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Milk Fever common Meatabolic Disease of Livestock- A Review

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Abstract:

Now a day's metabolic disorder is a major cause of concern in high yielding livestock and poultry. Due to high productivity and environmental concern metabolic disorder are very common in lactating dairy animals and other livestock, so analytical approach with accurate diagnosis is very important for quick diagnosis and as per diagnosis treatment of livestock which leads to better health and productivity from livestock. Out of many metabolic disorder, milk fever is one of the most important disorder which not only reduces the production performance of dairy animals but also create problems for other metabolic disease occurrence and infertility or repeat breeding problem in future. So proper feeding management is planned during advance pregnancy to reduce risk of milk fever. Metabolic profiling tests, which are using specific parameters known to be responsive to dietary intake, can be used to complement dietary evaluation of current feeding programme adequacy or a response to a feeding programme change.

Introduction

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. Compounding the problem are the ever-changing nutritional needs of the cow, her lactation/dry period needs, feed quality changes, and the producer's personal management practices. Herd health programs, as recommended by the veterinarian, must include a way to avoid metabolic disorders and prevent or control infectious disease. Frequently when metabolic disease increases, opportunistic infectious disease also increases.

Stress from metabolic problems may decrease the cow's resistance and compromise immune system function. If these diseases are not prevented, very costly consequences in the

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reproductive, milk production and human resource areas will occur. In some herds there have been death losses of up to 20-25 percent reported over a year's time, in addition to other related costs, as a result of these disease implications.

The production diseases of the dairy cow are a manifestation of the cow's inability to cope with the metabolic demands of high production, and they continue to be a cause of economic loss to the dairy industry and an animal welfare concern (Mulligan and Doherty, 2008). According to Radostits *et al.* (2000) the production diseases comprised of diseases associated with imbalances between the rate of input of essential dietary nutrients and the output of the production such as milk fever, ketosis, hypomagnesaemia and mastitis etc.

Milk Fever (Synoynms: Parturient paresis, Milk fever, Parturient apoplexy, and Aclampsia)

This metabolic disorder usually occurs just after parturition and is due to a failure in calcium homeostatic mechanism, which is severely stressed by onset of milk synthesis. The disease is precipitated by decrease in blood calcium from normal levels of 8.5-11mg/dl to less than 5 mg/dl it is often accompanied by a paralysis and is fatal unless treated.

Milk fever is an important production disease occurring most commonly in adult cows within 48-72 hours after parturition, which is characterized clinically by hypocalcemia, general muscular weakness, circulatory collapse and depression of consciousness (Radostits *et al.*, 2000). The name milk fever is misleading since the cow does not have a fever. This disease has been known by a number of terms including parturient paresis, milk fever, parturient apoplexy, eclampsia, and paresis peurperalis. The term "Parturient hypocalcemia" (PH) is to refer to the classic clinical syndrome. When milk fever is results due to imbalance in blood Ca, P and Mg levels, known as "Milk fever complex) (Sharma *et al.*, 2005). Generally the milk fever is sporadic but on individual farms the incidence may rarely reach 25 to 30% of susceptible cows. The incidence of milk fever is higher in dairy cows than beef cows and increases with age and yield. Milk fever undoubtedly increased in incidence during the 1970s and 1980s when levels of around 9 per cent per annum were being reported. Goff (2006) recently reported that incidence of milk fever in US was 5.9% in 1995 and 5.2% in 2001. The incidence of milk fever in organic cows has been reported as being low (Weller and Cooper, 1996). One of the main reasons for this may be the generally lower milk yield on organic dairy farms (Pryce *et al.*, 1999). The disease does appear to be more common when dry cows are fed grass rather than conserved fodder. Milk fever is a common

