

# Bile acids

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Analysis of various clinical chemistry parameters allows laboratory evaluation of liver cell damage. Bile acids assay is a valuable diagnostic tool to assess liver function in-house in a timely manner.

## Enterohepatic circulation of bile acids

Bile acids are synthesized by the liver and stored in the gall bladder. They are then secreted via the bile duct into the intestines. Within the intestines bile acids are responsible for dissociation of lipids to facilitate fat digestion. Majority of secreted bile acids are reabsorbed via the portal vein. Hepatocytes filter the portal venous blood and thereby absorb bile acids back into the liver, closing the enterohepatic circulation (Fig. 1).

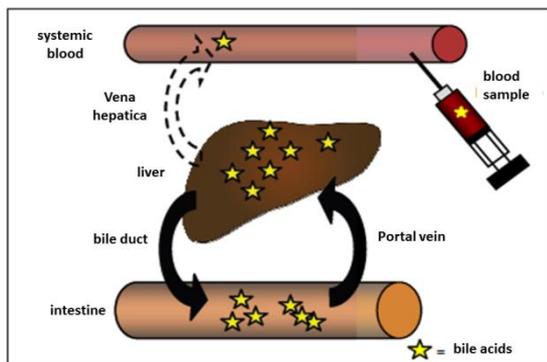


Fig. 1: Enterohepatic circulation of bile acids

The process of enterohepatic circulation is so efficient that in health only minimal amounts of bile acids enter the systemic blood stream.

In healthy patients bile acids within the blood resemble the small amount of bile acids which escape the enterohepatic circulation.

In fasting state, only minimal enterohepatic bile acid circulation takes place. Therefore the amount of bile acids in plasma is low. Food ingestion leads to gall bladder contraction and release of increase amounts of bile acids in the enterohepatic circulation. Subsequently, increased bile acid concentrations can be detected in plasma.

## Laboratory examination of bile acids

As bile acid secretion into the intestine is stimulated by food ingestion, bile acid evaluation should always be performed out of blood of fasted patients. Owners are advised to not feed the patient for at least 12h prior to the blood sampling procedure.

The result of a measurement performed at a randomly chosen timepoint has no diagnostic significance as actual status of enterohepatic bile acid circulation is unknown.

## The bile acid stimulation test

In dogs and cats, a bile acid stimulation test is often performed. Thereby bile acid concentration of 2 samples is evaluated. The first sample (basal or fasted value) is taken after an at least 12h fasting period. Then, food with a high fat content is given to the patient. Two hours post feeding a second sample is taken (post-prandial value). This stimulation test increases sensitivity to evaluate liver capacity for resorption of bile acids out of the enterohepatic circulation.



### Reference value

For the detection of bile acids out of a fasted sample after 12h food deprivation, results of  $<25 \mu\text{mol/l}$  (dog) and  $<20 \mu\text{mol/l}$  (cat) are generally used as upper reference limit.

In the bile acid stimulation test a basal/ fasted concentration of  $<7.9 \mu\text{mol/l}$  (dog) and  $<15 \mu\text{mol/l}$  (cat) and a post-prandial value of  $<25 \mu\text{mol/l}$  (dog) and  $<15 \mu\text{mol/l}$  (cat) can be seen as physiologic. Questionable results of  $>25 \mu\text{mol/l}$  for a basal value, and a post-prandial result between 20-40  $\mu\text{mol/l}$ . A result of  $>40 \mu\text{mol/l}$  is pathologic for a postprandial value.

### Interpretation of pathologic results

Increased bile acid concentrations in systemic blood can be seen when enterohepatic circulation is disrupted. Possible reasons are the following:

#### 1. Reduced absorption of bile acids out of portal blood

Hepatobiliary disease may lead to loss of functional liver mass and diminished absorption of bile acids out of portal blood (Fig. 2). Increased amounts of bile acids are released from enterohepatic circulation in the systemic blood flow. Increased bile acid concentrations can be detected in the blood and resembles a sensitive possibility to detect hepatobiliary disease. A remarkably increased fasting bile acid concentration is consistent with a pronounced hepatic dysfunction. Mild deteriorations in liver function can be better detected by performing a bile acid stimulation test.

