***Review Article***

**Fatty liver syndrome in dairy cattle – A Comprehensive Review**

**ABSTRACT**

Fatty Liver Syndrome (FLS), also known as hepatic lipidosis, is a metabolic disorder affecting high-producing dairy cows, particularly during the early weeks of lactation. It is most prevalent in systems where all cows, regardless of their milk yield potential, are fed the same ration. This condition is more common in adult cows than in heifers and typically manifests within the first two weeks postpartum, though it can develop upto a month after calving. FLS occurs when high-producing dairy cows become over-conditioned during late pregnancy or in the dry period, resulting in a body condition score (BCS) greater than 3.5 at calving. At calving, these dairy cows experience a negative energy balance due to the sudden energy demands of lactation. Consequently, the body mobilizes excess fat reserves to meet the energy requirements. However, cows with a high BCS often have reduced appetite, leading to lower energy intake. This reduced intake exacerbates fat mobilization, overwhelming the liver's capacity to process the mobilized fat. The excess fat accumulates in the liver, impairing its function and leading to hepatic lipidosis. Early intervention is critical to prevent severe complications and to improve recovery outcomes. Implementing these preventive and management strategies can significantly reduce the incidence and impact of Fatty Liver Syndrome in dairy herds, leading to improved animal health and farm productivity.

**Key words**: Fatty Liver Syndrome, hepatic lipidosis, body condition score, negative energy balance.Top of FormBottom of Form

1. **INTRODUCTION**

The incidence of fatty liver is strongly associated with the occurence of other metabolic, infectious, digestive and reproductive disorders. These also share a common precipitating cause viz., ‘a severe negative energy balance’ during the transition period. A known metabolic issue of this imbalance is the fat cow syndrome, also known as fatty liver disease. This condition develops when non-esterified fatty acids (NEFAs) are absorbed by the liver and accumulate as excess triacylglycerols (TAGs). The build-up of fat, primarily TAGs, in hepatocytes is known as fatty liver. Long-chain fatty acids are first released from adipose tissues and subsequently taken up by the liver to create them. Fatty liver or hepatic steatosis is categorized as mild, moderate or severe based on the amount of fat in the liver (Zhang et al., 2023). A deficient amount of energy intake during early lactation causes fat metabolism to increase, resulting in the accumulation of extra amount of fat in the liver. Thus fatty liver is the main metabolic illness that affects dairy cows during the early stages of lactation. An abrupt spike in energy requirements especially after calving is the cause of this syndrome. This disorder mostly affects obese periparturient cows and happens to cause a combination of digestive, reproductive, metabolic, and infectious problems. During the early lactation period, due to a lack of energy, fat metabolism is increased, and excess fat is deposited in the liver. The condition is also associated with a large number of disadvantages such as increased veterinary costs, prolonged calving intervals, reduction in milk production and decreased average life span of cows. In severely affected cases, cows may develop hepatic encephalopathy, which is marked by depressed consciousness, ataxia, somnolence, coma and death. Clinically it can lead to metritis, mastitis, ketosis, downer cow syndrome, retained placenta, and infertility (Andrew et al., 2008). Research shows that metabolic problems and mild fatty liver mainly occur after calving due to the mobilization of adipose tissues in early lactation as the cows attempt to gain high energy needs (Djoković et al., 2013). The transition period in dairy cows are the last 21 days before expected parturition to 21 days postpartum, including the parturition, which is marked by several physiological (metabolic, endocrine, immune, digestive) adaptations which are required so that the cows must experience to achieve adequate lactational and functional performance (Melendez and Cisco, 2022). In this intricate context, the liver is considered a central regulatory organ in regulating the entire metabolism, particularly in high-producing dairy cows, which may surpass its normal function, leading to a series of local and systemic inflammatory and degenerative processes compromising integral animal health. In fact, hepatic fibrosis has been frequently reported as a common pathological finding in cows with fatty liver, a condition associated with oxidative stress, hepatocyte death, and inflammation (Zhang et al., 2023). Consequently, affected cows become more susceptible to a range of developing secondary diseases, including ketosis, displaced abomasum (DA), mastitis, retained fetal membranes (RFM), metritis, reduced fertility, and decreased milk production (Melendez and Cisco, 2022).

