CHAPTER 31

KETOSIS IN DAIRY ANIMALS

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INTRODUCTION

Ketosis is also known as acetonemia characterized by the presence of ketone (acetone, acetoacetate and 3-hydroxybutyrate) compounds inside the blood and these compounds are eliminated through urine and milk. Generally, ketosis is a metabolic disorder, but in dairy animals it is a lactation syndrome correlated with high milk yielding cows having negative energy balance. Ketosis occurring in the dairy animals is of two types i.e., clinical, and subclinical with signs and without signs respectively.

The transition period (three weeks before and after calving) is important one in high milk producing dairy cattle. During this period (late gestation and early lactation), there is need of more energy. National Research Council also recommended that sufficient nutrients should be included in the diet of animals particularly in the form of bypass nutrients (Marghazani 2012; Das et al. 2014; Gyanendra et al. 2019). To avoid from environment stress, more care should be practiced during last three weeks of pre-partum in dairy animals (Gerloff 2000). It is found that due to intake of energy deficient diet, the huge metabolic burden shifted on the liver due to import of non-esterified fatty acids (NEFA). NEFAs are liberated out from fat stores (triacylglycerol) due to negative energy balance or shortage of glucose. The more concentration of NEFAs into the liver led to increase in oxidation process that finally buoy up liver-connected diseases i.e., ketosis and hepatic lipidosis. Taken together, more acceleration in the gluconeogenesis contributes glucose utilization by the mammary glands (lactose synthesizes) that in turn cause stress in the hepatic tissue of early-lactating animals (Ringseis et al. 2015).

There are two main types of ketosis i.e., clinical with visible signs and subclinical without signs (Youssef et al. 2010). There are many factors involved in the establishment of ketosis during lactating period including body condition score and release of fat during calving (Busato et al. 2002). Ketosis is not considered as life threatening disease (death uncommon) but its negative impact on high yielding dairy cattle have been observed that includes decreased milk production, increased culling rate of early lactating animals, occurrence of displaced abomasum, chances of metritis, less fertility rate, and economical losses (Rajala-Schultz et al. 1999; Oetzel 2013; Steeneveld et al. 2020). More frequency in cases of ketosis, even at normal level imparts overall impact on economic losses to the dairy industry.

Classification of Ketosis

Generally, there are two types of ketosis primary and secondary which differs on the basis of disease source (Herdt 2000). Most of evidence show the occurrence of ketosis in starting days of calving or during early lactating phase (McArt et al. 2012). The terms subclinical and clinical are also commonly used for ketosis classification. Clinical form of ketosis is manifested by increased ketones in biological fluids (blood, urine, milk) along with other symptoms including appetite, decreased weight, and dryness of dung. While the subclinical form of ketosis shows high level of ketones in the blood, milk, and urine, along with absence of major signs. The reason is loosed-type housing system in majority of dairy forms which causes difficulty in observing the signs in specific or individual animal. It was thought that clinicalor subclinical forms of ketosis should be according to the b-hydroxybutyrate (BHB) level inside the blood. Though, it was experienced after careful observation of the animals that increased ketonemia condition did not show clinical signs. Each animal tolerance to clinical ketosis were different and accordingly some animals show clinical signs whilst others may not show (Herdt 2000). It is long-established that term hyperketonemia is best for description of ketosis rather than its clinical or subclinical forms.

Biochemistry and Cycle of Ketones Production

The production source of ketones is associated with fatty acids and amino acids from the fat reservoir tissues in the body and feed (Coelho et al. 2013; Kohlmeier 2015). The process of ketogenesis happens in mitochondria of hepatocytes. Adipokine signal triggering the release of fatty acid from the fat reservoirs results in increasing level of glucagon and epinephrine and decrease in the concentration of insulin. Such happening led to development of hypoglycemic and fasting states (Owen 2005). Coenzyme A is attached with fatty acids and transported to mitochondria. Fatty acids through beta-oxidation splits 2 carbons from the acyl-CoA compound in each cycle for the formation of acetyl-CoA. This acetyl-CoA transported into citric acid cycle for the formation of citric acid, and then citric acid incorporated into the tricarboxylic acid cycle (TCA), finally high energy produced (Stryer 1995). These mechanisms are shown in flow diagram (Figure-2). Every cell of the body can metabolize the acetyl-CoA by TCA cycle,

