KETOSIS

- Ketosis is a common disease of adult cattle.
- It typically occurs in dairy cows in early lactation and is most consistently characterized by partial anorexia and depression. Rarely, it occurs in cattle in late gestation, at which time it resembles pregnancy toxemia of ewes.
- In addition to inappetence, signs of nervous dysfunction, including pica, abnormal licking, incoordination and abnormal gait, bellowing, and aggression, are occasionally seen.

ETIOLOGY AND PATHOGENESIS

- It requires the combination of intense adipose mobilization and a high glucose demand.
- Both of these conditions are present in early lactation, at which time negative energy balance leads to adipose mobilization, and milk synthesis creates **a high glucose demand.**
- Adipose mobilization is accompanied by high blood serum concentrations of nonesterified fatty acids (NEFAs). During periods of intense gluconeogenesis, a large portion of serum NEFAs is directed to ketone body synthesis in the liver.

- Thus, the clinicopathologic characterization of ketosis includes high serum concentrations of NEFAs and ketone bodies and low concentrations of glucose.
- In contrast to many other species, cattle with hyperketonemia do not have concurrent acidemia.
- The serum ketone bodies are **acetone**, **acetoacetate**, and **β-hydroxybutyrate** (BHB).

TYPE I KETOSIS

- Spontaneous or underfeeding ketosis is the classic form of ketosis that occurs in cows that are 3 to 6 weeks post-calving.
- It is named type I ketosis because of its similarities to its related metabolic disorder, type I diabetes mellitus.
- In both conditions blood insulin concentrations are low, although for different reasons.
- Low Insulin level
  - type I diabetes ➡ pancreatic defect
  - type I ketosis ➡ chronic hypoglycemia due to a shortage of glucose precursors.

- Type I ketosis occurs between 3 and 6 weeks post-calving because cows are at their highest milk energy outflow at this time.
- Sometimes these cows simply cannot keep up with energy demand because of some deficiency in nutritional management.
- Type I ketosis is most common in component-fed herds, because it is very difficult to minimize negative energy balance without causing ruminal acidosis with component feeding.

- Cows with type I ketosis are able to make glucose from precursors (mostly propionate from the rumen and amino acids from the small intestine). The limiting factor is the supply of glucose precursors. Blood ketone concentrations become very high and blood glucose concentrations very low under these conditions (Figures 4 and 5).

