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Milk Fever and its Economic Consequences in Dairy Cows: A Review

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Abstract: Nutritional imbalances, deficiencies, or erratic management of feeding programs for dairy cows can create large numbers and various types of health problems generally categorized as metabolic diseases. High producing dairy cows are the most susceptible to metabolic diseases during the periparturient period. During this period the animal is tremendously challenged to maintain calcium homeostasis because of physiological and pathological factors. Those that fail can develop milk fever, a clinical disorder that is life threatening to the cow and predisposes the animal to a variety of other disorders. The aims of this manuscript were to review milk fever and its economic consequences in dairy cows. Milk fever (parturient paresis) is an important metabolic disorder of dairy cattle around the time of calving. Because of the high volume of milk produced during this time and subsequent demand for calcium, these cows often develop hypocalcaemia, or abnormally low levels of calcium in the blood. Since calcium is required for the release of acetylcholine at the neuromuscular junction, affected animals will begin to experience muscle weakness. As this hypocalcaemia worsens, the cow will become too weak to stand and will eventually become comatose over a matter of hours. Parturient paresis is treated intravenously with calcium borogluconate. Affected cows have an excellent prognosis if treated early and properly. However, the worse the symptoms, the worse the prognosis tends to be. Any preventive measure must be aimed at regulating calcium haemostasis and eliminating the precipitous fall in blood calcium at parturition. For assessing economic losses caused by milk fever cost of medicines, cost of additional labour utilized, loss due to reduction in milk output cost of animal dead and culled as well as increased susceptibility of cows to other metabolic and infectious disease should be considered. Furthermore, as the dairy profitability is determined by the biological cycles of milk production and reproduction emphasis should be given on the nutritional management of dairy cows in the dry period as well as at parturition.

Key words: Calcium Borogluconate · Dairy Cows · Milk Fever And Parturient Paresis

INTRODUCTION

Milk fever (MF) is one of the most common mineral-related metabolic conditions affecting dairy cows at parturition, a disorder that occurs immediately after or close to calving as a result of a low level of calcium in the blood (hypocalcaemia). A mild degree of hypocalcaemia develops in the majority of cows during the peripartum period and has been linked to calving problems, retained placenta, uterine prolapse, metritis, mastitis, ruminal stasis, depression of the immune system and generally reduced reproductive performance, resulting in reduction of productive life by 3.4 years and/or death if left untreated [1]. In a small proportion of animals, hypocalcaemia becomes severe and results in paresis, recumbency and, occasionally, death [2].

About 50% of dairy cows in their second lactation and greater have blood Ca concentrations that fall below the threshold for subclinical hypocalcemia after calving [3]. This inadequate blood calcium concentration can cause a cow to lose the ability to rise to her feet as calcium is necessary for nerve and muscle function. These results in the metabolic disease known as milk fever, although it is more properly termed hypocalcaemia

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or parturient paresis, as an elevated body temperature is not typically observed. It is a common metabolic disorder in dairy cattle that generally affects older, high producing cows [4].

Mechanisms that may explain the detrimental effects of hypocalcaemia include impaired energy balance, which is reflected with higher serum NEFA concentrations [3] and direct impairment of immune cell responses to an activating stimulus [5]. The parathyroid hormone is the primary regulator of blood calcium, its failure in milk fever is caused by either parathyroid inadequacy which resulting in the lack of sufficient hormone secretion, or by the presence of some metabolic condition in the tissues at parturition that renders the parathyroid hormone temporarily inactive [6].

There are risk factors for the precipitation of milk fever in the dairy cows to occur including age, breed, body condition, length of dry period, milk yield, parity and dietary factors [7, 8]. Milk fever is a disease of considerable importance for dairy cow welfare and economy. Although treatment with intravenous infusion of calcium salt solutions cure most clinical cases of hypocalcaemia. It has been proposed that a specific control program is relevant when the incidence of milk fever increases to above 10% among high risk cows that is cows entering third or later lactations. So strategically prevention of milk fever is economically important to the dairy farmer because of minimize production loss, death loss and veterinary costs associated with clinical cases of milk fever [9].

Although milk fever was known to occur sporadically in dairy cows and recently it is dramatically increased in small holder dairy farms, there has been no emphasis given on the extent of the disease, methods of prevention and control and factors that influence its occurrence. Furthermore, the occurrence of milk fever predisposes the cow to productive problems, especially among highly productive dairy cows. These were the points which initiated the authors to review on of milk fever. Therefore, the main objectives of this paper are to review general aspect of milk fever and describe its economic consequences in dairy cows.

