***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**

Dairy animals during the transition period undergo significant changes like physiological and metabolic and these changes enhance their susceptibility to a wide spectrum of ailments like metabolic, infectious, digestive and reproductive disorders. During this period of transition these disorders are significantly affected by the energy balance and the ability of the animal’s body to adapt to the increased energy demands of early lactation. ‘A severe negative energy balance’ is a common precipitating cause that influences these adaptation mechanisms, which can lead to elevated levels of cortisol and disturbances in calcium homeostasis. One of the known metabolic changes of the negative energy balance is the fat cow syndrome or fatty liver disease or hepatic lipidosis. 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. During the early lactation period, due to 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 is 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) which is more than 3.5 before parturition and less than 3.5 after parturition (Truman et al., 2022). 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). Monensin often reduces blood ketones, but it has not been shown to reduce hepatic fat accumulation ([Duffield et al., 2008](https://www.ncbi.nlm.nih.gov/books/NBK600607/)). Supplementing rumen-protected choline during the peripartum period can reduce liver fat concentrations ([Zenobi et al., 2018](https://www.ncbi.nlm.nih.gov/books/NBK600607/)). Niacin has antilipolytic properties, but unless supplemented at very high rates, it usually does not affect plasma NEFA concentrations ([Grummer, 2008](https://www.ncbi.nlm.nih.gov/books/NBK600607/)). Supplementing peripartum cows with rumen-protected niacin has reduced plasma NEFAs but has not markedly affected liver lipid concentrations ([Yuan et al., 2012](https://www.ncbi.nlm.nih.gov/books/NBK600607/)). 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 induces 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 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 promotes 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 causes 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 release fat from adipose tissues to meet energy demands. 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 such as obesity and showing 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 (Bombik et al., 2021). Fatty liver syndrome is more vulnerable in heifers than older cows (Bombik et al., 2021). The disease is most common in late pregnancy (7-9 months) or immediately after parturition (Radostits et al., 2007).

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 (Bombik et al., 2021). Cortisol levels in the circulation during pregnancy remain relatively low until just before parturition when they markedly increase due to stress. After calving, blood cortisol levels decrease, particularly in acetonemic cows. Namely, under low blood cortisol levels in puerperal cows, under intense lipomobilization, the ability of liver cells to synthesize glucose through gluconeogenesis decreases, while ketogenesis and lipogenesis in the liver become intensified (Forslund et al., 2010). It is believed that under negative energy balance and hypoinsulinemia during early lactation catabolic processes dominate and lipomobilization increases, likely leading to ketosis and fatty liver (Djokovic et al., 2014). Dairy cows suffer a reduction of ~70% in plasma insulin-like growth factor-I (IGF-I) during the transition from pregnancy to lactation despite elevated plasma growth hormone ([Rhoads et al., 2004](https://joe.bioscientifica.com/view/journals/joe/195/1/1940049.xml#RHOADS-ETAL-2004)). This fall in plasma IGF-I is thought to reflect decreased GH-stimulated IGF-I transcription in liver as a consequence of GH receptor (GHR) loss ([Kim et al., 2004](https://joe.bioscientifica.com/view/journals/joe/195/1/1940049.xml#KIM-ETAL-2004)). Hepatic GHR loss is associated with reduced abundance of the liver-specific GHR1A transcript, whereas the ubiquitously expressed GHR1B and 1C transcripts remain unaffected ([Kim et al., 2004](https://joe.bioscientifica.com/view/journals/joe/195/1/1940049.xml#KIM-ETAL-2004)). These observations suggest a model whereby the energy deficit of early lactation decreases the activity of the promoter responsible for GHR1A synthesis, leading to a decreased hepatic GHR abundance and IGF-I production ([Kim et al., 2004](https://joe.bioscientifica.com/view/journals/joe/195/1/1940049.xml#KIM-ETAL-2004)). 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 (Bombik et al., 2021).

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 results in 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 induce 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 (Djoković et al., 2013). 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).

Step-by-Step diagnostic process for detecting fatty liver in dairy cows

1. Identifying the animals which are in the transition period.
2. Commonly those cows with high BCS, showing signs of inappetence with reduction in the milk yield.
3. Measure the enzyme levels including AST, GGT, GDH and OCT. These markers lack sensitivity and specificity and only after severe liver damage, the values of these enzymes will rise, hence for the early diagnosis their use is very limited (Melendez et al., 2018).
4. A strong indicator of the negative energy balance is the elevated level of NEFA (>1 mmol/l) and BHB. But NEFA and BHB shows decreased association with liver TG content in comparison to direct methods (Fry et al., 2018).
5. Imaging based assessment by using transcutaneous ultrasound which will be helpful for analyzing the structural changes primarily when the TG content surpasses 10%. The specificity of this method is suitable for the diagnosis of moderate to severe fatty liver (Weijers et al., 2012). However, if the findings from this method are associated with other variables like AST, glucose and the backfat thickness, then it will improve the diagnostic surety.
6. Fine Needle Aspiration Cytology (FNAC) is a minimally invasive technique that is rapid and inexpensive for assessing fatty infiltration (Komemushi et al., 2015). For detecting TG content greater than or equal to 2% it has shown sensitivity of 73% and specificity of 85%, which makes it effective for early diagnosis of fatty liver. (Melendez et al., 2018). Receiver Operating Characteristic curve analysis further confirmed FNAC's diagnostic accuracy across TG thresholds of 5%, 10%, and 15% (Fry et al., 2018).
7. The gold standard for assessing liver TG content is liver biopsy with histopathology or fat extraction. Flotation and histological grading techniques provides definite confirmation. Liver biopsy due to its invasive nature and risks like haemorrhage, adhesion formation and infection, hence it is performed for research or complex cases (Bobe et al., 2004; Swecker et al., 2014).
8. Other non-invasive indicators which are primarily experimental or supportive tool and may lack consistency at TG content <5% includes OCT >25 U/L, GDH >8.9 U/L, NEFA >1 mmol/L (Kalaitzakis et al., 2010) and reduced liver propionate to glucose conversion (McCarthy et al., 2015).
9. **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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