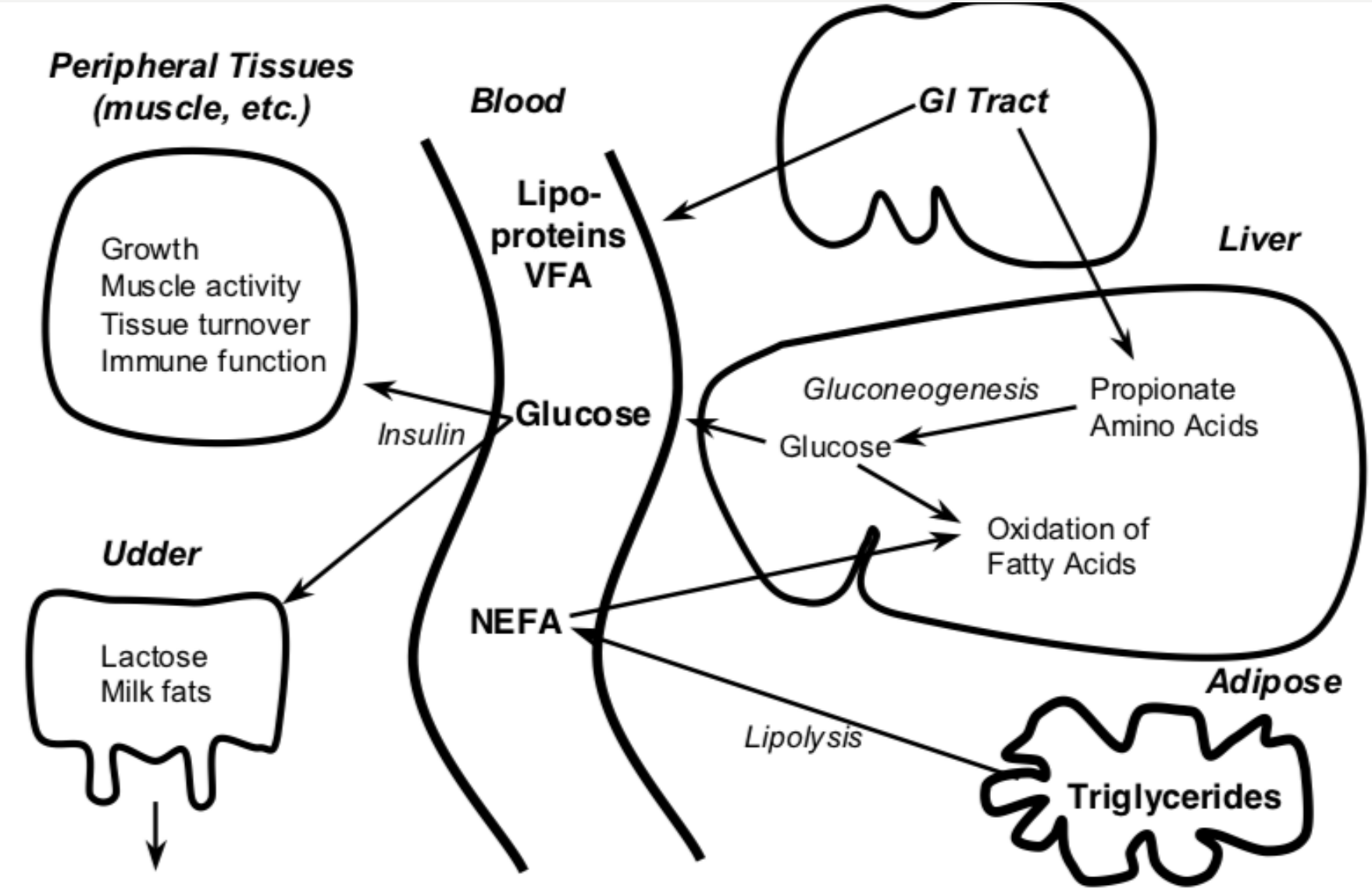

Figure 4. Schematic of glucose metabolism in a normal dairy cow.

