Hepatic lipidosis in turkeys

Hepatic lipidosis, also called fatty liver and hepatic steatosis, is a pathological condition that can affect turkey breeder hens and meat-type turkeys. The exact cause of the condition, which typically affects apparently healthy birds, is yet to be determined.

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Hepatic lipidosis is characterised by the excess accumulation of lipids in hepatocytes (liver cells). Triglycerides are the lipids most involved in hepatic lipidosis. In turkeys, hepatic lipidosis usually occurs in turkey breeder hen replacements between the ages of 12 and 24 weeks. However, the condition has also been reported in commercial, meat-type turkey hens and toms. Turkeys affected with this condition may die suddenly without preceding clinical signs, or they may exhibit signs of dyspnea and cyanosis shortly before death.

Metabolising lipids

In order to understand the pathogenesis of hepatic lipidosis, it is important to understand lipid metabolism. The consumed dietary lipids (predominantly triglycerides and neutral fats) are digested in the small intestine through emulsification by the bile and then enzymatic digestion by the pancreatic enzymes. The major products of lipid digestion - fatty acids and monoglycerides - enter intestinal epithelial cells where they are used to synthesise triglycerides, which are then packaged with cholesterol, lipoproteins, and other lipids to form the chylomicrons. The predominant lipids of chylomicrons are triglycerides, which are esters of fatty acids and glycerol. The chylomicrons enter the blood stream, and in the capillaries of adipose tissue and muscle, they are removed from the triglyceride by the action of lipoprotein lipase, which is found on the surface of the endothelial cells of the capillaries. The free fatty acids are then absorbed by the adipose tissue and liver to synthesise triglyceride, and the glycerol is returned to the blood circulation.

In the liver, free fatty acids are esterified to triglycerides, converted to cholesterol or phospholipids, or oxidised to ketone bodies. Triglycerides form complexes with specific lipid acceptor proteins called apoproteins, and the formed lipoproteins are then transported from the liver into the plasma.

Energy from fat keeps the body running whenever it runs out of its main source of energy (glucose). When there is a demand for energy, fatty acids can also be mobilised from the adipose tissue in a process called lipolysis in which the triglyceride is hydrolysed into free fatty acids and glycerol.

Oxidation of fatty acids

In the liver and muscle cells, the fatty acids released from the adipose tissue are oxidised through a cyclic series of reactions referred to as β-oxidation (occurring mostly within the mitochondria of the cells) to generate acetyl-CoA. Acetyl-CoA then enters the citric acid cycle to generate adenosine triphosphate (ATP) that is used as a primary source of energy. The series of reactions in β-oxidation involve several enzymes that are encoded by different genes. A substance called carnitine is required to transport activated fatty acid from the cell cytoplasm into the mitochondrial matrix for oxidation. Carnitine is synthesised primarily in the liver and kidney from the amino acids lysine and methionine, with iron, magnesium, and vitamins B2, B6, C, and niacin as required cofactors. Normally small amounts of ketone bodies (acetoacetate, β-hydroxybutyrate, and acetone) are generated from acetyl-CoA. Acetoacetate can be used as a source of energy in the extrahepatic tissue. The heart muscle in particular uses acetoacetate in preference to glucose as a source of energy. However, if a large amount of fatty acid is delivered to the liver, then the amount of the generated acetyl-CoA may exceed the capacity of the citric acid cycle, and the...
result is the synthesis of large amounts of ketone bodies, a condition referred to as ketosis.

**Cause of hepatic lipidosis**

The cause of hepatic lipidosis in turkeys is uncertain. The following are the most important causes of an excess of triglycerides in liver cells:

- Excess energy consumption (energy from fats or carbohydrates) and reduced energy combustion may increase lipid storage in the liver. So basically, there is an over-storage of excess energy from fats and carbohydrates in the hepatocytes when the consumed energy exceeds the energy combustion capabilities of the fatty acid oxidation system in the liver. It is important to note that fatty acids can also be formed in the liver from glucose in a process called lipogenesis, which is stimulated by insulin and glucose in the blood.

- Excess fatty acid influx into the liver from lipolysis of adipose tissue in obese individuals and animals.

