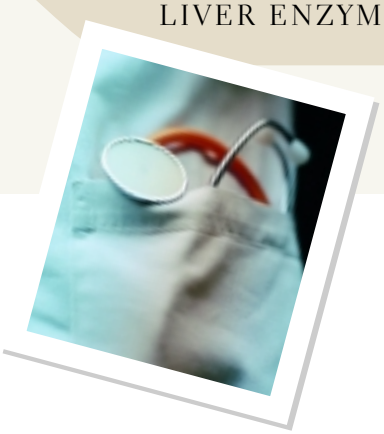

Interpretation of Serum Alkaline Phosphatase in Dogs

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Profile

DEFINITION

An increase in serum ALP activity is a common, nonspecific finding in dogs that is associated with drug induction (corticosteroids, anticonvulsants), extrahepatic diseases (pancreatitis, endocrinopathies), or primary liver pathology (including nodular hyperplasia in older dogs).

PROBLEMS

What is the clinical significance of an increase in total ALP? Is the increase in serum total ALP associated with hepatobiliary disease or primary bone disorders or due to drug induction from corticosteroids or phenobarbital? Are increases due to corticosteroid or phenobarbital resulting from enzyme induction or drug-induced hepatotoxicity?

When increases in total ALP are due to hepatobiliary disease, are they associated with primary hepatobiliary disease, or do they represent secondary involvement of the liver? Conditions in which total ALP may be elevated without the presence of clinically significant hepatobiliary disease are listed in the **Box**.

INCIDENCE/PREVALENCE

Unknown, but increased total ALP is one of the most common abnormalities detected on biochemical profiles in dogs.[1]

SIGNALMENT

Young dogs have increases in bone isoenzymes due to increased osteoblastic activity in growing bones.

Conditions Other Than Primary Liver Disease Associated with Increased Serum Total ALP Activity

- Bone disorders
  - Young animals (normal physiologic-related finding)
  - Osteosarcoma
  - Osteomyelitis
- Endocrinopathies
  - Diabetes mellitus
  - Hypothyroidism
  - Hyperadrenocorticism
- Gastrointestinal disease
  - Pancreatitis
  - Inflammatory bowel disease
- Hypoxia/Hypotension
  - Congestive heart failure
  - Hypotensive crisis
  - Severe hemolytic anemia
  - Status epilepticus
- Neoplasia
  - Hepatic metastasis
  - Paraneoplastic induction
- Drug induction
  - Corticosteroids
  - Phenobarbital
- Systemic infections

Breed-specific hepatopathies in Labrador retrievers, Doberman pinschers, Dalmatians, cocker spaniels, Bedlington terriers, and Skye terriers should alert the clinician to the possibility of a primary hepatobiliary disorder.

Nodular hepatic hyperplasia is a common, age-related, incidental lesion in dogs with a reported incidence from 70% to 100% in dogs older than 14 years of age.

CAUSE/RISK FACTORS/PATHOPHYSIOLOGY

The primary clinical asset of serum total ALP determination is its sensitivity (80%) for hepatobiliary disease.[2] (Sensitivity is the ability of the test to detect animals that have hepatobiliary disease.) The major limitation in interpreting serum total ALP is its low specificity (51%) for hepatobiliary disease. (Specificity is the ability of the test to exclude the presence of hepatobiliary disease.) The low specificity of serum total ALP is due to presence of several ALP isoenzymes (bone, liver, corticosteroid-induced) and the unique susceptibility of the enzyme to induction by drugs.

Bone ALP accounts for about one third of normal serum total ALP and is elevated with conditions associated with increased osteoblastic activity, such as bone growth in young dogs, or with pathologic conditions, such as osteomyelitis, osteosarcoma, or renal secondary hyperparathyroidism.[3] Typically, bone ALP elevations in these conditions are mild to moderate (three to five times the upper limit of normal). Liver ALP is a membrane-bound enzyme present on biliary epithelial cells and hepatocytes. Increases in serum liver ALP are

ALP = alkaline phosphatase

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due to elution of the enzyme from the membrane following hepatobiliary damage. The largest increases are seen with focal or diffuse intrahepatic or extrahepatic cholestasis. Mild to moderate increases are seen with chronic hepatitis and hepatic necrosis.

Corticosteroid-induced ALP is produced by the liver and is found on hepatocyte membranes.[4–6] This enzyme increases from de novo synthesis of the enzyme in dogs exposed to endogenous or exogenous corticosteroid excess.

Dx Diagnosis

Clinical findings can be used as an aid in identifying the source of total ALP elevation. Similarly, diagnostic imaging can be helpful in determining the root of the problem, as can laboratory analysis and biopsy. The following indicators are important.