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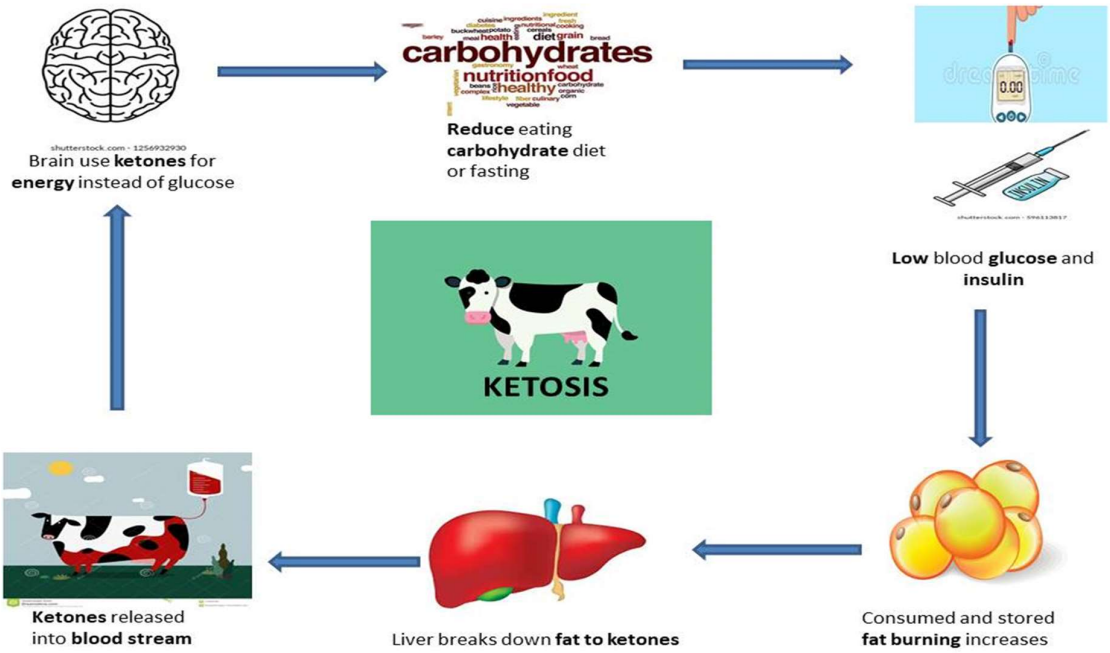

Fig. 1: Factors leading to Ketosis in dairy animals (Zhang and Ametaj, 2020).

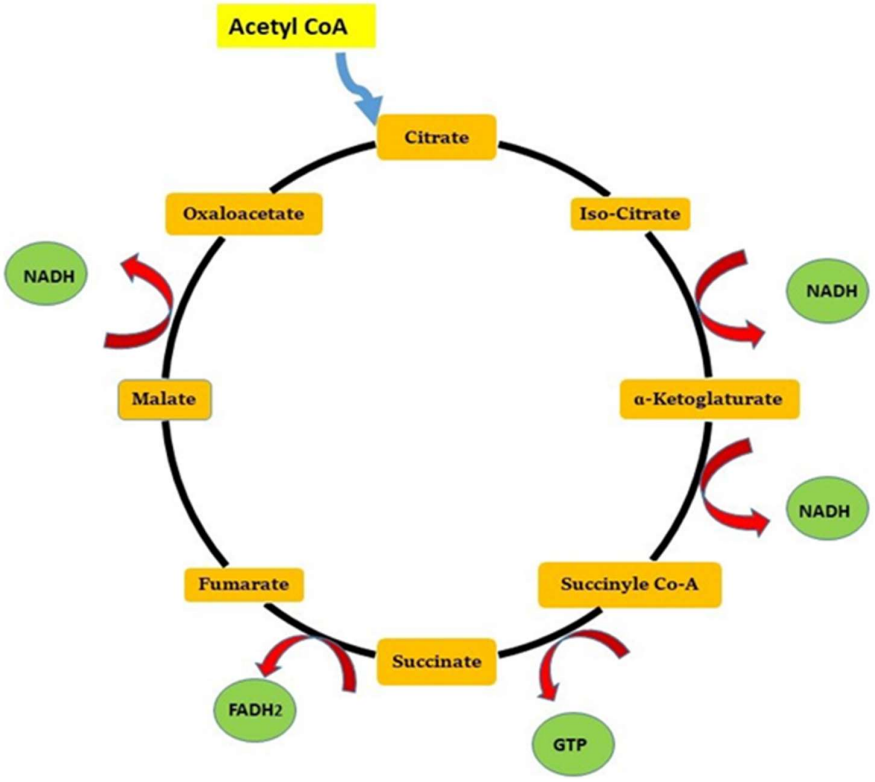

Fig. 2: Kreb's Citric Acid Cycle (Tri-Carboxlic Acid Cycle): (Martínez and Chandel 2020; Protasoni and Zeviani 2021)

