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Liver & gastoenterology test

Key Points for Clinical Investigation

Central Role in Biochemistry: Liver and GI abnormalities lead to significant diseases due to their pivotal biochemical functions.

Laboratory Studies:
1.Synthetic Function: Tests to assess protein production and other synthetic activities.
2.Excretory Function & Cholestasis: Evaluates bile flow and liver excretion.
3.Hepatocellular Injury: Identifies liver cell damage.
4.Detoxification & Ammonia Levels: Assesses liver's role in detoxifying substances.

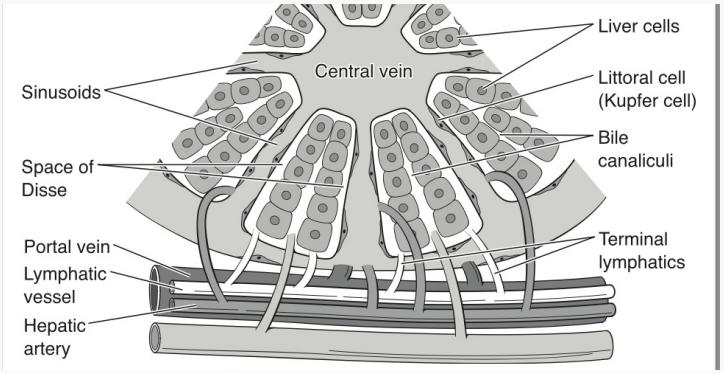
Disease-Specific Tests:
•Viral hepatitis, primary biliary cirrhosis (PBC), hemochromatosis.
Nonhepatic GI Tests: Includes diagnostics for pancreatitis, H. pylori infection, and C. difficile colitis

Liver

•**Blood Sources**:
- **Hepatic Artery**: Oxygen-rich blood from the aorta.
- **Portal Vein**: Nutrient- and toxin-rich venous blood from intestines.

Structure
•Composed of lobules with radiating hepatocyte plates.
•Bile canaliculi between cells lead to bile ducts → common duct → gallbladder or duodenum.

Functions
•**Protein Synthesis**: Albumin, clotting factors.
•**Amino Acid & Carbohydrate Processing**: Stores glycogen, prevents hypoglycemia.
•**Lipid & Cholesterol Metabolism**: Primary site for lipid processing.
•**Detoxification**: Breaks down drugs, toxins, hormones, and byproducts like ammonia.
•**Medication Metabolism**: Liver failure can impact drug dosing due to reduced detoxification.



Pancreas

•**Functions**
- **Exocrine Role**:
  - Enzymes (trypsin, chymotrypsin, lipase, amylase) digest proteins, fats, and carbohydrates.
  - **Pancreatic Insufficiency**: Leads to malabsorption, weight loss, and diarrhea.
- **Endocrine Role**:
  - Hormones (insulin, glucagon) regulate blood sugar levels.
  - **Insufficient Insulin**: Causes diabetes mellitus.

•**Reserve Capacity**
- Significant glandular destruction (>90%) needed before clinical symptoms (e.g., diabetes, insufficiency) appear.

Introduction to Liver Function Tests (LFTs)

Purpose of LFT Panel
•Initial investigation for liver disease; includes key markers:

- **Aminotransferases (AST, ALT)**: Reflect liver injury.
- **Bilirubin**: Indicator of bile metabolism and liver excretion.
- **Alkaline Phosphatase (ALP)**: Linked to bile duct health.
- **Albumin**: Measures liver's synthetic function.

Understanding LFT Categories

•**Cholestatic Diseases**: Issues with bile secretion and flow (e.g., bile duct blockage).
•**Hepatocellular Diseases**: Direct hepatocyte damage (e.g., viral hepatitis).

Introduction to Liver Function Tests (LFTs)

- **Key Considerations**

- Misnomer: Not all LFTs measure liver *function* (e.g., aminotransferases measure liver *injury*).

- **Overlap**: Severe hepatocellular disease can affect bile flow.
- **Reference Ranges**: Adult norms vary slightly across labs; pediatric values differ.

