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Bovine ketosis: A comprehensive review on pathophysiology, diagnosis, monitoring strategies, therapeutics, and prevention in dairy cattle

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Abstract
Ketosis remains one of the most prevalent metabolic disorders in high-producing dairy cows, particularly during the early postpartum period when negative energy balance (NEB) induces excessive mobilization of adipose reserves. This leads to elevated concentrations of ketone bodies primarily β-hydroxybutyrate (BHBA), acetoacetate, and acetone in blood, milk, and urine. Subclinical ketosis (SCK), defined by BHBA ≥1.2 mmol/L without overt clinical signs, affects a significant proportion of herds and predisposes animals to secondary conditions such as displaced abomasum, metritis, and reduced reproductive performance. Diagnosis typically relies on ketone quantification in body fluids, with BHBA as the gold standard. However, recent research indicates that inflammatory biomarkers (e.g., serum amyloid A, haptoglobin, LPS-binding protein) and metabolomic signatures may serve as early predictors of disease risk. Therapeutic interventions involve administration of glucogenic precursors like propylene glycol or glycerol, the latter also modulating rumen fermentation and hepatic gluconeogenesis. Preventive strategies include precise nutritional management, maintenance of optimal body condition scores, and minimization of periparturient stressors. Emerging data suggest that ketosis involves not only metabolic dysregulation but also systemic inflammatory responses and gut-derived endotoxemia. This review integrates current knowledge on the pathogenesis, clinical and subclinical manifestations, diagnostic advancements, economic ramifications, and evolving preventive paradigms for ketosis, with contextual relevance to Indian dairy production systems.

Keywords: Ketosis, subclinical ketosis, β-hydroxybutyrate (BHBA), negative energy balance, dairy cows, periparturient diseases

1. Introduction
Lactating bovines undergo three major physiological stages: lactation, gestation, and transition. Among these, the transition period defined as the interval spanning from three weeks before to three weeks after parturition is the most critical phase influencing subsequent milk production and reproductive efficiency (Smith and Risco, 2005) [80]. This period is characterized by substantial metabolic and endocrine adjustments, including reduced dry matter intake (DMI), which coincides with a dramatic rise in energy requirements for fetal development and lactogenesis (Castillo *et al.*, 2005; Sordillo *et al.*, 2007 and Sharma *et al.*, 2011) [12, 78, 81].

During this time, the animal experiences intense physiological changes such as mammary gland growth, differentiation of secretory parenchyma, and initiation of milk synthesis and secretion. These processes demand not only increased metabolic energy but also elevated oxygen consumption, which results in enhanced production of reactive oxygen species (ROS) byproducts of normal metabolism that, when produced in excess, surpass the neutralizing capacity of the body's antioxidant defense systems (Gitto *et al.*, 2002) [29]. The accumulation of ROS leads to oxidative stress, which, along with negative energy balance (NEB), contributes to several periparturient disorders including ketosis, milk fever, retained fetal membranes, and mastitis (Castillo *et al.*, 2005 and Dimri *et al.*, 2010) [12, 17].

Trace minerals such as selenium (Se), copper (Cu), zinc (Zn), manganese (Mn), and iron (Fe)

play pivotal roles in antioxidant defense. These minerals are integral to the activity of enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase, which mitigate the harmful effects of ROS. SOD (Cu-, Zn-, Mn-dependent) converts superoxide radicals into hydrogen peroxide, which is then broken down by catalase (Fe-dependent) and GSH-Px (Se-dependent) into water, thereby neutralizing oxidative damage (Bowman *et al.*, 2008) [10].

High-yielding dairy cows often enter a state of negative energy balance in early lactation due to the mismatch between energy intake and the demands of milk production. This metabolic imbalance triggers the mobilization of body fat reserves and leads to hypoglycemia, predisposing animals to metabolic conditions such as fatty liver and ketosis (Bobe *et al.*, 2004; Djokovic *et al.*, 2011) [8, 18, 45]. Factors like age, genetics, over-conditioning, and inadequate prepartum nutrition further exacerbate NEB (Bobe *et al.*, 2004 and Le Blanc *et al.*, 2005) [8]. The downstream consequences include increased incidence of reproductive disorders, displaced abomasum, immune suppression, and decreased feed intake and milk yield (Houe *et al.*, 2001; Ingvartsen *et al.*, 2003 and Le Blanc, 2008) [41, 42].

Ketosis, in particular, represents a significant metabolic disorder characterized by elevated levels of ketone bodies β-hydroxybutyrate, acetoacetate (AcAc), and acetone (Ace**)** in the blood, urine, and milk. The condition typically arises shortly after parturition when NEB is most pronounced. Reduced glucose availability leads to increased lipolysis and the release of non-esterified fatty acids (NEFAs) from adipose tissue, which are transported to the liver. There, they are incompletely oxidized due to limited oxaloacetate availability and are instead converted to ketone bodies. While these ketones serve as alternative energy sources, especially for the brain, their accumulation impairs feed intake, suppresses immune function, and increases the risk of concurrent diseases. Diagnosis of ketosis in the early or subclinical stage is vital for preventing production losses, yet there remains a need to correlate blood biochemical markers including glucose, NEFAs, and ketone concentrations for effective monitoring.

2. Conventional view of ketosis

Transition dairy cows undergo profound physiological and metabolic changes as they move from late gestation to early lactation. This phase, commonly referred to as the transition period, is critical for the health and productivity of dairy cows, yet it is frequently associated with metabolic disorders most notably ketosis. Ketosis is a prevalent condition characterized by elevated levels of ketone bodies acetoacetate (AcAc), acetone (Ac), and β-hydroxybutyrate in blood, urine, and milk during early lactation (Oetzel, 2004 and Tehrani-Sharif *et al.*, 2011) [64, 85]. Since the late 1990s, ketosis has surpassed other metabolic disorders such as ruminal acidosis and milk fever, becoming one of the most significant challenges to metabolic health in North American dairy herds (Oetzel, 2007) [63].