but it is also involved in ketogenic process in the hepatocytes (Laffel 1999). During decreased level of glucose inside the blood, oxaloacetate intermediate compound of TCA cycle transported and is utilized in the production of glucose (gluconeogenesis). Oxaloacetate is used in gluconeogenesis prevent its condensation with acetyl-CoA, hence no entrance of acetyl-CoA into the TCA cycle. In nutshell, the energy was generated in the form of ketones from acetyl-CoA. In ketone occurring process, acetyl-CoA 2 molecules converted into acetoacetyl-CoA by condensation with the help of thiolase. In short, acetoacetyl-CoA plus a new molecule of acetyl-CoA produced the hydroxy-β-methylglutaryl (HMG)-CoA with the help of HMG-CoA synthase. HMG-CoA converted into acetoacetate (ketone body) with HMG-CoA lyase enzyme. D-β-hydroxybutyrate type of ketone formed from acetoacetate through D-β-hydroxybutyrate dehydrogenase action. Due to

result of continuous degradation of acetoacetate, acetone (ketone) and CO_2 produced. In the end, ketone compounds not used as fuel of energy by the liver but transported as energy source towards brain and other tissues of body. Primarily ketones not only produced from fatty acids, but also produced from ketogenic amino acids. These amino acids are converted into the intermediate compounds of citric acid cycle through deamination (Kohlmeier 2015).

Causes and Factors Involved in Ketosis

In context of particular biochemical and physiological etiology of ketosis, no proven data is available till date. There is no single cause, while it is well established that misbalancing in nutrient availability, particularly low energy, is a crucial factor. It is proved that glucose deficiency is associated with the occurrence of ketosis during early lactation phase of dairy cattle. Because 60-85% glucose is utilized by the udder for the collecting lactose contents in milk (Reynolds 2005). Deficiency in ACTH or cortisone hormones is also one of the causes of ketosis that cause pathological changes in adrenal gland (Dressler et al. 2019). Another possible cause of ketosis is the deficiency of oxaloacetic acid (OAA) in hepatic tissues (Bach 1978).

Some risk factors are associated directly or indirectly with occurrence of ketosis. Decreased milk yield and production is affected by the presence of ketones inside the body fluids (Dohoo and Martin 1984). Reported reproductive pathological conditions also associated with ketosis (Dohoo and Martin 1984). Ketotic dairy animal were seen with reduction in conception rate during first artificial insemination shot. This may help in culling of dairy animal at early phase of milking (Oetzel 2013). High milk producing ketotic animals had chance of displaced abomasal disease (Koeck et al. 2013). Among feeding management factors, the dairy cows at calving should not be fatty enough, otherwise it may cause reduced feed intake during early lactation. It is found that body condition score of 2.5-3.0 on a 1-5 scale is optimal and any increases in it enhance risk of ketosis (Melendez et al. 2004). Due to occurrence of associated other diseases, ketosis thought to be gateway disease during starting milking phase. Prevention and treatment of ketosis could decrease the possible chance of associated diseases.

Signs of Ketosis

Ketosis is related with the presence of ketones in fluids and characterized by hypoxia along with drop in milk yield. Decreased intake of diet by lactating animal is indication of first clinical sign during ketosis. In some cases, change in rumen motility (active to inactive) was also observed.

Other important clinical signs observed during ketosis were anorexia, decline in milk yield, body weight loss, poor body appearance, dry dung, and sometimes nervous signs. Nervous dysfunction signs are observed in nervous ketosis type which includes not normal licking, pica, absence of normal gait, incoordination, bellowing and aggression. While in cases of subclinical form of ketosis, less signs or no signs are found (Herdt 2019).

Diagnosis

In ketosis, hypoglycemic condition appeared due to less carbohydrate diet intake by the dairy animals. As a result, body produce one chemical named as Beta-hydroxybutyrate (BHB), which facilitate provision of energy when body is in need of sugar. The common approach related with diagnosis of ketosis in dairy animal is blood, milk, and urine testing. In normal circumstances, quantification of BHB level in biological fluid with the help of specialized meter indicates the occurrence of ketosis. The cut off value of BHB considered for non-ketotic cows is <1.2 mmol/L whilst level of BHB >1.2 mmol/L in cows are considered as ketogenic (Itle et al. 2015).