- **Fundamental Distinction**
- Recognizing cholestatic vs. hepatocellular patterns is essential for diagnosis.

PROCESS	MOST CLOSELY RELATED TESTS
Protein synthesis	Albumin
	Prealbumin
	PT/INR (clotting factors)
Excretion into the bile ducts and drainage into the duodenum (impairment of this process is defined as cholestasis)	Bilirubin
	ALP
	5'-nucleotidase
	GGT
Hepatocellular injury	Aminotransferases:
	AST
	ALT
Detoxification	Ammonia (NH_3+)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transpeptidase; INR = international normalized ratio; PT = prothrombin time.

Tests Of Synthetic Liver Function

The liver synthesizes key blood proteins, including albumin and clotting factors, and their levels indicate the liver's protein production capacity.

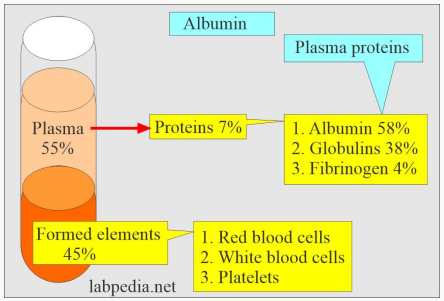
Synthetic function tests do not detect mild liver damage

Reduced protein synthesis mainly indicates advanced cirrhosis, often from chronic alcohol use, hepatitis, or severe liver injury.

Albumin

Normal Range: 4–5 g/dL (40–50 g/L)
Functions:
•Maintains oncotic pressure.
•Binds/transports hormones, ions, drugs, and fatty acids.

Clinical Interpretation:
•**Chronic Liver Dysfunction**: Low albumin levels often indicate cirrhosis or chronic liver failure.
•**Other Causes of Low Albumin**: Malnutrition, protein loss (gut, kidney, skin), IV fluid overload, systemic inflammation (e.g., infection, cancer).
•**Severely Ill Patients**: Low levels may signal poor prognosis, requiring context-specific interpretation.



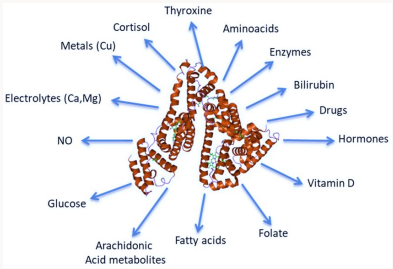
Albumin

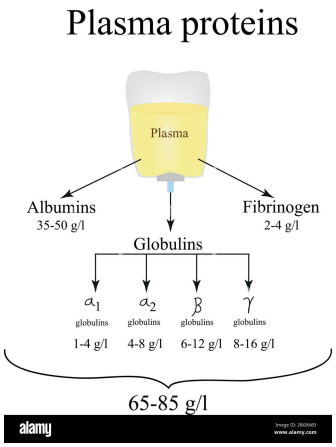
Implications of Low Albumin:

- **Symptoms**: Severe hypoalbuminemia (<2–2.5 g/dL) can cause edema, ascites, pulmonary edema.
- **Drug Binding**: Increases free (active) drug levels for highly protein-bound medications (e.g., phenytoin, warfarin).
- **Calcium Correction**: Requires adjustment in total calcium interpretation.

Hyperalbuminemia:

- Rare, often due to dehydration or steroid use; asymptomatic.





Plasma proteins

INR & Prothrombin Time (PT):

Normal Ranges: INR 0.9–1.1, PT 12.7–15.4 sec

Purpose:
•Measures coagulation speed in the extrinsic pathway.
•**INR**: Standardized measure; adjusts for lab reagent variations.

Liver's Role in Clotting:
•Synthesizes clotting factors (except factor VIII), many needing vitamin K.
•**Hepatic Impairment or Vitamin K Deficiency**: Increases PT/INR values.

