Abnormal release of pancreatic enzymes and their premature activation
- The main pancreatic enzyme is trypsinogen
- Trypsinogen is activated to trypsin
- Trypsin converts other enzymes to active form such as kallikrein, phospholipase A₂, elastase, etc.
- Effects of abnormal release of enzymes: autodigestion of pancreas, vasodilation, respiratory failure, etc.

Enzymatic diagnosis of pancreatic diseases:

Measurement of pancreatic enzymes:

- Amylase
- Lipase
- Trypsinogen

Amylase

- Elevated serum amylase level is a diagnostic indicator of acute pancreatitis
 - Amylase level greater than 10 times the upper limit indicates acute pancreatitis
- The test has low specificity because elevated serum amylase level is also present in other diseases
- Amylase appears in the serum within 2-12 hours after abdominal pain
- Free amylase (unbound form) is rapidly cleared by the kidneys

High ALT and AST in liver diseases

- Alcohol abuse
- Medication
- Chronic hepatitis B and C
- Steatosis and steatohepatitis
- Autoimmune hepatitis
- Wilson's disease
- α_1 -antitrypsin deficiency
- Malignancy
- Poisons and infectious agents

Serum enzymes used in the assessment of liver function:

- Markers used in hepatocellular necrosis
 - Alanine aminotransferases
 - Aspartate aminotransferases
- Markers used in cholestasis
 - Alkaline phosphatase
 - 5'-nucleotidase
 - γ -glutamyl transferase

Alanine aminotransferase (ALT)

- Mostly present in liver
- Small amounts in heart
- More specific for liver disease than AST
- Major diagnosis: liver disease

Aspartate aminotransferase (AST)

- Widely distributed in heart, liver, skeletal muscle, kidney
- Small amounts in erythrocytes
- High serum activity of AST found in:
 - Liver disease, heart disease, skeletal muscle disease, hemolysis
- Major diagnosis: myocardial infarction, liver and muscle diseases

plasma proteins as markers (albumin)

Functions

- **Oncotic pressure** (pressure exerted by plasma proteins that pulls water into the circulatory system)– 80% of plasma oncotic pressure is maintained by albumin
 - Fluid distribution in and outside cell, maintains plasma volume
- **Buffering** – some buffering function
- **Transport** – lipid-soluble molecules, hormones, calcium, drugs, etc. in blood

plasma proteins as markers

Hypoalbuminemia – Causes

- Decreased albumin synthesis – failure of synthesis due to genetic reasons and malnutrition
- Increased volume of albumin distribution – in liver disease
- Increased losses of albumin – increased catabolism in infections, nephrotic syndrome, hemorrhage, severe burns, etc.

plasma proteins as markers

Hypoalbuminemia – Effects

- Edema due to low oncotic pressure
 - Albumin level drops in liver disease causing low oncotic pressure
 - Fluid moves into the interstitial spaces causing edema
- Reduced transport of
 - Substances in plasma
 - Drugs (free form – more active)

plasma proteins as markers

Hyperalbuminemia – causes

- Dehydration is a major cause of hyperalbuminemia

tumor markers

- A molecule secreted by a tumor that is measured for diagnosis and management of a tumor
- α -fetoprotein
- Prostate specific antigen (PSA)

α -fetoprotein

- In newborn babies α -fetoprotein levels are very low
- High conc. are observed in:
 - hepatocellular carcinomas (hepatoma)
 - testicular carcinomas
 - Gastro Intestinal tract carcinomas
- However, high serum levels are also found in benign (non-cancerous) conditions e.g. hepatitis
- High concentration are not always suggestive of a tumor

prostate specific antigen (PSA)

- A serine protease enzyme also called kallikrein III, seminin
- Produced by prostate gland
- Liquefies ejaculate
- High serum PSA levels are observed in prostate cancer
- Less specific in diagnosis
 - High serum levels are also observed in benign prostatic hypertrophy (enlarged prostate gland)

Take Home message

- A biochemical marker is a biological molecule found in body fluids or tissues that indicates a disease or a condition
- A biomarker is measured to diagnose, follow up or monitor a disease or treatment
- Assays to measure biomarkers should be sensitive, specific, fast, and using samples that are easy-to-obtain.
- Examples of biomarkers are enzymes, plasma proteins, and tumor markers

THANK YOU!