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cause of death and is probably the most common cause of apparent sudden death in dairy cows. It is also a common cause of dystokia and hence stillborn calves. Hypocalcemia or low blood Ca (not just milk fever) impairs abomasum contraction leading to more metabolic disorders. Hypocalcemia cause secretion of cortisol which impairs the immune system of the fresh cow (Wang *et al.,* 1991). Cows developing milk fever have higher plasma cortisol concentrations than do non-milk fever cows (Goff *et al.*, 1989). Muscle tone decreases in most body systems, particularly in the cardiovascular, reproductive, and digestive systems, and possibly in the mammary system. Blood flow to the extremities is reduced, causing the characteristic cold ears of a cow suffering from milk fever. Jonsson and Daniel (1997) found that there was also a significant reduction in blood flow to the ovaries of sheep with induced hypocalcemia. This would result in suppressed ovarian function, including progesterone synthesis and follicular development. Unfortunately, the highest incidence of hypocalcemia is during the first 6 weeks after calving, a critical time for resumption of ovarian activity. Milk fever cows also exhibit a greater decline in feed intake after calving than non-milk fever cows (Goff and Horst, 1997), exacerbating the negative energy balance commonly observed in early lactation. In addition, hypocalcemia prevents secretion of insulin (Littledike *et al.*, 1970), preventing tissue uptake of glucose which would exacerbate lipid mobilization at calving, increasing the risk of ketosis.

Etiology

The onset of lactation places such a large demand on the calcium homeostatic mechanisms of the body that most cows develop some degree of hypocalcemia at calving. In some cases, plasma calcium concentrations become too low to support nerve and muscle function, resulting in parturient paresis or milk fever. Milk fever occurs when calcium leaves the blood to support milk production faster than Ca can be put back into the blood from the diet, skeletal Ca stores, and renal conservation of calcium. The onset of lactation places such a large demand on the calcium homeostatic mechanisms of the body that most cows develop some degree of hypocalcaemia at calving (Goff, *et al.*, 1987; Horst *et al.*, 1994). The entire extracellular pool will have only 8 to 9g Ca. In some cases, plasma calcium concentrations become too low to support nerve and muscle function, resulting in parturient paresis or milk fever. A cow producing 10 kg of colostrum (2.3g of Ca/kg) will loss 23g of Ca in a single milking. This is about 9 times as much Ca as that present in the entire plasma Ca pool of the

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cow. Normally extracellular Ca concentration is around 10,000 greater than intracellular resting Ca concentration. A 50% decline in extracellular ionised Ca concentration, typical of the cow with milk fever. This hypocalcemia is caused by an imbalance between Ca output in the colostrum and influx of Ca to the extracellular pool from intestine and bone.

In order to prevent blood calcium from decreasing, the cow must replace calcium lost to milk by withdrawing calcium from bone or by increasing the efficient absorption of dietary calcium. Various physiological factor and hormonal regulation are involved in milk fever as explained:

1. Plasma Ca concentration is under the control of parathyroid hormone, calcitonin, and the metabolites of vitamin D (Goff *et al.*, 1995). Bone calcium mobilization is regulated by parathyroid hormone (PTH) produced by the parathyroid glands. Whenever there is a drop in blood calcium, blood PTH levels increase dramatically. Renal tubular reabsorption of Ca is also enhanced by PTH. However, the total amount of Ca that can be recovered by reducing urinary Ca excretion is relatively small.
2. A second hormone, 1, 25-dihydroxyvitamin D, is required to stimulate the intestine to efficiently absorb dietary calcium. This hormone is made within the kidney from vitamin D in response to an increase in blood PTH (Goff, 2006). Milk fever occurs when cattle do not remove enough Ca from their bones and the diet to replace Ca lost to milk. This occurs because a key hormone involved in Ca metabolism, parathyroid hormone, acts only poorly on bone or kidney tissues when the blood pH is high (Goff and Horst, 1997). Blood pH of cattle is often alkaline because forage K is often excessively high.
3. Oestrogens also inhibit calcium mobilization and as oestrogen levels rise at parturition this will have a negative effect on the adaptation process to maintain calcium levels. Milk fever does occasionally occur during lactation, usually in association with oestrus. This again would be due to the inhibitory effect of oestrogens.

In conclusion, milk fever is caused due to disturbance in Ca homeostasis. Calcium homeostatic mechanism is influenced by mainly 3 factors- a) excessive loss of Ca++ in the colostrums beyond the capacity of absorption from intestine, b) impairment of absorption of

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Ca++ from intestine at parturition, and c) mobilization of Ca++ from storage in skeleton may not be sufficiently rapid to maintain normal serum level (Sharma *et al.*, 2006).

