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Review Article

Calcium Requirement about Milk Fever of Dairy Animals

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ABSTRACT

The objective of this review paper is to compile recent findings and give an overview of dairy animals' calcium requirement for milk fever. Dietary imbalance and inadequate management of dairy cow feeding programs can cause a wide range of health problems, termed metabolic disorders. Periparturient hypocalcemia, often known as milk fever, is a metabolic condition that affects dairy cows around the time they give birth. Dairy animals' calcium requirements are moderate throughout the dry period but skyrocketed when lactation begins at calving. If the cow body fails to respond to the demand immediately the blood calcium concentration falls below a crucial level, causing clinical or subclinical milk fever, because plasma calcium is essential for neurotransmission affected animals will develop muscle weakness. Sometimes cows develop recumbency, and eventually coma and death. Therefore, administering intravenous calcium salt infusion is the best and fastest way to restore normal plasma calcium levels, and the use of different nutritional approaches has a remarkable role in preventing the sharp drop of blood calcium that occurs during parturition and also avoiding economic loss.

Keywords: Calcium Requirement, Dairy Cow, Milk Fever, Nutrition

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INTRODUCTION

The high-yielding dairy cow demands a diet that meets its nutritional requirements for synthesizing milk and milk components. Carbohydrates, amino acids, fatty acids, minerals, vitamins, and water are all essential elements. Thus, successful dairy cattle feeding requires a thorough understanding of their physical and chemical properties as well as their interactions (Ericksona, and Kalscheur, 2020). Even the nutritional requirement of dairy animals depends on biological and non-biological factors, physiological status and milk production potential are critical ones. These nutritional fractions require for maintenance, reproduction, and production, for instance, water is the most necessary ingredient for life and the formation of milk (Heinrichs and Zanton 2016; Kononoff *et al*., 2017), amino acids are used by cattle to make enzymes, milk proteins, immunoglobulins, muscle, and a variety of other organs and tissues (Schwab and Broderick, 2017) and fat as a source of energy and increase milk yield (Ericksona, and Kalscheur, 2020). Whereas it harms the rumen microorganisms during hydrogenation, which results in decreased milk fat synthesis, dry matter intake, and productivity.

Moreover, all kinds of living organisms require inorganic substances for their normal life processes, including structure, nerve impulses, and osmotic balance. Some minerals act as reaction catalysts or are required for enzyme function (e.g. glutathione peroxidase) (Schwab and Broderick, 2017). Based on the nutritional role of living org minerals are classified as major or macro-minerals; required in quite large quantities (calcium, phosphorus, magnesium, sodium, potassium, chloride, and sulfur) and trace minerals or micro-minerals; required in extremely minute levels. Mineral requirements are described in terms of how much of the mineral is absorbed. Because genuine mineral absorption varies widely depending on source, antagonist presence, food concentrations, and animal mineral status, stating mineral requirements on an absorbed basis is theoretically reasonable (Weiss, 2020).

Furthermore, mineral nutrition is critical for the effectiveness of lactation in dairy cattle (Ericksona, and Kalscheur, 2020). Among these calcium is the most abundant mineral in an animal's body, with the majority of it (99%) concentrated in the bones. It is a major component of vertebrates' skeletal structure, and it is essential for muscle movements and healthy nervous system function. The intracellular calcium fraction plays a role in cell signaling, while the calcium in the bones is constantly exchanged with extracellular fluids. An adequate level of ionized calcium is required in the bloodstream of an animal for maintaining normal body function (Cecilia, 2011), thus, a sufficient amount of calcium must be fed for dairy animals to meet their maintenance, production, and reproduction requirements. According to NRC mineral requirement standard recommendations, lactating cow must get 0.6% to 1.1 % of calcium from their diet (NRC, 2001).

On the other hand, when the cow tends to parturition demand for calcium dramatically increases because the synthesis of a high volume of milk and secretion of colostrum requires much amount of calcium. Thus a substantial amount of calcium is mobilized from the animal's body in the days before and after parturition (Martinez *et al*., 2012). When the amount of calcium needed for milk production exceeds the body's ability to mobilize calcium reserves or the total blood calcium level is less than 2.0 mmol/L during this period the cow becomes hypocalcemic, a condition is known as milk fever or parturient paresis (Wilhelm *et al*., 2017). It's one of the metabolic disorders that strike adult cows within 48 hours of giving birth, however, it can happen weeks before or after (Ericksona, and Kalscheur, 2020) and it can be severe or mild.

Clinical milk fever affects 5-10% of dairy cows while the prevalence of subclinical hypocalcemia was 30-50 %(Reinhardt *et al*., 2011). The incidence of milk fever increases the risk of mastitis, retained placenta, endometritis, slower uterine involution, delayed first ovulation after calving, ketosis, displaced abomasum, and reduced gastrointestinal motility. In the rear case, it results in paresis, recumbency, and occasionally death. Manipulating nutrition and management reduce the risk of incidence and economic loss because incidence has a significant relation with nutrition, production potential, age, and breed of the animal. Furthermore, there have been numerous studies on the occurrence of milk fever, as well as prevention techniques and risk factors. However, there is no comprehensive data on calcium requirements in dairy cows about milk fever. Therefore, the goal of this review study is to compile recent findings on the calcium requirements of dairy animals about milk fever.