Literature Review:

General Aspect of Milk Fever in Dairy Cows: Grummer *et al*. [10] suggested that the success of the production cycle of a cow is determined by its production level, the postpartum recovery reproductive function and absence of pathology. Undoubtedly, the achievement of these objectives depends largely on the state of animal in its early days postpartum. So that the level of production output, the level of feed intake and blood parameters (NEFA, ketone bodies) in the first week postpartum are good indicators of the quality of initiating lactation. The initiation of lactation challenges the dairy cow's metabolic capabilities at maintaining normocalcemia due to reduced DMI [11] and calcium (Ca) loss in colostrum and milk [12, 13]. According to most recent NAHMS [14] report for dairy cows, the leading causes of morbidity in dairy cattle are clinical mastitis, lameness, infertility, retained placenta, milk fever, reproductive problems and displaced abomasum. They are generally known as periparturient diseases and they have a negative impact on milk yield, reproductive performance and overall animal well-being [15, 16].

The metabolic diseases or disorders of production are caused by an imbalance of nutrients (such as proteins, minerals and water), fault in metabolism and excess loss of minerals through feces, urine, milk and fetus. Nutritional imbalances affecting livestock are produced because the supply or use of feed does not meet nutritional demands for maintenance, growth, production and reproduction [17]. During last 2 to 4 weeks of gestation there is an increase substantial energy demand due to fetal development and the needs of colostrum synthesis. These two circumstances are often responsible for the development of a negative energy balance that initiates a few weeks before delivery. Cattle have the ability to compensate for deficits energy through the mobilization of body fat. However, an excess mobilization of fat leads to metabolic disease and reproductive problems [18].

The birth and early lactation are periods of too much stress for dairy cows due to the large metabolic challenges that occur in this period. During the last 2 weeks pre-calving, non-concentrated feed especially fiber consumption decreased and result in negative energy balance due to fetal development and decreased rumen motility, in the last days before calving, the balance of other nutrients such as protein, vitamins and minerals may also be compromised. The depletion of Ca^{++} stores within the cells likely begins several days before calving [5]. But the reduction in serum calcium concentrations usually occurs about 12 to 24 hours after calving [5, 4]. Major physiological, nutritional, metabolic and immunological changes occur within this time frame as the production cycle of the cow shifts from a gestational nonlactating state to the onset of copious milk synthesis and secretion [19]. These alterations are related to increases in energy requirements driven by both fetal needs and lactogenesis, endocrine and metabolic

preparing cows for childbirth and lactation as a result a condition known as milk fever, caused by hypocalcaemia occur in the animal [20, 21].

Low blood calcium level interferes with muscle function throughout the body, causing general weakness, depression and death. It is more common in older dairy cows which have reduced ability to mobilize calcium from bone and in high milk producing breeds [19]. Additionally, the major complications in the occurrence of hypocalcemia is that as the Ca^{++} is responsible for impulse transmission of nerve and muscle contractions [5], it causes calving problems due to muscle inactivity of reproductive organs at parturition. Cows that fail to return to normal plasma Ca^{++} concentrations may develop clinical signs of hypocalcemia known as milk fever. Hypocalcemia seems to negatively affect multiparous cows at the onset of lactation more profoundly than primiparous cows [3].

The mean incidence of clinical milk fever in published field studies was about 3.5% for North American and Australian studies and about 6.2% for European studies [22]. About 50% of second and greater lactation cows have blood Ca concentrations that fall below the threshold for subclinical hypocalcemia after calving [3]. Hypocalcemia may lead to reduced feed intake, poor rumen and intestine motility, increased risk for displaced abomasum, reduced milk yield, increased susceptibility to infectious diseases and increased risk for early lactation removal from the herd [4, 23].

Etiology: Initiation of lactation challenges a dairy cows' ability to maintain calcium (Ca^{++}) homeostasis as the demand of colostrum and milk synthesis increases around parturition and DMI transiently decreases, the result is a transient period of hypocalcemia [3]. Calcium is eliminated from the cow to endogenous fecal Ca^{++}, clearance in glomerular filtration, placental Ca^{++} transport to the fetus, bone deposition and Ca^{++} secretion in the mammary gland [24]. When approximately 50% of the circulating blood Ca^{++} is lost, a hypocalcemic event, which is known as milk fever, is likely to occur [22]. Thus hypocalcemia occurs as the dairy animal's complex mechanisms for maintaining calcium homeostasis fail during a sudden and severe calcium outflow [7].

Milk fever is caused by a severe deficiency of metabolizable calcium ion (Ca^{++}) in the circulation [25]. Deficiency of calcium ion in the tissue fluids and fall in serum calcium level at calving due to the onset of lactation is the major biochemical defect in parturient paresis. Serum calcium level falls in all adult cows at calving [6]. On the other hand the delay in the operation of calcium homeostatic mechanisms is vital in causing milk fever. Calcium homeostasis is affected by three factors and variations in one or more of them are instrumental in causing the disease in any individual. These are excessive loss of calcium in the colostrums beyond the capacity of absorption from the intestines and mobilization from the bones to replace, impairment of absorption of calcium from the intestine at parturition and insufficiency of mobilization of calcium from storage in the skeleton, which could arise because of parathyroid insufficiency since the gland is relatively quiescent due to the decreased calcium and phosphorus metabolism of the dry period [26].