Clinical signs

The main clinical manifestations are divided into three stages.

A).First stage or Stage of excitement:

- Anorexia (decreased appetite)
- Nervousness or hypersensitivity
- Mixed excitement or tetany without recumbency
- Weakness or weight shifting
- Stiffness of hind legs
- Rapid heart rate
- Rectal temperature is usually normal or above normal (>39^0 C)

B**). Second stage or Stage of sternal recumbency:**

- Sternal recumbency comprising down on chest and drowsiness
- Characteristic "S" shaped posture- sitting with lateral kink in neck or head turned to lateral flank.
- Depression
- Fine muscle tremors
- Rapid heart rate with decreased intensity of heart sounds
- Cold extremities
- Decreased rectal temperature (35.6 to 37.8 C)
- Decreased gastrointestinal activity
- Pupils dilated and unresponsive to light

C).Third stage or Stage of lateral recumbency:

- Lateral recumbency, comprising of almost comatose condition, progressing to loss of consciousness
- Severe bloat
- Flaccid muscles
- Profound gastrointestinal atony

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- Rapid heart rate
- Impalpable pulse and almost inaudible heart sounds.

Diagnosis

1. **History taking**
   - Occurs in mature cows usually 5-9 years old, within 72 hours after parturition.
   - Occurs in highest milk producing period.
   - Higher incidence in the Jersey breed.
2. **Clinical examination**

Blood calcium levels in healthy and milk fever cows-

Normal Lactating cow	8.4-10.2 mg/dl
Normal at calving	6.8-8.6 mg/dl
Slight milk fever	4.9-7.5 mg/dl
Moderate milk fever	4.2-6.8 mg/dl
Severe milk fever	3.5-5.7 mg/dl

Treatment

In 1806, Price recommended the use of hot packs and blanketing to cause the affected cow to sweat profusely (Horst *et al.*, 1997). In 1814, Clater recommended prepartum bleeding (4 to 5 L/d for 8 to 10 d) (Horst *et al.*, 1997). Other treatments mentioned were pouring cold water on the head or rubbing the legs with cayenne pepper and alcohol. As summarized by Hibbs (1950), the first successful treatment for milk fever was proposed in 1897 when Schmidt suggested that milk fever was caused by a viral infection of the udder. To destroy the infection, he suggested that potassium iodide be injected into the udders of "infected" cows. This treatment reduced the mortality rate to 60 to 70%. Marshak (1956) later realized that these udder insufflations techniques prevented milk formation and, therefore, prevented the loss of Ca from plasma (Horst *et al.*, 1997). Treatment during the first stage of the diseases, before the cow is recumbent, is the ideal situation (Radostits *et al.*, 2000).

The treatment of choice for milk fever is slow, intravenous infusion of 8-12 g of calcium as soon as possible after the onset of clinical signs. Heart rate should be closely monitored for toxic effects. Calcium borogluconate containing products with or without

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added magnesium and phosphorus are mostly used in the India: usually 400 ml of 40% calcium borogluconate. For cattle 400-800 ml of 25% solution is the usual dose. Intravenous therapy to elevate calcium levels quickly is important to avoid downer cow syndrome, often seen when cows are treated subcutaneously. Subcutaneous injection may be useful for maintaining blood levels. Solution containing dextrose should not be given subcutaneously because of abscess formation.

- During cold weather the solution should be warmed to body temperature. Warming the calcium solution seems to reduce toxic effects also.
- Approximately 85% of cases will respond to one treatment, in many cases cows recumbent from milk fever will rise within 10 minutes of treatment and others will get up 2-4 hours later.

It is essential to sit the cow in a sternal recumbency position and turn her so that she is lying on the side opposite to the one on which she was found. She should be turned to lie on the opposite side every two hours. Provide shelter or cover with rugs in exposed situations. If a response is not evident by 5-6 hours, the diagnosis should be reassessed, and, if necessary, a further intravenous infusion of 8-12 g of calcium administered. Relapses of milk fever occur in 25% of cases treated. Twelve hours after treatment, all calcium administered, whether by the intravenous or subcutaneous route, has been eliminated from the body. The treatment is only a holding operation until the normal adaptation process is in full operation. Cases of relapse usually occur at 18-24 hour intervals and should be treated in the same way. Removal of the calf and advice not to milk the cow for 24 hours except to check for the presence of mastitis may help to prevent relapses (Eddy, 1992). Massive dose of vitamin D (20-30 million unit daily) in feed in 5-7 days before parturition.