LITERATURE REVIEW

Role and Metabolism of Calcium

Calcium (Ca) is the most prevalent mineral in the body, with 99 % found in the skeleton; nonetheless, the small amount of calcium outside the skeleton that is necessary for living is crucial (Suttle, 2010). “Calcium in extracellular fluid maintains its physiologic equilibrium in three forms namely ionic, protein-bound and complex” (Kumar and Kaur, 2017). Smooth muscle function and nerve impulse both require calcium, it also prevents blood clotting ((Østerud, 2010; Diamond, 2013) and facilitates the dynamics of enzyme function (Pandey, 2011; Kumar and Kaur, 2017). Calcium is necessary for optimal milk production and development rates (Sureka, 2020), preservation of cell membrane integrity, intestinal movement, conversion of light to electrical impulses in the retina, and enzyme and hormone metabolism (Pandey, 2011).

Moreover, calcium is required for the preservation and strengthening of bones, skeletons, and teeth. It allows vital nutrients to go in and out of the body's cells. Calcium is also beneficial to sleep. As a result, calcium not only plays an important

function in bone growth but also interacts with other sections of the body. The targeted cells then produce new bone to replace the "missing" bone, when the body lacks sufficient calcium, the lost bone is not regenerated. As a result, without calcium, humans, and animals (or any other living thing) would lose their shape (Goff, 2007; Pandey, 2011). Calcium has also been shown to decrease cholesterol and blood pressure (Pandey, 2011).

Furthermore, calcium is crucial for young cattle to grow properly. If the needed calcium intake is not met, the rate of growth is slowed. The deficiency of calcium causes illnesses, such as a weak skeleton or even bone fractures, and rickets in growing cattle. To maintain a normal extracellular calcium concentration, calcium will be taken from the bones (Sureka, 2020). If dietary calcium is substantially insufficient for a long time, the animal will develop severe osteoporosis and fractures, although plasma calcium will only be slightly lower than usual due to the strong desire to maintain a normal extracellular calcium concentration in mature animals (Sureka, 2020). As a result, hypo-calcemic cows face difficulty in removing the placenta because their uterus is unable to contract. Mastitis can also develop when the keratin plug (an antibacterial physical barrier found in the streak canal) slips out owing to muscular relaxation at the teat end. As a result, bacteria can enter the hypocalcemic cow's teat and gland cisterns. Ketosis can arise as a result of decreased gastrointestinal tract motility and inadequate calorie intake (Erickson and Kalscheur, 2020). Likewise, calcium metabolism during calving (in cattle) is one of the most critical animal health parameters that affect production, reproduction, and feed conversion efficiency (McClearn *et al*., 2020).

Calcium is absorbed across the intestinal mucosa by active transport (transcellular) and passive diffusion (paracellular) (Bronner, 2009). The action of calcitriol and the intestinal vitamin D receptor is required for active calcium transport (VDR). Calcitriol activates the transcellular pathway, which accounts for the majority of calcium absorption at low and moderate consumption levels. Transcellular transport occurs largely in the duodenum, where the VDR is expressed at its highest level and is reliant on the upregulation of responsive genes such as the calcium transport protein transient receptor potential cation channel, vanilloid family member 6, or TRPV6 (Li *et al*., 1993; Xue and Fleet, 2009). These characteristics of upregulation of VDR and TRPV6 are more noticeable when high calcium absorption efficiency is required. The transport of calcium between mucosal cells, known as passive diffusion or paracellular uptake, is influenced by luminal: serosal electrochemical gradients. Passive diffusion is more common with higher calcium intakes (i.e., when luminal concentrations are high) and can happen anywhere along the intestine's length (Ireland and Fordtran, 1973). Passive diffusion rates, on the other hand, are determined by the permeability of each intestinal segment. Calcium diffusion is greatest in the duodenum, jejunum, and ileum (Weaver and Heaney, 2006b).

On the other hand, bone calcium mobilization is regulated by parathyroid hormone (PTH), which is produced whenever blood calcium levels fall. While the primary function of PTH is to raise blood calcium levels by initiating Ca release from the skeleton, it also enhances the reabsorption of Ca in the renal distal and kidney tubules (Felsenfeld *et al*., 2007; Goff, 2007). Because only small amounts of calcium are lost to urine each day, the total amount of calcium that can be reclaimed by reducing urinary Ca excretion is limited. A second hormone, 1, 25-dihydroxy vitamin D, is required to assist the intestine to absorb dietary Ca effectively. This hormone is synthesized in kidneys from vitamin D, but only when blood PTH levels rise (Ireland and Fordtran, 1973). Research findings revealed that 1, 25 dihydroxy vitamin D receptors were reduced in older cows and they become less efficient in Ca absorption from the intestine than calves (pre-weaned calves have a 90% efficiency) (Ericksona, and Kalscheur, 2020). In a non-hypocalcemia cow, lower blood calcium levels responded by raising PTH and consequently, 1, 25(OH) $_2$ D_3 concentrations. Then calcium absorbs from the intestine, resorption from bone, and reabsorption of renal tubular increased. However, the capacity of cows to respond to the increased metabolic demand of Ca by the rate of increased absorption from the intestine and the bones is limited (DeGaris, and Lean 2009). Similarly, the absorption of Ca from the rumen is uncertain, while sufficient Ca is provided because of the buffering action of the rumen and which acts as a reservoir for Ca (Ramberg, 1972). Thus, the cows experience a negative Ca balance until they are post-peak (Ericksona, and Kalscheur, 2020).

