For Vet Professionals only
Face2Vet
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Hypocalcaemia in Dairy Animals

The incidence of production disease in dairy cattle increases and is directly proportional to increase in milk production. The incidence rapidly increases during late periparturient period, peaks on the day of parturition, and then rapidly declines until 7th day of lactation (Fig-1).

This critical seven days window starting with parturition has a tremendous influence on morbidity, production, reproductive performance and mortality.

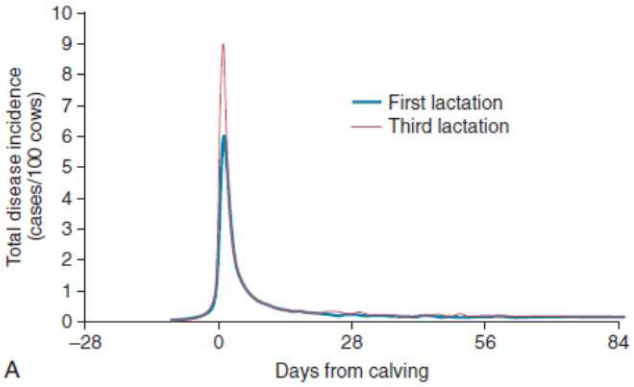

Fig-1: Incidence of production disease during peripartum period

Milk Fever (Parturient Paresis)

Milk fever is a condition caused by low blood calcium levels (hypocalcaemia) in cows. During the final months of pregnancy and early lactation, there is a considerable drain of cow's blood calcium levels to supply the developing calf and to build up milk for upcoming lactation. If the cow is unable to sustain the optimal blood calcium levels it suffers with Milk fever or Parturient Paresis.

- Normal concentration of Calcium in blood is about 9 to 12 mg/dl.
- Constant plasma concentrations of calcium are easily maintained during non-lactation. Daily need is typically less than 20 gm/day and during late gestation it is 10 gm/day.
- Loss of plasma calcium to milk takes place during lactation (up to 50 gm/day).
- 2 gm of calcium is drained out in 1 kg of milk and 2.3 gm of calcium in 1 kg of colostrum.

Predisposing Factors

There are several predisposing factors that influence the occurrence of milk fever:

1. Breed

More Susceptible Breeds: Jersey, Swedish Red and White and Norwegian Red breeds
Susceptible Breeds: Holstein–Friesian cows
Less Susceptible: Indigenous cows

The increased susceptibility and incidence is correlative with the following facts:

- Higher Calcium concentration in milk from Jersey compared with Holstein cows.
- Intestine of Jersey cows possesses 15% fewer receptors for 1, 25 dihydroxy-Vitamin D_3 than intestine of Holstein cows. Lower receptors result in loss of target tissue sensitivity to 1, 25 dihydroxy-Vitamin D_3.
- At parturition, plasma 1, 25 dihydroxy-vitamin D_3 is elevated as the animal becomes hypocalcemic.
- Normally, the elevated 1, 25 dihydroxy-vitamin D_3 would result in enhanced bone Calcium resorption and intestinal Calcium absorption.
- With reduced number of 1, 25 dihydroxy-vitamin D_3 receptors, the activation of genomic events by vitamin D_3 is less efficient, resulting in increased susceptibility to milk fever.
- It is also related to relatively high production level for a small breed *viz.* Jersey.

2. Age

- The risk of developing milk fever increases with age.
- It is rare in first and second calving and increases dramatically in third and greater lactations.
- Aging results in decline in ability to mobilize Calcium from bone stores and decline in active transport of Calcium in intestine, as well as impaired production of 1, 25 dihydroxy-vitamin D_3.
- The bones of heifers are still growing. Growing bones have large numbers of osteoclasts present, which can respond to parathyroid hormone more readily than bones of mature cows. Lower number of active osteoblasts in older cows means fewer cells to respond to PTH and mobilize bone Calcium.
- Collectively, these impairments result in an inability to respond to acute Calcium stress.