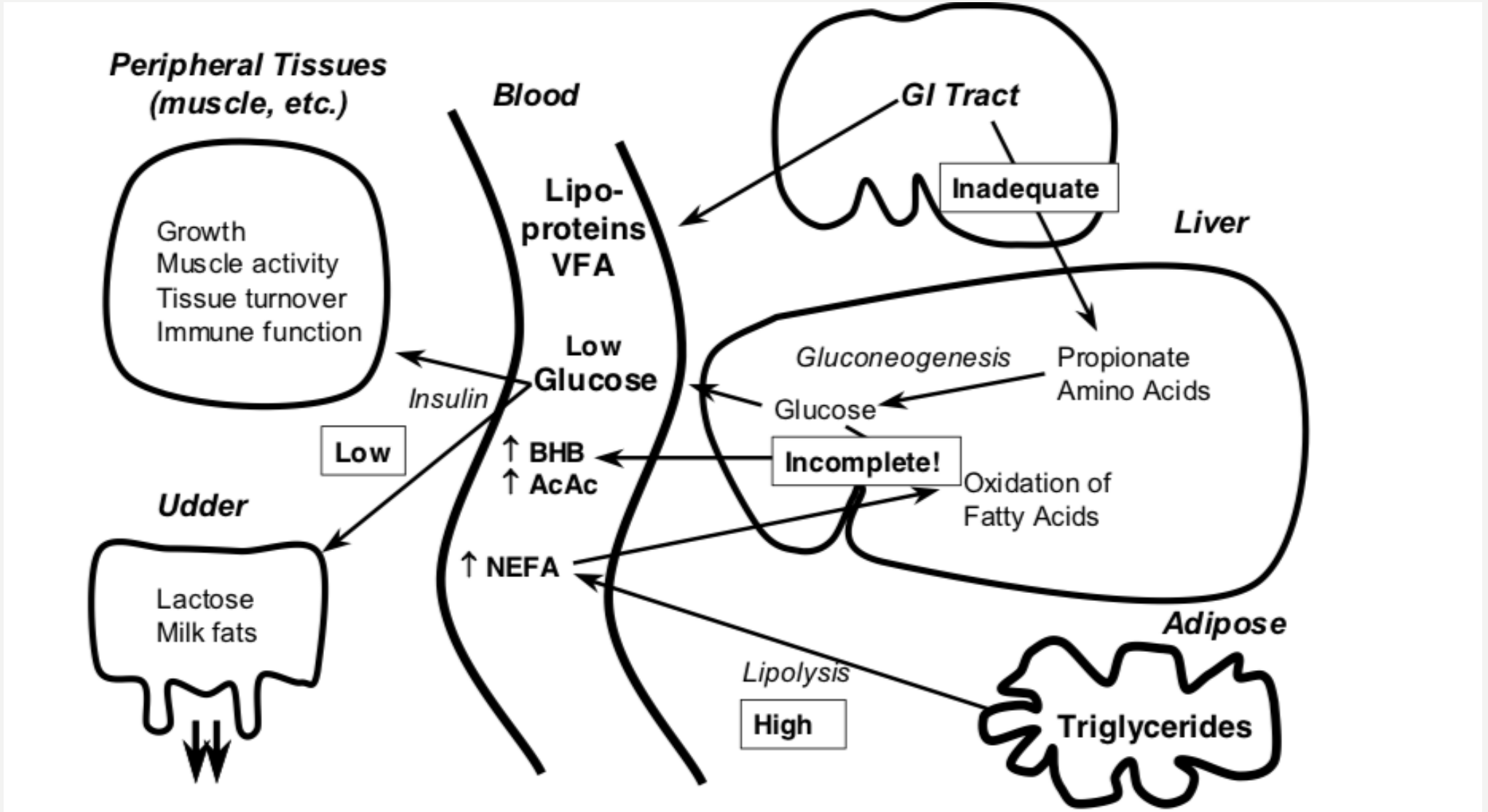

Figure 5. Schematic of glucose metabolism and ketone body formation with type I ketosis.

- Cows with type I ketosis generally respond well to a variety of ketosis treatments.
- The key to preventing type I ketosis is to **maximize energy intake in early lactation**. In some herds, this might be as simple as feeding a little more grain in early lactation. Alternatively, a little less grain might be the correct solution if the cows simultaneously have subacute ruminal acidosis (SARA) causing depressed dry matter intake.
- Over-crowding and/or lack of bunk space can be another cause of insufficient energy intake in early lactation cows

TYPE II KETOSIS

- This form of ketosis includes the older designation of "fat cow syndrome," but encompasses more than just overly fat dry cows.
- It includes any cows that develop negative energy balance and begin mobilizing body fat prior to or at calving.
- Fat cows are at the highest risk for this problem because they are prone to dry matter intake depression around calving but thinner cows are also at risk if nutritional management during the pre- fresh and/or maternity period is poor.

- Maintaining positive energy balance up to the time of calving can be difficult, since dry matter intake is naturally depressed for about the five days prior to parturition

- As for post-fresh cows, maintaining energy intake is a matter of both energy density and dry matter intake. Nutrient densities for pre-fresh groups have to be set with the lowest expected dry matter intakes (i.e., just prior to calving) in mind. Formulating pre-fresh diets for the average intake of the group will result in negative energy balance in those cows approaching calving.

- Moving cows to a different pen just prior to calving, over-crowding cows prior to calving, frequent disruptions of pens by adding new cows, moving cows to different pens frequently after calving, and over-crowding after calving are important risk factors for type II ketosis.
- Inadequate maternity pen management also increases the risk for type II ketosis.

- Fatty infiltration of the liver is largely complete by the time of calving, but waits to manifest itself clinically after until calving. It impairs the liver's gluconeogenic capacity, which greatly increases a cow's risk for ketosis once lactation starts. Affected cows develop ketosis within the first week or two after calving.

The quality of their post-fresh management has limited bearing on the risk for type II ketosis; affected cows were programmed to get ketosis based on their energy balance and stress just before or soon after calving.