1. **ETIOLOGY**

Fatty liver or hepatic lipidosis is a common metabolic disorder or disease in dairy cows around parturition that leads to reduction of milk production, decreased fertility, and high risk of culling and even death. In addition to this, fatty liver is related to a higher incidence of infections and inflammatory responses, which further alters the overall health and productivity performance of the affected cows (Contreras et al., 2018). Fatty liver develops when there is an excessive NEFA uptake by the hepatocytes, which surpasses the oxidation capacity and exporting mechanism of newly assembled **TAGs** as **very low-density lipoproteins (VLDL)**. Increased concentrations of plasma NEFA resulting from an increased rate of lipolysis, particularly occurring in cows with excessive abdominal fat and/or high BCS (Contreras et al., 2018). Additionally, in dairy cows, especially those with high BCS, there is mostly a progression towards a state of insulin resistance around the parturition time, which is also contributing to a higher rate of mobilization of fat depots and further risk of hepatic lipidosis (De Koster et al., 2016). Insulin resistance may increase the condition of fatty liver by consequently, excessive lipo-mobilization in early postpartum cows, which leads to a high concentration of NEFA in the bloodstream, an important factor in the development of hepatic lipid accumulation. Hence, managing the excess fat during the period is essential for decreasing the incidence of metabolic diseases like hepatic lipidosis (Contreras et al., 2018).

1. **PATHOGENESIS**

In the response of energy deficiency, stored fat is released from adipose tissues in the form of free fatty acids, also known as NEFAs which can be oxidized as a source of energy or re-esterified into triglycerides (TG) in the liver, where they are either accumulated in the liver cells or transported as VLDL. Due to the limited capacity of liver, possibilities of synthesis of triglycerides and their transport as VLDL, an excess amount of mobilized fat results in the accumulation of fat in hepatocytes which leads to the development of hepatic lipidosis. Serum fatty acid level begins to increase from about 2 weeks prepartum, reaching a peak level upto 2 days postpartum, and returns to normal levels by the 3rd week of lactation (Nowak et al., 2006). A fatty liver is closely associated with a negative energy balance, which normally happens during the first few weeks postpartum. The syndrome occurs when metabolism of the body cannot be adequately adjusted to meet the body requirements. During the normal physiological conditions, the fat level in the liver increases a few weeks prepartum to reach approximately 20% in the 1st week postpartum, and then slowly decreases to less than 5% by 26 weeks post-partum. However, the hepatic fat content can range widely from almost 0% to 70% in the 1st week after parturition. Fat mobilization begins 2–3 weeks prepartum and is most likely triggered by hormonal changes which are caused by parturition, not by energy deficiency. Liver changes are functional, reversible, and closely dependent on metabolic demands during late pregnancy and early lactation. In cows with experimentally induced fatty liver, the intensity of glycogenesis in liver during the perinatal period is higher in comparison to that in cows without steatosis. Low level of glucagon leads to reduction in blood glucose concentrations, low level of insulin, and increased fatty acid mobilization, contributing to severe fatty liver syndrome.

1. **RISK FACTORS**

Obesity in pregnant cows is an essential predisposing factor in the development of postpartum liver steatosis, which increases the risk of metabolic disturbances during the critical transition period. Postpartum fat cows often show a reduction in appetite, which leads to negative energy balance during early lactation. This triggers increase in lipolysis of adipose tissues to meet the ever increasing energy demands (Kirovski and Sladojevic, 2017). Appetite loss in excessively overconditioned cows in the postpartum period results in increased fat mobilization, causing severity in the development of fatty liver. Fat accumulation in liver increases upto three weeks before and after calving (Andrew et al., 2008). The nutritional factor that leads to obesity plays an important role in the development of a fatty liver. Over fat cows show a higher decrease in feed consumption as that of healthy cows in the perinatal period (transition time), leading to a significant loss of energy in early lactation. Loss of appetite and energy deficiency leads to increased lipolysis to meet increasing energy demands of the body (Kirovski and Sladojevic, 2017). Researchers showed that cows in early lactation have morphological and physiological abnormalities in hepatic function, which causes a mild form of fatty liver (Krsmanović et al., 2016). The peak of milk production is 4-7 weeks postpartum, while the highest feed consumption reaches 8-10 weeks after parturition. Due to the result of energy deficiency, the cow in order to meet the energy demands for milk production releases fat stored in adipose tissues. Body condition at the time of parturition plays a significant role on the health, milk production and fertility of cows. Dairy cows with a long dry period have problems like obesity and shows an increased tendency towards development of fatty liver in the postpartum period. The disease that is also known as pregnancy poisoning is rare in beef cows, occurring in approximately about 1%, but has a 100% death rate. Fatty liver syndrome is more vulnerable in heifers than older cows. The disease is most common in late pregnancy (7-9 months) or immediately after parturition (Radostits et al., 2007).