Epidemiology and Risk Factors for Hypocalcaemia: With the onset of lactation, most lactating dairy cows enter a stage of negative Ca^{++} balance [3]. The cow will spend the next six to eight weeks of her lactation period increasing Ca^{++} intake by increasing calcium rich feed intake and improving intestinal Ca^{++} absorption [11]. Parturient paresis is a disease of high producing dairy cattle. It is estimated that 3 to 8% of cows are affected by this disease with some herds having prevalence as high as 25 to 30%. It occurs before calving, but most cases occur within the first 48 hours following calving [27]. The risk factors for hypocalcaemia could be grouped into intrinsic risk factors, which are associated within the animal itself and extrinsic risk factors, which are outside of the animal's body which are commonly known as environmental factors [28].

According to Roche and Berry [29] the factors that contribute to occurrence of milk fever and which influence the incidence and severity of milk fever includes; 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) [30-32] breed, body condition, length of dry period and diet composition [33, 34].

Age: The risk of a cow developing milk fever will increase with age [35, 36]. From the third lactation onwards, dairy cows produce more milk, resulting in a higher calcium demand. In addition to increased milk production, ageing also results in a diminished ability to mobilize calcium from bone stores and a decline in the active transport of calcium in the intestine, as well as impaired

production of 1,25-$(OH)_2D_3$ [36]. The skeletal bones of heifers are still in a growth phase and therefore have a large number of osteoclasts present, which can respond to PTH more readily than the bones of mature cows [35]. Increased age also causes a decrease in the number of 1,25-$(OH)_2D_3$ receptors [36].

The hypocalcaemia at calving is age related and most marked in cows from third to seventh parturition; it is infrequent at the first parturition. This is because while some degree of hypocalcaemia occurs during the first few days of lactation, they are able to adapt rapidly to the high demands of calcium for lactation [37]. With increasing age, this adaptation process is decreased and results in moderate to severe hypocalcaemia in most adult cows. The adaptation mechanism is directly related to the efficiency of intestinal absorption of calcium, which decreases with increasing age. Most cases occur in animals older than five years of age. This is as a result of increasing milk production with age and decreasing efficiency of dietary calcium absorption and bone resorption [9, 38].

Breed: Certain breeds of dairy cows have been shown to be more susceptible to milk fever than others. For instance cross breed cows are more susceptible to milk fever than local breeds. This could be attributed to high milk yield and low ability to maintain calcium homeostasis in cross breed cows compared with local breeds [8]. It was shown that Jerseys had lower numbers of intestinal receptors for 1,25-$(OH)_2D_3$ than same-aged Holsteins. Lower receptors would result in a loss of target tissue responsiveness and sensitivity to 1,25-$(OH)_2D_3$. At calving the plasma 1,25-$(OH)_2D_3$ levels are increased due to the hypocalcaemic state of the dairy cow. Normally, the elevated levels would result in enhanced bone calcium resorption and intestinal calcium absorption, but with the reduced number of receptors available in an older animal, the activation of genomic events by 1,25-$(OH)_2D_3$ is less sufficient, resulting in increased tendency to become hypocalcaemic [39]. Additionally, there is a genetic predisposition of cows to milk fever and this is well recognized in certain breeds of high producing Jersey and other breeds. This is associated with higher milk production per unit of body weight, reduction of intestinal vitamin D3 receptors as Jersey's age and a higher than normal production of parathyroid hormone related proteins by the mammary gland, which increases calcium transport from bone to milk [9].

Body Condition Score: According to Ostergaard *et al*. [40] high BCS enhance the risk of milk fever. Dairy cows that are over conditioned at calving are up to four times more likely to develop milk fever. This is due to dairy cows with higher BCS at calving have a higher calcium output in milk, making them more prone to milk fever and over conditioning results in decreased feed intake during gestation period (i.e they take small amount of calcium containing feed especially cereals) this is caused by reduced appetite in the critical period around calving which predisposes them to the development of hypocalcaemia [41]. Bewley and Schultz [42] suggested that cows with excessive body condition at calving, or excessive weight loss after calving, demonstrate overall decreased reproductive performance and increased likelihood of dystocia, retained placenta, metritis, milk fever, cystic ovaries, lameness and mastitis as well as metabolic disorders, fatty liver and ketosis.

