INTERACTIONS OF CALCIUM, PHOSPHORUS, MAGNESIUM AND VITAMIN D THAT INFLUENCE THEIR STATUS IN DOMESTIC MEAT ANIMALS

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ABSTRACT

Known and possible interactions between Ca, P, Mg, parathyroid hormone (PTH), calcitonin (CT), vitamin D and its metabolites, and interactions of each of these with other factors plus complexities and possible variations between and within domestic animal species, such as age, sex, physiologic state (i.e., pregnancy, lactation and growth) and diet, make Ca, P and Mg metabolism extremely dynamic and complex. Many advances have been made in understanding these interactions and how each of these factors is controlled, secreted or metabolized within the body. Some interactions among these factors are discussed in detail, mostly with a view to understanding mechanisms by which homeostasis of Ca, P and Mg is maintained. Also, three of the major diseases of mineral metabolism of cattle (milk fever, grass tetany and wheat pasture poisoning) provide excellent models to study the complex soil, plant and animal interrelationships among Ca, P, Mg and the factors that influence and control the ultimate utilization of these minerals in animals. These diseases are used to illustrate some of the interactions among many of the factors that influence Ca, Mg and P metabolism in domestic animals.

(Key Words: Calcium, Phosphorus, Vitamin D, Animals.)

Introduction

Calcium (Ca), phosphorus (P) and magnesium (Mg) are important components of bone, and also intracellular and extracellular fluids of the body. Extracellular Ca is essential for maintenance of nerve tissue, resting membrane potential, blood clotting mechanisms, myocardial contraction and myoneural junctional transmission. Intracellular Ca, directly or indirectly, regulates activity of many enzymes, microtubule assembly, generation of ATP, release of hormones and neurotransmitters and muscle cell contraction (Rasmussen, 1986). Magnesium is an essential cofactor of many enzymes, especially phosphate-transferring enzymes involved in ATP generation and the adenylate and guanate cyclases, and is essential for normal function of nerve tissues. Phosphorus is a component of phospholipids, phosphoproteins and nucleic acids and is a major component of energy-transferring molecules such as ATP. Alterations in intake or mobilization of Ca, Mg, P or vitamin D lead to a variety of diseases such as milk fever, grass tetany, wheat pasture poisoning and rickets.

Calcium Metabolism

In mammals, normocalcemia ranges between 9 and 11.5 mg/dl. About 50% of Ca in plasma is ionized and is in equilibrium with extracellular fluid Ca. Both hypocalcemia and hypercalcemia are incompatible with normal function of many biological processes; thus, a complex homeostatic mechanism is needed to maintain normocalcemia. Figure 1 illustrates some of the major changes in Ca metabolism that maintain Ca homeostasis as Ca input varies.

Calcium leaving the extracellular Ca pool via urine, feces, milk and the developing fetus is non-retrievable and must ultimately be replenished by dietary Ca. Calcium deposited in bone and intracellular organelles of soft tissues.
Figure 1. Mechanism of adaptation to alterations in dietary calcium. The dashed line represents a response that occurs in rats but not in ruminants (Horst, 1986).

