ALKALINE PHOSPHATASE (ALP)

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Synonyms: None

Specimen Type: Serum or plasma (lithium heparin; do not use EDTA or citrated or oxalated plasma)

Reference Interval: Cisgender/transgender female and male (adults) 35–125 IU/L*

Factors that Influence Reference Interval:

- Age: Alkaline Phosphatase (ALP) activity is higher in newborns and peripubertal children. Physiological increases in ALP occur during childhood, due to the growth of bones. For children and adolescents, age-specific reference intervals are strongly recommended.
- Sex: In adults, ALP activity may be slightly higher in males depending on the population.
- Multiple studies demonstrate that hormone replacement therapy does not have a significant effect on ALP activity level.

**Note: Reported reference intervals will vary due to manufacturer platform used.*

Physiological Significance

ALP is a family of four isoenzymes, each encoded by a different gene. ALP is family of four isoenzymes, each encoded by a different gene; tissue-non-specific (ALPL), which is expressed primarily in the bone, live and kidney, intestinal (ALPI), placental (ALPP) and germ cells (APL2).

ALP is present in all tissues and catalyzes the hydrolysis of phosphate monoesters at basic pH values. Three metal ions, two zinc and one magnesium, are contained in the catalytic site, and both ions are required for enzymatic activity. ALP is part of the CMP and often interpreted in conjunction with AST, ALT, and gamma glutamyl transferase (GGT). Measurement of ALP isoenzymes can also be used to distinguish between hepatic, bone, intestinal, and placental origin.

Methods for Measurement*

i. colorimetric: At alkaline pH, ALP catalyzes the colorless 4-nitrophenylphosphate (p-NPP) substrate to PO_4 and 4-nitrophenoxide (yellow). The change in absorbance is measured at ~400–500 nm (reference method).

ii. fluorometric

iii. electrochemical

iv. chemiluminescence

Previously, deficiencies of magnesium and zinc caused artifactually low ALP activity since ALP requires magnesium and zinc cofactors for full *in vivo* and *in vitro* activity. The current ALP assay formulations use the IFCC method, which include sufficient concentrations of magnesium and zinc such that this is largely no longer an issue.

**Note: Certified reference material is available.*

Causes of Elevated ALP

i. cholestatic liver disease (often >5x upper limit of normal)

ii. bone diseases with increase in osteoblastic activity

- Paget's disease (isolated increase of ALP, often >5x upper limit of normal)
- osteomalacia (often >5x upper limit of normal)
- rickets (often >5x upper limit of normal)

iii. malignancy (metastases of bone or liver)

iv. renal osteodystrophy

v. healing fractures

vi. primary hyperparathyroidism with bone involvement

vii. tumors of the head of the pancreas

viii. intrahepatic cholestasis of pregnancy (often >5x upper limit of normal)

ix. cirrhosis

x. inflammatory bowel disease

xi. benign transient hyperphosphatasemia

xii. viral hepatitis (mildly elevated)

xiii. alcoholic hepatitis

xiv. asfotase alfa/enzyme replacement therapy

xv. macro-ALP: artifactual

- immunoglobulin-ALP complex that accumulates due to decreased clearance, resulting in artifactually elevated ALP activity. Clinically benign.

Causes of Decreased ALP

i. hypophosphatasia

ii. malnutrition

iii. hypophosphatemia

iv. treatment with steroids

v. hypothyroidism

vi. Wilson's disease

vii. post-cardiac surgery and post-pulmonary bypass surgery

viii. severe aplastic anemia

ix. pernicious anemia

x. achondroplasia

xi. massive blood transfusion

xii. cleidocranial dysplasia

xiii. osteochondrodysplasia

xiv. magnesium deficiency

xv. osteogenesis imperfecta IIC

xvi. EDTA Contamination: artifactual

- EDTA chelates Mg^{2+} and Zn^{2+} which is required for ALP enzyme activity, yielding a decreased result.
- EDTA contamination can be caused by errors during sample collection or handling, such as:
  - incorrectly collecting into an EDTA tube instead of serum or lithium heparin tube
  - collecting an EDTA tube before a serum or heparin tube (it should be collected after a serum or heparin tube)
  - pouring a sample collected in an EDTA tube into a serum or heparin tube

GAMMA-GLUTAMYL TRANSFERANSE (GGT)

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Synonyms: Glutamyl transpeptidase

Specimen Type: Serum or plasma

Reference Interval: Cisgender/transgender females (adults): <40 U/L; Cisgender/transgender males (adults): <70 U/L

Factors that Influence Reference Interval:

- Age: Gamma-Glutamyl Transferase (GGT) activity level tends to be higher in newborns. In adults, GGT increases with age. Age-specific reference intervals may be needed, depending on the patient population.
- Sex: Males tend to have higher activity levels of GGT than females.
- Studies have shown that transgender patients on stable hormone therapy shift toward the affirmed gender.

Physiological Significance

GGT is a key enzyme involved in extracellular catabolism of glutathione, permitting amino acid transport across cell membranes and re-synthesis of intracellular glutathione. It maintains intracellular concentrations of glutathione, which is a major antioxidant. Its catalytic function entails the transfer of the gamma-glutamyl group from a donor substrate, such as peptides or peptide-like compounds, to an acceptor group. GGT is found in the proximal renal tubule, liver, pancreas, seminal vesicles, and intestine. Its serum activity originates from the hepatobiliary system, where it is found in the biliary pole of the hepatocytes. GGT is often ordered in conjunction with other liver enzymes like AST, ALT, and ALP to detect hepatobiliary diseases. In cases of intrahepatic or post-hepatic biliary obstruction, serum GGT activity may be elevated by 5–30x the upper limit of normal. GGT can aid in identification of elevated ALP of biliary vs bone origin.

Method for Measurement

The International Federation of Clinical Chemistry (IFCC) reference measurement uses the enzymatic activity of GGT, facilitating transfer of the gamma glutamyl group from a substrate to produce 5-amino-2 nitrobenzoate, which is measured at 410 nm. This conversion is expressed as its enzymatic activity.

Causes of Elevated GGT

i. hepatobiliary disease

ii. primary or secondary metastatic liver neoplasm

iii. hepatitis (moderate increases)

iv. non-alcoholic fatty liver disease (NAFLD)

v. alcoholic hepatitis (chronic or heavy alcohol use)

vi. increased body weight and obesity

vii. medications (e.g., phenytoin, phenobarbital, furosemide, heparin)

viii. myocardial injury

ix. heart failure

x. pancreatitis

Causes of Decreased GGT

i. low GGT familial intrahepatic cholestasis