3. Parity

- Incidence of sub-clinical hypocalcemia (<8.0 mg plasma Calcium/dl) typically rises with increasing parity.
- Heifers are less susceptible because they have greater bone depletion/repletion activity and are more able to mobilize bone Calcium from their Calcium reserves than later parity cows.
- Additionally, later parity cows produce more colostrum and milk, making demand for Calcium greater.
- Complete milking in the first 48 hours after calving, as opposed to normal sucking by a calf, appears to be a precipitating factor.

4. Nutrition

Diet Causing Metabolic Alkalosis

- Metabolic alkalosis predisposes cows to milk fever and subclinical hypocalcaemia.
- Metabolic alkalosis reduces the response of the cow to parathyroid hormone (PTH).
- Parathyroid hormone (PTH) affects the surface of target bone and kidney cells.
- *In-vitro* studies suggest the conformation of PTH receptor is altered during metabolic alkalosis rendering tissues less sensitive to PTH (Fig-2).
- Lack of PTH responsiveness by bone tissue prevents effective utilization of bone calcium and prevents activation of osteoclastic bone resorption.
- Metabolic alkalosis is largely the result of a diet that supplies more cations (K, Na, Ca, and Mg) than anions (chloride (Cl), sulfate (SO_4) and phosphate (PO_4) to blood.
- Cows fed diets that are relatively high in potassium or sodium are in a relative state of metabolic alkalosis, which increases likelihood to develop milk fever.

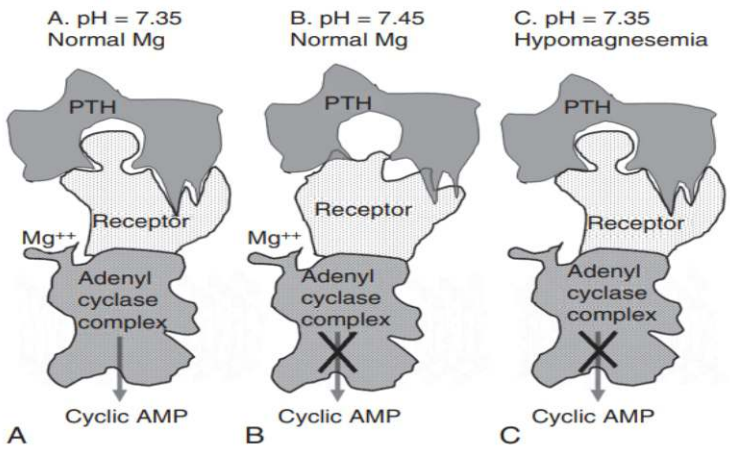

Fig-2: Effect of pH on PTH binding

A- Under normal conditions, PTH released in response to hypocalcemia interacts with its receptor, located on the surface of bone and kidney cells, in a lock and key fashion. This stimulates G proteins and adenylatecyclase (adenylatecyclase complex) resulting in production of cyclic AMP, which acts as a second messenger within the cytosol of target cells. This initiates mechanisms such as bone calcium (Ca) resorption and renal production of 1,25-dihydroxyvitamin D to restore blood Ca concentration to normal levels.

B- Alkalotic conditions induced by high-potassium diets induce a change in the shape of the PTH receptor protein so that it is less able to recognize and bind PTH, resulting in failure to activate the cell by producing cyclic AMP.

C- Magnesium is required for function of the adenylatecyclase complex. Hypomagnesemia reduces ability of PTH stimulated cells to produce cylic AMP, resulting in failure to activate the cell.

Calcium and Phosphorous during the Prepartum Period:

- Manipulation of dietary Calcium and Phosphorous is known to have dramatic effects on incidence of milk fever.
- High dietary Calcium fed to the cow before calving place the cow in such a state of positive Calcium balance that the parathyroid gland atrophies, rendering it too sluggish to adequately respond during onset of lactation, placing the cow into negative Ca balance.
- Studies have shown that feeding low Calcium diets or adjusting the ratio of dietary Calcium to Phosphorous to 2:1, lowered the incidence of milk fever.