HISTORY / PHYSICAL EXAMINATION

- History of drug administration: Particularly corticosteroids (oral, parenteral, or topical) or phenobarbital, but also other potentially hepatotoxic drugs, such as potentiated sulfonamides and nonsteroidal antiinflammatory agents
- Bone pain: Osteomyelitis, osteosarcoma
- Polyuria/polydipsia: Hyperadrenocorticism, diabetes mellitus, chronic liver disease, congenital portosystemic shunts
- Dermatologic disorders: Hyperadrenocorticism, hepatocutaneous syndrome
- Diffuse cerebral signs: Hepatic encephalopathy from chronic liver disease or congenital portosystemic shunts
- Pot belly: Abdominal wall muscle atrophy with centripetal redistribution of fat in hyperadrenocorticism
- Jaundice: Prehepatic (hemolytic anemia), hepatic, or posthepatic hyperbilirubinemia
- Abdominal effusion: Chronic liver disease, neoplasia, pancreatitis, congestive heart failure
- Hepatomegaly: Primary liver disease, steroid hepatopathy, passive congestion, hepatic lipidosis
- Dyspnea/increased lung sounds: Congestive heart failure
- Abdominal pain: Pancreatitis, cholecystitis, gastric ulceration
- Chronic intermittent gastrointestinal signs: Gastric ulceration secondary to chronic liver disease, congenital portosystemic shunts, chronic pancreatitis, inflammatory bowel disease

IMAGING

Radiography.

- Hepatomegaly: Steroid hepatopathy, congestive heart failure, hepatic lipidosis, and focal and diffuse hepatobiliary disease
- Microhepatica: Chronic end-stage hepatobiliary disease, congenital portosystemic shunts
- Choleliths: 50% are visible radiographically and may be associated with secondary cholecystitis.
- Decreased abdominal detail: Ascites
- Cardiomegaly and signs of pulmonary edema: Congestive heart failure
- Lytic bone lesion: Bone tumor or infection

Ultrasonography.

- Focal or multifocal hepatic lesions: Hepatobiliary neoplasia, nodular hyperplasia, metastatic disease, abscess
- Diffusely hyperechoic liver: Steroid hepatopathy, hepatic lipidosis, lymphosarcoma
- Diffusely hypoechoic liver: Passive congestion, lymphosarcoma, suppurative hepatitis
- Normal liver: Does not rule out primary hepatic disease
- Gallbladder/biliary tree: Gallbladder mucocele, distention of intra- and/or extrahepatic biliary tree, bile duct mineralization, choleliths
- Portal vasculature: Single or multiple acquired portosystemic shunts, portal vein thrombosis, passive congestion
- Pancreas: Enlarged hypoechoic, surrounded by hyperechoic fat with pancreatitis
- Thickened gastrointestinal wall with retention of normal layering: Inflammatory bowel disease
- Hepatic metastasis: Primary neoplasia of spleen, stomach, pancreas, intestine, or adrenals

LABORATORY ANALYSIS

- Hyperadrenocorticism: Mild polycythemia, mild thrombocytosis, mild to moderate increase in ALT and GGT, hypercholesterolemia
- Primary liver disease: Concurrent increases in serum ALT, AST, and GGT; hypoalbuminemia; low blood urea nitrogen; hypocholesterolemia; hypoglycemia. *Note: The specificity of the total ALP for hepatobiliary disease can be improved to 94% if used in combination with serum GGT.*
- Chronic liver disease: Pure transudate or modified transudate as evidenced by abdominal tap
- Acute pancreatitis: Acute nonseptic neutrophilic inflammation as evidenced by abdominal tap; increase in serum amylase and/or lipase
- Diabetes mellitus: Persistent hyperglycemia
- Malignancy: Malignant effusion as evidenced by abdominal tap. High protein fluid with exfoliated neoplastic cells (pancreatic, intestinal, adrenal adenocarcinoma, or lymphoma). Absence of neoplastic cells, however, does not rule

ACTH = adrenocortical hormone–stimulation test; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST aspartate transaminase; GGT = γ-glutamyl transpeptidase; LDDS = low-dose dexamethasone suppression; PCV = packed cell volume

out cancer. Hemorrhagic effusion with ruptured hemangiosarcoma.