Epidemiological studies indicate that nearly 40% of dairy cows in North America develop some form of ketosis within weeks of parturition, with prevalence varying widely across farms and peaking as high as 80% in certain herds (Duffield, 2000) [23]. The repercussions of ketosis are far-reaching, including reduced milk yield, poor reproductive performance (e.g., infertility), and increased susceptibility to periparturient diseases such as displaced abomasum, mastitis, metritis, lameness, and retained placenta. These effects also contribute to a higher culling rate and economic losses (Duffield *et al.*, 2009; Ospina *et al.*, 2010; McArt *et al.*, 2011 and Raboisson *et al.*, 2014) [56, 66, 70]. The economic cost of a single case of ketosis has been estimated at approximately CAD $50-100 per affected cow (Duffield, 2000) which is approximately 3000- 6000 Indian Rupees [23].

Despite decades of research and comprehensive reviews on ketosis (Duffield, 2000; Ospina *et al.*, 2010 and Gordon, 2013) [23, 31, 66], the precise pathophysiology remains incompletely understood. One prevailing theory emphasizes the development of negative energy balance (NEB) around parturition due to reduced dry matter intake (DMI) and the high energy demands of milk synthesis (Herdt, 2000) [40]. During NEB, adipose tissue mobilizes free fatty acids into circulation, mainly as non-esterified fatty acids (NEFAs), which follow one of four hepatic metabolic pathways: (1) Complete oxidation via the tricarboxylic acid (TCA) cycle to produce energy, (2) Incomplete oxidation resulting in ketone body production, (3) Re-esterification into triacylglycerols (TAGs) for storage, or (4) Export from the liver as very low-density lipoproteins (VLDL) (Grummer, 2008) [35].

Although these hepatic adaptations are essential to meet the energy demands of the postpartum cow, the liver's gluconeogenic capacity is often insufficient. Between 60% and 85% of circulating glucose is directed toward the mammary gland for lactose synthesis, limiting systemic glucose availability (Knowlton *et al.*, 1998) [48]. This glucose deficit contributes to hypoglycemia and hypoinsulinemia, which further promote lipolysis and ketogenesis (Gordon, 2013) [31]. Hepatic ketogenesis, in turn, leads to the accumulation of ketone bodies that serve as alternate energy substrates, particularly for extrahepatic tissues such as the brain (Newman and Verdin, 2014) [62]. However, excessive ketone production can overwhelm homeostatic mechanisms and impair liver function, resulting in TAG accumulation, fatty liver, and further disruption of gluconeogenesis.

Interestingly, fat accumulation in the liver can begin during the dry-off period or even the previous lactation, potentially predisposing cows to ketosis in the subsequent calving cycle (Drackley *et al.*, 2001 and Hayirli, 2006) [21, 39]. Although most research has focused on postpartum measurements of ketone bodies for the diagnosis of ketosis, limited studies have investigated prepartum metabolic markers in blood and urine that may predict postpartum ketosis. Further research is necessary to elucidate the metabolic alterations during the prepartum phase and to better understand the underlying pathobiology of ketosis in transition dairy cows.

3. Classification of Ketosis

The classification of bovine ketosis varies among researchers, with two primary frameworks commonly employed in both clinical and academic settings. The first approach classifies ketosis based on the concentration of β-hydroxybutyrate in the blood and the presence or absence of clinical symptoms, while the second system categorizes the disorder based on its etiology and the timing of onset during lactation.

3.1 Classification by Clinical Manifestation: Subclinical vs. Clinical Ketosis: One widely accepted method differentiates between subclinical ketosis (SCK) and clinical ketosis (CK). This classification relies primarily on measuring BHBA levels in the blood and assessing the presence of outward clinical signs. In subclinical ketosis, cows exhibit elevated ketone body concentrations—typically in the range

of 1200 to 1400 µmol/L BHBA—but do not show visible signs of illness. These animals generally maintain their appetite and dry matter intake (DMI), and may go unnoticed without metabolic testing (Duffield, 2000) [23].

In contrast, clinical ketosis is characterized by more severe hyperketonemia (BHBA between 2600 to 3000 µmol/L), hypoglycemia, and clear clinical signs. These signs include anorexia or reduced appetite, marked body weight loss, decline in milk production, dry, firm feces, and general lethargy. CK is more readily diagnosed due to these visible indicators. However, it is important to note that the distinction between clinical and subclinical forms is not always clear-cut. Studies have shown that cows with high ketone levels may not always display symptoms, while those with comparatively low levels may exhibit clear illness (McArt *et al.*, 2011) [56]. Thus, the individual cow's ability to tolerate and metabolize ketone bodies plays a pivotal role in symptom expression (Herdt, 2000) [40].

In large, loose-housed herds, clinical assessment becomes increasingly challenging, making BHBA-based testing a more objective and practical approach for herd-level monitoring. This has led to the proposal that the disorder may be more accurately termed hyperketonemia, encompassing both symptomatic and asymptomatic cases, rather than maintaining a rigid dichotomy of subclinical and clinical forms.

3.2 Classification by Etiology and Timing: Type I, Type II, and Butyric Acid Silage Ketosis: An alternative and more pathophysiologically-oriented classification divides ketosis into three main types: Type I, Type II, and Butyric Acid Silage Ketosis.

Type I Ketosis: This is the classic form of ketosis and generally occurs 3 to 6 weeks postpartum, coinciding with peak milk production. It is analogous to Type I diabetes mellitus in humans, where there is a deficiency of insulin and chronic hypoglycemia. In this type, cows experience insufficient gluconeogenesis due to limited availability of glucose precursors, primarily propionate from rumen fermentation and amino acids from muscle protein breakdown. As a result, energy demands exceed supply, triggering lipolysis and subsequent ketone body formation to compensate for glucose scarcity. Type I ketosis is typically associated with normal to low insulin levels and occurs in otherwise healthy cows during high milk output.