Vitamin D Deficiency:

- Vitamin D deficiency causes reduction in production of 1, 25 dihydroxy-Vitamin D_3, resulting in increased risk for milk fever. Normal cows have plasma 1, 25 dihydroxy-Vitamin D_3 concentrations between 20 and 50ng/ml.
- Dietary factors can greatly influence the incidence of milk fever in dairy cows. Feeding a low calcium diet prepartum stimulates parathyroid hormone secretion and 1,25 dihydroxy-Vitamin D_3 production prior to parturition, activating calcium transport mechanism in bone and intestine that would be needed to adapt to lactational Calcium demand.

Hypomagnesemia

- Low blood magnesium can reduce PTH secretion from parathyroid glands and alter responsiveness of tissues to PTH.
- High dietary potassium reduces ruminal magnesium absorption in addition to causing metabolic alkalosis.
- Hypomagnesemia affects Ca metabolism in two ways.
    - Moderate hypomagnesemia (<1.6 mg/dl) interferes with PTH action on tissues.
    - Other is inadequate absorption of dietary Mg, is the second most common cause of milk fever in cows around the time of calving and is the most common cause of "midlactation milk fever" (downer cows that respond to intravenous Ca)
- In these syndromes blood Magnesium concentration falls slowly over time until such point that PTH secretion is impaired.
- It is at this point that blood Calcium concentration declines precipitously and clinical symptoms, such as tetany, become apparent.

Mechanism

- Initiation of lactation places the greatest stress on calcium homeostasis (Fig-3) and is associated with hypocalcemic parturient paresis among high producing dairy cows.
- On the day of parturition, dairy cows commonly produce ten litres or more colostrum containing 23 gm or more of Calcium that is six times as much as the extracellular pool contains.
- In order to prevent blood calcium from decreasing, the cow must replace calcium lost to milk by withdrawing calcium from bone or by increasing efficient absorption of dietary calcium.
- Plasma Calcium concentration is under control of parathyroid hormone, calcitonin and metabolites of Vitamin D.
- Most cows in first and second lactations adapt to Calcium stress by rapidly increasing intestinal absorption and bone Calcium resorption,

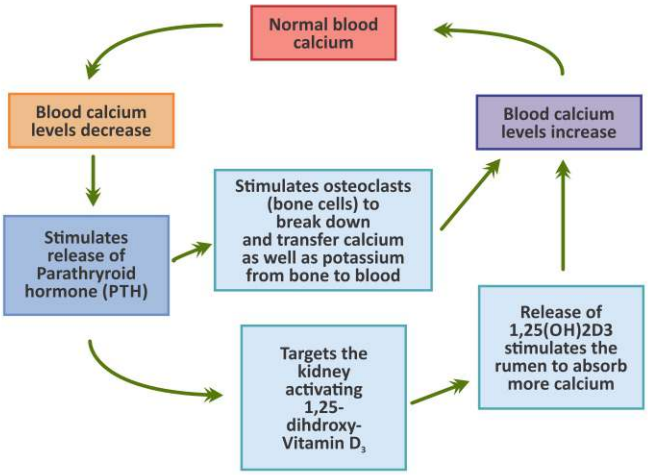

Fig-3: Regulation of blood calcium levels in body

activities regulated by parathyroid hormone and 1, 25 dihydroxy-Vitamin D_3.

- PTH increases renal reabsorption of calcium from glomerular filtrate. If the perturbation in blood calcium is small (less than 1 gm Calcium/day), blood calcium returns to normal and PTH secretion returns to baseline levels.
- If calcium drain from extracellular pool is large, continued PTH secretion stimulates resorption of calcium stored in bone. This calcium comes from both dissolved calcium in solution within bones as well as from calcium released by osteoclastic activity on organic bone collagen matrix.
- Parathyroid hormone, acts only poorly on bone or kidney tissues when blood pH is high. Blood pH of cattle is often alkaline because forage potassium is often excessively high.
- Oestrogens also inhibit calcium mobilization. Oestrogen levels rise at parturition which has negative effect on the adaptation process to maintain calcium levels.
- Calcium is absorbed across intestine and forestomachs by both 1, 25 dihydroxy-Vitamin D_3 dependent and 1, 25 dihydroxy-Vitamin D_3 independent means.
    - 1, 25 dihydroxy-Vitamin D_3 independent absorption of calcium is primarily by passive diffusion.
    - 1, 25 dihydroxy-Vitamin D_3 dependent absorption is by active transport; it occurs when dietary calcium is low or when calcium demand is very high.
- The activity of renal enzyme responsible for converting 25- hydroxy Vitamin D to the 1, 25 dihydroxy-Vitamin D_3 is stimulated by and tightly regulated by PTH.
- The most important function of 1, 25 dihydroxy-Vitamin D_3 is its ability to stimulate active transport of dietary calcium across intestinal epithelium.