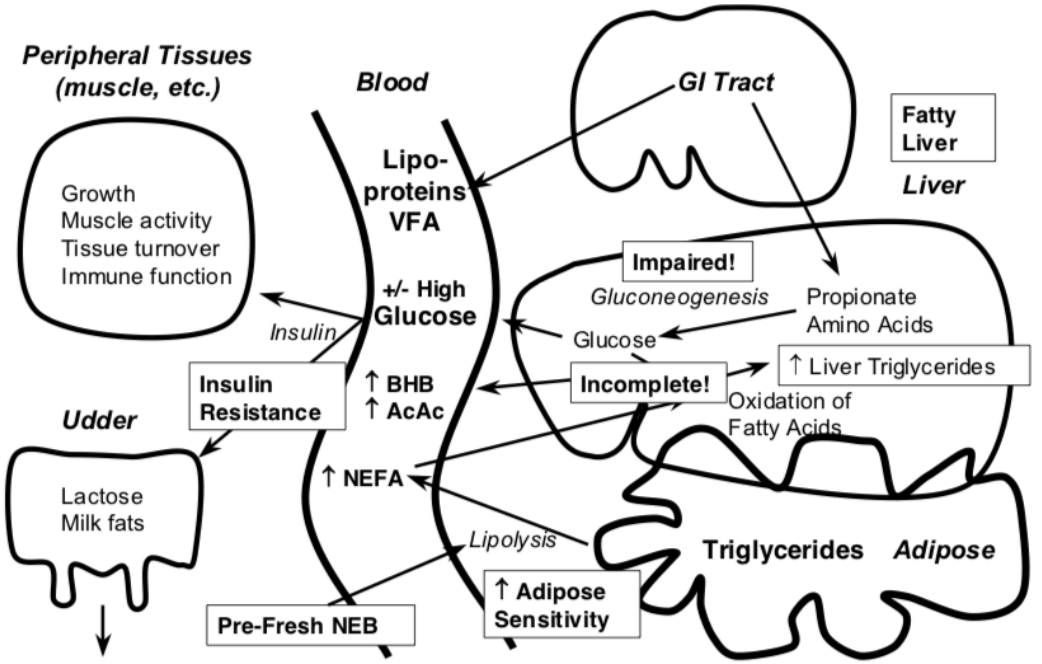

Figure 6. Schematic of glucose metabolism and ketone body formation with type II ketosis.

- Type II ketosis is named for type II diabetes mellitus, its metabolic counterpart. In both conditions blood insulin and glucose concentrations are high
- Insulin resistance may also characterize both conditions. **Obesity** is a particularly important factor in the development of insulin resistance.
- Further accumulation of body fat is restricted when tissues are insulin resistant; however, insulin resistance has grave consequences once the cow faces an energy crisis in early lactation and desperately needs to move glucose into her cells.
- It appears that insulin resistance is not present at the time these cows develop ketosis; however, it may have been a factor in the development of the disease.

- Obese cows are also prone to increased adipose sensitivity, which is the tendency to mobilize body fat very rapidly under conditions of stress or negative energy balance.
- This further exacerbates the cow's problems, because excessive mobilization of body fat increases fatty liver infiltration, drives ketone production, and depresses appetite even more. Very fat cows fall into a downward metabolic spiral soon after calving that leads to high mortality.
- .Obese heifers are also more prone to **dystocia, retained placenta, and metritis than older cows**. Mortality in replacement heifers can be high when they are obese and when transition cow management is not excellent.

- Blood ketone concentrations are not as high in type II ketosis as for type I. Yet, the prognosis for recovery in type II cases following treatment is poor, because treatment does little to improve the cow's underlying lesion of fatty liver infiltration and loss of gluconeogenic capacity. Cows with type II ketosis often remain ketotic for 1 to 3 weeks.
- Besides impairing gluconeogenic potential, fatty liver also impairs immune function by hepatocytes. Severe negative energy balance also suppresses immune function by itself, because immune cells and functions are voracious consumers of energy. The net result is a cow that is not only persistently ketotic, but also immune suppressed. Many cows with type II ketosis die from infections (metritis, mastitis, pneumonia) that their immune systems would normally have been able to combat.

- Type II ketosis is prevented by excellent pre-fresh nutritional management combined with prevention of obesity in dry cows. Preventing negative energy balance prior to calving requires good dry matter intakes as well as proper energy density of the pre-fresh diet. As for the post-fresh cows, nutritional management issues that increase dry matter intake are of more practical importance than increasing diet energy density.

BUTYRIC ACID SILAGE KETOSIS

- Some herds have persistent ketosis problems that are caused by feeding ketogenic silages. Hay crop silages that are chopped too wet (insufficient wilting time or direct-cut silages) or that are low in water-soluble carbohydrates favor growth of *Clostridium sp*. bacteria. These bacteria ferment some carbohydrates to butyric acid instead the desired lactic acid. Corn silage or ensiled corn grain rarely supports clostridial growth, presumably because of their relatively high water-soluble carbohydrate content.

- Silages that have undergone clostridial fermentation are easy to recognize because of the distinctive odor of butyric acid and protein degradation products that accompany this fermentation pattern.
- A silage fermentation (VFA) analysis can confirm the presence of and the amount of butyric acid present in the silage.