Numerous diagnostic tests (strips, kits, powders, and tablets) are used for the detection of ketosis which give results within seconds and minutes. Acetoacetate from urine (Ketostix strip, Bayer, Leverkusen, Germany) and BHB from milk or blood (Ketolac, Biolab, München, Germany) could be detected by using strips. These tests qualitatively confirm the presence of ketone in body fluids (Geishauser et al. 1998, Geishauser et al. 2000; Carrier et al. 2004; Oetzel 2007). The quantitative confirmatory methods of ketosis detection are using electronic BHB meter, digital devices, and high technological equipment (thin layer chromatography, high resolution gas chromatography and flame ionization detector/mass spectrometer (HRGC-FID/MS). With these techniques, fatty acids profile can be quantified inside the blood and milk and their connection with BHB level (BHB < 1.2 mmol/L). The fatty acids could be valued biomarker that guides in predicting the future occurrence of hyperketonemia (Zhang et al. 2012; Zhang et al. 2013; Li et al. 2014; Zeng and Cao 2018). Diagnosis before occurrence of ketosis may be helpful in the productive and profitable management of lactating animals. In advance, inclusion of various feed additivesor supplements and pharmaceutics could prevent the ketosis.

Prevention and Treatments

Various factors are associated with ketosis including glucose utilization in the formation of lactose (Kronfeld 1972), excess fat on animal body during calving (Smith et al. 1997), less energy diet in post calving period (Dann et al. 2005), not normal hepatic function (Tendler et al. 2007), endocrine glands illness such as ACTH or glucocorticoids, more or less inclusion of proteins diet, mineral and vitamins deficits, and more inclusion of ketogenic diet. Ketosis can be prevented effectively by avoiding these along with few other factors.

One of the approaches for the prevention of ketosis is inclusion of forages (rich in carbohydrates) in the diet of high milk yielding cows during transition period. It will also prevent the occurrence of hypoglycemic cows (Vickers et al. 2013). Second approach, addition of feed additives (supplements, pharmaceutics, herbal) in the diet can also avoid the ketosis in dairy cows (Mammi et al. 2021).

There are shortcomings in well-planned treatment regimens of ketosis and in efficacious ketosis treatment. The most of focused studies were done on treatment of ketosis rather than improvement of production or yield of dairy animals. Variety of treatments had been practiced in dairy cattle industry, with variable outcomes. More treatments had been reported along with other existing diseases but specifically and common one treatment only for ketosis practiced in dairy animals is described hereinafter.

It was proved in 1930s that hypo-glycemic condition occurred in ketosis (McSherry et al. 1960). From that period, glucose/dextrose is used primarily for treating the ketosis. Dextrose treatment play role in correcting the physiology of

the animal as glucose connected with the milk production further corrected the hypoglycemia and fat metabolism (Herdt 2000). It is believed that concentration of glucose is more in 500 ml bottle (50% dextrose). 50% dextrose will boost the glucose level inside the blood eight times more than normal level immediately after injection and normal after 2 hours (Sakai et al. 1996). Due to dextrose administration, the impact on BHB levels is short lived (<24 hours) and dextrose should be repeated for additional impacts (Wagner and Schimek 2010). It had been reported that continuous dextrose administration resulted in hyperglycemia and abomasum dysfunction by decreasing its motility (Holtenius et al. 2000; Zadnik 2003; Sahinduran and Albay 2006; Šamanc et al. 2009). Though, dextrose administration single treatment in connection with onward effects yet not well-known. Dextrose should be selected by the veterinary clinicians as secondary treatment ketonemia. Dextrose could provide reverse effect in animals which were hypoglycemic along with associated signs in nervous system. Later on, animals were administered with specific treatment regime for long period of time (Herdt and Emery 1992; Wagner and Schimek 2010).

Glucocorticoids is one of the corticosteroids that practiced in managing ketosis due to its impact on increasing level of glucose (Herdt and Emery 1992). It is proven that steroids having lessening effect on insulin whist increasing influence on breakdown of fat and protein reservoirs. Dexamethasone injection resulted in increased level of glucose and insulin hormone after 48 hours (Jorritsma et al. 2004). Corticosteroids were not recommended for long term usage in ketosis, due to less efficacious effects along with chances of side effects.