Moreover, Calcium mobilization from bone by parathyroid hormone takes at least a week, while calcitriol takes a day or two to increase calcium absorption efficiency. As a result, practically all animals experience hypocalcemia after giving birth, while high-yielders are more prone to get milk fever (Fekata, 2021). The role of parathyroid hormone (PTH) is to regulate calcium homeostasis, which is closely associated with the pathogenesis of milk fever. Besides, adequate magnesium and a slightly less alkaline blood pH (known as metabolic acidosis) are required for PTH to be produced and properly bind to its receptor (Amaral-Phillips, nd.), as a result, providing a sufficient amount of Mg in dairy animals' feed has a significant role to maintain cation-to-anion difference (DCAD) and prevent hypocalcemia. Simply put, hypocalcemia and milk fever occur in cattle that cannot be absorbing enough calcium from their bones and feed to compensate for the calcium lost in milk (Goff, 2008).

Generally, calcium has a significant role in the survival of any organism, including production reproduction, skeletal formation, and body function. Changes in Ca metabolism due to lactation are more important than parturition in the pathophysiology of parturient paresis, with blood Ca losses exceeding 50 g per day (DeGaris and Lean, 2009).

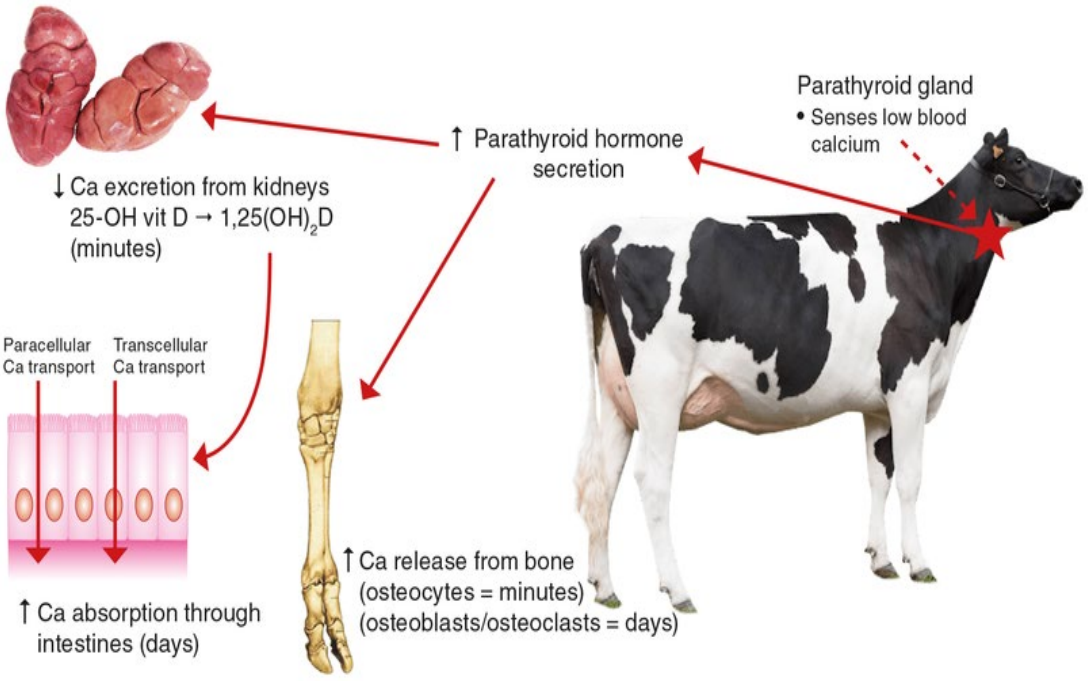

Figure 1: Schematic diagram showing the homeostatic response of a cow to low blood calcium concentration. These mechanisms act in parallel to increase blood calcium to a normal concentration (McArt, 2019).

Calcium Requirement of Dairy Animal

The amount of dietary Ca required is determined by the amount of Ca available in the feed and the efficiency with which it is absorbed in the intestine. NRC reported that 30 percent of Ca absorption from forages and 60 percent from concentrates (Taylor, 2007). Due to variations in DHVD receptors, the effectiveness of Ca absorption varies with age and breed (Horst *et al*., 1990). Jerseys have fewer DHVD receptors in their intestines than Holsteins, reducing their ability to absorb dietary Ca effectively (Goff *et al*., 1995). Besides dairy animal calcium requirement depends on physiological status, level of production, calcium absorption efficiency, and parity.

Moreover, the type and amount of feed also affect the Ca requirement. For instance, the amount of fat fed to the animal also has a significant effect on the calcium requirement of lactating cow, meaning that when the amount of fat in a cow's feed increases the calcium requirement also increases from 0.61 percent of the diet (DM basis) to 1% (NRC 2001). About 16-18 g of Ca is required for a peri-parturient cow to maintain normal blood Ca concentrations for a 650 kg dairy cow (Goff, nd). Jessica McArt (2019) reveals that a single colostrum milking requires an extra 23 g of calcium and a cow producing 45 kg of milk per day requires an extra 56 g of calcium per day, whereas, Goff (nd.) reported a lower level of Ca requirement (17.25 g) for first colostrum production. Each kilogram of colostrum produced requires 2.1 g of absorbed calcium (NRC, 2001). Thus, a total of 50 g of calcium might be lost from the

blood between calving and 14 hours following calving. Correspondingly, Sue Macky (2011) asserts that the minimum calcium requirement for dry, early, mid, and late lactating cows is 0.6 percent of the dietary dry matter, however, a lower Ca requirement reported by SNV (2017) for dry, early, mid, and late lactating cows were 0.44 %, 0.48%, 0.79%, 0.60%, 0.61%, and 0.62% respectively.