In later lactations, because of decline in ability to mobilize calcium from bone stores and a decline in the active transport of calcium in intestine, as well as impaired production of 1, 25 dihydroxy-Vitamin D_3 results in inability to respond to acute Calcium stress and milk fever develops (Fig-4).

Calcium Homeostatic Mechanism is influenced by mainly three factors:

a) Excessive loss of Calcium in colostrum beyond capacity of absorption from intestine
b) Impairment of absorption of Calcium from intestine at parturition
c) Mobilization of Calcium from storage in skeleton may not be sufficiently rapid to maintain normal serum level

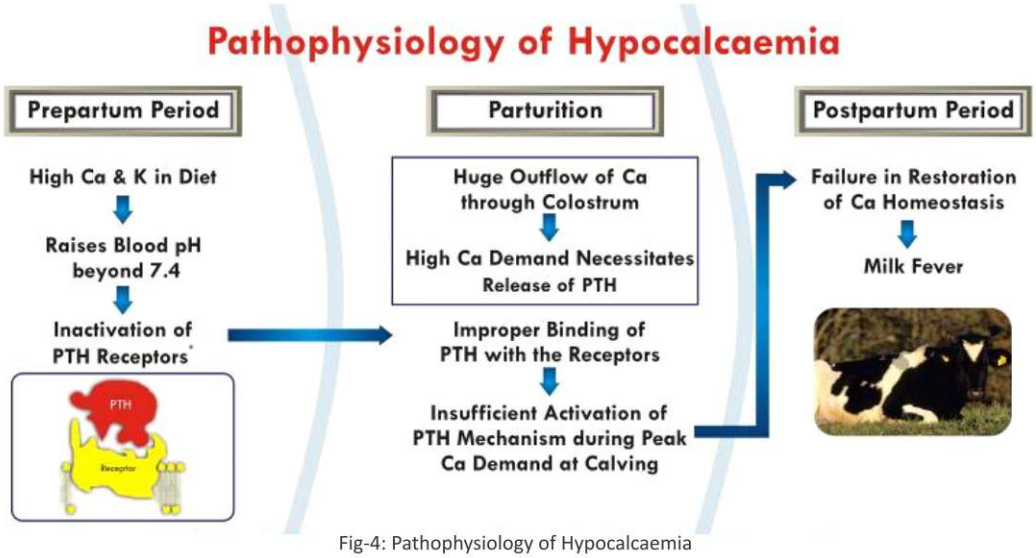

Fig-4: Pathophysiology of Hypocalcaemia

Signs and Symptoms

Milk Fever Stage	Description	Signs and Symptoms
Stage I	Early Stage Sub-clinical	Loss of appetite, nervousness, hypersensitivity, weakness and shuffling of hind feet
Stage II	Sub-clinical	Lying down with head outstretched or layed in flank, moderate depressed, coordination disorder, trembling muscles, constipation and fast heart rate
Stage III	Clinical	Lying flat on ground, severely depressed, progressive loss of consciousness, comatose, death

Clinical Signs are divided into three stages. Clinical signs usually occurs within 72 hours of parturition.

First Stage:

Fig-5: 'S' shaped posture of cow suffering with Milk Fever

- Serum calcium- 6.5-8.0mg/dl.
- Early signs without recumbency.
- This stage may go unnoticed as signs are subtle and transient.
- Affected cattle may appear excitable, nervous or weak.
- May shift their weight frequently and shuffle their hind feet.
- Stiffness of hind legs.
- Rapid heart rate.
- Rectal temperature is usually normal or above normal (>39°C).