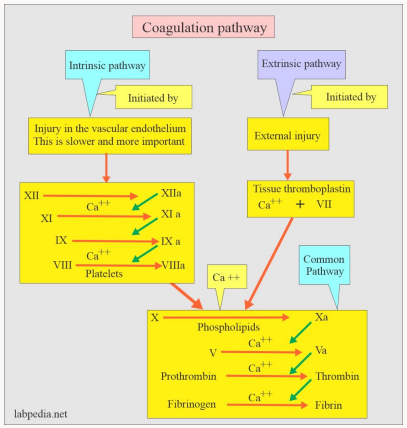
Factors Affecting PT/INR:
•**Vitamin K Deficiency**: Due to poor diet, malabsorption, gut flora loss, or warfarin use.
•**Liver Failure**: Severe liver damage (>80% capacity loss) affects clotting factor production, prolonging PT/INR.

COAGULATION AND LIVER FUNCTION TESTS

INR & Prothrombin Time (PT):

•**Prognostic Value**:
- PT/INR responds rapidly (within 24 hours) to liver status changes, often indicating liver failure early.
- Elevated PT/INR in liver disease (e.g., acetaminophen overdose) provides critical prognostic data.

•**Management of Elevated PT/INR**:
- **Vitamin K Supplementation**: Used to identify cause of elevation.
- **Fresh Frozen Plasma**: Temporarily corrects PT/INR in significant bleeding or surgical risk.



Cholestatic Liver Disease:

Definition: Impaired excretory function of the liver, disrupting bile flow from hepatocytes to the duodenum.

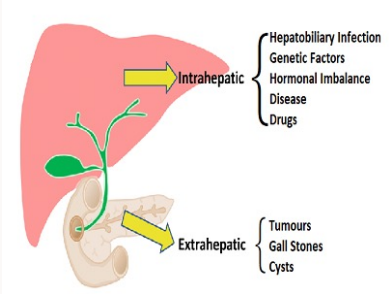
Functions of Bile:
•**Excretion**: Removes lipophilic toxins, drugs, and endogenous substances.
•**Digestion**: Bile salts aid absorption of fat-soluble vitamins (A, D, E, K).

Consequences of Cholestasis:
•**Accumulation**: Leads to jaundice (bilirubin), pruritus (bile salts), and xanthomas (lipid deposits).
•**Vitamin Deficiencies**: Impaired absorption can cause:
- **Vitamin D**: Osteoporosis risk.
- **Vitamin K**: Elevated PT/INR and bleeding risk.

Cholestatic Liver Disease:

Types of Cholestasis:
- **Intrahepatic**: Dysfunction of hepatocytes/microscopic ducts.
- **Extrahepatic**: Anatomic obstruction of larger bile ducts.

Diagnostic Approach:
- **Initial Imaging**: RUQ ultrasound to identify bile duct dilation and differentiate between intra- and extrahepatic cholestasis.



Lab Tests

- **Alkaline Phosphatase (ALP)**
- **5'-Nucleotidase**
- **γ-Glutamyl Transpeptidase (GGT)**
- **Bilirubin**

•**Key Points**:
- Labs alone cannot differentiate between **intrahepatic** and **extrahepatic** cholestasis.
- **Imaging** (CT, MRI, or ultrasound) is required to identify duct dilation and obstruction.

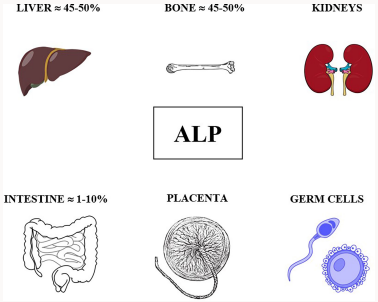
•**Radiologic Findings**:
- **Extrahepatic Cholestasis**: Bile duct dilation above the obstruction due to the damming effect.

Alkaline Phosphatase (ALP):

Normal Range: 33–96 units/L (0.55–1.6 µkat/L)

Source:
- Found in liver, bone, intestine, kidneys, placenta, and leukocytes.
- In adults, 80% of serum ALP comes from liver and bone.

Clinical Interpretation:
- **Elevations** suggest cholestatic liver disorders but don't distinguish between intra- and extrahepatic causes.
- **>4x Normal**: Strongly suggests cholestasis.
- **Mild Elevations (<1.5x Normal)**: May be nonspecific.