According to the report from McGill University Department of Animal Science (nd.), the calcium requirement of a dairy animal in early, mid and late lactation will be 0.8-1.1, 0.8-1.0, and 0.7-0.9 % DM respectively with an average daily milk yield of 40, 30, and 20 litter. Furthermore, the calcium requirement of dairy animals increases when the volume of milk produced and the milk solids in the milk increase. Evidence in the literature reveals that one litter of milk having 4.0% fat contains about 1.22 grams of calcium (Sue Macky, 2011), which indicates that the level of milk fat and protein in milk is positively correlated with calcium requirement. Likewise, the amount of calcium produced per kilogram of milk varies significantly depending on the amount of protein in the milk, which varies by breed. Holstein cows require 1.22 g of absorbed calcium per kg of milk produced, Jersey cows require 1.45 g, and other breeds require 1.37 g (NRC, 2001).

For a non-lactating cow, the daily calcium maintenance requirement (the quantity required for regular body functioning) is about 21 g (McArt, 2019). Besides, the findings of Visek *et al*., (1953) and Hansard *et al*., (1957) demonstrated that about 0.0154 g/kg body weight of absorbed calcium is required for nonlactating cattle maintenance, however, about 0.031 g/kg live BW calcium is required for maintenance of lactating animals (Martz *et al*., 1990). On the other hand, heifers the age of 6, 12, 18, and 24 months old require 0.47%, 0.41%, 0.44 %, and 0.40 % calcium of the DM (SNV, 2017). Even though there is no concert evidence about the Ca requirement of dairy Zebu cattle, 4.64%, 5.66%, and 4.41% of calcium is required for beef type bull, steers, and heifer of zebu breed respectively, whereas about 4.20%, 5.21%, and 4.52% calcium were need for crossbreed bull steer and heifer and 5.34% required for pasture-based production of this breed.

Cattle require more calcium when they are young and actively accruing bone, and less as they grow older and their skeletal size decreases. The Agricultural and Food Research Council (1991) created an allometric equation that will be used in this model to describe the calcium demand of growing calves.

The requirement for absorbed calcium/kg average daily gain is:

$Ca\ (g/day) = (9.83 * (MW^{0.22}) * (BW^{-0.22})) * WG$

Where MW = expected mature live body weight (kg), BW = current body weight, and WG weight gain.

In late pregnancy, the fetal skeleton begins to calcify when the period of parturition closes and the developing fetus requires a high amount of calcium, whereas, at the beginning of pregnancy up to 190 days the requirement of calcium is insignificant.

The exponential equation of House and Bell (House and Bell, 1993) best describes the absorbed calcium required to meet the demands of the uterus and concepts for any given day of gestation beyond day 190:

$$\mathbf{Ca\ (g/day) = 0.02456\ e^{(0.05581-0.00007\ t)\ t} - 0.02456\ e^{(0.05581-0.00007(t-1))\ (t-1)}}$$

Where t = day of gestation.

Generally, literature revealed that total Ca contents in normal blood plasma are 9-10 mg% and are strictly regulated (Goff, 2017). If the level of Ca is below the needed amount, calcium can be mobilized from bone, hence lactating cows will affect by a short-term Ca deficiency. Long-term deficiencies can lead to fractured bones and other skeletal issues (Weiss W.P., 2014).

Moreover, the approximate daily requirement for Ca before calving is only 30 g, with 15 g lost through fecal and urine waste and 15 g going to fetal growth (DeGaris and Lean 2009). Due to circulating blood Ca reserves being limited, this demand for Ca can only be met by boosting absorption from the rumen or intestines and mobilizing Ca from tissue, particularly bone reserves.

The total amount of calcium absorbed from all food ingredients must equal the total amount of calcium required:

Maintenance Ca requirement + lactation Ca requirement = Ca absorbed from corn silage + Ca absorbed from alfalfa + Ca absorbed from CaCO3.

Hypocalcemia

Mammalian metabolism undergoes significant changes during the periparturient phase. An increase in nutrient demand for milk production at the onset of lactation, as well as the associated metabolic load required for the production of this much amount of milk exceeds the animal's adaptive capacity, which causes for incidence of several metabolic diseases (Paudyal *et al*., 2018). calcium homeostasis can be influenced by three key factors; excessive calcium loss in the colostrum beyond the capacity of intestinal absorption and mobilization from the bones to replace it, reduced calcium absorption from the gut during parturition, and insufficient mobilization of calcium from skeletal storage, which could be caused by parathyroid insufficiency because the gland is relatively dormant during the dry season (Mulligan *et al*., 2006). Thus, the failure of maintaining calcium homeostasis during a sudden and severe calcium outflow in dairy cows after the partition leads to hypocalcemia (Oetzel, 2011).

Hypocalcemia decreases rumen and abomasal motility increasing the risk of abomasal displacement, increases body fat mobilization in early lactation by reducing feed intake, reduces all muscle contractions including the teat sphincter muscle responsible for the closure of the teat orifice after milking, thus increasing the risk of mastitis and hinder immune cell response to an activating stimulation (Kimura et al., 2006). It also affects cow health, future milk production, and reproductive performance.