Phosphorus Metabolism

Dietary P deprivation and the hypophosphatemia it induces has been reported to affect renal 1α-hydroxylase activity and plasma 1,25-(OH)₂D₃ concentration (Tanaka and DeLuca, 1973; Hughes et al., 1975; Sommerville et al., 1978; Gray and Napoli, 1983). Figure 2 illustrates some of the changes that may be associated with P deficiency. Feeding a low P diet may or may not result in an increase in renal 1α-hydroxylase activity or an increase in plasma 1,25-(OH)₂D₃ levels even though hypophosphatemia may develop (Henry et al., 1974; Montecuccoli et al., 1977; Henry, 1981; Engstrom et al., 1982; Nagode and Steinmeyer, 1982). The increase in renal 1α-hydroxylase and in plasma 1,25-(OH)₂D₃ that occurs may be determined by the amount of dietary P, availability of P in the diet, time on the diet, age of animals and concentration of Ca in the diet (Engstrom et al., 1985). Also, differences in receptor binding or turnover rate of 1,25-(OH)₂D₃ would affect the correlation between 1α-hydroxylase activity and plasma 1,25-(OH)₂D₃ levels. Table 1 shows effects of feeding young pigs four diets with different levels of P for 39 to 41 d (Engstrom et al., 1985). Renal 1α-hydroxylase activity increased six- to sevenfold and plasma 1,25-(OH)₂D₃ levels increased threefold in pigs fed the low (.085%) P diet compared with pigs fed a normal (.6%) control diet. Renal 24-hydroxylase activity was not affected by variations in dietary P. Plasma 24,25-(OH)₂D₃ concentrations were significantly lower at the .085% dietary P level. Plasma P decreased as dietary P decreased, but plasma Ca concentration increased as dietary P decreased. Factors by which dietary P deprivation increases renal 1α-hydroxylase activity and plasma 1,25-(OH)₂D₃ levels are different from those that increase 1α-hydroxylase activity and plasma 1,25-(OH)₂D₃ during dietary Ca deprivation. Stimulation of renal 1α-hydroxylase activity and increased plasma 1,25-(OH)₂D₃ due to low dietary Ca requires PTH (Garabe-
TABLE 1. RENAL 1α- AND 24R-HYDROXYLASE AND PLASMA ALKALINE PHOSPHATASE, CALCIUM, PHOSPHORUS AND VITAMIN D METABOLITES OF PIGS FED DIETS VARYING IN CONCENTRATION OF PHOSPHORUSB

<table>
<thead>
<tr>
<th>Variable</th>
<th>.085% P (2)C</th>
<th>.3% P (2)C</th>
<th>.6% P (4)C</th>
<th>1.2% P (4)C</th>
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<tr>
<td>1α-Hydroxylase, pmol·min⁻¹·g⁻¹e</td>
<td>136.3 ± 17.0</td>
<td>48.6 ± 10.2</td>
<td>21.2 ± 5.8</td>
<td>11.5 ± 2.7</td>
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<tr>
<td>24R-Hydroxylase, pmol·min⁻¹·g⁻¹</td>
<td>13.4 ± .2</td>
<td>9.6d</td>
<td>8.6 ± 2.2</td>
<td>10.1 ± 1.8</td>
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<tr>
<td>25-OHD₃, ng/ml</td>
<td>16.1 ± 1.1</td>
<td>17.0 ± 1.1</td>
<td>18.4 ± 2.3</td>
<td>16.8 ± 1.2</td>
</tr>
<tr>
<td>1,25-(OH)₂D₃, pg/ml</td>
<td>496.7 ± 69.7</td>
<td>525.0 ± 61.7</td>
<td>168.5 ± 11.2</td>
<td>139.6 ± 26.5</td>
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<tr>
<td>Calcium, mg/dl</td>
<td>.2 ± .2</td>
<td>3.3 ± .7</td>
<td>5.1 ± 1.7</td>
<td>2.6 ± 1.3</td>
</tr>
<tr>
<td>Phosphorus, mg/dl</td>
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<td>9.2 ± .2</td>
<td>9.0 ± .2</td>
<td>8.6 ± .2</td>
</tr>
<tr>
<td>Alkaline phosphatase, IU/liter</td>
<td>3.1 ± .1</td>
<td>5.1 ± 1.1</td>
<td>5.3 ± .3</td>
<td>7.4 ± .5</td>
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aEngstrom et al. (1985).
bMean values ± SE for pigs fed diets for 39 to 41 d before euthanasia.
cNumber of pigs in parentheses.
dValue for one pig.
eWet weight.

Corresponding changes in plasma vitamin D metabolites occurred, with reduced plasma 1,25-(OH)₂D₃ in low P, and an increase in plasma 24,25-(OH)₂D₃.