Second Stage (Stage of Sternal Recumbency):

Fig-6: Dilated pupils

- Serum calcium- 4.0-6.0mg/dl.
- Sternal recumbency comprising down on chest and drowsiness.
- Characteristic 'S' shaped posture, sitting with lateral kink in neck or head turned to lateral flank (Fig-5).
- Depression, fine muscle tremors.
- Rapid heart rate with decreased intensity of heart sounds.
- Cold extremities and decreased rectal temperature (35.6-37.8°C).
- Decreased gastrointestinal activity.
- Pupils dilated and unresponsive to light (Fig-6).

Third Stage or Stage of Lateral Recumbency:

Fig-7: Cow in Lateral Recumbency during Stage III of Milk Fever

- Serum calcium- <4.0 mg/dl
- Lateral recumbency, comprising of almost comatose condition, progressing to loss of consciousness (Fig-7).
- Severe bloat, flaccid muscles, profound gastrointestinal atony.
- Rapid heart rate, impalpable pulse and almost inaudible heart sounds.
- They will die within few hours without treatment.

Consequences of Hypocalcaemia

Fig-8: Uterine prolapse seen during hypocalcaemia

- Reduces milk yield.
- Reduces productive life of cow by as much as 3.4 years.
- Increased risk for displaced abomasum.
- Dystocia and hence stillborn calves.
- Impairs contractions of rumen and abomasum leading to increase in blood nonesterified fatty acids (NEFAs) resulting in more metabolic disorders.
- Hypocalcaemia causes secretion of cortisol which impairs immune system.
- Contributes to metritis, mastitis and retained placenta by negatively affecting uterine and teat sphincter contractility.
- Prolapse of uterus is a common complication of milk fever (Fig-8).
- Reduces blood flow to extremities, causing characteristic cold ears of cow suffering from milk fever.
- Milk fever cows also exhibit a greater decline in feed intake after calving than non-milk fever cows, exacerbating the negative energy balance commonly observed in early lactation.
- Prevents secretion of insulin, preventing tissue uptake of glucose which would exacerbate lipid mobilization at calving, increasing the risk of ketosis.
- Hypocalcemia become a “Downer Cow Syndrome” due to mineral imbalances:
    - Hypocalcemia—plasma Ca< 5 mg/dL
    - Hypomagnesemia—plasma Mg < 1.2 mg/dL
    - Hypophosphatemia—plasma P < 1.5 mg/dL
- The mineral deficiency may lead to Fractures, Coxofemoral luxation and Rupture of gastrocnemius muscle.

Management

- Treatment is usually initiated based on clinical signs only.
- Treatment is directed towards restoring serum calcium level to normal as soon as possible to avoid muscular and nervous damage and recumbency.
- This would minimize the associated problems of hypocalcaemia.

Oral Calcium Supplementation

- Oral calcium supplementation is best approach for hypocalcaemic cows that are still standing, such as cows in Stage 1 hypocalcaemia or who have undetected subclinical hypocalcaemia.
- A cow absorbs an effective amount of calcium into her bloodstream within about 30 minutes of supplementation.
- Blood calcium concentrations are supported for only about 4-6 hours for most forms of oral calcium supplementation.
- Oral calcium gel like **CALRIZE** are effective in hypocalcaemic conditions as they provide high concentration of calcium. The oral calcium administration should be done at an interval of 12 hours before and after parturition.

Intravenous(I/V) Calcium Treatment

- Stage II and Stage III cases of milk fever should be treated immediately with slow I/V administration of 450 ml of a 25% calcium borogluconate solution.
- Treatment with I/V calcium should be given as soon as possible, as recumbency can quickly cause severe musculo skeletal damage.
- The thumb rule is when the animal is showing signs of peripheral vascular failure, hypothermia and cold extremities, calcium borogluconate should be administered intravenously.
- Intravenous Calcium is administered at 2.2 g/100 kg body wt.
- To reduce the risk for relapse, recumbent cows that respond favourably to I/V treatment need additional oral calcium supplementation once they are alert and able to swallow, followed by a second oral supplementation about 12 hours later.
- Heart rate should be closely monitored for toxic effects while giving I/V calcium.
- The response to properly administered calcium therapy is quite characteristic.
- 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.
- The cow's symptoms will appear to reverse themselves as they had previously progressed. The laterally recumbent cow will sit up to sternal position, and then it will often begin to have tremors over its body. As all body functions affected by hypocalcaemia begin to reverse, the affected animal may urinate, belch, and then begin the wobbly effort to rise.
- Repeated treatment may be necessary in 12 hours if cow is still unable to rise.

