ELEVATED LIVER ENZYMES-WHAT DO THEY MEAN AND WHAT SHOULD I DO

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INTRODUCTION
After history taking and a clinical examination, blood tests to assess liver enzyme activity and liver function are usually the simplest next step in the investigation of an animal with suspected liver disease. Unfortunately it is never possible to make a diagnosis of liver disease based on results of blood tests alone, and these should form part of the investigation as a whole. In most cases, a tentative diagnosis of liver disease can be made from the combined results of laboratory tests and imaging. However definitive diagnosis of liver disease in most cases ultimately relies on histological examination of a liver biopsy.

LIVER ENZYMES
Liver enzyme activity, as measured in serum, can be classified into two major groups. Leakage markers, which are hepatocellular enzymes released as a result of cell damage (ALT, AST), and biliary enzymes whose synthesis is induced by retained bile and drugs (ALP, GGT).

Liver enzyme activity should be measured in all cases of suspected liver disease. In general, liver enzymes are sensitive indicators of liver disease or injury but are not specific. There are far more animals in which elevated liver enzyme activities are detected than actually have clinically significant liver disease. This lack of specificity arises from a combination of the susceptibility of the liver to secondary or ‘reactive’ disorders, the ability of certain hormones or drugs, such as corticosteroids, to induce production of particular liver enzymes and the presence of isoenzymes within tissues other than liver. These secondary or reactive hepatopathies are listed in the following Table.

It is also vital to remember that liver enzymes are not a test of liver function. Liver enzymes may be extremely high following a toxic insult, but due to immense reserve capacity liver function may be normal. Liver enzymes also remain high during hepatocyte regeneration after such an insult. Conversely, an animal with cirrhosis may have normal liver enzymes as there is insufficient hepatic mass to synthesis enzymes, but liver function may be markedly reduced.
Table: Some secondary (‘reactive’) hepatopathies associated with elevations in liver enzymes

<table>
<thead>
<tr>
<th>Disease</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Hyperadrenocorticism or glucocorticoid treatment (DOGS only)</td>
<td>• Direct enzyme induction of ALP or secondary to cholestasis induced by hepatocyte swelling (glycogen accumulation)</td>
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<td>• Usually, but not always, see large elevations in ALP +/- milder elevations in ALT, GGT and bile acids</td>
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<td>Diabetes mellitus</td>
<td>• Associated with the development of a secondary hepatic lipidosis</td>
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<td>• ALP and ALT can be mild to moderately elevated</td>
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<tr>
<td>Hyperthyroidism</td>
<td>• Mild to moderate elevations in ALT +/- ALP</td>
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<td>Anticonvulsant medication particularly phenobarbitone</td>
<td>• Often due to enzyme induction.</td>
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<td>• Some dogs may develop morphologic liver injury and functional impairment, although this generally occurs only at higher doses</td>
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<td>• Majority only develop increased serum activities of ALP +/- ALT, AST, GGT (usually only increase by approx. 2-fold). Bile acids usually remain normal</td>
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<td>Congestive heart failure (CHF)</td>
<td>• Associated with chronic congestion and hypoxia of hepatocytes.</td>
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<td>• Mild to moderate increases in ALT and ALP</td>
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<tr>
<td>Pancreatitis</td>
<td>• Increased ALP, GGT and sometimes jaundice due to biliary tract obstruction by pancreatic swelling and/or fibrosis</td>
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<td>• Hepatocellular enzymes may be mildly to moderately elevated due to local and systemic inflammation</td>
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INDIVIDUAL LIVER ENZYMES

ALANINE AMINOTRANSFERASE

Alanine aminotransferase (ALT) is a cytosolic enzyme that is released into the serum from hepatocytes with increased hepatocyte membrane permeability or following hepatocellular necrosis. This enzyme is considered to be a sensitive indicator of hepatocellular injury in dogs and cats and is also considered to be the most liver-specific enzyme in these species. Although ALT is also found in cardiac and skeletal muscle and the kidneys, this is not generally of clinical significance as the isoenzymes found in these other locations either have short half-lives or are present at low concentrations. However, occasionally severe muscle injury can result in ALT elevation.

The half-life in dogs is around 24-48 hours, whereas in a cat it is several hours. In general, with hepatic injury a reduction in the enzyme activity of approximately 50% every 2-3 days would be viewed as a good prognostic sign. Elevated ALT activity can also occur with cholestasis due to the damaging effect of accumulated bile acids on hepatocyte membranes. Certain drugs can also result in ALT enzyme increases, for example anticonvulsant drugs or corticosteroids; these elevations tend to be dose-dependent but also show considerable inter-individual variation.