Moreover, the prevalence of hypocalcemia is significantly affected by parity. Hypocalcemic cows had a serum calcium content of less than 2.0 mmol/L. Despite being cautious, DeGaris and Lean (2008), Reinhardt *et al*., (2011), and Wilhelm *et al*. (2017) have all agreed on threshold cut-off. Higher criteria have been proposed in recent investigations. Hypocalcemia measured at 2.1, 2.2, and 2.3 mmol/L was linked to a negative health outcome such as displaced abomasum and metritis (Chapinal *et al*., 2011, 2012; Martinez *et al*., 2012) or an increased risk of culling (Seifi *et al*., 2011; Roberts *et al*., 2012).

Furthermore, the finding reported by Venjakob *et al.,* (2017) only 5.7% of cows have subclinical hypocalcemia whereas, 29.0, 49.4, and 60.4 % of cows were found subclinical hypocalcemia, second, third, and fourth lactations, respectively based on the 2.0 mmol/L threshold. According to a recent study, subclinical hypocalcemia affected 51, 54, and 42% of fourth, fifth, and sixth parity cows, respectively (Reinhardt *et al*., 2011). Similarly, Venjakob *et al.,* (2017) observed that subclinical hypocalcemia prevalence of 52.1, 51.1, and 41.7% in fourth, fifth, and sixth parity cows, respectively, are nearly equal. When comparing dairy cows with multiple parties (> 3 up to 7 times) to those with fewer parities (3 times), around three fourth of those with multiple parties were the most affected by hypocalcemia (Saed *et al*., 2020).

According to Klingbeil (2015), multiparous cows have a higher calcium output due to a higher volume of colostrum than primiparous cows, which could explain why they have a higher prevalence of subclinical hypocalcemia. However, because their colostrum yield was not different, the calcium output does not explain the rise in the prevalence of hypocalcemia in multiparous cows as they get older. The parity-related rise could be owing to a reduction in active osteoclasts and osteoblasts in multiparous cows, resulting in less bone remodeling. Define *et al*., (2022) reveal that the prevalence of subclinical hypocalcemia was higher in cows with poor body conditions, however, this report disagrees with Saed *et al*., (2020) who observed that dairy cows with BCS ≥ 3.5 were significantly affected. The serum calcium content of Holstein, Simmental, and Jersey cows did not differ (Venjakob *et al.,* 2017).

Milk Fever (Clinical Hypocalcemia)

Milk fever is a metabolic disorder that affects dairy cows and is manifested by low calcium levels in the blood. When the calcium required for milk production surpasses the body's ability to mobilize reserved calcium in the early few days of lactation, it is most prevalent, usually within 72 hours (Tadesse and Belete, 2015). However, instances might appear up to 10 days before and after calving and even sometimes during late lactation (Radostits *et al*., 2007; Roche and Berry 2006). It occurs when the serum calcium concentration decreases below 1.625 mmol/L (Thirunavukkarasu *et al*. 2010). Body temperature is frequently below normal throughout the sickness,

therefore the term "fever" is misleading. According to DeGaris and Lean (2008), milk fever occurs when roughly 50% of the circulating blood calcium is lost. Research findings reveal that when the total blood Ca level is less than 1.4 mmol/L causes clinical hypocalcemia or milk fever (Thirunavukkarasu *et al*. 2010). Low blood calcium levels impair muscle function all across the body, resulting in overall weakness, depression, and mortality. It's more common in older dairy cows, each lactation increases the risk of milk fever by about 9% (DeGaris and Lean) with a reduced ability to mobilize calcium from their bones, as well as in breeds that produce a lot of milk (Venjakob *et al*., 2017).

Milk fever is considered a gateway sickness that significantly reduces the chances of a full lactation's productivity. The most serious problem of hypocalcemia is that Ca is responsible for nerve and muscle contraction impulse transmission. Mild milk fever is caused for calving problems, retained placenta, uterine prolapse, metritis, mastitis, ruminal stasis, immune system depression, and reduced general reproductive performance in the majority of cows during the peripartum period, resulting in a 3-4 year reduction in productive life (Bhanugopan and Lievaart, 2014). While the death of affected animals is insignificant (5%) the productive life of affected cows has been reported to be diminished (Krehbiel, 2014) and causes significant economic loss.

Moreover, evidence in the literature, the average prevalence of clinical milk fever was about 3.5% in North American and Australian studies and about 6.2 % in European investigations (Reinhardt *et al*., 2011), and this rate can reach up to 80% of calving cows in individual herds (DeGaris and Lean 2008) however, there is no relevant information on the prevalence of milk fever in Ethiopia and most developing countries. It has recently become much more common in small-scale dairy farms. Besides, the prevalence of milk fever is highly significant in high-producing dairy animals during calving (Crivei *et al*., 2021) and several risk factors also were described in different literature.

Furthermore, Roche and Berry(2006) illustrated that milk fever is caused by several factors, all of which have an impact on its occurrence and severity such as; parturition or number of parity (9% increased risk for each successive lactation), stage of lactation(first-lactation dairy cattle rarely develop milk fever because they produce less colostrum and because they can rapidly mobilize calcium from bone owing to the high osteoclastic activity in their growing skeleton), age (older cows are more sensitive than younger), milk yield (cows with higher yield are more predisposed than cows with lower yield) (Fleischer *et al*., 2001; Rehage and Kaske, 2004) breed, body condition, length of the dry period and diet composition (Angassa, 2019).