Dietary Factors: Boda and Cole [43] indicated that diets providing dry cows a high daily intake of calcium are associated with an increased incidence of parturient paresis. At this level the maintenance requirement of calcium can be met predominantly by passive absorption since active absorption of dietary calcium and bone resorption are then suppressed. Cows in this condition are not able to quickly replace plasma calcium lost in milk and become severely hypocalcaemic. Excessive dietary phosphorus intake (>80 g day) during late gestation can also induce milk fever and the severity of hypocalcaemia by raising blood phosphorus concentrations to the point that phosphorus directly inhibits renal synthesis of 1,25-(OH)2D3 and thus reduces the intestinal calcium absorption mechanisms [7]. Pre-partum diets high in cations like sodium and potassium are associated with an increased incidence of milk fever while diets of high in anion, especially chlorides and sulfides are associated with decreased incidence of the disease. The addition of anions to the diet of dairy cows prior to parturition effectively reduced the incidence of milk fever by inducing a metabolic acidosis, which facilitates bone resorption of calcium [38].

Pathophysiology: Calcium (Ca) is a macro-mineral that has important functions in the body; among them are the bone matrix, the process of muscle contractor and transmission of nerve impulses and Ionized calcium (Ca^{++}) is also necessary for vital cellular functions such as signaling, neurotransmission, muscle contraction, metabolism,

growth and proliferation and activation of immune responses [44, 45]. Normal blood Ca^{++} in the adult cows is maintained between 8.5 and 10 mg/dl [4]. Maintenance of blood Ca^{++} within the acceptable range is a balancing act between the Ca^{++} demand of milk production and the cow's homeostatic mechanisms to maintain blood Ca^{++} [31]. During the dry period, the supply of calcium through the diet is usually more than adequate to maintain homoeostasis without activating the calcium mobilization system, which is thus usually not activated until parturition. Therefore, dry period is the phase most important in the development of milk fever [18, 22]

According to DeGaris and Lean [22], the pre-partum demand for Ca^{++} is about 30g per day, allowing 15g for fecal and urinary loss and the remaining 15g to be available for the gestating calf. When intake and homeostatic mechanisms cannot meet the increased demands for Ca metabolism, the pathogenesis of hypocalcemia is initiated. The level of calcium in plasma is well regulated and when the level decreases, the parathyroid gland will excrete parathyroid hormone (PTH). This increases the mobilization of calcium from the skeleton and also raises the renal threshold for calcium in the kidneys [46]. The regulation of serum Ca^{++} is controlled by three potent calcitropic hormones: parathyroid hormone (PTH) secreted from the parathyroid gland, 1,25-$(OH)_2$ D_3, a metabolite of vitamin D produced in the kidney [4] and calcitonin, while calcitonin plays a valuable feedback relationship with hypercalcemia, or managing blood Ca^{++} concentrations after an intravenous calcium treatment, it has a lesser impact on calcium homeostasis [24].

Factors such as the production of milk, age and breed are predisposing cows to have the metabolic disturbance, since cows for producing more secreted calcium should have efficient metabolism to meet increased demand [18]. The great demand of calcium in early lactation to produce 10 liters of colostrum, cow losses 23g of calcium in a single milking (2.3 g/L) which is about nine times more present in the plasma compartment [39]. The calcium lost from the plasma compartment should be replaced by intestinal calcium absorbed and bone reabsorption. During the dry season these mechanisms are inactive and all cows undergo hypocalcemia in the first days after birth until the intestines and bones are adapted. The adaptation starts with increased PTH and 1,25-$(OH)_2D_3$ at the beginning of hypocalcemia. About 24 hours of stimulation of 1,25-$(OH)_2D_3$ is required for intestinal calcium transport increase significantly. Bone reabsorption (osteoclast recruitment and activation) is not increased until 48 hours after the stimulation of PTH. When these compensatory mechanisms are prolonged, clinical hypocalcaemia or milk fever develops. Consequently, most cows with clinical hypocalcaemia have higher levels of PTH and 1,25-$(OH)_2D_3$ [47].

Mechanisms that may explain the detrimental effects of hypocalcemia include impaired energy balance, which is reflected in higher serum NEFA concentrations [3] and direct impairment of immune cell responses to an activating stimulus [5]. According to Iggo [48] Hypocalcaemia affects muscular contraction mainly in three ways. Firstly, calcium has a membrane stabilizing effect on the peripheral nerves. Hyperesthesia and mild tetany seen in early stages of milk fever are due to lack of nerve cell membrane stabilization. Secondly, calcium is required for the release of acetylcholine at the neuromuscular junction. The inability to release acetylcholine, due to hypocalcaemia causes paralysis by blocking the transmission of nerve impulse to the muscle fibers. Thirdly, calcium is directly required by muscle cells for contraction. Paralysis of various muscle types results in the clinical signs of parturient paresis [9]. Currently it is known that the pathogenesis of the disease is much more associated with the action of PTH on cells responsible for demineralization (osteoclasts), cells of the intestine responsible for absorption and kidney cells responsible for the reabsorption of calcium in the tubules [18].