If hypomagnesaemia is a complicating factor of milk fever then the addition of the magnesium may be helpful. However, in cases of clinical hypomagnesaemia more than 1.0 g of magnesium will be required.

The presence of the phosphorus has no doubt been added because of the finding that the blood levels of phosphorus in cases of milk fever are also depressed. However, it has been shown that plasma phosphorus levels return to normal within a few hours after successful treatment with calcium borogluconate (CBG) without the addition of phosphorus.

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Administration of ammonium chloride (@ 50-100 g/day, orally) produce acidosis and enhance blood calcium mobilization and ionization.

Prevention and Control

Prevention of milk fever is economically important to the dairy farmer because of reduced production loss, death loss, and veterinary costs associated with clinical cases of milk fever. In order to understand how to prevent this condition, one must understand why it becomes a problem. The onset of milk production drains on the animal's blood calcium levels and she is unable to replace this calcium. The body loses its ability to mobilize reserves of calcium in bone and absorb calcium from the gastrointestinal tract. As a result, hypocalcemia affects the cow's muscle contractions and rumen motility. The key to prevention of milk fever is management of a close-up dry cow or management during late pregnancy. The traditional way of preventing milk fever is to limit Ca intake during the dry period. This will allow the dry cow to adapt to Ca deficiency and make her better able to respond to milk Ca demand in early lactation.

Feeding high Ca forages (alfalfa hay and silage) should be restricted during the dry period. Replacing part or all of the alfalfa forages with grass hay or silage, cuts Ca consumption during the dry period and helps prevent milk fever. In cows fed limited amount of Ca and P during the dry period, bone and small intestine respond better to stimulation from parathyroid hormone and active vitamin D.

- Restricted Ca feeding to less than 50 g per day (less than 0.5% of the diet) during dry period.
- Phosphorus intake to less than 45 g per day (at 0.35% of the diet) during late pregnancy.

An important determinant of the risk for milk fever is the acid-base status of the cow at the time of parturition. Metabolic alkalosis predisposes cows to milk fever and sub clinical hypocalcemia. The traditional method of preventing milk fever in fresh dairy cows is to restrict dietary intake of Ca during the prepartum period. Cations have a positive charge like sodium (Na), potassium (K), calcium (Ca) and magnesium (Mg). Cations in the diet promote a more alkaline (higher blood pH) metabolic state which has been associated with an increased incidence of milk fever. Anions have a negative charge such as chloride (Cl), sulfur (S) and phosphorus (P). It has been discovered that milk fever can be effectively

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treated and/or prevented by feeding (dairy cows during the close up period (14 to 21 days pre-calving) a diet containing substantial amounts of negative ions (i.e. anionic salts) (Markandeya *et al.*, 2009).

Metabolic alkalosis impairs the physiologic activity of PTH and induces conformational changes in the PTH receptor, which prevents tight binding of PTH to its receptor. Anionic salts reduce the incidence of milk fever by increasing the mobilization of Ca from bones. They are helpful when there is a high incidence of milk fever or when it is difficult to control Ca consumption during the dry period. Anionic salts are effective in rations with high Ca levels (150 g per day). They should not be fed when Ca intake is low. Therefore it is very important to analyze feed ingredients especially forages, as book values on mineral content can be misleading. Urine pH is affected by changes in the cow's acid-base status and therefore, checking urine pH can help producers monitor the effectiveness of a ration containing anionic salts. It had been reported that addition of anionic salts reduced the incidence of clinical milk fever from 18.5% to 7.7% and the incidence of parturient hypocalcemia from 50.0% to 28.2%. When cations exceed anions in a solution the pH is increased and vice-versa. Blood pH is ultimately determines by the number of positive and negative charges entering the blood from the diet. The major cations present in feeds and the charge they carry are Na^{+}, K^{+}, Ca^{2+} and Mg^{2+}. The major anions and their charges found in feeds are Cl^{-}, S^{2-}, P^{3-}. The difference between the number of cation and anion particles absorbed from the diet determines the general acid-base balance of the body and therefore, the pH of the blood. The cation-anion difference of the diet is commonly described in terms of mEq/kg of just sodium, potassium, chloride and sulfate as follows:

Dietary Cation-Anion Difference (DCAD)= (mEq Na^{+} + mEq K^{+}) – (mEq Cl^{-} + mEq S^{2-})

This equation is useful, although it must be kept in mind that Ca, Mg and P, absorbed from the diet will also influence blood pH. Metabolic alkalosis is largely the result of a diet that supplies more cations (K, Na, Ca and Mg) than anions (Cl, SO4 and PO4) to the blood.

Under this though examine the animal after collecting the detail history. Clinical signs include early excitement and tetany, hypothermia, flaccidity pupil dilation, impalpable pulse, no rumen movement, soft heart sounds, fast heartbeats are fast (80-100 per minutes), decreased reflex, depression coma, bloated and death.

Following things to taken into account to prevent milk ferver:

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1. Feeding of prepatal diets low in calcium (no more than 100-125 gm/day) feeding of high calcium diets before calving is contraindicated and may increase incidence of milk fever. A natural excess of calcium in the diet may predispose cow to milk fever because it promoter dependence on gastrointestinal absorption and not skeletal mobilization. It is the efficiency of latter which governs cow's ability to maintain homeostasis.
2. Maintenance of appetite and the avoidance of alimentary tract stasis in late pregnancy appear to be important preventive measures calcium absorption.
3. Administration of large quantities of phosphate in ration should result in increased phosphate, and concurrently calcium excretion in urine.

So negative balance of calcium can be be expected to stimulate activity of parathyroid. Bode & Cora have made use this physiological mechanism.

Ca: P ratio	% of cows developed parturient paresis
6:1	30%
1:1	15%
1:3.3	No cases

4. But if negative balance of calcium is prolonged if may contribute to development of osteoporosis.

Calcium gel dosing - As drench @ 150 gm/day – 3 doses

1st dose - 24 hours before calving

2nd dose - 1-2 hours before calving

3rd dose - 10-14 hours after calving

5. Administration of Vitamin D and its metabolites and analogues oral dosing with 20 million units of vitamin D_2 per day for 5 days to cows immediately prior to calving greatly reduce the expected incidence of of parturient paresis.

Disadvantages: Exact date of calving is often difficult to determine.

a. Metastasic calcification may occur
b. 25-hydroxycholecalciferol – 8 mg I/m for 3-10 days before calving
c. 1,25 –Dehydrozy vitamin D_3 given in 200mg daily, orally, to calving cows reduces development of hypocalcaemia but not completely milk fever.

6. Increasing ration acidity by feeding mineral acids or ammonium chloride daily.

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Disease Control of Calcium/Phosphorus Imbalance:

The most important and critical time to adjust imbalances causing metabolic problems due to calcium/phosphorus is the month prior to calving.

Requirements include:

1. Limit precalving calcium intake. Feeding an excess tends to inhibit normal calcium mobilization from the bones.
2. Total calcium requirement for a 1,200-pound dry cow is approximately 40 gm/day. In general, try not to feed in excess of 0.40 percent calcium (percent of ration dry matter) to dry cows.
3. Nutrients fed to the cow should be generally low in calcium. For example, alfalfa contains approximately 6 grams of calcium per pound. The calcium intake could easily be in excess if alfalfa was the only feed.
4. If milk fever problems persist, limit total calcium to less than 60 grams per head per day. If herd problems of hypocalcemia continue on, reduce the precalving ration further to 20-25 gm per day.
5. Avoid feeding high phosphorus levels. Phosphorus requirement is 28-30 gm/day and should be maintained near this level. Try to feed approximately 0.24 percent phosphorus as a percentage of ration dry matter.
6. Keep pre-calving potassium levels as low as possible because high forage potassium levels may predispose cows to milk fever regardless of calcium intake. Forages lows in Potassium are usually low in calcium. If this is not practical, consult with a nutritionist about feeding anionic salts to dry cows.