Age

The incidence of milk fever significantly increases with age and the effect is particularly obvious in cows above the third parturition. It is not common in the first

lactation, this is because young stocks can rapidly adjust to the high calcium demands of lactation even if it occurs in the first lactation. Venjakob *et al*. (2017) reported that the prevalence of clinical milk fever was 1.4%, 5.7%, and 16.1% for 2nd, 3rd, and ≥ 4th parity cows, respectively. The relationship between age and milk fever is studied by several researchers and they provide concrete evidence. According to Rezac (2010), dairy cows give more milk after the third lactation, resulting in a higher calcium need. The disease is more common in cows that produce more than 25 liters of milk each day (Aberaw, 2017). In addition to increased milk production, aging causes a decrease in the ability to mobilize calcium from bone storage, a decrease in active calcium transport in the colon, and a decrease in 1,25-dihydroxy vitamin D (1,25$[OH]_2$D; calcitriol) synthesis by 50%. Another finding concludes that the growth of the skeletal bones of heifers is not completed yet, thus they have a lot of osteoclasts, which are more responsive to PTH than older cows' bones ((NRC, 2001). Besides increased age also causes a decrease in the number of 1, 25-(OH) D receptors (Rezac, 2010). Therefore, we can conclude that there is a significant relationship between milk fever, party/age, and milk yield in dairy cows.

Breed

Milk fever susceptibility varies by breed. Cows have a hereditary tendency to milk fever, which is well documented in some high-producing Jersey and other breeds. High-producing dairy cows, such as Jerseys and Guernseys, are more susceptible to the disease than Holstein and Brown Swiss breeds. This could be because the most sensitive breeds produce more milk per unit of body weight. Jersey cows were said to be 2.25 times more susceptible to milk fever than Holstein-Friesian cows (Lean *et al*. 2006), this is because Jersey cows have fewer vitamin D receptors (Goff, 2008), which are responsible for intestinal calcium absorption and bone calcium resorption. On the other hand, Prapong *et al*., (2005) also discovered that the secretory enzyme Ca2+-ATPase concentrations in mammary tissue and milk fat globule membranes are proportional to the prevalence of milk fever. These changes in Ca2+-ATPase concentrations could also play a role in the occurrence of milk fever among different breeds.

Body Condition Score (BCS)

Dairy animals with excessive BCS before calving are more susceptible to metabolic disease. Based on the finding of Ostergaard *et al*., (2003) there is a significant relationship between milk fever and BCS, higher BCS increases the risk of milk fever. The prevalence is four times more in over-conditioned cows before calving. Cows having a BCS of 3.00 at dry-off had a lesser incidence of milk fever than cows with a BCS of 3.25 (Contreras *et al*., 32), whereas, cows having a BCS above 2.5 at calving had an increased risk of milk fever (Roche and Berry). This is because dairy cows

with a higher BCS at calving have a higher calcium output in milk, making them more prone to milk fever, while over-conditioned cows take a small amount of calcium due to lower appetite during the critical period around calving, predisposing them to hypocalcemia. Similarly, Bewley and Schultz (2008) demonstrated that cows with excessive body condition at calving or excessive weight loss after calving, have lower reproductive performance and are more likely to develop dystocia, retained placenta, metritis, milk fever, cystic ovaries, lameness, and mastitis, as well as metabolic disorders, fatty liver, and ketosis. Chapinal *et al*., (2012), on the other hand, observed no link between a dry BCS of 3.75 and the outcome of milk fever. The development of milk fever in over-conditioned cows may be owing to a reduction in DMI, which, when combined with a reduction in calcium intake, results in hypocalcemia upon calving.

Diet

Dietary calcium and phosphorus modification have been shown to have a significant impact on the occurrence of milk fever. A higher prevalence of parturient paresis has been linked to diets that provide dry cows with a high daily calcium intake. Because active dietary calcium absorption and bone resorption are inhibited at this level, the calcium maintenance requirement can be supplied mostly by passive absorption. Cows in this situation are unable to restore the calcium lost in milk in their plasma and become severely hypocalcemic (Bhanugopan and Lievaart, 2014). Thus, the total amount of dietary calcium was more important than the dietary ratio of calcium and phosphorus.