Clinical Signs: Goff [4] showed that many cases of milk fever do not externalize the clinical signs in animals. Hypocalcaemia can be clinical or subclinical based on whether an animal may or may not show clinical signs. Clinical milk fever (hypocalcaemia) is the most severe hypocalcaemia results in a cow that is unable to rise (from lying to stand position) and is the most easily recognized form of hypocalcaemia with blood Ca^{++} concentration less than 5 mg/dl. Subclinical hypocalcaemia results in less severe disturbances in blood Ca^{++} and does not have any outward signs of milk fever. During subclinical hypocalcaemia, blood Ca^{++} concentration ranges between 5.5 and 8.0 mg/dl. Clinical MF has very serious economic point of view because if not rapidly controlled may lead to loss of the affected animal; on the other hand, subclinical hypocalcaemia assumes a more insidious role leading to loss of production and fertility. Subclinical hypocalcaemia in which concentrations of calcium in the blood does not decline as severely affects about 50% of lactating dairy

cows. According to Oetzel [7], animals that are supplemented with minerals prior to calving have reduced risk of milk fever and the hypocalcaemia percentage of cows is reduced to about 15 to 25%. He also stated that based on the degree of hypocalcaemia and time of occurrence the clinical sign of milk fever in dairy cattle around calving can be divided into three stages;

Stage I: Stage I milk fever is early signs without recumbency. It may go unnoticed because its signs are subtle and transient. Affected cattle may appear excitable, nervous, or weak. Some may shift their weight frequently and shuffle their hind feet.

Stage II (Sternal Recumbency): Cows in Stage II milk fever are down but not flat out on their side. They exhibit moderate to severe depression, partial paralysis and typically lie with their head turned into their flank [7]. The clinical signs of stage II milk fever can last from 1 to 12 hours. This is frequently seen with lateral kink or S-shape neck curvature in which the cow tends to lie with her head tucked into her flank. Her temperature is subnormal, her muzzle dry, coldness of skin and extremities. The heart rate will be rapid exceeding 100 beats per minute, gastrointestinal atony predisposes to constipation and mild bloating; In addition the animal exhibits incoordination when walking [9].

Stage III (Lateral Recumbency): Stage III hypocalcemic cows are flat out on their side, completely paralyzed, typically bloated and are severely depressed (to the point of coma). They will die within a few hours without treatment [7]. Generally this stage is characterized by inability to stand and a progressive loss of consciousness leading to coma. There is a marked fall in temperature and heart sounds become nearly inaudible and the heart rate increases to 120 beats per minute or more. Cows will not survive for more than a few hours without treatment in this stage [6].

Diagnosis and Treatment

Diagnosis: Diagnosis of milk fever can be based on the history of the animal at birth, clinical signs, age of dam and response to intravenous calcium borogluconate solution. The occurrence of paresis and depression of consciousness in cows that have recently given birth to young are diagnostic signs for the disease. The diagnosis is confirmed by laboratory examination of the blood and rapid characteristic response to treatment with calcium borogluconate. The most notable changes occurring in the blood are a decrease in blood calcium and blood phosphorus levels and an increase in blood magnesium levels [6]. Cows with serum calcium lower than 7.5 mg/dl are as considered as hypocalcaemic. Animals with serum calcium level of 5.5 to 7.5 mg/dl show sign of stage I hypocalcaemia. Stage II hypocalcaemia seen with calcium levels of 3.5 to 6.5 mg/dl and stage III seen when calcium concentration falls to as low as 2 mg/dl. Prolonged recumbency results in ischemic muscle necrosis and increases in the serum muscle enzymes CPK and AST. The value CPK normally ranges between 105 to 409 IU/L, a value greater than 1000 IU/L indicates severe muscle damage from being down and AST levels over 500 IU/L indicates severe muscle damage [38].

Typical signs and indications that differentiate milk fever from hypoglycemia includes in hypocalcaemia there is rapid progression of the disease with death after 6 to 12 hours, but in hypoglycemia there is slow progression of the disease with death 5 to 7 days. Elevation of the chin (star gazing posture) with slow progression to recumbency over 2 to 3 days after onset of initial signs is seen in hypoglycemia but during hypocalcaemia rapid recumbency over 3 to 4 hours with sternal recumbency. In response to treatment, in hypoglycemia there is no response to hypocalcaemia treatment dose rates and usually poor and slow doses of glucose or energy. However, during hypocalcaemia response is rapid and good recovery is seen after injection of treatment doses of commercial calcium doses [9].

On the other hand, during peripartum period there are common metabolic and non-infectious diseases those results in the same symptom with milk fever which are commonly known as Downer cow's syndrome (an animal that is unable to rise to a standing position). They can be divided into 3 categories: (a) cows that are unresponsive to standard hypocalcaemic or milk fever therapy and do not exhibit other complications but remain alert; (b) alert recumbent animals that have traumatic musculoskeletal and nerve problems; (c) and recumbent animals that are affected with systemic diseases related to metabolic, toxic, alimentary, or neurologic conditions [42].