Metabolic Profile Tests to detect Metabolic/Production Disease:

Metabolic profile test is the detection of low molecular weight metabolites and their intermediates from biofluids or tissues. It is used widely in many fields, such as pharmacology, toxicology, and diagnostics, and its use and technological development have increased rapidly (Zhang *et al.*, 2012). Clinical or sub clinical metabolic disease problems in dairy herds can be corroborated with metabolic profile testing. Metabolic profile testing of a herd to finding the prevalence of SARA, sub-clinical ketosis (SCK), parturient hypocalcaemia (clinical plus subclinical milk fever), displaced abomasum and etc. in early lactation or other times is useful in almost any dairy herd, and particularly if the herd is

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experiencing a high incidence of displaced abomasum or high removal rates of early lactation cows (Oetzel, 2004).

Usually the metabolic profile measures glucose, urea, albumin, cholesterol, beta-hydroxybutyric acid (BHBA) and non-esterified fatty acids (NEFA) as well as some minerals (Na^{+}, K^{+}, Cl^{-}, Ca^{2+}, Mg^{2+},P^{3-}). These parameters can help assess total protein and energy intake, the bal-ance between protein and energy, and the net energy balance. Utilising a metabolic profile also allows screening for production limiting nutrients (Lager & Jordan, 2012). Some problems may not be diagnosable from a metabolic profile alone; therefore it may be necessary to add other tests such as vitamin A and E, trace minerals, or routine chemistry panels (Anonymous, 2018).

Samples and Analysis of Metabolic Profile Tests Results:

Urine and blood serum or plasma are the most commonly used biofluids for metabolic-based studies for the simple reasons that they both contain hundreds to thousands of detectable metabolites and can be obtained non- or minimally invasively. A number of other fluids such as cerebrospinal fluid, bile, seminal fluid, amniotic fluid, synovial fluid, gut aspirate and saliva have also been studied (Bollard ME., *et al.* 2005). More recently, metabolic profiling of intact tissue and its lipid and aqueous metabolites extracts is gaining more importance for biomarker detection (Griffin JL., *et al*, 2007).

Serum is the required specimen for metabolic profiling and most of the trace mineral and vitamin testings. It is essential to collect blood and harvest serum appropriately and in a timely manner to avoid sample haemolysis and obtain consistent results. A significant delay in harvesting the serum from the clot can significantly change electrolyte results. It will also increase phosphorous, potassium, albumin and magnesium levels. In addition, haemolysis is a cause of misleadingly low blood glucose. Finally, haemolysis may contribute to unreliable non-esterified fatty acids (NEFA) and betahydroxybutyric acid (BHBA) results. If possible, blood samples should be centrifuged within 2–4 h, the sera separated and stored at –20 °C (–4 °F) until shipment (Anonymous, 2018).

After evaluation of samples, data must be statistically analysed via accurate data analysis method. The aims of data analysis in metabolic profiling will depend on the scientific objectives of the study which typically fall into one or more of the following categories. Firstly, one of aims is to reveal the relationships between groups of both samples and

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variables. For example, this could include clustering individuals, or detecting significant correlations between variables. A second aim could be to identify a significant difference between groups related to the effect of interest. Finally, and perhaps most importantly, metabolites responsible for these changes should be found out. There are several statistical methods for analysis of metabolic profile tests introduced by different scientists (Butler& Denham, 2000), also several metabolic profile analysis software packages are available (Davies, 1998). Statistical methods for analysis of metabolic profile test including principal components analysis, principal components regression, partial least squares, etc. are reviewed in details by De Iorio*et al*. (2008).

Finally, analysed results are compared to reference values. Different reference values of metabolic profile parameters for different breed, different production level, different ages, etc. of cows were repeatedly reported in different countries (Lager & Jordan, 2012; Anonymous,2018).

Conclusion:

Metabolic disease milk fever not only reduces production and hamper reproduction and fertility of animals and huse economic loss to the dairy farmers. The goal for good production is to prevent feeding management diseases, provide the cow with a clean, dry, comfortable environment, and good water sources to maximize the intake of a palatable, well-balanced ration that meets her present production needs. Proper feeding and other management during advance pregnancy and early lactation can reduce the milk fever in high yielding dairy cows.

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