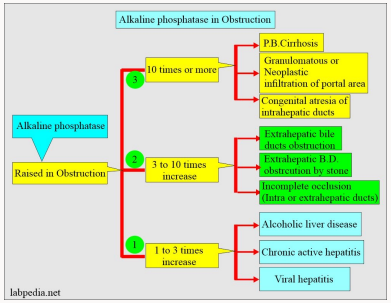


Alkaline Phosphatase (ALP):

Diagnostic Approach:
- Measure **5'-nucleotidase** or **GGT** to confirm hepatic origin.
- Elevated **GGT or 5'-nucleotidase** with ALP indicates liver involvement.

Nonhepatic Causes:
- Bone disorders, hyperthyroidism, renal failure, neoplasms, etc.
- Elevated ALP can occur after a fatty meal in blood type O or B.

Lowered ALP:
- Conditions include hypothyroidism, hypophosphatemia, or certain deficiencies (e.g., zinc, magnesium).



5'-Nucleotidase

Normal Range: 0–11 units/L (0–0.18 µkat/L)

Source:
•Found in multiple tissues (liver, brain, heart, blood vessels).
•Elevated levels primarily associated with liver disease.

Clinical Use:

•**Parallels ALP**: Helps differentiate hepatocellular vs. cholestatic liver disease.
•**Specific to Liver**: An elevated ALP with normal 5'-nucleotidase suggests a nonhepatic cause.

Interpretation:
•**Elevated 5'-Nucleotidase** confirms hepatic origin of elevated ALP, aiding in diagnosing cholestasis.

Gamma-Glutamyl Transpeptidase (GGT)

Normal Range: 9–58 units/L (0.15–0.97 µkat/L)

Role:
•Biliary excretory enzyme; parallels ALP and 5'-nucleotidase in liver disease.
•**Specific to Liver**: Not elevated in bone disorders, adolescence, or pregnancy.

Clinical Use:

•Confirms hepatic origin of elevated ALP.
•**GGT/ALP Ratio >2.5**: Strong indicator of alcohol abuse.
•Decreases by 50% within two weeks of alcohol abstinence.

Gamma-Glutamyl Transpeptidase (GGT)

Sensitivity vs. Specificity:

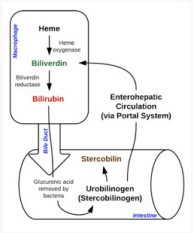
•**Most Sensitive** for cholestatic disorders but lacks specificity.
•Elevated in liver and other conditions (e.g., pancreatic diseases, myocardial infarction, certain cancers, COPD).

Confounding Factors:
•Medications (e.g., phenytoin, barbiturates) and non-hepatic conditions can elevate GGT.
•Requires careful interpretation alongside 5'-nucleotidase and patient history.

Bilirubin

Normal Ranges:

•**Total Bilirubin**: 0.3–1.3 mg/dL (5.1–22.2 µmol/L)
•**Indirect (Unconjugated)**: 0.2–0.9 mg/dL (3.4–15.4 µmol/L)
•**Direct (Conjugated)**: 0.1–0.4 mg/dL (1.7–6.8 µmol/L)



Biochemical Pathway:

•**Origin**: Breakdown of heme from erythrocytes, primarily in the spleen.
•**Transport**: Indirect bilirubin is lipophilic, carried to the liver bound to albumin.
•**Conjugation**: Liver converts indirect bilirubin to water-soluble direct bilirubin via glucuronyl transferase.
•**Excretion**: Direct bilirubin is secreted into bile, then eliminated in feces (gives stool its brown color).

Indirect vs. Direct Bilirubin: Key Differences

•**Total Bilirubin** = Direct + Indirect fractions
•**Direct Bilirubin (Conjugated)**
- **Water-soluble**, reacts quickly in van der Bergh assay.
- Can be detected in **urine**; urine dipsticks are sensitive to direct bilirubin.
- Elevation suggests bile duct obstruction or liver excretion issues.