Treatment: The treatment should be carried out as quickly as possible. Administration of calcium borogluconate by oral route is the best approach to hypocalcemia cows that are still standing, but the intravenous (IV) calcium administration is not recommended for the treatment of cows that are still

standing, since this application if not done correctly can result in dead animal by cardiac complication. For cows in stage II and III of milk fever should be treated immediately with a slow IV administration of 500 ml of a solution of calcium borogluconate 23%. This gives 10.8g of elemental calcium, which is more than sufficient to correct the deficit whole cow's calcium (about 4 to 6 grams) [7]. In general early intravenous calcium borogluconate is the treatment of choice for severely affected patients. The solution must be given slowly because rapid calcium infusion may result in cardiac arrest. Concurrent use of subcutaneous calcium borogluconate may prevent recurrence, by slow release of biologically available calcium from the tissues into the bloodstream [9].

The prognosis is excellent if cows are treated early and properly. As the symptoms worsen so does the prognosis. Cows down for more than 48 hours may develop muscle inflammation and never be able to stand [9]. The prognosis of milk fever depends on the stage of the condition; stage 1 is less severe and the animal is able to stand but staggering. In stage 2, the cow is recumbent on sterna recumbency, while in stage 3, there is progressive muscular paralysis that may lead to coma and death if prolonged [50].

Prevention and Control: Multiple strategies have been utilized to prevent hypocalcemia and mobilize Ca^{++} in dairy cows through nutritional management including: feeding anionic salts, low calcium ion diets, low potassium forages and vitamin D supplementation [51]. Most of the literatures suggest that when the incidence of milk fever increases above 10% in their third or latter lactation, considerations should be given to a specific control program [8]. It has been proposed that a specific control program is relevant when the incidence of milk fever increases to above 10% among high-risk cows, i.e. cows entering third or later lactations

Thilsing-Hansen [52] indicated as several principles for milk fever control. However, due to a variety of reasons only four of these are widely used on commercial dairy farms today. These are:

- Oral drenching around calving with a supplement of easily absorbed calcium.
- The feeding of acidifying rations by anionic salt supplementation during the last weeks of pregnancy.
- Feeding low calcium rations during the last weeks of pregnancy.
- Prepartum administration of vitamin D, vitamin D metabolites and analogues.

Other possible but less specific control measures for the prevention of milk fever include management practices such as: Dietary magnesium level control peripartum, Body condition control, controlling dietary carbohydrate intake peripartum, Shortening of the dry period, Prepartum milking and reduced milking in early lactation [52].

Body Condition Score (BCS) Management: Achieving the correct BCS at calving and drying-off is critical for the prevention of milk fever. It has been reported that dairy cows that are over-conditioned at calving are up to four times more likely to develop milk fever [40]. It is unclear why this is the case, but several hypotheses have been suggested to explain this effect. Firstly, it has been suggested that dairy cows with higher BCS at calving have a higher Ca^{++} output in milk, making them more prone to milk fever. Secondly, it is widely appreciated that over-conditioned dairy cattle have a reduced feed intake relative to thinner cows, in the last week or ten days pre-calving. This may reduce their intake of Ca and Mg to levels which predispose them to the development of hypocalcaemia. Finally, it has been shown, in human patients suffering from non-alcoholic fatty liver disease that serum concentrations of 25-OH-vitamin-D3 are lower than healthy controls. Thus one wonders if over-conditioned dairy cows are capable of producing sufficient amounts of the active form of vitamin-D3 to prevent hypocalcaemia [9]

Magnesium Supplementation: Ensuring adequate magnesium supplementation is vital for the prevention of milk fever. Because magnesium (Mg) plays a very important role in Ca metabolism, as it is a key intermediate in the resorbtion of Ca from bone by parathyroid hormone. In a recent review, increasing Mg supplementation was found to have the greatest influence amongst dietary strategies for the prevention of milk fever [53]. Therefore, dietary Mg concentration for pregnantdairy cattle should be in the region of 0.4% of dry matter (DM) [27, 52].

Dietary Cation Anion Balance (DCAB) and Potassium: One common prevention strategy is supplementing anionic salts to reduce diet cation-anion difference [54]. The goal of this type of supplementation is to reduce absorbable cations (Na^+ and K^+), while increasing available anions (Cl^- and SO_4^{2-}) in the diet [4]. The concept of dietary cation-anion balance [(Na + K) – (Cl + S)] has focused attention on the level of potassium (K) that is contained in the feed of pre-calving dairy cattle.