1. **HEMATO-BIOCHEMICAL ALTERATIONS**

Cebra et al. (1997) in a study involving 59 cows, found that 50% of cows required treatment for secondary ketosis and 50% showed biochemical results indicating a fatty liver, with levels at least twice the normal range for two or more of the following enzymes: GGT AST, SDH (succinate dehydrogenase), and total bilirubin. The authors in another study revealed that in severe fatty liver disease, serum levels of sorbitol dehydrogenase activity or bilirubin concentration were abnormally elevated in only 8%, of cases while AST levels were 83% sensitive and 62% specific for diagnosis. Andrew et al. (2008) revealed that the levels of free fatty acids, bilirubin, and AST increase, while there is decrease in glucose, cholesterol, albumin, magnesium, insulin, and leukocyte levels. Al-Fartosi et al. (2010) conducted a study in southern Iraq; the mean AST level in cattle was 54 ± 9.53 U/l in males and 53.12 ± 8.26 U/l in females. Klebaniuk and Rocki, (2011) found no changes in AST activity in various stages of lactation or during pregnancy in dairy cows with an average yield of up to 6000 l of milk per year. Đoković et al. (2012) in a study, showed that the highest correlation was recorded between fatty liver and AST (r = 0.69). Moreover the other correlations between fatty liver and choosed individual enzymes were as follows: NEFA r = 0.51; BHB r = 0.58, TG r = - 0.55; cholesterol r = - 0.34; albumin r = - 0.53; glucose r = - 0.69; bilirubin r = 0.5. This reveals the association of these markers as indicators of fatty liver in dairy cows. With a significant fatty liver, the levels of enzymes produced are decreased, which causes a reduction in levels of blood glucose, total protein, albumin, globulin, cholesterol, triglycerides and urea. In addition, the secretions of hepatocytes are reduced, which leads to an increase in total bilirubin, ammonia and bile acid in the bloodstream. Joksimović et al. (2012) revealed that 15 days prepartum, levels of NEFA was significantly lower than in other groups (P < 0.05). The highest NEFA level was noted on the 15th day of lactation (0.41 mmol/L), which was higher than on the day of calving (0.32 mmol/L) and on day 45 of lactation (0.3 mmol/L). Increased levels of NEFA are a consequence of changes in the energy balance and are associated with intensification of lipolysis of adipose tissue due to energy deficiency. This condition often appears in the second month of lactation, although other studies havefound an increase between the 17th and 2nd day prepartum. In an investigation, AST was 91.69 ± 8.90 to 96.21 ± 7.75 U/L; ALT was 29.69 ± 5.91 to 31.14 ± 5.84 U/L, and GGT was 21.89 ± 2.47 to 23.00 ± 2.75 U/L, which is within the normal physiological range. These results were same as of other studies, in which high-yielding dairy cows (producing more than 25 l/day) showed AST levels upto 97.1 U/L, compared to 69.3 U/L in cows with lower milk productivity. Additionally, GGT was 22.7 ± 3.11 U/L in early lactation, which further supports the enzymatic profile. GGT is a membrane bound enzyme found mostly in cells with high metabolic activity like absorption or secretion. High GGT activity has been reported in the organs like liver, kidneys, pancreas, intestine and spleen. Djoković et al. (2013) in a study compared two groups: those in early lactation and in late pregnancy. The levels of NEFA and β-hydroxybutyrate (BHB) were statistically higher (P < 0.05) in cows during early lactation than those in late pregnancy. AST levels were significantly higher in early lactating cows as compared to mid or late lactating cows. Although the mean GGT value was higher in late pregnancy, the difference was statistically insignificant (P > 0.05). NEFA content more than 0.4 mmol/L indicates problems with the energy balance, which leads to the intense mobilization of fat from adipose tissues. Elevated levels of NEFA are a good indicator of energy balance disturbances and may indicate increased fat mobilization from adipose tissues. More than 50% of cows near calving are at risk of developing severe metabolic disorders. When hepatic lipidosis occurs and changes appear in the liver tissues, the activity of the hepatic enzymes like AST, GGT and GLDH (glutamate