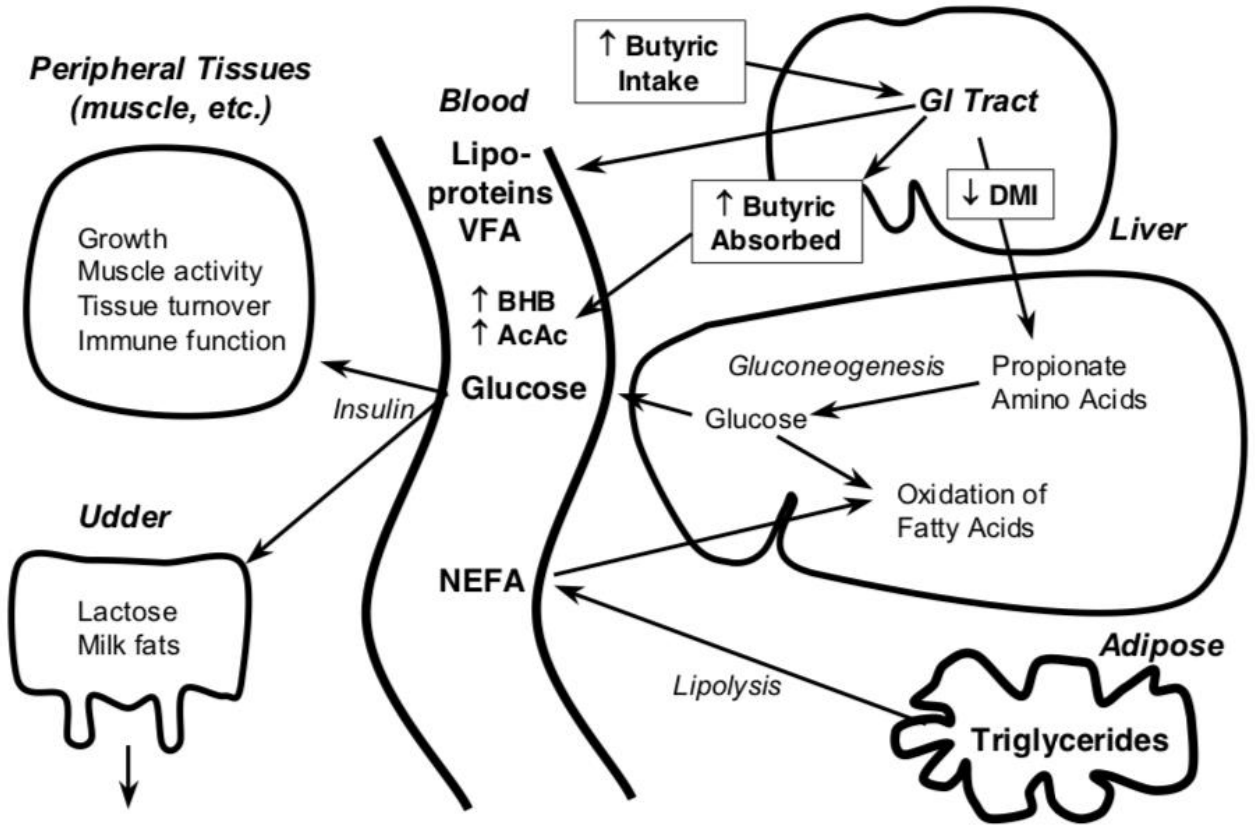

Figure 7. Schematic of glucose metabolism and ketone body formation in a dairy cow consuming excessive butyric acid from silage.

Cows are equipped to metabolize the butyrate produced by ruminal fermentation (about 750 g/day), mostly by using it as metabolic fuel for the ruminal musculature

About 75% of the additional ruminal butyrate is converted to blood BHBA, the direct cause of ketosis (Figure 7).

The liver then can convert BHBA to AcAc and vice versa. Thus, there is no "safe" dose of dietary butyric acid for dairy cows.

Any amount of additional dietary butyric acid increases a cow's risk for ketosis. Whether or not dietary butyric acid causes ketosis depends on the dose of butyric acid consumed and on whether other risk factors for ketosis (early lactation, high production, low dietary energy, high dietary protein, ruminal acidosis, etc.) are also present.

Table 1. Summary of types of ketosis observed in dairy herds

	Ketosis Type:		
Outcome	**Type I**	**Type II**	**Butyric Acid Silage**
Description	Spontaneous; Underfeeding	Fat Cows; Fatty Liver	Wet silages
Blood BHBA	Very high	High	Very high or high
Blood NEFA	High	High	Normal or High
Blood glucose	Low	Low (may be high initially)	Variable
Blood insulin	Low	Low (may be high initially)	Variable
Body condition	Probably thin	Often fat (or may have lost fat)	Variable
Fate of NEFA	Ketone bodies	Liver triglycerides initially, then ketone bodies	Variable
Liver gluconeogenesis	High	Low	Variable
Liver pathology	None	Fatty liver	Variable
Highest risk period	3 to 6 weeks after calving	1 to 2 weeks after calving	Variable
Prognosis	Excellent	Poor	Good
Key diagnostic test	Post-fresh BHBA	Pre-fresh NEFA	Silage VFA analysis
Key intervention	Post-fresh management and nutrition	Pre-fresh management and nutrition	Destroy, dilute or divert the silage