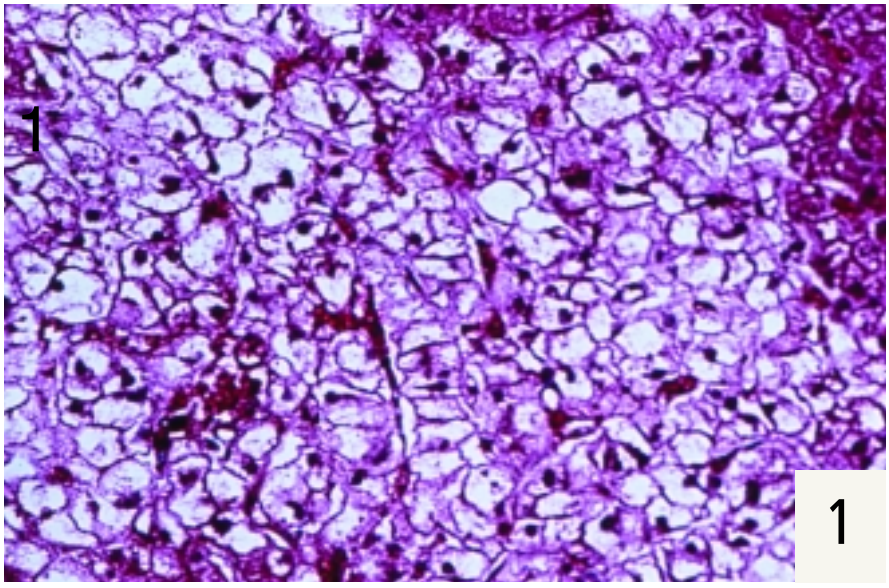
DEFINITIVE DIAGNOSIS

Disease-specific.

- Hyperadrenocorticism: Failure to suppress on an LDDS test. Exaggerated response to an ACTH-stimulation test.
- Hepatobiliary disease: Abnormal hepatic function test: Elevated total serum bile acids. Hyperbilirubinemia with a normal PCV is due to hepatic or posthepatic disease. Blood hyperammonemia confirms the presence of hepatic encephalopathy. Increased prothrombin time or partial thromboplastin time can accompany severe hepatobiliary disease.
- Nodular hyperplasia: Asymptomatic patient, typically older than 8 years of age with mild to moderate increase in total ALP. Other serum liver enzymes and hepatic function tests are normal. Ultrasonography shows multifocal nodules. Hepatic biopsy shows well-circumscribed nodules with normal but often vacuolated hepatocytes surrounded by normal hepatic tissue. Wedge biopsy works best, since nodular hyperplasia must be differentiated from regenerative nodule in a cirrhotic liver, which requires the finding of fibrosis and/or inflammatory changes in surrounding hepatic parenchyma.

Laboratory testing.

- ALP isoenzyme analysis: Determination of corticosteroid-induced increases in ALP by levamisole inhibition is a sensitive (95%) but not specific (18%) indicator of excess exposure to corticosteroids.[7] Many dogs with primary hepatobiliary disease have increases in both corticosteroid-induced ALP and liver ALP.[8,9] Corticosteroids induce increases in both liver and bone ALP along with corticosteroid-induced ALP. Phenobarbital increases liver ALP.
- Hepatic biopsy: Identify primary hepatic disease, such as lipidosis, neoplasia, vascular, or inflammatory/fibrotic disease. Steroid hepatopathy is characterized by the presence of vacuoles in hepatocytes, which most studies suggest are filled with glycogen[5] (**Figure 1**). May be associated with endogenous or exogenous administration of corticosteroids or with endogenous excess of other adrenal steroids, such as 17-hydroprogesterone.[10]



Steroid hepatopathy in a dog on immune-suppressive doses of prednisone

Tx Treatment

Treatment is tailored to the specific disorder. Asymptomatic patients with an increase in serum total ALP or patients with primary hepatic disease on corticosteroids or phenobarbital are particularly problematic. Management of such patients is reviewed in the following discussion.

PATIENT MONITORING

Asymptomatic patients.

Look for signs of occult hyperadrenocorticism. Perform an LDDS or ACTH-stimulation test. Measure cortisol levels initially with ACTH stimulation; if indicated, pursue testing for other adrenal steroids, such as 17-hydroxyprogesterone. If there are no signs of other disease but total ALP is less than 2 times upper limit of normal, monitor total ALP monthly. If total ALP is persistently elevated or more than 4 times upper limit of normal, perform abdominal ultrasonography and evaluate as follows:

- Focal or diffuse liver disease: Hepatic biopsy
- Bile duct obstruction in the absence of pancreatic disease: Surgical decompression of biliary tract
- Gallbladder mucocele: Cholecystectomy
- Choleliths (without obstruction) and/or thickened gallbladder wall: Perform cholecystocentesis with bacterial culture and bile sensitivity testing, or give a therapeutic trial of antibiotics and choleretics (ursodeoxycholate).

Dogs on corticosteroids.