Magnesium Metabolism

There is no strong evidence to indicate that any single hormone or vitamin is concerned principally and directly with Mg homeostasis or metabolism. As described in excellent reviews (Walser, 1967; Wacker and Parisi, 1968; Todd, 1969; Littlefield and Cox, 1979; Littlefield et al., 1983), alterations in dietary or blood Ca, P, potassium (K), some of the vitamin D metabolites, PTH, CT and aldosterone can influence Mg metabolism. Conversely, changes in Mg metabolism can influence secretion or metabolism of most of these factors. These complexities and possible variations in animal species, age, sex, physiologic state (i.e., pregnancy, lactation, and growth) and diet make Mg homeostasis extremely dynamic and complex.

Normal Mg concentrations in plasma of cattle are 1.7 to 3.3 mg/dl (Allcroft, 1947, 1960). A limit of 1.8 mg/dl has been reported (Rook and Balch, 1958; Butler, 1963). The kidneys play a key role in maintaining Mg homeostasis, especially under conditions of hypermagnesemia. Thus, oral or intravenous Mg loads are rapidly excreted in the urine (Chesley and Tepper, 1958). Storry and Rook (1963) estimated renal threshold values in two cows to be 1.46 mg/dl. Wilson (1969) estimated the renal threshold of Mg in sheep to be 2 mg/dl. Rook and Balch (1958) reported that urinary Mg of lactating cows fed a low Mg ration decreased to very low levels before serum Mg decreased below 1.8 mg/dl. The correlation between absorption and urinary excretion of Mg reported by Gerken and Fontenot (1967) and Ammerman et al. (1972) would suggest that excretion of Mg in urine reflects availability of Mg in the diet. Kemp et al. (1961) found the daily excretion of Mg in urine to be
a better measure of Mg status than Mg concentration in blood of mature cows.

Studies that involve feeding experimental Mg-deficient diets are difficult to interpret because inappetence commonly develops in hypomagnesemic animals. Thus, changes seen in animals fed these diets may be due to inappetence rather than consumption of a low Mg diet. Fasting is known to have marked effects on serum Ca and Mg in several species (Dale et al., 1954; Halse, 1958; Herd, 1966; Estep et al., 1969). This is especially the case if animals are subjected to a Ca and Mg demand during fasting. Figure 3 shows the dramatic changes associated with fasting in a lactating Jersey cow (Littledike and Cox, 1979). Plasma Ca and Mg markedly decreased even though lactational Ca and Mg demand were progressively reduced as fasting continued. Plasma PTH increased only minimally even though significant hypocalcemic stimulus was present. Upon refeeding, PTH levels increased markedly in spite of an increasing plasma Ca level. Thus, fasting apparently interferes with appropriate PTH secretion and normal Ca and Mg homeostasis may not be maintained. Other lactating cows (not shown) that were fasted, but not milked during the fasting period, maintained normal or increased Ca and Mg levels in their plasma.

Lavor (1976) suggested that redistribution of Mg from the extracellular to the intracellular pool, or inhibition of release of Mg from the intracellular pool, may promote hypomagnesemia. No depletion of the Mg content of soft tissues has been demonstrated in hypomagnesemic cattle (Wacker and Parisi, 1968); thus, intracellular Mg apparently does not serve as a significant readily mobilizable store of Mg to replenish extracellular Mg.

Bones of young calves raised on Mg-deficient diets can serve as a major source of Mg because of their rapid rate of bone remodeling. As bones of young calves fed Mg-deficient diets are remodeled, Mg-poor bone mineral replaces the original bone mineral containing normal amounts of Mg and the freed mineral is available to meet the other Mg needs of the calf (Blaxter and Rook, 1954; Blaxter, 1956). In older animals, bone has much less significance as a labile source of Mg to maintain extracellular fluid Mg concentration because their bones usually have a lesser percentage of active exchangeable surface than that of young animals. Because of the small amount of Mg in bone (Ca:Mg ratio about 50:1), a large amount of bone has to be remodeled to yield significant amounts of Mg. Because the Ca:Mg ratio in milk is about 13:1, a highly selective mechanism would be required.