Type II Ketosis

Occurring immediately postpartum, Type II ketosis is often associated with obesity, overfeeding during the dry period, and concurrent disorders such as fatty liver syndrome. It resembles Type II diabetes mellitus in humans, being linked to insulin resistance, where cows present with elevated levels of both glucose and insulin at the time of ketosis diagnosis. The excessive energy intake during the dry period promotes adipose tissue deposition, which is mobilized rapidly after parturition. The liver becomes overwhelmed with NEFAs, leading to triglyceride accumulation, impaired gluconeogenesis, and hepatocellular dysfunction. Type II ketosis tends to have a more complicated metabolic profile and is often more difficult to manage than Type I.

Butyric Acid Silage Ketosis

This form of ketosis is associated with the consumption of silage containing high levels of butyric acid, a potent ketogenic precursor. Butyric acid silage results from improper fermentation, often due to clostridial contamination under moist or carbohydrate-deficient ensiling conditions. Clostridial activity leads to an accumulation of butyric acid, which is absorbed by the cow and directly contributes to increased ketogenesis. The clinical expression of this type of ketosis depends on the amount of silage consumed, lactation stage, and the nutritional balance of the overall diet. Risk factors such as early lactation, ruminal acidosis, high milk yield, low dietary energy, and excess dietary protein may further predispose animals to this form.

3.3 Clinical Relevance of Classification

Although distinctions between the types of ketosis help understand its underlying pathophysiology, the most practical and widely used categorization remains the division into subclinical and clinical forms, especially for on-farm diagnostics (Duffield, 2000) [23]. The variable presentation of clinical signs relative to blood BHBA levels further complicates classification, supporting the argument for adopting the broader term hyperketonemia (Herdt, 2000) [40]. From a clinical management perspective, this approach provides a more inclusive framework for addressing the metabolic complexity of ketosis and implementing timely intervention strategies.

4. Incidence of ketosis

The incidence of ketosis in India has been extensively studied by various researchers, shedding light on its prevalence among dairy cows. Different studies conducted by researchers have reported varying rates of occurrence of both subclinical and clinical ketosis.

Duffield (2000) [23] highlighted that the early phase of lactation stands as a critical period, noting a prevalence of 40 to 60% cases of subclinical ketosis and an incidence of clinical ketosis ranging from 2% to 15% in cows.

Studies conducted by Bihani *et al.* (2002) [7] indicated a lower prevalence of ketosis at 9.90% during the second to fifth parity, specifically occurring within 60 to 80 days postpartum, with the highest prevalence recorded during the months of November to January (Akamatsu *et al.*, 2007). Mir and Malik (2002) [1, 61] noted varying prevalence rates, with the highest incidence observed in cows aged 8-9 years (47.36%) during the third lactation phase (45.10%) and within 1-2 months post-partum (42.10%).

Singh (2002) [79] described ketosis as a common metabolic disease occurring within the first 10-60 days postpartum. High-producing Holstein cows were reported to have a higher prevalence of subclinical ketosis (38%) compared to low producer dairy cows (Pourjafar and Heidari, 2003) [69]. Chakrabarti (2006) [13] documented a higher prevalence of ketosis in high-yielding cows, generally occurring within a month after calving.

Other studies, such as those conducted by Sakha *et al.* (2007) [77], Arya (2008), Thirunavukkarasu *et al.* (2010, 2011) [2, 86], and various researchers, showed prevalence rates ranging from 9.38% to 37.25%, with variations observed based on seasons, with higher incidences during the summer and rainy seasons compared to winter.

Research by LeBlanc (2010), Ospina *et al.* (2010), Asl *et al.* (2011), Borchardt *et al.* (2012), Chapinal *et al.* (2012), and McArt *et al.* (2012) [3, 9, 15, 51, 55, 66] further highlighted varying prevalence rates of ketosis, showcasing the significance of post-partum BHBA concentrations in determining the incidence, with different thresholds used for detection in different studies.

Overall, these studies collectively emphasize the substantial impact of ketosis on dairy cattle, particularly during the postpartum and transition periods, with prevalence rates varying based on factors like lactation phase, age, parity, breed, and seasonal influences.

5. Impact of Ketosis on Health, Reproduction, Milk Production, and Economics in Dairy Cows

Ketosis, both in its clinical (CK) and subclinical (SCK) forms, imposes significant physiological, productive, and economic burdens on dairy cows and the dairy industry at large. A vast body of literature confirms that ketosis adversely affects the health, fertility, milk output, and milk quality in dairy animals, thereby impairing farm profitability (Duffield, 2005; LeBlanc *et al.*, 2005; Duffield *et al.*, 2009; Ospina *et al.*, 2010; McArt *et al.*, 2011 and Gordon, 2013;) [22, 24, 31, 52, 56, 66].

Subclinical ketosis, in particular, is often underdiagnosed due to the absence of overt clinical symptoms, yet it has been consistently associated with a higher risk of subsequent periparturient diseases. These include displaced abomasum, retained placenta, metritis, endometritis, mastitis, lameness, cystic ovarian disease and impaired immune response (Hammon *et al.*, 2006; Duffield *et al.*, 2009; Ospina *et al.*, 2010; Suthar *et al.*, 2013 and Raboisson *et al.*, 2014) [24, 38, 66, 70, 83]. The cascade of disease progression due to SCK frequently results in decreased reproductive efficiency, extended calving intervals, increased services per conception, and higher rates of early culling during early lactation (McArt *et al.*, 2012) [55]. While clinical ketosis manifests with obvious signs, SCK silently deteriorates performance across multiple physiological parameters.