Typical findings include hepatomegaly, diffusely hyperechoic hepatic parenchyma on ultrasonography, steroid hepatopathy on hepatic biopsy, moderate to marked increases in total ALP (3 to 64 times upper

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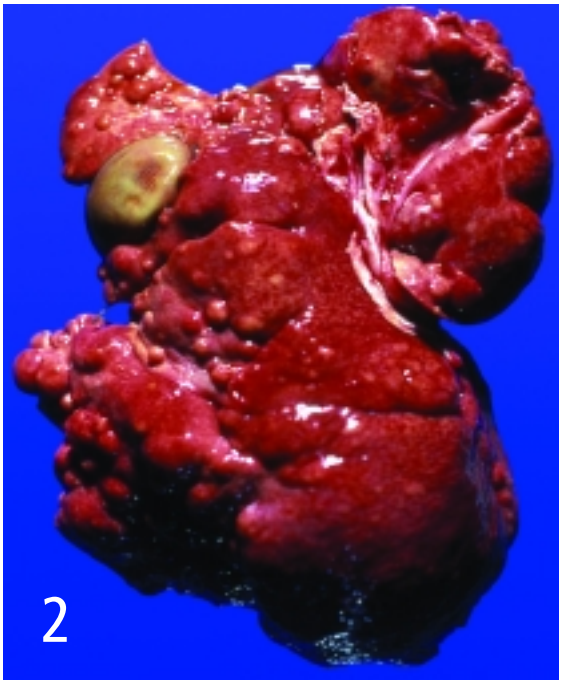
limit of normal), mild to moderate increases in ALT and GGT (2 to 6 times upper limit of normal) with little to no increase in AST (< 2-fold increase).

Signs of possible hepatotoxicity include abnormalities of hepatic function tests, such as increased total serum bile acids, hyperbilirubinemia, hypoalbuminemia, coagulopathy, ascites, or hepatic encephalopathy. Hepatic biopsy shows vacuolar hepatopathy with areas of focal necrosis, cholestasis, and degeneration of hepatocytes.

Treatment involves discontinuing corticosteroids and substituting an alternative immunosuppressive, antiinflammatory agent, such as azathioprine or chlorambucil.

Dogs on phenobarbital.
The liver of a dog with cirrhosis due to chronic hepatotoxicity from phenobarbital is shown in **Figure 2**. Typical findings include increased total ALP usually less than 5 times upper limit of normal, with ALT usually less than 2 times upper limit of normal. GGT, AST, total serum bile acids should be within the normal range.[11,12] Ultrasonography yields normal findings, and most dogs do not have hepatomegaly. Biopsy shows diffuse cytoplasmic granularity due to proliferation of smooth endoplasmic reticulum.

Signs of possible hepatotoxicity include abnormal hepatic function tests. ALT, GGT or AST elevations more than 2 times the upper limit of normal. Hepatic biopsy shows chronic inflammatory/fibrotic disease.[13] Treatment involves weaning from phenobarbital and onto alternative antiseizure medications, such as potassium bromide; controlling the complications of hepatic failure; and initiating hepatoprotective therapy with ursodeoxycholate and/or S-adenosylmethionine.



Cirrhotic liver in a dog secondary to chronic hepatotoxicity from phenobarbital

Follow-up

PROGNOSTIC SIGNIFICANCE OF ALP

Increases in serum total ALP with primary hepatobiliary disease are indicative of active hepatobiliary disease. The increase is usually—but not always—proportional to the severity of ongoing damage. In end-stage fibrotic liver disease, however, total ALP may not be elevated in proportion to the degree of hepatic disease because of enzyme depletion secondary to replacement of normal hepatocytes by fibrosis.

Since the liver has large regenerative capacity and great functional reserve, the magnitude of elevation of total ALP is not indicative of the degree of functional impairment and is not prognostic. However, the prognostic significance of total ALP can be improved by sequential evaluation, especially in conjunction with hepatic biopsy or function tests. Since the half-life of ALP in dogs is 72 hours, a 50% decrease in total ALP over a 3- to 4-day period may indicate resolution of acute injury. In the absence of hepatotoxicity, serum total ALP elevations due to phenobarbital should return to normal in 2 to 4 weeks after discontinuation of the drug. Increases in total ALP due to corticosteroid excess, however, may take several months to normalize.

Elevations in bone ALP are associated with shorter survival time in appendicular osteosarcoma.[14]

See Aids & Resources, back page, for references, contacts, and appendices.

Dx at a glance…

Serum Total ALP

- Hepatobiliary, bone, and corticosteroid-induced isoenzymes contribute to total serum alkaline phosphatase levels in dogs.
- Elevation in the bone isoenzyme is associated with increased osteoblastic activity; in osteosarcoma, the degree of bone ALP elevation predicts survival time.
- Definitive diagnosis of induction of the corticosteroid isoenzyme is made by medication history along with the presence of clinical or laboratory signs suggestive of hyperadrenocorticism in combination with abnormal LDDS or ACTH stimulation.
- Total ALP is a sensitive but relatively nonspecific indicator of hepatobiliary disease. Specificity for primary hepatobiliary disease is increased when it is used in series with other liver enzymes.

ACTH = adrenocortical hormone–stimulation test; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST aspartate transaminase; GGT = γ-glutamyl transpeptidase; LDDS = low-dose dexamethasone suppression