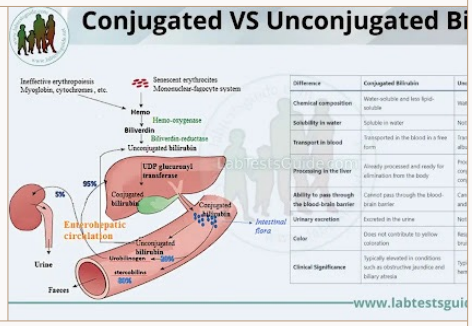
•**Indirect Bilirubin (Unconjugated)**
- **Water-insoluble**, requires dissolving agents for detection in assays.
- Cannot be excreted in urine.
- Elevation indicates increased RBC breakdown or impaired liver conjugation.

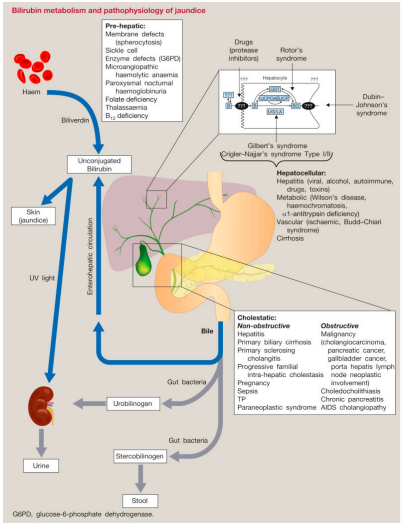
Indirect vs. Direct Bilirubin: Key Differences

Clinical Presentation:
•Elevated bilirubin causes **jaundice** (yellowing of skin/eyes), visible when total bilirubin >2–4 mg/dL.
•**Carotenemia** (e.g., from excessive carrot intake) can mimic skin jaundice but spares the eyes.
•High bilirubin (>20 mg/dL) can be **neurotoxic** in infants, but toxicity is rare in adults.

Key Takeaway

- **Unconjugated bilirubin** is fat-soluble and needs liver processing for excretion.
- **Conjugated bilirubin** is water-soluble and represents the liver's ability to modify and excrete bilirubin efficiently.





Bilirubin

Clinical Insights:

- **Elevated Indirect Bilirubin**: Suggests increased RBC breakdown or liver uptake issues.
- **Elevated Direct Bilirubin**: Indicates impaired liver excretion or bile duct obstruction.
- **Pale Stools**: Sign of bile duct obstruction or liver failure.

Hepatocellular Injury

Overview:

•Hepatocytes are susceptible to injury due to their role in toxin/drug metabolism, biochemical homeostasis, and close contact with the bloodstream.
•**Hepatitis**: Inflammation of hepatocytes, clinically marked by elevated **aminotransferases (ALT, AST)**.

Common Causes:

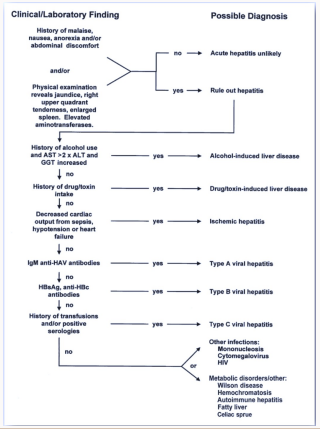
1.Viral Hepatitis: Includes hepatitis A, B, C, D, E, G, and less commonly EBV, herpes, CMV.
2.Drug-Induced Hepatitis: Acute or chronic; can involve numerous drugs (e.g., heparin, tamoxifen, amiodarone).
3.Fatty Liver/NASH: Affects 30–40% of U.S. adults; linked to obesity, rapid weight loss, or certain drugs.

Hepatocellular Injury

Evaluation:

•Careful **history** (drugs, alcohol, toxins), physical exam, and lab tests are essential.
•**Imaging** or **liver biopsy** may be needed for diagnosis, therapy planning, and prognosis.

Prognosis:
•Hepatocellular injury can be **mild/transient** or signal chronic liver disease.
•Potential progression to **cirrhosis**, especially with conditions like NASH.



ALGORITHM FOR DIFFERENTIAL DIAGNOSIS OF SUSPECTED HEPATITIS.