Regarding milk production, several pivotal studies have quantified the production deficits linked to ketosis. Dohoo and Martin (1984) [19] reported a 4.4% to 6.6% decline in daily milk yield (approximately 1.0 to 1.4 kg/day) in ketotic cows compared to healthy animals. Similarly, Duffield *et al.* (2009) [24] noted milk losses of 1 to 2 kg per day in cows with ketosis. McArt *et al.* (2012) [55] provided additional granularity, showing that for every 0.1 mmol/L increase in β-hydroxybutyrate BHBA beyond the SCK threshold of 1.2 mmol/L, cows experienced a further 0.5 kg/day milk reduction during the first 30 days in milk (DIM). These cumulative milk losses are especially detrimental in high-yielding dairy herds, directly impacting total lactation yield and profitability.

Ketosis also alters milk composition, which can have marketing and processing implications. Research by Kauppinen (1984) and Miettinen (1994) [47, 59] demonstrated that cows with CK or SCK tend to have a higher milk fat percentage. This is believed to be a metabolic consequence of increased lipolysis and fat mobilization. However, the milk protein percentage was found to decrease in SCK-affected cows (Miettinen & Setala, 1993) [60], indicative of compromised protein metabolism and imbalanced nutrient partitioning. These changes can negatively influence milk quality and its suitability for processing, thereby affecting the market price.

The economic cost of ketosis is considerable. According to Duffield (2000) [23], each case of SCK incurs a cost of approximately CAD $50 to $100, which translates to ₹3,050 to ₹6,100 per cow. Geishauser *et al.* (2001) [27] estimated a similar cost of CAD $78 per case (~₹4,750). Liang (2013) [53] projected that the combined cost of SCK and CK could range between USD $55.19 to $123.94, equivalent to ₹4,580 to ₹10,290 per case. These estimations incorporate losses due to reduced milk production, treatment costs, veterinary visits, labour, and impaired fertility.

When considered at the herd level, the economic burden becomes even more significant due to the high prevalence of the condition. Studies have shown SCK affects between 26.4% and 55.7% of cows within a herd, while CK incidence ranges from 2% to 15% during the first month postpartum (Gordon *et al.*, 2013 and Oetzel, 2013) [31, 65]. In a 100-cow herd, for instance, 40-60 cows may be affected by ketosis, potentially leading to cumulative financial losses exceeding ₹3 to ₹6 lakhs per lactation cycle, depending on severity and management.

Given the economic and physiological implications, it is imperative that ketosis be detected early and managed proactively. Comprehensive monitoring of BHBA levels, appropriate transition feeding strategies, and minimizing negative energy balance are essential to safeguard cow health and optimize dairy farm economics.

6. Risk Factors of Ketosis in Dairy Cows

Ketosis, particularly in its subclinical form (SCK), is a pervasive metabolic disorder in dairy cattle, posing challenges to animal health, fertility, and milk production. Understanding the risk factors associated with this condition is essential for developing effective prevention and management strategies. Various physiological, nutritional, and environmental determinants have been identified across multiple studies (Gillund *et al.*, 2001; Lievaart *et al.*, 2005; Duffield *et al.*, 2009; Ospina *et al.*, 2010; McArt *et al.*, 2012; Suthar *et al.*, 2013; Roche *et al.*, 2013; Raboisson *et al.*, 2014; Berge & Vertenten, 2014; Rathbun *et al.*, 2017; Zbinden *et al.*, 2017; Chandler *et al.*, 2018;) [6, 14, 28, 55, 66, 70, 72, 73, 83, 93].

6.1. Breed Susceptibility

Breed is a significant determinant in the risk of developing ketosis. Studies indicate that Jersey cows have a higher prevalence (19%) compared to Holsteins (14%), with crossbred Jerseys also showing elevated ketone levels (Raboisson *et al.*, 2014) [70]. Additionally, Swedish Red and White cows have been observed to produce higher levels of acetone and total ketone bodies in milk than Swedish Friesians (Raboisson *et al.*, 2014) [70]. According to Dohoo and Martin [19], Holsteins and Ayrshires were 3.6 and 2.8 times more likely, respectively, to develop ketosis compared to Guernsey cows (Raboisson *et al.*, 2014) [70].

6.2. Parity (Number of Lactations)

Multiparous cows (especially in third lactation or beyond) face increased metabolic demands, predisposing them to ketosis. Rathbun *et al.* (2017) [72] reported that the incidence of ketosis increased from 8.6% in first-lactation cows to 22.2% in cows with three or more lactations. However, Chandler *et al.* (2018) [14] observed that primiparous Jersey cows had the highest prevalence, suggesting that breed-specific physiology may influence parity effects.

6.3. Days in Milk (DIM)

Ketosis is most prevalent within the first two weeks postpartum, with a peak around day five of lactation and also documented that approximately 80% of SCK cases occur within this window McArt *et al.* (2012) [55]. Herd-level data from Canada and Germany also show a marked decline in SCK prevalence after 30 days in milk (Lievaart *et al.*, 2005 and Duffield *et al.*, 2009) [24].

6.4. Prepartum NEFA Levels and Body Condition
Elevated prepartum non-esterified fatty acids (NEFA) and high body condition scores are predictive of increased ketosis risk. Excessive lipid mobilization due to negative energy balance (NEB) leads to hepatic lipidosis and impaired gluconeogenesis, predisposing cows to metabolic disorders (Ospina *et al.*, 2010) [66].

6.5. Nutritional and Feeding Practices
Transition cow nutrition plays a pivotal role in ketosis development. Inadequate or imbalanced energy intake during the close-up dry period can trigger ketosis (McArt *et al.*, 2012 and Berge & Vertenten, 2014) [6, 55]. Swedish studies found that partial mixed rations (PMR) were associated with higher SCK prevalence compared to total mixed rations (TMR) or separate forage-concentrate feeding (Lievaart *et al.*, 2005). In pasture-based systems, such as those in Australia and New Zealand, individual feed intake is difficult to monitor, increasing the risk of undetected NEB (Roche *et al.*, 2013 and Raboisson *et al.*, 2014) [70, 73].