- Decreased synthesis of lipid acceptor proteins with subsequent accumulation of triglycerides and other lipids in the hepatocytes. As mentioned earlier, the triglycerides that are synthesised in hepatocytes must be complexed with apoproteins before they are released into the plasma. Insufficient dietary protein, including certain amino acids, or damage to hepatocytes by an infectious agent or a hepatotoxin (e.g. a mycotoxin) can result in failure of hepatocytes to synthesise lipid acceptor proteins.

- Increased synthesis of fatty acids from glucose (lipogenesis) in the hepatocytes. It has been shown that lipogenesis is regulated independently by insulin and glucose. Elevated glucose level in the blood causes increased secretion of insulin from the pancreas. Insulin activates lipogenesis by inducing certain molecules in the hepatocytes, and these molecules activate key genes encoding enzymes necessary for the conversion of excess glucose to fatty acids. Over-expression of one or more of these molecular mediators (as seen in transgenic mouse) increases lipogenesis in the liver. Furthermore, high glucose and insulin have also been shown to inhibit fatty acid oxidation. There is no study to show whether turkeys with hepatic lipidosis have high glucose and/or insulin levels. It is also unknown whether the hepatic lipidosis in turkeys has a genetic component, as there is no data to show whether the incidence of hepatic lipidosis is high in the progeny of turkey hens with hepatic lipidosis.

- Reduced or impaired ß-oxidation of fatty acid in the mitochondria of cells. In humans, there are different conditions of “fatty acid oxidation disorders” in which the cells cannot oxidise fatty acids due to defects in the genes encoding fatty acid oxidation. These conditions are inherited in an autosomal recessive pattern. However, similar conditions have not been reported in turkeys.

**Gross lesions**

Birds that die of hepatic lipidosis are in good body conditions with abundant visceral (abdominal) fat. A yellow-tinged fluid may be found in the abdominal cavity. The liver is typically enlarged and its surface is mottled due to numerous hemorrhagic foci. Some livers have irregularly shaped, discrete or confluent, pale areas that represent lipid accumulation (Figures 1 and 2). Other lesions that have been described in affected turkeys are hemorrhages on the surface of the heart and the fat around the gizzard, and congestion and oedema of the lungs.

**Microscopic lesions**

There are variations in the microscopic lesions in affected livers. In some areas, the normal architecture of the liver is distorted by marked vacuolation of the cytoplasm of hepatocytes (Figure 3). The cytoplasmic vacuoles represent lipid droplets that were dissolved during tissue processing, thus called lipid vacuoles. Because of cytoplasmic vacuolation, individual hepatocytes are difficult to recognised. In other areas, groups of vacuolated hepatocytes and proliferating bile ductules are separated by hemorrhagic areas (Figure 4). In most cases, however, the predominant lesions are massive or submassive necrosis of hepatocytes with hyperplasia (proliferation) of bile ductules and with or without necrohemorrhagic areas that are either multifocal or extensive, confluent and separate areas of hepatocellular necrosis (Figures 5, 6, 7). Dying hepatocytes are shrunk and rounded and their nuclei may be pyknotic or karyorrhectic (Figure 8). Dead hepatocytes are anucleated (lost their nuclei) and appears as ghost cells (coagulative necrosis). Enlarged hepatocytes with a single, large vacuole that replaces the cytoplasm and peripherally displace and compressed the nucleus may be seen among the necrotic cells. There is no inflammatory response to the necrosis of hepatocytes. Because liver necrosis and hemorrhage are striking lesions in many cases, it is more appropriate to call the condition hepatic lipidosis and necrosis syndrome. The fatty vacuolation of hepatocytes, hepatocellular necrosis, hemorrhage, hyperplasia of bile ductules, and absence of inflammatory response suggest a toxic etiology (e.g. a mycotoxin) that causes injury to hepatocytes. Swelling and fatty vacuolation of hepatocytes indicate a sublethal, reversible injury. If the insult continues, or if it is more severe, the injury may progress to the point of cell death (necrosis). Because of extensive necrosis of hepatocytes, the meshwork of reticulin fibres, which support the hepatocytes and sinusoid lining cells, collapses in some areas, resulting in extravasation of blood from sinusoids (hemorrhages). Affected birds likely die from liver failure.

It is important to mention that hepatic lipidosis in turkeys is different from fatty liver-hemorrhagic syndrome in caged table-egg chickens. More researches are needed to determine the cause and pathogenesis of the condition, and to investigate whether it has any genetic components. Future research should primarily focus on investigating the possibility of exposure to a toxin.