Aminotransferases: AST and ALT

Normal Ranges:

•**AST**: 12–38 units/L (0.2–0.64 µkat/L)
•**ALT**: 7–41 units/L (0.12–0.68 µkat/L)
•Gender-specific: <30 units/L (men), <20 units/L (women)

Clinical Role:
•Elevated in **hepatocyte damage** (sensitive but nonspecific).
•Reflects **active** liver injury; decreases rapidly after hepatocellular damage ends.

Patterns of Elevation:
•**Mild/Moderate**: Nonspecific; seen in many liver disorders.
•**Severe (>1000 units/L)**: Associated with acute hepatitis, toxic reactions, or ischemic liver injury.
•**AST/ALT Ratio >2**: Suggests **alcoholic hepatitis**; GGT may also be elevated.

ASSESSING HEPATOCELLULAR INJURY

Aminotransferases: AST and ALT

Differentiation:

- **ALT** is more liver-specific;
- **AST** also found in muscle, heart, and other tissues.

- Elevated AST alone suggests **non-liver** causes (e.g., muscle disease, myocardial infarction).

Confounding Factors:

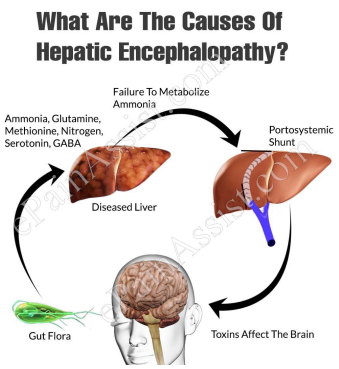
- Medications, exercise, uremia, hemolysis, and muscle injury can affect results.
- Retesting and multiple enzyme elevation help confirm liver injury in low-risk patients.

AST / ALT

Elevations above the upper limit of normal

<5x	5-10x	>10x
NAFLD	EtOH	Viral Hepatitis
Drug Induced	Drug Induced	Acetaminophen
EtOH	Biliary Disease	Shocked Liver
		HELLP
		Autoimmune

ASSESSING HEPATOCELLULAR INJURY



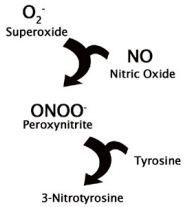
Hepatic Encephalopathy

Definition: Metabolic brain dysfunction associated with **acute or chronic liver failure**.

- Clinical range: **Personality changes → coma → death**.

Pathophysiology:

- **Ammonia** plays a central role:
  - Produced in intestines (bacterial protein breakdown, glutamine conversion).
  - Normally >90% cleared by liver; in liver failure, bypasses liver metabolism and reaches the brain.
- Other toxins may also contribute to neurological impairment.



Hepatic Encephalopathy

Clinical Diagnosis:

- **Serum ammonia**: Standard lab test, though not always correlated with severity.

Emerging markers:

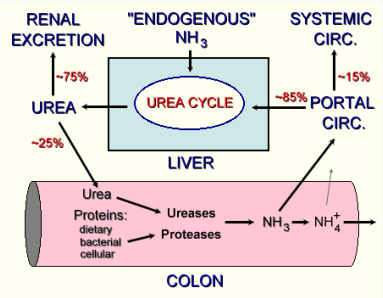
- **3-nitro-tyrosine**: Potential marker for minimal hepatic encephalopathy, showing high sensitivity (93%) and specificity (89%).

Clinical Manifestations:

- Subtle cognitive changes to severe neurologic impairment.
- Requires early detection and management in liver disease patients.

Ammonia

- **Normal Range**: 19–60 mcg/dL (13.6–42.8 µmol/L)
- **Correlation with Hepatic Encephalopathy (HE)**:
- **Chronic Liver Disease**: Poor correlation with HE; influenced by increased blood-brain barrier permeability.
- **Acute Liver Failure**: High levels correlate with HE severity and mortality; may help predict need for emergent liver transplant.



Ammonia

Clinical Use:

•**Very High Levels (>250 mcg/dL)**: Suggestive of HE, but most cirrhotic patients have normal/slightly elevated levels.
•**HE Diagnosis**: Primarily clinical, supported by history, exam, and psychometric tests.