6.6. Season of Calving
Calving season affects ketosis risk, likely due to forage quality and climatic factors. In Sweden, spring-calving cows showed higher prevalence due to poor silage quality (Berge & Vertenten, 2014). Other studies have associated increased risk with autumn and winter, depending on regional management systems (Suthar *et al.*, 2013; Rathbun *et al.*, 2017) [6, 72, 83].

6.7. Herd Size and Management
Larger herds generally exhibit lower ketosis prevalence, attributed to structured management, regular health monitoring, and group-based nutrition strategies (Duffield *et al.*, 2009; Zbinden *et al.*, 2017) [93]. Smaller herds may lack these resources, resulting in delayed detection and intervention (Lievaart *et al.*, 2005).

6.8. Housing System
Housing type influences cow comfort, feed intake, and metabolic health. Cubicle housing systems are linked with lower SCK prevalence, while free-stall barns with straw floors and grazing systems are associated with higher risk, due to inconsistent monitoring and feeding (Duffield *et al.*, 2009) [24].

6.9. Colostrum Yield and Lactation History
High colostrum production and extended lactations prior to dry-off increase metabolic stress postpartum. Additionally, longer dry periods before calving are associated with higher ketosis incidence due to over-conditioning and increased lipo-mobilization postpartum (Gillund *et al.*, 2001 and Roche *et al.*, 2013) [28, 73].

7. Diagnosis of Ketosis
Accurate and timely diagnosis of ketosis is crucial for minimizing production losses and preventing secondary health complications in dairy cows. Over the years, diagnostic approaches have evolved from traditional clinical observations to advanced biochemical and metabolomic tools.

7.1 Blood β-Hydroxybutyrate (BHBA) Measurement
Quantifying β-hydroxybutyrate (BHBA) in blood is widely regarded as the most reliable diagnostic approach for ketosis. Among the three major ketone bodies—BHBA, acetoacetate, and acetone—BHBA demonstrates the greatest stability and persistence in circulation, making it the preferred biomarker (Duffield *et al.*, 2009; Suthar *et al.*, 2013) [24, 83]. Typically, blood BHBA levels above ~1.2 mmol/L indicate subclinical ketosis, whereas values exceeding 3.0 mmol/L are often associated with clinical disease (Oetzel, 2004; McArt *et al.*, 2012) [55, 64]. Laboratory assays, especially enzymatic-spectrophotometric methods, provide precise quantification with high diagnostic accuracy (Grünberg, 2014).

7.2 Milk BHBA Testing
Milk is an attractive diagnostic matrix due to its routine collection and non-invasive nature. Although BHBA levels in milk are lower compared to blood, a strong positive correlation between the two has been established, validating its use for herd-level screening (Enjalbert *et al.*, 2001) [26]. Technologies such as Fourier Transform Infrared (FTIR) spectroscopy now permit high-throughput milk BHBA assessments, allowing integration of ketosis surveillance into regular milk quality testing (Dórea *et al.*, 2018; Gruber & Mansfeld, 2019) [20, 34].

7.3 Blood Glucose Assessment
Although not specific for ketosis, blood glucose measurement remains a useful adjunct tool for assessing energy balance. Declining glucose concentrations in early lactation often signal a negative energy balance and may precede hyperketonemia (Zahra *et al.*, 2006; Duffield, 2000) [23, 92]. Veterinary-adapted portable glucometers allow on-farm testing, although validation is essential due to potential species-specific variations (Iwersen *et al.*, 2009).

7.4 Urine Ketone Detection
Urine-based tests, such as Ketostix® or Acetest®, are widely employed in field conditions for their affordability and ease of use. These tests rely on a colorimetric nitroprusside reaction that detects acetoacetate, with the intensity of the color change reflecting ketone levels (González & Schelcher, 1999). While rapid and inexpensive, they are less specific and subject to user interpretation. Additionally, urine collection can be challenging, limiting their utility for large-scale screening (Duffield, 2000) [23].

7.5 Laboratory Enzymatic Assays
Enzymatic colorimetric methods remain the gold standard for research and diagnostic laboratories. These assays, which detect BHBA in both blood and milk, are highly sensitive and reproducible, though less practical for routine field application (Enjalbert *et al.*, 2001; Grünberg, 2014) [26].

7.6 Advanced Diagnostic Technologies
FTIR spectroscopy has become a valuable tool for herd-level monitoring, simultaneously evaluating multiple milk components, including ketones, without destroying samples (Dórea *et al.*, 2018) [20]. Fluorometric assays, such as those described by Larsen and Nielsen (2005), measure BHBA via enzymatic oxidation linked to fluorescence generation, enabling high-throughput application.

Gas-liquid chromatography (GLC), nuclear magnetic resonance (NMR), and gas chromatography-mass spectrometry (GC-MS) are also employed in research settings for precise quantification of ketone bodies and related metabolites (Kristensen *et al.*, 2007; Dettmer *et al.*, 2007). Though highly accurate, these techniques are cost-intensive and less feasible for routine farm use.

7.7 Cow-Side Rapid Tests

Handheld blood ketone meters, such as Precision Xtra® (Abbott), provide immediate and highly accurate BHBA results under field conditions. When compared with laboratory assays, these meters have demonstrated excellent sensitivity and specificity at clinically relevant cutoffs (Iwersen *et al.*, 2009; Grunberg, 2014). Milk-based strips such as KetoTest™ also allow non-invasive BHBA testing but are comparatively more expensive (Suthar *et al.*, 2013) [83].

7.8 Alternative Monitoring Parameters

The milk fat-to-protein (F:P) ratio has been proposed as an indirect marker of negative energy balance, with values exceeding 1.35-1.50 suggesting increased risk of ketosis (Richardt, 2004; Jenkins *et al.*, 2015) [43]. Similarly, milk urea nitrogen levels may reflect imbalances between dietary protein and energy intake (Jonker *et al.*, 2002).