Figure 3. Response of plasma calcium, magnesium and parathyroid hormone (PTH) associated with fasting of a lactating Jersey cow.
for Mg uptake from bone and transfer of Mg to milk to be a significant source of milk Mg, and no such mechanism has been described.

The occurrence of major hypomagnesemic and hypocalcemic diseases of cattle is associated with increased Mg and Ca demands of lactation. Figure 4 shows effects of alternate periods of milking (4 d) and not milking (3 d) on plasma Ca, P, Mg and PTH in a Jersey cow (Littledike, 1976). Initiation of milking was associated with hypocalcemia, hypomagnesemia and hypophosphatemria. A similar series of changes occurs in postpartum cows associated with initiation of lactation, as will be shown later. However, if diets are low in Mg, then little hypermagnesemia, and possible hypomagnesemia, is found during initiation of lactation during the peripartal period in cows (Barber and Wright, 1983).

Parathyroid Hormone

Biosynthesis of PTH consists of several steps: Pre-Pro-PTH, a 115-amino acid peptide, is converted to Pro-PTH (90 amino acids), which is transported to the Golgi apparatus and enzymatically cleaved to PTH-(1-84). This PTH-(1-84) is incorporated into membrane-bound granules where it is stored until secreted. No Pro-PTH is incorporated into secretory granules (Habener et al., 1976; Habener, 1981).

Up to 70% of newly transcribed PTH-(1-84) is not incorporated into secretory granules within the Golgi apparatus, but is released into the cytoplasm. There the PTH-(1-84) is vulnerable to proteolysis and is cleaved to inactive fragments (Morrissey et al., 1980). Intracellular degradation of PTH-(1-84) is stimulated by high extracellular concentrations of Ca, whereas low extracellular Ca concentrations inhibit extracellular destruction of PTH (Chu et al., 1973; Habener et al., 1975). The only biologically active form of PTH secreted by the parathyroid gland is PTH-(1-84). Numerous inactive carboxy terminal fragments are also secreted (Mayer et al., 1979). The amount of parathyroid tissue present is dependent on Ca status of the animal. Chronic hypocalcemia stimulates hyperplasia of the parathyroid glands with concomitant increases in PTH production (Habener, 1981). Conversely, chronic hypercalcemia results in a decreased mass of parathyroid tissue and perhaps a decreased ability to secrete active PTH in response to a Ca drain, such as occurs at onset of lactation. Circulating PTH consists of intact PTH-(1-84) and carboxy- and amino-terminal fragments of PTH-(1-84) (Berson and Yalow, 1968). Metabolism of intact hormone by peripheral organs, primarily liver, kidney and bone, contributes greatly to the heterogeneity of the circulating PTH (Canterbury et al., 1975). While PTH-(1-84) is fully active on renal tissue, increasing evidence suggests that PTH-(1-84) must be cleaved to PTH-(1-34) before it will stimulate bone resorption.
An inverse sigmoidal relationship exists between PTH secretion and extracellular Ca concentration. A basal level of PTH secretion exists that cannot be suppressed by Ca. Likewise, at some low extracellular Ca concentration, the chief cells are maximally stimulated, and further reduction in Ca does not result in increased secretion of PTH (Mayer and Hurst, 1978; Brown, 1983).

Parathyroid hormone causes a rapid increase in urinary excretion of P while inhibiting urinary excretion of Ca and Mg. These effects are mediated by cAMP generated as a result of PTH stimulation of adenylate cyclase within the tubular epithelium (Chase and Aurbach, 1968; Sutton and Dirks, 1978). The net effect is to reduce plasma P concentration and increase plasma Ca and Mg concentrations.