Other Causes of Elevated Ammonia:
•**Reye Syndrome**, urea cycle disorders, valproic acid, renal impairment, ureterosigmoidostomy, or UTI with urea-splitting bacteria.
•**Cirrhosis Triggers**: High protein intake, GI bleeding, constipation, H. pylori infection.

Pancreatitis: Overview, Causes, and Diagnosis

Definition: Inflammation of the pancreas, can be **acute** or **chronic**.

•**Acute Pancreatitis**: Severe midepigastric pain, often radiating to the back, with nausea, vomiting, and potential complications (e.g., anemia, hypocalcemia, hypoxia).
•**Chronic Pancreatitis**: Long-term inflammation leading to fibrosis, calcification, possible diabetes, and malabsorption.

Common Causes:

•**Gallstones** and **alcohol abuse**: Account for 60–80% of cases.
•Other factors: Medications, autoimmune diseases, trauma, hypercalcemia, hypertriglyceridemia, and pancreatic tumors.

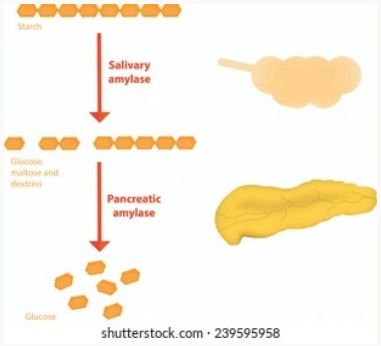
Amylase

Normal Range: 20-96 units/L (method dependent)

- **Function**: Enzyme that breaks down starch into glucose.

Clinical Use:
- Primarily used to diagnose **acute and chronic pancreatitis**.
- Rises **2–6 hours** after onset, peaks at **12–30 hours**, and normalizes in **3–5 days** if uncomplicated.

Interpretation:
- **High levels (up to 25x normal)**: Suggest acute pancreatitis but may overlap with other conditions (e.g., opiate-induced Oddi sphincter spasms).
- **Low Sensitivity & Specificity**: 20% of pancreatitis cases have normal amylase, especially in **alcoholic pancreatitis** or **hypertriglyceridemia**.



Amylase

Elevated Amylase:
•Can occur in GI, salivary, gynecologic, renal, neoplastic, and metabolic disorders.
•Influenced by drugs (e.g., aspirin, thiazides, oral contraceptives).

Macroamylasemia:
•Benign, with serum amylase elevated but urine amylase normal/low.
•Due to amylase complexes too large for kidney filtration.

Urine Amylase:
•Peaks later and persists longer (7–10 days) than serum levels, useful for delayed diagnosis.
Limitations:
•Hypertriglyceridemia can mask serum amylase elevation; serial dilution may clarify results.
•**Lipase** is often preferred for its longer half-life and fewer confounding factors.

Lipase

Normal Range: 31–186 units/L (0.5–3.2 µkat/L)

Function:
•Secreted by the pancreas, aids in **fat digestion** by breaking down triglycerides into fatty acids and glycerol.

Clinical Use:
•Rises within **12–30 hours** in acute pancreatitis, similar to amylase.
•Longer half-life (**7–14 hours**), normalizes in **8–14 days**, useful for delayed pancreatitis diagnosis.

Comparison with Amylase:
•**Superior Specificity** for pancreatitis.
•Combined amylase and lipase testing increases diagnostic accuracy; different factors affect each enzyme.

Lipase

Interpretation:

•**Elevated Lipase with Normal Amylase**: May suggest non-pancreatic causes or delayed testing.
•Elevation >3x normal suggests pancreatitis; lower elevations may indicate other abdominal disorders or conditions (e.g., renal failure, DKA).

Non-Pancreatic Causes:

•Conditions like **abdominal aortic aneurysm rupture**, **intestinal infarction**, **renal failure**, and certain drugs (e.g., opioids, NSAIDs) can elevate lipase.
Macrolipasemia:
•Rare, due to immunoglobulin-bound lipase complexes, preventing renal clearance and causing elevated serum lipase.