CLINICAL FINDINGS

- Reduced feed intake
- Refuse grain before forage
- Reduced milk production
- Lethargy, and an "empty" appearing abdomen
- Slightly dehydration
- Rumen motility is variable, being hyperactive in some cases and hypoactive in others.
- CNS disturbances are noted in a minority of cases. These include abnormal licking and chewing, with cows sometimes chewing incessantly on pipes and other objects in their surroundings.

DIAGNOSIS

- A variety of cowside tests are available for ketosis monitoring of dairy herds. However, none of the cowside tests have perfect sensitivity and specificity compared to blood BHBA
- Cow-side tests for the presence of ketone bodies in urine or milk are critical for diagnosis.
- Dipstick tests are convenient, but those designed to detect acetoacetate or acetone in urine are not suitable for milk testing.
- Therefore, the gold standard ketosis test (blood BHBA) is the most accurate for herd monitoring, and is particularly warranted for investigating herds with presumptive ketosis.

- Cowside ketosis tests have the advantages of **lower cost, less labor**, and **immediate results** when compared to blood BHBA testing. This makes them particularly useful for making (or excluding) a clinical diagnosis of ketosis in individual, sick cows. However, testing herds for ketosis requires a very different testing strategy compared to diagnostic decision-making for sick cows.
- The **BHB concentration in milk is always higher** than the acetoacetate or acetone concentration, making the tests based on **BHB more sensitive** than those based on acetoacetate or acetone

TREATMENT:

- Reestablishing normoglycemia
- Reducing serum ketone body concentrations

- Bolus IV administration of 500 mL of 50% dextrose solution
- Administration of glucocorticoids, including dexamethasone or isoflupredone acetate at 5–20 mg/dose, IM, may result in a more sustained response, relative to glucose alone.
- Propylene glycol administered orally (250–400 g/dose [8–14 oz]) once per day acts as a glucose precursor and is effective as ketosis therapy.
- Overdosing propylene glycol leads to CNS depression.

HYPOCALCEMIA

- The normal blood calcium concentration in adult cows is between 8.5 and 10 mg/dL
- PTH is considered a common denominator in the skeletal, renal, and intestinal regulation of calcium homeostasis, aiming to keep plasma levels within a range that maintains critical muscular, nervous, and other cellular functions.

- The normal physiologic response to decreasing ionized calcium levels is to produce PTH, which acts to increase osteoclastic bone resorption (direct PTH effect), increase intestinal absorption (via 1,25-dihydroxyvitamin D3), and enhance renal tubular resorption of calcium. PTH secretion is exquisitely sensi- tive to small decreases in plasma ionized calcium, but the response can be blunted by hypomagnesemia, partly explain- ing the well-documented link between clinical hypomagne- semic tetany and hypocalcemia, even in nonlactating cattle.

- There are several other important factors that interfere with PTH activity at a tissue level that can serve to blunt the individual's ability to respond efficiently to the increased demands of lactation, despite appropriate PTH secretion
- **Metabolic alkalosis** predisposes to both milk fever and subclinical hypocalcemia principally because it interferes with skeletal calcium resorption by decreasing readily available calcium in bone fluid as well as lessening intestinal absorption by conformationally altering the PTH–receptor interaction at the tissue level
- **Alkalosis increases albumin binding** of serum calcium, hence lowering ionized, biologically available, serum calcium.

- **Other factors** also contribute to the development of hypocalcemia in dairy cattle, specifically age, breed, and endocrinologic factors such as estrogen levels.

- With increasing age, there is a reduced pool of calcium available for absorption from bone, and decreased vitamin D receptors predisposing older, high-producing cows, to milk fever.
- Freshening heifers, that generally give less milk than multiparous cows and have higher osteoblastic activity and calcium availability, rarely suffer from clinical milk fever.

- Further age-related changes include a reduction in PTH receptors in the peripheral tissues of older cattle alongside decreased intestinal absorption of calcium.
- Although **estrogen** increases predictably in the last few days of gestation and this hormone has a negative effect on calcium mobilization from bone, it does not appear to be a significant contributor to the incidence of milk fever nor the severity of hypocalcemia

CLINICAL SIGNS

- Parturient hypocalcemia or milk fever mostly occurs from about 24 hours before to 72 hours after parturition with a majority of cases occurring within 24 hours after calving.
- It can contribute to dystocia, uterine prolapse, retained fetal membranes, metritis, abomasal displacement, and mastitis.