Milk fatty acid profiling offers further insight, as increased long-chain fatty acids, particularly oleic acid, are indicative of lipid mobilization associated with ketosis (Van Haelst *et al.*, 2008). Advanced FTIR systems now permit large-scale fatty acid monitoring during routine milk analysis (Gruber & Mansfeld, 2019) [34].

7.9 Emerging and Complementary Approaches

Non-esterified fatty acid (NEFA) measurement is increasingly recognized as a valuable predictor of ketosis risk, especially when measured prepartum (Ospina *et al.*, 2010; LeBlanc, 2010) [66]. However, its application is limited by the need for laboratory processing and higher costs.

Exhaled breath analysis represents another promising non-invasive approach, with acetone levels correlating strongly with BHBA concentrations (Dobbelaar *et al.*, 1996; Kuntzel *et al.*, 2012). Similarly, metabolomic profiling using NMR or LC/GC-MS has revealed unique biochemical signatures predictive of ketosis, offering deeper insights into its multifactorial pathogenesis (Zhang *et al.*, 2013; Tran *et al.*, 2020). Although currently limited by cost and technical complexity, metabolomics holds great potential for precision dairy herd health management.

7.9.1 Cowside Testing Methods

7.9.1 Urine Ketone Tests

Cow-side urine testing for acetoacetate utilizes nitroprusside-based reagents. Acetest® and Ketostix® (Bayer Corp.) are commonly used, offering high sensitivity but variable specificity (Oetzel, 2004) [64]. Limitations include difficulty in urine collection—only 50% of cows can be induced to urinate—and cost per test (₹17), which restricts their use in large herds (González and Schelcher, 1999; Duffield, 2000) [23]. Furthermore, prolonged sample-reagent contact may yield false positives.

7.9.2 Milk Ketone Tests

Milk testing is more practical on-farm due to ease of sample collection. Nitroprusside powders such as Utrecht powder and KetoCheck™ detect milk acetoacetate, though with poor sensitivity and limited diagnostic value (Oetzel, 2004) [64]. In contrast, BHBA-specific test strips like KetoTest™ offer better accuracy, enabling both individual cow diagnosis and herd-level screening. These tests are more expensive (₹142 per test) but are preferred for non-invasive monitoring (Suthar *et al.*, 2013) [83].

7.9.3 Blood Ketone Meters

Handheld ketone meters like Precision Xtra® (Abbott) are increasingly used for rapid, accurate detection of BHBA. Validated against laboratory gold standards, they provide 100% sensitivity and specificity at the 1.4 mmol/L BHBA cutoff (Iwersen *et al.*, 2009). Despite requiring venipuncture, these meters are portable, do not require calibration, and yield immediate results. Concerns remain regarding animal handling and the need for trained personnel (Grunberg, 2014 and Gruber and Mansfeld, 2019) [34].

7.10 Alternative Monitoring Parameters

7.10.1. Fat to Protein Ratio (F:P) in Milk

Milk fat and protein levels change with energy status during lactation. The fat-to-protein (F:P) ratio increases during negative energy balance due to elevated lipolysis (Gross *et al.*, 2011) [33]. Ratios above 1.35-1.50 are associated with increased ketosis risk (Richardt, 2004 and Jenkins *et al.*, 2015) [43]. However, dietary factors and sensor calibration issues can affect accuracy, limiting its sensitivity and specificity (Kamphuis *et al.*, 2013 and King *et al.*, 2018) [46].

7.10.2 Urea Content in Milk

Milk urea levels reflect dietary protein and energy intake. Low urea and protein concentrations in early lactation indicate insufficient nutrient supply and impaired rumen function (Gruber and Mansfeld, 2019) [34]. High urea with low protein suggests protein excess with energy deficit (Jonker *et al.*, 2002 and Burgos *et al.*, 2007).

7.10.3 Fatty Acid Profiles in Milk

Milk fatty acids originate from diet, de novo synthesis, and lipolysis. NEB leads to higher long-chain FA (notably oleic acid) and reduced short-chain FA synthesis (Palmquist *et al.*, 1993) [68]. Elevated oleic acid levels may indicate subclinical ketosis (Van Haelst *et al.*, 2008). FTIR technology facilitates large-scale FA profiling during milk testing (Gruber and Mansfeld, 2019) [34].

7.11. Emerging and Complementary Methods

7.11.1 Non-Esterified Fatty Acids (NEFA)

NEFA concentrations increase with adipose mobilization in early lactation. Elevated prepartum NEFA levels predict ketosis risk (Ospina *et al.*, 2010; LeBlanc, 2010) [66]. NEFA is more stable than BHBA throughout the day, but laboratory processing is costly (₹920/sample). Misreadings may occur due to stress or sample mishandling (Duffield, 2000) [23].

7.11.2 Exhaled Breath Analysis

Acetone in exhaled breath correlates with blood BHBA ($r = 0.81$) and milk ketones (Dobbelaar *et al.*, 1996). Breath sampling devices have been developed for cattle, enabling non-invasive detection of volatile organic compounds associated with ketosis (Kuntzel *et al.*, 2012).