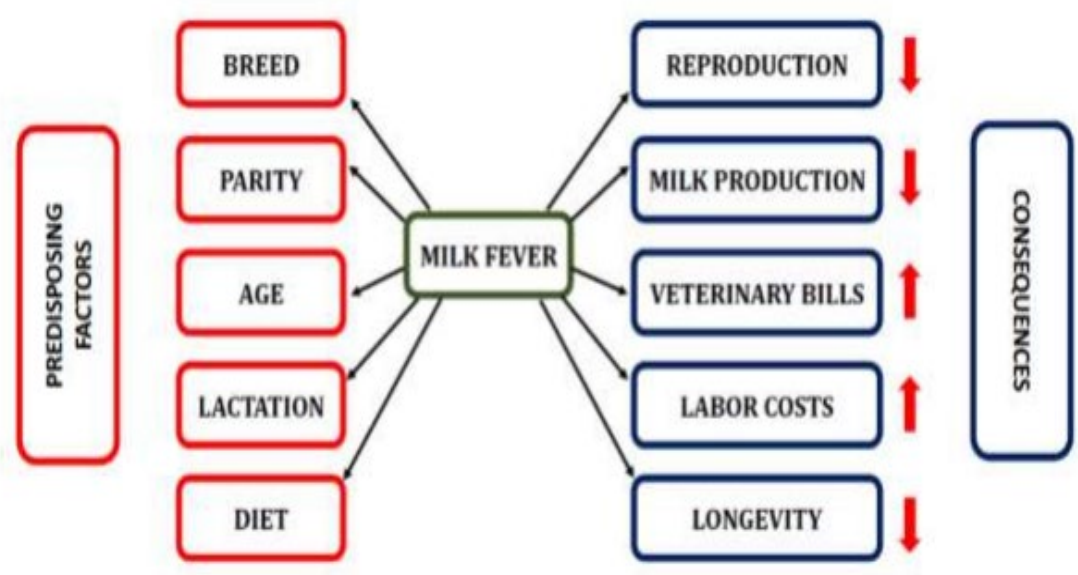

Figure 2. Predisposing factors for milk fever and its economic consequences (Dervishi E. *et al*., 2017)

Moreover, milk fever and the severity of hypocalcemia are both increased by phosphorus-rich diets at the start of lactation. A higher level of phosphorus in the diet affects the formation of 1, 25 dihydroxy vitamin D3 and so inhibits the absorption of calcium in the intestine (Horst, 1996). Milk fever incidence is also strongly linked to pre-partum cations diets such as sodium and potassium, while diets with high anion, particularly chlorides and sulfides, are linked to a lower prevalence. Anions added to dairy cows' diets prior to parturition effectively reduced the incidence of milk fever by producing metabolic acidosis, which aids calcium resorption in the bones (Bradford, 1996).

Clinical Diagnosis of Calcium Level

A combination of information gathering, clinical examination, and laboratory testing is used to diagnose milk fever; cow's age, breed, lactation stage, milk yield, calving day, and response to intravenous calcium borogluconate solution were obtained during history tracing (Wubishet *et al*., 2016). Milk fever is common in mature dairy cows (>5 years old) within 72 hours of parturition. It occurs more frequently in dairy cows that produce much volume of milk (Radostits *et al*., 2007). Paresis and weakness depression in cows that have recently given birth to young are diagnostic indications of the condition. Whereas laboratory investigation of blood calcium levels and a positive response to intravenous calcium solutions is the most accurate technique to diagnose a case of milk fever. The blood calcium level should be between 8 and 10 mg/dL (Thirunavukkarasu *et al*., 2010). Cows having blood calcium levels less than 7.5 mg/dL are classified as hypocalcaemic. Hypocalcaemic cows have a blood calcium concentration of less than 7.5 mg/dl. Stage II hypocalcemia is defined as calcium levels ranging from 3.5 to 6.5 mg/dl, whereas stage III is defined as calcium concentrations as low as 2 mg/dl. Bradford (1996) states that prolonged recumbency causes ischemic muscle necrosis as well as an elevation in the serum muscle enzymes CPK and AST. CPK levels typically vary between 105 and 409 IU/L, with values larger than 1000 IU/L indicating serious muscle injury from being low, and AST levels greater than 500 IU/L indicating severe muscular damage.

Recently a study group from Germany diagnosed subclinical hypocalcemia by taking the historical clinical impression of “cold ears” and using an infrared thermometer to determine the skin temperature of ears in fresh cows. However, diagnosis of subclinical hypocalcemia by ear temperature is an unreliable method, because the results were greatly affected by the ambient temperature (McArt, 2019).

Prevention

The incidence of milk fever or hypocalcemia is a predisposing factor for the occurrence of several metabolic and physiological disorders. Therefore, the prevention of milk fever is vital for dairy farmers to increase profitability by reducing production

loss, death loss, and veterinary expenditures. After extensive investigation researchers suggested a variety of nutritional management techniques to control hypocalcemia and mobilize calcium in dairy cattle such as feeding anionic salts, low calcium ion diets, and vitamin D supplementation (Amaral-Phillips D., 2017).

Feeding of Low-Calcium Diets

One method of preventing milk fever is to feed low-calcium diets throughout the dry period (Jesse *et al*., 2018) which promotes the release of parathyroid hormone. This increases bone osteoclasts, enhances calcium resorption from bone, and reabsorption in renal tubules from urine, and initiates the synthesis of 1, 25-dihydroxy vitamin D. thus the calcium homeostatic pathways become active and capable of preventing hypocalcemia when lactation begins (Oetzel, 2011). This can be achieved by providing less than 50 g/ each day. As a result, calcium-rich forages such as alfalfa should be removed from the animal's diet. Corn silage and grass hay should be fed often throughout the dry period to help lower calcium levels (Angassa, 2019). According to Bhanugopan and Lievaart (2014), feeding hay, straw, and grain during the dry season is a common nutrition method employed by all farmers. Grain feed helps the rumen acclimatize to the high-energy diets given post-calving, and grain is also low in calcium, thus it minimizes the risk of MF.

Feeding Dietary Cation-Anion Balancing

It is a dietary technique for minimizing milk fever in early lactation while also enhancing the cow's health and productivity (Patel *et al*., 2011). It is a basic preventative approach that entails administering anionic salts to reduce the cation-anion difference in the diet, and it has been effectively implemented in dairy farms (MartínTereso *et al*., 2014). Reducing the number of absorbable cations in the diet and increasing the number of accessible anions like chlorine and sulfur monoxide is the main goal of this type of supplementation (Goff, 2008). Orally supplements with calcium around parturition and 2 subcutaneous calcium infusions in the first 18 hours postpartum is the recommended prevention strategies (Bhanugopan *et al*. 2014; Amanlou *et al*. 2016), magnesium supplementation is also crucial for reducing milk fever (Jesse *et al*. 2018). It has been identified as the most effective technique for reducing milk fever.