Intramuscular Calcium Injection:

- Intramuscular Calcium injection is another option for providing ready source of calcium to the hypocalcaemic cattle.
- The intramuscular Calcium injections are available as Calcium Gluconolactobionate and Calcium Levulinate.
- Each ml of Calcium Gluconolactobionate offers 9 mg of ionisable calcium and each ml of Calcium Levulinate Preparation offers 10 mg of ionisable calcium.
- The calcium levuinate is an excellent source for 20% to 60% of the calcium ions. Because it is non-irritating, it dilutes the irritating effect of the lactate and chloride salts.
- **INTACAL- IM** with Calcium levulinate offers rapid Calcium support during hypocalcaemia.

Subcutaneous Calcium Treatment

- Subcutaneous calcium can be used to support blood calcium concentrations around calving, but has substantial limitations.
- Absorption of calcium from subcutaneous administration requires adequate peripheral perfusion.
- It may be ineffective in cows that are severely hypocalcemic or dehydrated.
- Subcutaneous calcium injections are irritating and can cause tissue necrosis; administration should be limited to approximately 75 ml (50- 125ml).
- Calcium solutions that also contain glucose should not be given subcutaneously. Glucose is very poorly absorbed when given by this route. Abscessation and tissue sloughing may result when glucose is given subcutaneously.
- The kinetics of subcutaneously administered calcium indicate that it is well-absorbed initially, but that blood concentrations fall back to baseline values in about 6 hours. Thus, repeat doses would be necessary to equal the sustained blood calcium support that is possible with oral calcium boluses.

Prevention and Control

Traditional Method- Restricting Dietary Calcium

- Aim is to limit the calcium intakes to below 30- 50 gm in last three weeks precalving.
- It is believed that low calcium in precalving diet triggers the PTH hormone.
- This reduces the chances of milk fever after calving as calcium homeostatic mechanism has already started to act to increase blood calcium levels.

Supplement Magnesium in Close-up Dry Cow Diet

- Magnesium is needed for calcium homeostatic mechanisms to work effectively around parturition.
- Magnesium is known to participate in calcium homeostasis via release of parathyroid hormone and the synthesis of the active form of Vitamin D (1,25 dihydroxy-cholecalciferol).
- Total intakes of about 40-50 gm of dietary Mg (about 0.30-0.45% of diet dry matter, depending on total dry matter intake) have been suggested.

Supplementation of Ionic Oral Calcium at Calving

- As per this method, large amount of calcium is given to the cow at the time of calving which supplies readily available source of Calcium just when the cow needs it the most.
- **CALRIZE**, an oral calcium gel is effective for administering the cows which are under the risk category of Milk Fever.

Avoid Excessive Drain of Calcium immediately after Calving

- Once the cow calves, her calcium requirements increases 2-3 fold due to high calcium levels in milk.
- Excessive or inappropriate milk withdrawal can drain too much calcium from the system resulting in Milk Fever.
- Cows should not be milked in pre-calving period.
- Complete milking should be avoided for first few days of calving.

DCAD Diet

- DCAD is Divalent Cation- Anion Difference.
- The cows approaching parturition are fed with negative DCAD diet *i.e.* anions in diet is higher than cations.
- DCAD diets are made of combination of salts.
- Cations have positive charge like sodium (Na), potassium (K), calcium (Ca) and magnesium (Mg). Cations in diet promote more alkaline (higher blood pH) metabolic state which has been associated with 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 treated and/or prevented by feeding dairy cows during the close up

period (14 to 21 days precalving) a diet containing substantial amounts of negative ions (i.e. anionic salts).