Parathyroid hormone has a biphasic effect on bone mineral mobilization. The initial effect is to stimulate the osteocyte-osteoblast pump, which moves Ca from the bone fluid compartment surrounding osteocytes, across the endothelial lining cells, and into the extracellular fluid compartment. Parathyroid hormone also stimulates osteoclastic resorption of bone. This effect is slower than the effect on the osteocyte-osteoblast pump, but is capable of releasing much greater quantities of Ca from bone (Capen and Martin, 1983). Antisera that have been used to measure PTH in animals have, in most instances, not been well characterized. Thus, the exact sequence or portion of the PTH molecule that these antibodies recognized is not known. As most of the antisera probably recognize and have different titers for more than one portion of the PTH molecule, the predominant reactivity of a given antiserum to various portions of the PTH molecule could vary with dilution of the antiserum in the assay and also the energy level of its binding to the various portions of the PTH molecule. With these uncharacterized PTH antisera, it is not known if the antiserum measures the C-terminal of the PTH molecule and thus measures inactive PTH fragments that circulate; or if the antiserum measures a mid-molecule portion of the PTH and thus reflects mostly intact PTH(1-84); or if the antiserum measures N-terminal portions of the PTH molecule representing either intact PTH molecule or the (1-34) biologically active species of the PTH molecule. Ideally, measurements of the N-terminal would most nearly represent active circulating PTH. Only 1 to 10% of circulating PTH, is 1-34 PTH, which is the form that is taken up and stimulates bone (Slatopolsky et al., 1981). Thus, PTH data in the literature may need to be reevaluated to be certain that the PTH that is measured represents active forms of PTH.

**Vitamin D Endocrine System**

Vitamin D is a pro-hormone formed by ultraviolet irradiation of skin (D₃) or plant material (D₂). A general scheme of vitamin D metabolism and the factors that influence production of 1,25-(OH)₂D and 24,25-(OH)₂D are shown in Figure 5. Vitamin D enters the blood from the gut (D₂ or D₃) or the skin (D₃) and rapidly accumulates in the liver and adipose tissue. In the liver, vitamin D is converted to 25-hydroxyvitamin D (25-(OH)D). This metabolite is the major circulating form of vitamin D under normal conditions and serves as the precursor of the other vitamin D metabolites (Horst and Littledike, 1982). Plasma 25-(OH)D concentration is an excellent indicator of vitamin D status (deficiency or toxicity) of animals. After exiting the liver, 25-(OH)D is transported in the blood bound to a specific transport protein (vitamin D binding protein) and is converted to 1,25-(OH)₂D by 25-(OH)D-1-α-hydroxylase (1-α-hydroxylase) located in the kidney. The 1,25-(OH)₂D is responsible for most of the biological activity attributed to vitamin D. Functions of other metabolites of vitamin D are unknown and may represent oxidative degradation steps for inactivation and excretion of vitamin D and its metabolites. The activity of the renal 1-α-hydroxylase enzyme is closely regulated. Hypocalcemia and(or) hypophosphatemia are the major stimuli for production of 1,25-(OH)₂D. Parathyroid hormone is necessary for full hypocalcemia-mediated stimulation of renal 1,25-(OH)₂D production (Trechsel et al., 1980). Stimulation of 1α-hydroxylase activity by severe hypophosphatemia is mediated via the pituitary gland (Gray, 1981) and does not require PTH.

A major physiological role of 1,25-(OH)₂D is to stimulate facilitated transport of Ca and P across the intestinal brush border (Wasserman and Taylor, 1976). Thus, 1,25-(OH)₂D initiates intestinal processes that permit adaptation to various dietary levels of Ca or P. In addition, 1,25-(OH)₂D also enhances bone resorption mechanisms, after they have been initiated by PTH.
Figure 5. Major pathways of vitamin D metabolism and factors influencing production of 1,25-(OH)₂D and 24,25-(OH)₂D (Horst, 1986).

Calcitonin

Calcitonin is a 32-amino acid peptide secreted by the ultimobranchial "C" cells (incorporated into the thyroid gland in mammals) and within the gastrointestinal tract. Calcitonin lowers blood Ca. It acts on bone to inhibit osteoclastic resorption (Weisbrode and Capen, 1974), and decreases renal tubular reabsorption of Ca, P and Mg. Secretion of CT is primarily stimulated by hypercalcemia or hypermagnesemia. However, the degree of hypermagnesemia that causes CT release is generally seen only under experimental conditions.