dehydrogenase) will show an increase indicating damage to the hepatocellular tissues. Biochemical results indicate that cows in early lactation have metabolic disturbances related to ketosis. Structural changes in liver tissue and the increased activity of BHB, NEFA, and AST can be helpful for the assessment of metabolic status in pregnancy and lactation. Changes in enzyme activity in the blood may be a result of an increase in activity in cells mainly hepatocytes, but can also result from cell damage. It was found that levels of AST was significantly (P < 0.05) higher in early lactation in comparison to that than in late pregnancy, confirming damage to the hepatic cells by steatosis and subsequent release of the enzyme into the blood. The level of AST in late pregnancy and early lactation was 78-132 U/l. Increased AST activity is correlated with liver damage caused through fatty infiltration. AST is the most sensitive indicator for assessing the condition of liver during the transition period in dairy cows. During the experiment the authors revealed a higher level of AST activity in early lactation compared to late pregnant cows. At the beginning of lactation, this condition may arise due to release of body fat and can lead to severe metabolic problems like mild fatty liver. The authorrecorded many values in dairy cows for lactation (L) and the dry period (D): NEFA - 0.38 mmol/L (L), 0.17 mmol/L (D); BHB 1.59 mmol/L (L), 1.14 mmol/L (D), and AST 69.46 IU/L (L), 33.55 IU/L (D). Insignificant changes in the values of GGT were found during the study. High-yielding dairy cows in the initial months of lactation can have metabolic problems, with almost 5-10% developing severe fatty liver disease and 30-40% having a mild form of fatty liver. These problems are seen along with higher activity of the hepatic enzymes such as AST, GGT, and GLDH due to reversible changes in hepatic tissues. Mohamed, (2014) showed that depending on the various physiological factors the mean Aspartate Aminotransferase (AST) and Alkaline Phosphatase (ALP) values varies. AST levels were recorded to be higher in early lactation in comparison to that in mid-lactation, while ALP levels was increased in mid-lactation relative to early lactation. There were no significant differences in the levels of ALT and GGT (gamma –glutamyl transferase) across these stages. Kubkomawa et al. (2015) revealed that AST levels show slight irregular changes during pregnancy and early lactation. During the time of late pregnancy, levels of this enzyme are higher as compared to that in the first weeks after calving. Dry cows generally shows higher AST levels than lactating cows most likely due to metabolic changes during pregnancy. Enhanced serum GGT levels are associated with damage to the liver and kidneys. The reference values for ALP are very broad and two consecutive results cannot be compared due to huge variability, making ALP useless in diagnosing liver diseases. Krsmanović et al., (2016) reported higher AST levels during early lactation as compared to the dry period and mid-lactation in dairy cows. This increase may be due to fatty liver, damage to the liver cells, and the subsequent release of AST into the blood. The study reveals that early lactating cows with a mild form of fatty liver exhibits morphological and physiological changes in liver function. The level of AST enzyme was 78-132 IU/L. The results found that AST is closely associated to the degree of fatty degeneration of the liver. AST was identified as the most sensitive determinant of liver condition and functioning in dairy cows. Gerspach et al. (2016) during standard surgery of abomasal displacement, liver tissue and blood samples were collected. Values of AST was significantly higher in cows with different degrees of hepatic lipidosis, compared to the control group with normal liver fat content, without fatty liver. Other biochemical parameters revealed statistically insignificant differences between the groups. Average levels of AST activity was as follows: control group 82.3 U/L; mild fatty liver 195.4 U/l; moderate fatty liver 180.1 U/l; and severe liver steatosis 201.8 U/l (p-value 0,003) which indicates a correlation between high AST values and the severity of hepatic lipidosis.