It is now widely accepted that the homeostatic mechanisms that result in milk fever prevention work more efficiently when DCAB is negative. The most common strategy employed to achieve this negative DCAB is the addition of anionic salts to the diet of pre-calving cattle [27]. He has stated also that it is very difficult to control hypocalcaemia if total ration of K is >1.8%. Since high potassium diets usually induce milk fever, pre-calving potassium levels should be kept as low as possible. As dry fodder contains more potassium, feeding of dairy animals with higher amount of dry fodder should be discouraged to prevent milk fever. Inclusion of silage and succulent / green fodder as a major portion of the dry cow's diet is essential, as it has lower potassium content [55].

Sakha *et al*. [56] in study to determine the effects of varying dietary cation-anion differences (DCAD) in prepartum period on milk fever, subclinical hypocalcemia and negative energy balance in dairy cows showed that use of anionic diets during three weeks before calving can protect dairy cows from clinical and subclinical hypocalcemia by increasing the calcium level in serum. To reduce the postpartum negative energy balance, replacement of anionic diet by cationic diet soon after calving is suggested.

Calcium Restriction and Milk Fever Prevention: One of the classical strategies often proposed for milk fever prevention is the restriction of calcium rich feed intake pre-calving. This has the effect of making sure that parathyroid hormone and the active form of vitamin-D3 are in higher concentrations in circulation on the day of parturition when Ca export in colostrums increases suddenly. This strategy does work and recent data where Ca binders were used to block Ca^{++} uptake from the gut have shown a reduced milk fever incidence on several farms in New Zealand [57]. However, in practical situations it is necessary to achieve a Ca^{++} intake of 30g per day or less for this strategy to work.

Vitamin D Supplementation: A practice by some farms is supplementing high amounts of vitamin D to prepartum dry cows either in the feed or parenterally. Supplementation requires that up to 10 million IU of vitamin D must be injected or fed daily for 10-14 days before calving. These vitamin D doses pharmacologically increased intestinal Ca^{++} absorption and sometimes prevented milk fever [4].

Economic Consequences of Milk Fever: Economically, milk fever is an important disease that can reduce dairy cow's productive life by 3.4 years. Mostly in untreated cases of milk fever, 60-70% cows die [34]. Economic losses due to clinical cases of milk fever are substantial and include losses from deaths (~8% of affected cows), premature culling (~12% of affected cows), treatment costs and decreased milk production in the subsequent lactation [1]. In addition, each episode of clinical milk fever increases the risk for other parturient diseases such as retained placenta, ketosis, displaced abomasums and environmental mastitis [7]. More recently it has been reported that both milk fever and subclinical hypocalcaemia exacerbate the level of immuno-suppression experienced by peri-parturient dairy cattle [5].

Milk fever in dairy production reduces the efficiency with which inputs are converted into out puts (milk yield and fertility) and hence result in decreased overall productivity. There are costs directly associated with the disease including the cost of veterinary treatments and the herdsman's time spent dealing with the affected animals. The indirect cost of the milk fever is due to increased risk to associated health problems, increased risk of calving problems and the possible risk of fatality [9]. Generally, it may lead to reduced feed intake, poor rumen and intestine motility, increased risk for displaced abomasum, reduced milk yield, increased susceptibility to infectious diseases and increased risk for early lactation removal from the herd [4, 23]

Milk Fever, Dystocia and Uterine Prolapse: It has been recognized for some time that milk fever and subclinical hypocalcaemia reduce the ability of the transition cow to effect smooth and skeletal muscle contraction [5]. Loss of uterine muscle tone due to hypocalcemia in cows suffering from milk fever is a major cause of uterine prolapse. Cows with milk fever are developing dystocia 6 times more than that of normal cows. This is because of a reduced ability of smooth and skeletal muscle contraction causes for cow's long period in labour, which predisposes to dystocia [9]. In some cases the increased odds of dystocia were reported as six times that of normal cows with other reports indicating an increased likelihood of around 2.5 to 3 times that of normal cows [58].

Milk Fever and Fertility: White-ford and Sheldon [59] reported that cows with clinical hypocalcaemia had a greater diameter of the gravid uterine horn and non-gravid uterine horn between 15 and 45 days post-partum (indicative of slower uterine involution) and a significantly reduced likelihood of having a corpus luteum (indicative of ovulation since parturition) than normal cows. These results in reduced fertility in dairy cows due to its effect on uterine muscle function, slower uterine

involution and reduced blood flow to the ovaries. There are also indirect effects of milk fever on fertility, which is mediated through dystocia, endometritis and retained placenta [60].