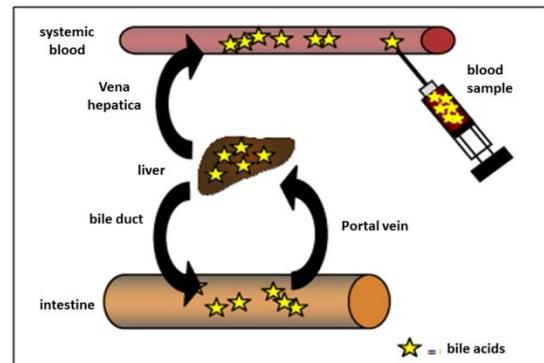


Fig. 2: Increase bile acid concentrations due to reduced liver mass

#### 2. Portosystemic Shunt

In patients with portosystemic shunt bile acids absorbed in the portal system are directly released in the systemic circulation (Fig. 3). In these patients a remarkable increase in bile acids can be detected as well.

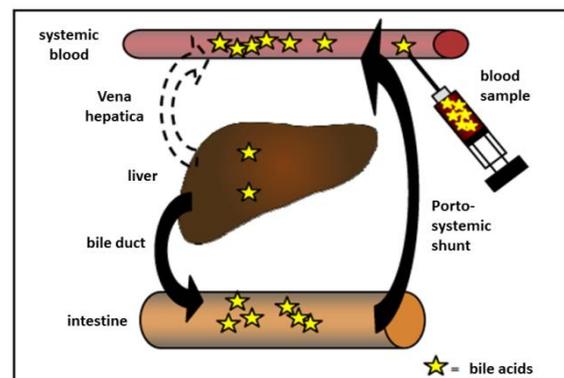
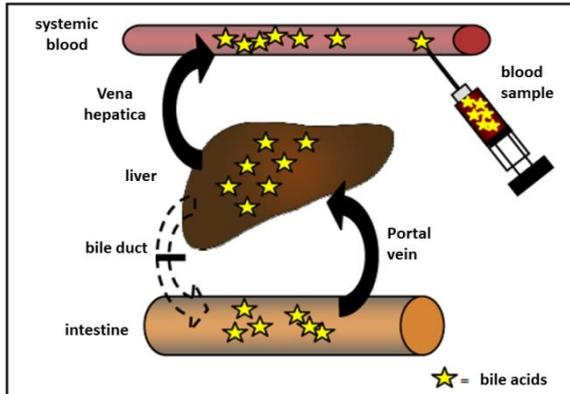


Fig. 3: Increased bile acid concentration in portosystemic shunt

#### 3. Reduced biliary excretion of bile acids

Is the patient suffering from a cholestatic disease, bile acids cannot be secreted in the intestine. (Fig. 4). Bile acids synthesized in the liver accumulate and are finally back-flushed in the systemic blood circulation. In this case increased bile acids can be detected. If a bile acid stimulation test is performed, usually basal as well as post-prandial bile acid concentrations are increased.





**Fig. 4: Increased bile acid concentration due to cholestatic disease**

## Result interpretation - Tips

### Increased basal bile acid concentrations

Rarely, high basal bile acid concentrations can occur. A grey area is present in bile acid concentrations between 20-50  $\mu\text{mol/l}$ . In these cases it is useful to look for extrahepatic disease or cholestasis as a reason for the increased bile acid concentration. Repetition of the bile acid stimulation test or repetition of fasting bile acid concentration after 2-4 weeks may also be of benefit. If the clinical picture or other examination results point to primary liver disease in these patients, further diagnostics in this direction are recommended. Basal concentrations of  $>50 \mu\text{mol/l}$  are highly suggestive of a primary liver function abnormality. If underlying disease had not been identified yet, further diagnostic workup including biopsy sampling may be warranted in these patients.

### Low post-prandial concentrations

Feeding is required prior to getting the post-prandial sample. Special care is warranted to assure ingestion of the food provided. If the food is not ingested properly, gall bladder contraction does not occur with subsequent failure of a postprandial bile acid peak. Only low bile acid concentrations will be detected.

If a gall bladder contraction took place during the 12h fasting period prior to performing the bile acid stimulation test, gall bladder will already be empty at the time of sampling. This condition is also associated with a low post-prandial bile acid concentration.

Small intestinal diseases (i.e. ileal malabsorption) may lead to reduced resorption of bile acids out of the intestine and lower bile acid concentrations in the peripheral blood.

Finally, individual differences in gastric emptying time, intestinal passage time and intestinal resorption can lead to changes in the timely occurrence of the post-prandial bile acid peak. It may occur later than 2h post food ingestion.

In general it is recommended to pay most attention to the stimulation test result with the highest bile acid concentration irrespectively of being the fasting or post-prandial result.

### Reference:

E. Villiers & J. Ristic, BSAVA Manual of Canine and Feline Clinical Pathology, 3rd Edition, 2016