Parturient Paresis Has Three Discernible Stages.

- **During stage 1**, animals are ambulatory but show signs of hypersensitivity and excitability.
- Cows may be mildly ataxic, have fine tremors over the flanks and triceps, and display ear twitching and head bobbing.
- Cows may appear restless, shuffling their rear feet and bellowing. If calcium therapy is not instituted, cows will likely progress to the second, more severe stage.

- **Cows in stage 2** are unable to stand but can maintain sternal recumbency. Cows are obtunded, anorectic, and have a dry muzzle, subnormal body temperature, and cold extremities.
- Auscultation reveals tachycardia and decreased intensity of heart sounds. Peripheral pulses are weak.
- Smooth muscle paralysis leads to GI stasis, which can manifest as bloat, failure to defecate, and loss of anal sphincter tone.
- An inability to urinate may manifest as a distended bladder on rectal examination. Cows often tuck their heads into their flanks, or if the head is extended, an S-shaped curve to the neck may be noted.

- **In stage 3,** cows lose consciousness progressively to the point of coma.
- They are unable to maintain sternal recumbency, have complete muscle flaccidity, are unresponsive to stimuli, and can suffer severe bloat. As cardiac output worsens, heart rate can approach 120 bpm, and peripheral pulses may be undetectable.
- If untreated, cows in stage 3 may survive only a few hours.

TREATMENT

- Restoring normal serum calcium levels as soon as possible to avoid muscle and nerve damage and recumbency.
- Concentrations of calcium, calcium salt formulations, and other elemental and carbohydrate components within the infusion solution vary widely according to personal preference and the perceived needs of the cow.
- Cows often eructate, defecate, or urinate during the IV administration of calcium, and many cows with truly uncomplicated stage 2 hypocalcemia are capable of standing before or shortly after the infusion is finished.

- A general rule for dosing is 1 g calcium/45 kg (100 lb) body wt.
- Most solutions are available in single-dose, 500-mL bottles that contain 8–11 g of calcium.
- In large, heavily lactating cows, a second bottle given SC may be helpful, because it is thought to provide a prolonged release of calcium into the circulation.
- SC calcium alone may not be adequately absorbed because of poor peripheral perfusion and should not be the sole route of therapy.

- Many solutions contain phosphorus and magnesium in addition to calcium. Although administration of phosphorus and magnesium is not usually necessary in uncomplicated parturient paresis, detrimental effects of their use have not been reported.
- Magnesium may protect against myocardial irritation caused by the administration of calcium.
- Magnesium is also necessary for appropriate parathyroid hormone (PTH) secretion and activity in response to hypocalcemia.

- Calcium is **cardiotoxic**; therefore, calcium-containing solutions should be administered slowly (10–20 min) while cardiac auscultation is performed.
- If severe dysrhythmias or bradycardia develop, administration should be stopped until the heart rhythm has returned to normal. Endotoxic animals are especially prone to dysrhythmias caused by IV calcium therapy.

- Administration of oral calcium avoids the risks of cardiotoxic adverse effects and may be useful in mild cases of parturient paresis; however, it is not recommended as the sole approach for clinical milk fever cases.
- Products containing calcium chloride are effective but can be caustic to oral and pharyngeal tissues, especially if used repeatedly.
- Calcium propionate in propylene glycol gel or powdered calcium propionate (0.5 kg dissolved in 8–16 L water administered as a drench) is effective, less injurious to tissues, avoids the potential for metabolic acidosis caused by calcium chloride, and supplies the gluconeogenic precursor propionate. Oral administration of 50 g of soluble calcium results in ~4 g of calcium being absorbed into the circulation.

- Regardless of the source of oral calcium, it is important to note that cows with hypocalcemia often have poor swallowing and gag reflexes. Care must be exercised during administration of calcium-containing solutions to avoid aspiration pneumonia.
- Gels containing calcium chloride should not be administered to cows unable to swallow.