7.12 Metabolomics

Metabolomics is a cutting-edge field of systems biology that focuses on the large-scale analysis of low-molecular-weight metabolites in biological fluids such as blood, milk, urine, and rumen fluid, offering a detailed snapshot of the metabolic state of the animal (Tran *et al.*, 2020). In the context of ketosis in dairy cows, metabolomics provides powerful tools for investigating the complex biochemical alterations induced by negative energy balance (NEB) during early lactation. Traditional markers such as β-hydroxybutyrate and non-

esterified fatty acids (NEFA) offer valuable but limited information, reflecting only specific metabolic shifts like lipolysis and ketogenesis. In contrast, metabolomics enables a holistic view of disrupted pathways, including glycolysis, gluconeogenesis, fatty acid metabolism, and amino acid turnover (Gross *et al.*, 2011 and Zhang *et al.*, 2013) [33]. Advanced analytical techniques such as nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS), often coupled with gas chromatography (GC-MS) or liquid chromatography (LC-MS), have been employed to generate comprehensive metabolic profiles of ketotic and healthy cows (Tran *et al.*, 2020). These methods are highly accurate and reproducible, although MS offers greater sensitivity and the ability to detect low-abundance metabolites compared to NMR (Van Haelst *et al.*, 2008). Metabolomic studies have identified significant changes in metabolites associated with fatty acid mobilization (e.g., increased oleic acid and acylcarnitines), impaired gluconeogenesis (e.g., decreased glucogenic amino acids such as alanine and valine), and elevated markers of oxidative stress and systemic inflammation (Gross *et al.*, 2011 and Zhang *et al.*, 2013) [33]. Notably, certain metabolites like oleic acid have been found to rise in milk before clinical onset of ketosis, making them valuable early biomarkers (Van Haelst *et al.*, 2008). Statistical tools such as principal component analysis (PCA) and partial least squares discriminant analysis (PLS-DA) have enabled the differentiation of ketotic from non-ketotic cows with high predictive accuracy, sometimes exceeding 90% (Zhang *et al.*, 2013; Tran *et al.*, 2020). Although metabolomics is currently limited by high costs, technical complexity, and the need for specialized laboratories, its potential for early diagnosis, improved understanding of pathophysiology, and precision herd management is immense. As on-farm technologies evolve, metabolomics is expected to become a valuable component of dairy cow health monitoring strategies, especially in identifying subclinical ketosis before it impacts productivity and welfare.

8. Effects of Hyperketonemia on Production and Health

Hyperketonemia (HYK), defined as elevated levels of β-hydroxybutyrate in blood (≥1.2 mmol/L), exerts significant detrimental effects on both productivity and overall health in early lactation dairy cows (Oetzel, 2020).

8.1. Impact on Milk Production

Multiple studies have reported that cows experiencing HYK show a 3-7% reduction in milk yield compared to normoketonemic counterparts (Ospina *et al.*, 2010; McArt *et al.*, 2011) [56, 66]. The severity of milk loss is directly proportional to BHBA concentration; for every 0.1 mmol/L increase in BHBA above the 1.2 mmol/L threshold, cows produced approximately 0.5 kg (1.1 lb) less milk (McArt *et al.*, 2011) [56]. Moreover, cows developing HYK within 3-7 days postpartum suffered greater production losses than those affected later (8-16 DIM).

8.2. Association with Displaced Abomasum (DA)

Hyperketonemic cows are at a significantly increased risk of developing DA, particularly those with early or severe cases. For example, cows with BHBA levels of 2.4 mmol/L had a 3.1 times greater risk of DA than cows at 1.2 mmol/L (McArt *et al.*, 2012) [55]. Additionally, cows diagnosed with subclinical ketosis (SCK) between 3-5 DIM had a 6.1-fold increased risk for DA compared to those identified later in lactation (McArt *et al.*, 2012) [56].

8.3. Risk of Metritis

Since metritis and HYK often occur concurrently in the early postpartum window, they are frequently interlinked. Studies suggest that HYK increases the odds of metritis by 3.4 times, although causality remains under debate (Duffield *et al.*, 2009) [24].

8.4. Herd Removal and Mortality

Cows diagnosed with SCK in early lactation are at higher risk for early culling or death. Specifically, each 0.1 mmol/L increase in BHBA raised the risk of removal by 1.4 times, and cows with BHBA levels of 2.4 mmol/L had a 57-fold higher risk of removal compared to those at 1.2 mmol/L (McArt *et al.*, 2012) [55]. Early detection and intervention are thus critical to herd retention.

8.5. Reproductive Performance

The relationship between HYK and reproduction is inconsistent across studies. Some have reported reduced conception rates and delayed first service in ketotic cows (Ospina *et al.*, 2010; Rutherford *et al.*, 2016) [66, 76], while others found no significant reproductive effect (Chapinal *et al.*, 2012) [15]. Synchronization protocols may mitigate some negative impacts on fertility, leading to variability in outcomes.

9. Treatment and Prevention

Preventing and treating ketosis, particularly subclinical ketosis (SCK), in dairy herds is critical due to its negative impact on animal health, reproductive efficiency, milk production, and overall farm economics. Ketosis has been associated with increased susceptibility to displaced abomasum (DA)—one of the most expensive diseases in dairy cattle, averaging approximately US$650 (₹54,275) per case (Liang *et al.*, 2017) [53]. As such, effective therapeutic strategies and proactive prevention protocols are essential components of herd health management. Traditionally, parenteral administration of dextrose has been a cornerstone in treating ketosis. Venkateshwarlu and Choudhuri (2000) [91] reported that intravenous administration of 540 ml of 25% dextrose over two days was superior in reducing recovery time and restoring milk yield compared to other combinations involving sodium propionate, methionine, nicotinic acid, propylene glycol, and jaggery. Similarly, Baishya *et al.* (2002) [4] observed that a regimen involving 10% fructose (500 ml I/V.) with Vetalog (6 mg I/M.), followed by dextrose and dexamethasone, yielded faster recovery in Jersey cows with SCK.

Despite its widespread use, propylene glycol (PG) has emerged as the most consistent and effective treatment for both clinical and subclinical ketosis. Studies by McArt *et al.* (2011), Ospina *et al.* (2013) and Capel *et al.* (2021) [11, 56] collectively demonstrate that PG alone is sufficient to resolve ketosis without requiring additional interventions like intravenous dextrose, which may carry risks such as jugular thrombophlebitis and increase labor demands. Recent trials have evaluated adjunct therapies to PG, including dexamethasone (Gordon *et al.*, 2013), insulin (Tatone, Gordon *et al.*, 2016) [31, 32, 84], and vitamin B12 (Tatone, Duffield *et al.*, 2016) [84], but these combinations have not consistently improved postpartum health or fertility outcomes beyond those achieved with PG alone (Jeong *et al.*, 2018) [44].