- The cation-anion difference of diet is commonly described in terms of mEq/kg of sodium, potassium, chloride and sulphate.

mEq/100g of Dry Matter = (Na + K) – (Cl + S)

- During peri-partum period objective is to provide negative DCAD diet *i.e* diet having higher anions in comparison to cations.
- For which it is important to achieve (-10) to (-15) mEq/100g of DM.
- Feeding of Anionic diets resets the blood pH and ensures proper binding of PTH to its receptors present on bone and kidney (Fig- 9).
- PTH binding takes care of the entire calcium homeostasis by triggering calcium mobilisation from bony reserves, absorption of calcium from intestines and reabsorption of calcium from urine in the kidneys thus restoring the normal level of calcium in the blood.

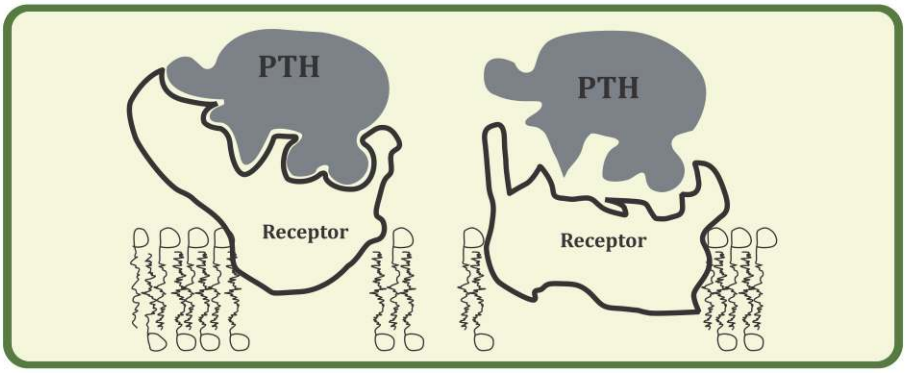

Fig-9: Anionic diets result in greater binding of PTH to its receptors at bones and Kidneys as shown on left side. PTH binding is impaired in Alkalosis conditions as shown on right side.

- Anionic diet supplementation increases activity of pre-existing osteoclasts and also stimulate proliferation of new osteoclasts. If more osteoclasts are present in parturient animal, there will be more osteoclasts present to respond to PTH as lactation begins, speeding the adaptation to high calcium diet.
- So the DCAD diet ensure that the animal's calcium mechanism is triggered and all set to face the upcoming lactation needs.
- The effective DCAD can be known by measuring the Urine pH of animal. A pH of 7.0 or greater would require balancing for cations-anions. The urine pH should not drop below 5.5 also. A urine pH of 6.0 to 6.5 indicates an effective DCAD diet.

DCAD	Urine pH	Dry Cow Acid-Base status	Lactating Cow Calcium status AD
Positive (>mEq/100g)	7.0 to 8.0	Alkalosis	Low Calcium
Negative (<mEq/100g)	5.5 to 6.5	Mild Metabolic Acidosis	Normal Calcium Level
Negative (<mEq/100g)	Below 5.5	Kidney Overload	Normal Calcium Level

- **HYPORID** is a negative DCAD dietary supplement that helps in lowering blood pH which enhances the activation and binding of PTH to its receptors. Thus helps in maintaining the calcium homeostasis in post-partum period.

Hypocalcaemia is an economically significant condition in Dairy cattle. The incidence are greater in high yielding animals. It is believed that nearly 50% of cow get affected with subclinical form of hypocalcemia at the onset of lactation.Hypocalcaemia has direct impact on milk production. The calcium homeostasis is regulated by Parathyroid hormone. PTH acts on bone, GI tract and kidneys to regulate the calcium levels in body. It is proven that the alkalosis during prepartum period affects the binding of PTH to its receptors and thus interferes with calcium homeostasis. The anionic dietary supplements [negative DCAD] effectively manages anionic environment in body which facilitates better binding of PTH to its receptors leading to effective calcium homeostasis thus DCAD dietary supplements should be included in the diets of prepartum animals.

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