1. **DIAGNOSIS**

Diagnosis of hepatic lipidosis is not easy as no single analytical test is accurate, fast, and reliable for diagnosing this condition. This limitation hinders the detection and management of the disease (Kalaitzakis et al., 2010). Traditional tests used to diagnose liver damage, to determine liver enzymes and other blood metabolites, have been widely used. However, their diagnostic utility for these biochemical profiles is often ineffective because of lag time between the onset of hepatic damage and changes in these biochemical enzymes. The increase in the values of hepatic enzymes and other metabolites occurs when there is already a significantly severe liver damage, which does not allow for correcting the problem timely and accurately. Therefore, the diagnosis of hepatic lipidosis should be done earlier than anticipated so as to take effective therapeutical and preventive interventions (Melendez et al., 2018). The Gold standard for estimating the hepatic TG content is fat extraction however; histopathology or flotation techniques to obtain liver biopsies in live animals can be used as an indirect method of assessment (Bobe et al., 2004). Moreover, liver biopsies are invasive techniques and have associated risks like hemorrhage, infection, and adhesion formation (Swecker, 2014). For diagnosing hepatic lipidosis Transcutaneous ultrasound is another technique used in cattle; but this method has low sensitivity when TG content is below 10%. This method is, hence, more accurate for the diagnosis of severe hepatic lipidosis (TG > 10%) (Weijers et al., 2012). A study aimed to identify peripartum biomarkers and weight loss fluctuations in body weight of dairy cows showing changes in hepatic ultrasonographic patterns likely of fatty liver (Grzybowska et al., 2023). This study reported that cows with hepatic lipidosis show a thicker backfat layer, increased blood NEFA and glucose concentrations, and altered AST activity compared to normal healthy cows. Fine needle aspiration cytology (FNAC) is one another technique that is reliable in clinical practice, which is being minimally invasive, less costly and additionally having rapid results compared with liver biopsy (Komemushi et al., 2015). FNAC in clinical settings have been proven to be effective in two studies (Fry et al., 2018, Melendez et al., 2018). Another study concluded that the FNAC with regard to diagnosis provides acceptable sensitivity of 73% and a specificity of 85% using a cut-off value of 2% for liver TG content (Melendez et al., 2018) by which an early detection of fatty liver (mainly in cows with TG infiltration 2–5%) can be achieved. In one study, Liver TG content was related more strongly with cytology scores than with NEFA or BHB concentration in serum, proving that FNAC is better than traditional tests (Fry et al., 2018). A receiver operating characteristic (ROC) curve analysis revealed that cytology had more effective diagnostic performance than either NEFA or BHB for correctly categorizing hepatic TG at threshold levels of 5%, 10%, and 15% (Fry et al., 2018). Based on the results from Melendez et al. (2018) and Fry et al. (2018), FNAC has proven as a rapid and inexpensive fatty liver diagnostic method that can be carried under field conditions. Besides the above mentioned methods some non-invasive techniques that help in the diagnosis of fatty liver in dairy cattle which includes the determination of circulating values of ornithine carbamoyl transferase (>25 U/L), glutamate dehydrogenase (>8.9 U/L), NEFA (>1 mmol/L) (Kalaitzakis et al., 2010) decreased liver propionate to glucose conversion (McCarthy et al., 2015) and altered transcutaneous ultrasound imaging (mainly when TG liver content is more than 10%) (Weijers et al., 2012). The reliability of these methods are less especially when the hepatic TG content is greater than 5%.

1. **CONCLUSIONS**

The occurrence of diseases of liver in dairy cows is of critical concern, as it can alter hepatic metabolic function, adversely affects overall health, and decreases both productive and reproductive performances. These metabolic disorders are particularly occuring during the transition period, a time of heightened metabolic demand and vulnerability. The incidence of fatty liver has increased significantly; this shift indicates a need to reconsider the current definitions, prevalence, and incidence of hepatic lipidosis in contemporary herds. Consequently, management strategies that aim to modulate negative energy balance (NEB) are critical. These include preventing excessive BCS, minimizing periparturient stress, ensuring adequate cow comfort, and improving dry matter intake (DMI). Besides, advancing our understanding of the molecular mechanisms underlying liver-associated diseases in transition dairy cows are essential. Such insights could inform the development of targeted strategies to prevent hepatic dysfunction, thereby improving animal health and enhancing both milk production and reproductive efficiency in modern dairy operations.

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