Moreover, it’s crucial to know how many cations and anions exist in an animal's diet, to maintain the balance of cations and anions. The DCAD is calculated by subtracting a sum of dietary cations (i.e. sodium and potassium) from anions (i.e. chloride and sulfur) (Greg *et al*., 1998). A negative DCAD diet has more anions than cation equivalents, whereas a zero DCAD diet has equal equivalents and a positive DCAD diet has more cation equivalents.

According to Bellini (2019) feeding a dry cow diet rich in anionic salts, chloride, and sulfur lowers DCAB, then the cow becomes acidotic and the blood and urine pH drops. This circumstance improves tissue response to PTH by improving the function of PTH receptors on bone and kidney cells, as well as boosting the generation of 1,25 (OH)2D3 and, as a result, enhancing active calcium transport across the gut. As a result, cows in metabolic acidosis are better able to mobilize calcium and satisfy rising demands without developing milk fever. Lowering DCAB is also achieved by lowing the levels of sodium and potassium.

Generally manipulating nutrition and management have a significant role to prevent all metabolic diseases as a whole and milk fever in particular.

Vitamin D Supplementation

Supplementing vitamin D in prepartum dry cows as a strategy to prevent milk fever is recommended by Bhanugopan and Lievaart, (2014). This approach requires injecting or ingesting up to 10 million IU of vitamin D each day for 10-14 days, boosting intestinal Ca++ absorption pharmacologically by these vitamin D dosages.

Moreover, maintaining appropriate BCS at calving and drying off is vital to avoiding milk fever and Zeolite supplementation also significantly increases the plasma Ca level before and after calving

Treatment

The goal of milk fever treatment is to restore the serum calcium content to a level sufficient to support cellular activity. Milk fever should be treated as soon as feasible, especially if recumbency is evident, as this can cause significant musculoskeletal damage (Oetzel, 2011). It is accomplished through intravenous injection of calcium salts such as borogluconate at a rate of 2 g/100 kg body weight, as well as oral calcium solutions and intravenous (IV) calcium borogluconate (Goof, 2008). However, intravenous (IV) calcium injection is suggested for the treatment of cows that are still standing, because if not done appropriately, an application can result in a dead animal due to a cardiac problem. An intravenous infusion of calcium salts is the fastest technique to restore normal plasma calcium content.

Cows in stages II and III of milk fever should be treated immediately with 500 ccs of 23 % calcium borogluconate administered slowly IV (Oetzel, 2011). Subcutaneous calcium injection can also be utilized to boost blood calcium concentrations during calving. Subcutaneous calcium injections are irritating and cause tissue necrosis; delivery should be limited to no more than 75 ml of a 23 percent calcium borogluconate.

CONCLUSION

The nutritional requirement of dairy animals depends on physiological status; stage of lactation, dry period, or pregnancy, milk production potential, and biological and other environmental factors. Different proportions of nutrients are required for maintenance, growth, production, and reproduction. Besides the calcium requirement of a dairy animal depends on physiological status, level of production, calcium absorption efficiency, and parity. The type and amount of feed also affect the Ca requirement, about 16-18 g of Ca is required for a peri-parturient cow to maintain normal blood Ca concentrations. This requirement rises (1.1% of DM) a few days after and before parturition due to colostrum secretion. During this period, high-producing dairy cows are the most susceptible to metabolic disorders. Pathophysiological difficulty in maintaining calcium homeostasis during a sudden and severe calcium outflow in dairy cows after the partition leads to hypocalcemia, a subclinical disorder that is life-threatening to the cow and predisposes the animal to a variety of other disorders.

Milk fever is a metabolic illness in dairy cows that is characterized by low serum calcium levels. It is most common in the early days of lactation when the calcium required for milk production surpasses the body's ability to mobilize retained calcium. It happens when the calcium concentration in the blood falls below 1.625 mmol/L. Low calcium levels in the blood affect muscle function, leading to general weakness, depression, and mortality. The incidence and severity of milk fever vary depending on factors such as parturition or age, lactation stage, and milk yield. Cows with higher body condition scores are also highly affected. The incidence of milk fever is diagnosed using a combination of data collection, clinical examination, and laboratory testing.

Prevention of milk fever is critical for dairy farmers to boost profitability by lowering output losses, death losses, and veterinary costs. Feeding anionic salts, low calcium ion diets, and vitamin D supplements are some of the nutritional management approaches used to control hypocalcemia and mobilize calcium in dairy cattle. Milk fever is treated intravenously with calcium borogluconate injections, subcutaneous calcium salts, and oral calcium administration. If treated early and appropriately, affected cows have a very high survival rate.

To recapitulate, milk fever is an economically important disease controlled by the nutritional manipulation of dairy animals and feeding adequate calcium. Therefore, nutritional mineral requirement standards should be developed for zebu cattle or cattle living in tropical climates and the pathophysiology of zebu cattle and the economic impact of milk fever in developing countries like Ethiopia should be further investigated.

CONFLICT OF INTEREST

The authors declare no conflict of interest regarding the publication of this paper.

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