Milk Fever and Mastitis: Both milk fever and subclinical hypocalcaemia cause an increase in the normal cortisol response at parturition. Cortisol is believed to be an important component of the suppressed immunity experienced by periparturient dairy cattle. Furthermore, It has been demonstrated that hypocalcaemia is associated with reduced intracellular Ca stores in peripheral blood mononuclear cells and that this exacerbates periparturient immuno-suppression [5]. Therefore, the epidemiological association found between milk fever and the occurrence of mastitis is easily supported by several potential biological mechanisms, some of which have been reported as being more relevant in periparturient dairy cows. Cows that have suffered from clinical milk fever are 8 times more likely to develop mastitis than normal cows. This phenomenon is mainly due to a reduction in smooth muscle function at the teat sphincter and hence an easy routine for infection after milking and an exacerbated suppression of immunity in milk fever cows when compared with normal cows. Cortisol is an important component of the suppressed immunity experienced by periparturient dairy cattle since milk fever cause an increase in the normal cortisol response at parturition [27].

Milk Fever and GIT Function: There is a reduction in the motility of rumen and abomasum in clinically hypocalcaemic cows. This reduction in ruminal and abomasal motility will likely cause a reduction in feed intake [59]. Furthermore, Goff [62] has indicated that low plasma Ca^{++} concentration around calving will result in reduced motility and strength of abomasal contractions and hence abomasal atony and distension of the abomasum. Therefore, milk fever has been implicated as a predisposing factor for many other transition cow disorders. It is difficult to think of any other factor that is associated with so many economically important veterinary complications of dairy cattle, particularly one that seems to sit as high as milk fever does in the cascade of possible events that cause problems for transition dairy cows [26].

Retained Placenta: Several studies indicated that increased risk for the occurrence of retained placenta following milk fever, with milk fever cows being up to three times more likely to experience retained placenta than normal cows [33]. The direct effect of milk fever on the occurrence of retained placenta (excluding any interaction for the effect of milk fever on dystocia) has been reported to double the odds of retained placenta occurring [26]. Furthermore there is also a large indirect effect of milk fever on retained placenta, as milk fever is a risk factor for dystocia and dystocia is a risk factor for retained placenta [58]. Melendez *et al*. [63] have reported a significantly lower plasma Ca concentration in cows with retained foetal membranes in comparison to cows with normal placental expulsion. The point should also be made that, in this case, the hypocalcaemia experienced by cows with retained foetal membranes was subclinical not clinical. There is, therefore, a clear link between milk fever and the occurrence of retained placenta.

Endometritis: The link between milk fever and periparturient immuno-suppression, provide a strong basis for the suggested association between milk fever and endometritis [5]. In support of this, Whiteford and Sheldon [59] observed a significantly higher incidence rate of endometritis in UK cows that suffered clinical hypocalcaemia in comparison to normocalcaemic cows. Therefore, there are several reports in the literature linking milk fever with complications occurring at or around parturition. This fact simply confirms what most people working with dairy cattle have probably already appreciated. However, it is very likely that many farm animal veterinarians deal with ongoing problems of retained placenta and poor fertility without considering milk fever and subclinical hypocalcaemia as possible predisposing factors [26].

CONCLUSION AND RECOMMONDITIONS

Metabolic diseases are of great economic impact; it usually affects the animals about to reach their maximum potential production. Dietary deficiencies as a result of poor ration formulation is the most probable cause of metabolic disorder. Milk fever or parturient paresis is a common metabolic disturbance in dairy cows resulting from hypocalcaemia that occurs in older, third to sixth lactation, high producing dairy cows that are near calving or have recently calved. It is mainly characterized by progressive muscle weakness and depression that progresses into coma if not treated promptly. Calving causes a high volume of milk production and with it, a high demand for calcium from the cow's body. If the body is unable to respond quickly to this demand,

the cow develops hypocalcaemia. Hypocalcaemic cows will begin trembling and will no longer be able to stand. Subsequently the cow becomes recumbent, first in the sternal position and then laterally. Parturient paresis is favorable to early treatment with intravenous calcium supplementation. Economically, it reduces milk yield and fertility. There are also losses due to cost of treatment, herdsman's time spent for dealing the diseased animal and increase the risk of associated health problems. As with most illnesses, prevention is the key. Dietary calcium levels must be low in the weeks leading up to calving. Management practices like body condition score management and shortening the dry period are also critical for the prevention of the disease.

Based on the above conclusion the following recommendations are forwarded:

- Owners should avoid over conditioning of cows around calving by either reducing the energy concentration of the ration or restricting the intake.
- A well monitored feeding strategy should have to be implemented for dairy cattle under challenge especially during the prepartum period.
- Education of dairy farmers should be taken into consideration to make frequent observations of cows prone to milk fever from 48 hours before to 72 hours after parturition for evidence of milk fever.
- Farmers should be enlightened about proper ration formulations and provision of mineral supplements to their dairy cows.
- At calving, the cow should receive an oral dose of a calcium salt in a gel, as set out later, followed by a diet with high calcium content.
- The owners of dairy farms and private animal owners should be aware of the disease and prepare themselves how to manage peripartum intake of calcium.
- Further study should be conducted on the epidemiology of the disease and its economic impact in dairy farms.

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