PREVENTION

- Prevention of parturient paresis has been approached by feeding low-calcium diets during the dry period. The negative calcium balance results in a minor decline in blood calcium concentrations. This stimulates PTH secretion, which in turn stimulates bone resorption and renal production of 1,25 dihydroxyvitamin D. Increased 1,25 dihydroxyvitamin D increases bone calcium release and increases the efficiency of intestinal calcium absorption. Although mobilization of calcium is enhanced, it is now known that feeding low-calcium diets is not as effective as initially believed.
- Furthermore, on most dairy farms today, it is difficult to formulate diets low enough in calcium (<20 g absorbed calcium/cow/day), although the use of dietary straw and calcium-binding agents such as zeolite or vegetable oil may make this approach more useful.

- The prevention of parturient paresis has been revolutionized by use of the dietary cation-anion difference (DCAD), a method that decreases the blood pH of cows during the late prepartum and early postpartum period. This method is more effective and more practical than lowering prepartum calcium in the diet. The DCAD approach is based on the finding that most dairy cows are in a state of metabolic alkalosis due to the high potassium content of their diets. This state of metabolic alkalosis with increased blood pH predisposes cows to hypocalcemia by altering the conformation of the PTH receptor, resulting in tissues less sensitive to PTH. Lack of PTH responsiveness prevents effective use of bone calcium, prevents activation of osteoclastic bone resorption, reduces renal reabsorption of calcium from the glomerulus, and inhibits renal conversion to its active form.t

- Use of synthetic bovine PTH may prove to be superior to administration of vitamin D metabolites. Vitamin D metabolites enhance GI calcium absorption, whereas PTH enhances GI calcium absorption and stimulates bone resorption. PTH is administered either IV 60 hr before parturition, or IM 6 days before parturition. Drawbacks to the use of PTH include increased labor requirements for administration, as well as the availability of such compound

HYPOCALCEMIC TETANY IN HORSES

- Mechanisms of hypocalcemia include;
  - decreased absorption from the intestines;
  - increased loss of calcium from the kidneys, sweat, or milk;
  - inhibition of osteolysis due to alterations in parathyroid hormone, calcitonin, or vitamin D.

- In lactating mares, high milk production and grazing of lush pastures appear to be predisposing factors.
- Hypocalcemia after prolonged physical activity (eg, endurance rides) results from sweat loss of calcium, increased calcium binding during hypochloremic alkalosis, and stress-induced high corticosteroid levels.
- Corticosteroids inhibit vitamin D activity, which leads to decreased intestinal absorption and skeletal mobilization of calcium.
- Stress and lack of calcium intake have been associated with transport tetany. Occasionally, hypocalcemic tetany may be precipitated by hypocalcemia after blister beetle ingestion

CLINICAL FINDINGS:

- The severity of clinical signs corresponds with the serum concentration of ionized calcium.
- Increased excitability may be the only sign in mild cases.
- Severely affected horses
  - synchronous diaphragmatic flutter,
  - anxious appearance,
  - signs of tetany,
  - increased muscle tone, stiffness of gait
  - muscle tremors
  - prolapse of the third eyelid, inability to chew, trismus, salivation, recumbency, convulsions, and cardiac arrhythmias.

In lactating mares, if not treated, the disease may take a progressive and sometimes fatal course over 24–48 hr.

Differential diagnoses include tetanus, endotoxemia, colic, exertional rhabdomyolysis or other muscle disorder, seizure disorder, laminitis, and botulism.

DIAGNOSIS

- A tentative diagnosis is based on clinical signs, history, and response to treatment.
- Definitive diagnosis requires demonstration of low serum levels of ionized calcium.
- Most laboratories measure only total (protein-bound and free) serum calcium, which is an acceptable diagnostic test in most cases.
- However, discrepancies may arise in alkalotic and hypoalbuminemic horses.

- Alkalosis increases albumin binding of calcium, which results in a decreased concentration of ionized calcium.
- Thus, alkalotic horses may have normal total serum calcium while exhibiting signs of hypocalcemia. Likewise, hypoalbuminemic or acidotic horses may have decreased total serum calcium without developing signs of hypocalcemia.
- Total serum calcium can be adjusted for albumin concentration by the following formula:

$$\text{adjusted } Ca^{2+} = \text{measured } Ca^{2+} - \text{serum albumin concentration} + 3.5$$

TREATMENT

- IV administration of calcium solutions, such as 20% calcium borogluconate or solutions recommended for treatment of periparturient paresis in cattle, usually results in full recovery.
- These solutions should be administered slowly (over 20 min) at 250–500 mL/500 kg, diluted at least 1:4 in saline or dextrose, and the cardiovascular response should be closely monitored.
- İncreased intensity of heart sounds is expected. If arrhythmias or bradycardia develop, the IV treatment should be discontinued immediately.
- Some horses require repeated treatments over several days to recover from hypocalcemic tetany.