However, innovative combinations, such as the one evaluated by Chirivi *et al.* (2023), show promising results. In their study, cows treated with PG + niacin + flunixin meglumine

showed greater improvements in metabolic status, higher resolution of hyperketonemia, reduced concentrations of NEFA and acute-phase proteins, and higher blood glucose and insulin levels. These findings suggest that a multi-targeted approach, addressing both ketogenesis and inflammatory lipolysis, may enhance treatment outcomes beyond standard therapy. Similarly, Tufani *et al.* (2011) [88] demonstrated that administering 25% glucose (1 L i.v., followed by 500 ml for 2 days), combined with B-complex vitamins and dexamethasone, achieved rapid recovery (mean: 1.7 ± 0.26 days). Gupta (2012) [36] further confirmed the superiority of PG over niacin-tannic acid-jaggery combinations in lactating buffaloes. Additional supportive therapies include yeast cultures such as *Saccharomyces cerevisiae*, which improve serum glucose, enhance milk yield, and reduce the incidence of periparturient disorders (Stanislaw & Przemyslaw, 2009; Bakr *et al.*, 2015) [5, 82].

Prevention of ketosis, especially SCK, relies on comprehensive herd-level strategies involving dietary optimization, metabolic monitoring, and management of body condition score (BCS). A strategically balanced feeding program, ensuring sufficient energy, protein, and micronutrient intake, is essential during the transition period. Both over-conditioning (high BCS) and excessive BCS loss prepartum increase the risk of postpartum ketosis (Melendez & Risco, 2021) [67]. Inclusion of gluconeogenic precursors like glycerol, calcium propionate, and propylene glycol in prepartum and early lactation diets has been shown to stimulate hepatic gluconeogenesis, increase circulating insulin, and reduce hepatic triglyceride accumulation and NEFA mobilization. These additives should be top-dressed on the total mixed ration to ensure equitable intake (Ospina *et al.*, 2013 and Melendez & Risco, 2021) [67].

Among nutritional interventions, monensin stands out as a preventive additive. As a ruminal ionophore, it shifts volatile fatty acid production toward propionate, a major gluconeogenic precursor. When administered as a slow-release bolus or powder, monensin has been shown to lower the incidence of ketosis, improve reproductive performance, and increase milk yield (Melendez *et al.*, 2007 and Duffield *et al.*, 2012) [57]. It is especially effective when used in cows with low BCS during the dry period, helping them calve with better metabolic reserves. Furthermore, the routine use of PG as a preventive supplement should be tailored based on the herd's history of ketosis incidence.

10. Conclusion

Ketosis, particularly subclinical ketosis (SCK), remains one of the most economically significant and biologically complex metabolic disorders affecting high-yielding dairy cows during the transition period. It is characterized by a negative energy balance (NEB) that drives excessive mobilization of body fat, leading to elevated concentrations of non-esterified fatty acids (NEFA) and β-hydroxybutyrate. These alterations not only impair liver function and reduce milk yield, but also predispose cows to secondary disorders like displaced abomasum, metritis, mastitis, immunosuppression, and reproductive inefficiency. Despite being often clinically silent, the subtle yet pervasive impact of SCK has prompted the evolution of diverse diagnostic, monitoring, and management strategies.

The diagnosis of ketosis has moved beyond traditional laboratory methods, with advancements enabling both high-precision laboratory assays and rapid cowside tests. Laboratory techniques such as enzyme catalysis, Fourier-transform infrared (FTIR) spectrometry, fluorometry, gas chromatography-mass spectrometry (GC-MS), and nuclear magnetic resonance (NMR) offer accurate quantification of ketone bodies, though are less feasible for routine field use. On-farm methods—such as dipsticks and portable blood ketone meters—provide cost-effective, real-time, and reliable monitoring tools. Additionally, emerging diagnostic approaches based on milk components like the fat-to-protein (F:P) ratio, milk urea nitrogen, fatty acid profiling, and predicted NEFA values, alongside breath analysis and metabolomics, hold promising potential for early detection and metabolic profiling.

Treatment strategies for ketosis are multifaceted, with propylene glycol firmly established as the cornerstone therapeutic due to its gluconeogenic efficiency, ease of administration, and consistent efficacy in resolving hyperketonemia and restoring energy balance. Adjunctive therapies, including intravenous dextrose, insulin, corticosteroids, B-complex vitamins, and feed supplements like *Saccharomyces cerevisiae*, have shown variable results, with recent studies supporting combinations such as propylene glycol, niacin, flunixin meglumine for enhanced metabolic and anti-inflammatory outcomes. Nevertheless, treatment success ultimately depends on timely intervention, accurate diagnosis, and appropriate case selection.

Importantly, prevention remains the most sustainable strategy in mitigating the widespread impact of ketosis. A proactive herd-level approach focusing on nutritional balance, maintenance of optimal BCS, cow comfort, and strategic supplementation during the dry and transition periods is essential. Preventive use of gluconeogenic precursors such as glycerol, calcium propionate, and propylene glycol, alongside monensin as a ruminal modulator, has shown robust efficacy in minimizing NEB, reducing the risk of ketosis, and improving reproductive and lactational performance. Modern tools like metabolomics and milk-based sensors further enable precision herd management and individualized nutritional interventions.

In conclusion, the effective control of ketosis lies in a balanced triad of early diagnosis, evidence-based treatment, and comprehensive prevention. With continued advancements in diagnostic technologies, a deeper understanding of metabolic pathways, and integration of precision nutrition and herd health practices, the dairy industry is well-positioned to mitigate the burden of ketosis. Through informed veterinary guidance, data-driven management, and strategic interventions, the goal of healthier cows, improved productivity, and enhanced farm profitability can be confidently achieved.

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