ASPARTATE AMINOTRANSFERASE

Aspartate aminotransferase (AST) is also a marker of hepatocellular damage within the group of ‘leakage’ enzymes, having a predominantly cytosolic location within hepatocytes. However in addition there is also a mitochondrial fraction, comprising about 30% of the total hepatic enzyme activity, which is only released during hepatocellular necrosis. The half-life of AST is about 4-20 hours in the dog and one hour in the cat. In general, in acute liver injury, elevations of AST mirror those of ALT although the overall values tend not to be as high (10-30-fold increases in the dog and up to 50-fold in the cat).
Elevations in AST also occur with skeletal muscle disease so any elevation occurring in the absence of ALT elevation should be cross-referenced with creatinine kinase measurement to exclude this possibility. In general, most biochemical profiles offer only one hepatocellular enzyme measurement, typically ALT, and the measurement of AST in addition to this is unlikely to offer a marked clinical advantage.

**ALKALINE PHOSPHATASE**

Alkaline phosphatase (ALP) is a membrane-bound enzyme that has been shown to have a high sensitivity (85%) but low specificity (51%) for the detection of hepatobiliary disease in dogs. The converse is true for cats with reported values of 48% sensitivity and 93% specificity.

In dogs and cats there are a variety of tissues known to exhibit ALP activity including intestinal mucosa, renal cortex, placenta, liver and bone. In the dog, the total serum ALP (T-ALP) measured on clinical biochemistry profiles reflects the combination of liver-ALP (L-ALP), bone-ALP (B-ALP) and glucocorticoid-ALP (G-ALP); other isoenzymes fail to contribute to this measurement due to a combination of their short half-life and/or low overall tissue activities. In the cat, T-ALP comprises L-ALP and B-ALP due to a lack of G-ALP in this species, although placental isoenzyme has also been detected late-term in this species. L-ALP is found predominantly within the periportal zone of the liver, bound to hepatocyte canalicular and sinusoidal membranes. The serum activity of this enzyme is increased in response to cholestasis (intra- and extra-hepatic) and induction of *de novo* synthesis.

The half-life of L-ALP is approximately 70 hours in the dog and 6 hours in the cat. This short half-life in the cat, combined with a lower ALP activity in feline liver, is important practically. Clinically significant elevations of ALP activity in the cat are considerably smaller those seen in the dog. Cats with hepatic disease may have ALP elevations twofold or three fold higher than normal as opposed to dogs where values are often more than four- or fivefold normal. This situation, in combination with the lack of G-ALP enzyme in the cat, results in the far lower sensitivity of ALP for liver disease in the cat (48%) but the enhanced specificity (93%). In view of this, the interpretation of ALP elevation in dogs and cats differs considerably. In dogs, ALP induction occurs in response to endogenous and exogenous corticosteroids and phenobarbitone. The response to corticosteroids is rapid and may occur following oral, topical and parenteral exposure. As with ALT, the level of ALP elevation observed does not correlate with the underlying disease process and persistent elevation is a source of more concern than a single abnormal value.

**GAMMA-GLUTAMYLTRANSFERASE**

Gamma-glutamyltransferase (GGT) is also a membrane-bound biliary enzyme. The serum GGT activity is largely derived from liver sources of the enzyme with increased activity resulting from *de novo* synthesis or increased elution from biliary membranes in response to cholestasis. In general GGT elevations parallel rises in ALP. GGT also shows corticosteroid induction, but unlike ALP, has no bone isoenzyme and shows less induction with phenobarbitone administration.

In one study in dogs GGT was found to be more specific for liver disease than ALP (87% compared to 51%), however it showed considerably less sensitivity (46% compared to 85%). In cats, the converse is true; GGT is more sensitive but less specific than ALP.

**SUMMARY**

There is no one specific clinical pathology finding that defines a specific diagnosis of hepatobiliary disease in dogs and cats. The clinician needs to interpret all of the tests together in the context of the patient and its clinical presentation. Consideration of pattern of abnormalities in the clinical pathology tests rather than individual tests in isolation can be helpful in increasing or decreasing the index of suspicion of different conditions. Once this type of interpretation has been considered, the use of diagnostic imaging allows further refinement and direction towards either the pursuit of potential extrahepatic causes of the animal’s signs and laboratory findings or more specific hepatic testing such as cytology or biopsy.
REFERENCES