At early stage of lactation, dairy animals are inherently considered as insulin resistant (Bauman 2000). In characteristics, it is in-fact part of the complex mechanism of homeorhesis. During negative energy balance, it allows early lactating animals to produce increased amount of milk. Increased insulin resistance is manifested in animals affected by ketosis than other healthy animals (Sakai et al. 1996). In ketosis affected animals, insulin is used for treatment of ketosis because of its anabolic effect. This hormone lessens breakdown of fat, increases synthesis of fat and use of ketone bodies as energy sources. This interconnected metabolic activity decreases the level and significance of ketonemia. Literature shows limited evidence in favor of insulin as therapy.

It is found that vitamin B_{12} (cyanocobalamin) is involved in the process of gluconeogenesis, that's why it is administered in ketonemia. It is speculated that vitamin B_{12} have ability in stimulation of methylmalonyl-coenzyme (CoA) A mutase, which is main component of krebs cycle and gluconeogenesis (Kennedy et al. 1990, Gordon et al. 2017). The increasing level of this enzyme will produce more efficient energy for the cells. Butaphosphan is one of the compound and precursor of phosphorus production administered in ketosis for its role in gluconeogenesis (Rollin et al. 2010). Phosphorus involved in the phosphorylation of variety of compounds which occurs during gluconeogenesis. Butaphophan-cyanocobalamin pharmaceutical product could be administered in management of ketosis if its impact on milk yield and risk on disease should be validated.

During 1954, it was discovered that ketosis can be treated with propylene glycol (Johnson 1954; Maplesden 1954). Propylene glycol 100% (300 ml) administered orally once a day upto the period of one week (Gordon et al. 2013). In rumen it is transported into the blood, or before converted into the propionate (Nielsen and Ingvartsen 2004). It is involved in the TCA cycle by boosting the oxidation of acetyle CoA, increasing the glucose formation and triggers the insulin (Studer 1993). Insulin level is increased after 15 minutes administration of propylene glycol, and hormone surge maintained into the blood for 2 hours (Studer 1993). Many veterinarians use the propylene glycol by incorporating it into the feed as feed additive (Nielsen and Ingvartsen 2004), so, ruminal environment slowly adjusted for long term till formation of propionate (Nielsen and Ingvartsen 2004). In relation with hepatic oxidation theory, this will result in reduced feed consumption, more fat utilization and prolonging the problem of ketosis, while the clinical significance of this has not been resolved (Allen et al. 2004).

Recently documented review article suggested that monensin is one of the ionotropic antibiotics popularized in developed countries (Europe, USA, and Canada) for the prevention of the ketosis in dairy cows. It produces impact by raising the level of propionate in rumen, by reducing the BHB level inside the blood and by improving the indicators of functional liver (Mammi et al. 2021).

The combined treatment regimens were practiced in resolving the ketosis. Implementation of multiple pharmaceutical products had showed good outcomes in comparison with usage of single product. One of the problems with usage of combined therapy is economically not sound. Taken together, in future research trials should be validated regarding application of each product individually. Additional research is needed for efficacious treatment plan of ketosis which should be economically sound and can be implemented in livestock sector.

Economic Losses Due to Ketosis

The economic losses associated with ketosis depend on individual and herd-level and also associated with other factors. According to one report, the cost for one case of clinical ketosis and subclinical ketosis in average way estimated as €709 and €150. Normal herd level ketosis rates (clinical plus subclinical) were €3,613 for a default farm and €7,371 yearly for a high-risked farm (Steeneveld et al. 2020). In another report, it is recorded that cost of ketosis is €21/cow/year (Van Soest et al. 2019). In Canada, one case of subclinical ketosis treatment cost is $203 (Gohary et al. 2016).

In earlier literature, it is also reported that the losses in dairy animals due to ketosis is about 2.2 to 3.1 lbs of daily milk (4.4 to 6.6%) (Dohoo and Martin 1984; Chapinal et al. 2012), 4.1 lbs daily decline (5.5%) in yield (Duffield et al. 2009), and 865 lbs during 305 days milking period (7%). At herd level, frequency of ketosis cases is about 25-60%. More frequency in cases of ketosis, even at normal level influences overall impact on economic losses to the dairy industry.

Conclusion

Ketosis is an important metabolic disease of early lactating dairy animals affecting production performance and consequent economic losses. This disease can be avoided by proper nutrition and good management of dairy cattle during transition period and at early stage of lactation. The application of quick detection tests can support in early management of problem and preventing more income losses.

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