The main function of CT in mineral metabolism is probably to prevent hypercalcemia after ingestion of a meal. When a high-Ca meal is ingested, CT secretion is stimulated, often before any hypercalcemia develops. This effect is mediated by intestinal hormones such as gastrin, glucagon and cholecystokinin, which act as secretagogues of CT (Care et al., 1970; Cooper et al., 1972).

Milk Fever

Milk fever (MF), also referred to as parturient paresis or parturient hypocalcemia (PPH), is a hypocalcemic disorder of dairy cattle that occurs during the peripartal period. Incidence of MF varies greatly among breeds. The incidence in the Jersey breed has been reported to be 12.4 to 30% and in the Friesian breed from 2.1 to 3.9% (Littledike, 1974). Individual herds may have 50 to 80% of the cows affected each year, depending on breed, age and diet.

At parturition, lactation creates a sudden, large demand for Ca. Since colostrum contains about 2.3 g Ca/liter, a cow producing 10 liters of milk on the day of calving would lose 23 g of Ca. This is about two or three times as much Ca as is present in the extracellular fluid. Almost all cows will experience some degree of hypocalcemia at this time, and plasma concentrations of PTH (Mayer et al., 1979) and 1,25-(OH)₂D (Horst, 1978b) increase as blood Ca concentrations decrease (figure 6). The kidney
Figure 6. Mean (± SE) of plasma calcium, magnesium, 1,25-(OH)₂D and parathyroid hormone (PTH) in seven aged Jersey cows that developed postparturient hypocalcemia.

Dietary factors and age may predispose cows to MF. The Ca content of the prepartal diet can greatly affect the incidence of MF (Boda and Cole, 1956). Diets that contain more than 100 g Ca/d provide much more Ca to the cow than is needed at the end of gestation. This surplus dietary Ca suppresses the Ca homeostatic processes to the point that full activation of these processes may require several days. In contrast, by providing less Ca (15 to 20 g/d) in the prepartal diet, MF can be prevented (Goings et al., 1974). The low-Ca diet stimulates prepartal production of PTH and 1,25-(OH)₂D and initiates bone resorption and intestinal Ca transport processes (Green et al., 1981). Cows so prepared are able to utilize successfully these mechanisms to restore normocalcemia during the prepartal period. When lactation ends, the necessity for supplying Ca for milk production is absent, and the homeostatic mechanisms that were used to meet those Ca demands become relatively quiescent. Thus, 1,25-(OH)₂D concentrations decline and bone resorption and intestinal Ca absorption mechanisms revert to a low, basal rate of activity. (Fetal Ca demands apparently stimulate only minimal response of the Ca homeostatic mechanisms in the bovine.) Aged cows are at greater risk of developing MF than are young cows because both basal and hormonally stimulated intestinal Ca absorption and bone resorption decline with age (Horst et
INTERACTIONS OF Ca, P, Mg AND VITAMIN D

Vitamin D and its metabolites have been used to prevent MF with some success. The prophylactic activity of the vitamin D metabolites resides mainly in their ability to enhance intestinal Ca absorption (Braithwaite, 1978; Hove, 1984). Because the active vitamin D metabolites increase intestinal Ca absorption, they would be most effective in preventing MF in herds fed a high Ca diet before parturition. Vitamin D metabolites do not increase bone resorption in these cows (Goff et al., 1986a). The hypercalcemia resulting from enhanced intestinal Ca absorption inhibits endogenous secretion of PTH necessary for increased bone resorption. Cows that develop MF subsequent to treatment with vitamin D metabolites may show an inhibition of the normal, endogenous 1,25-(OH)2D response to hypocalcemia (figure 7). Thus, when vitamin D or its metabolites are used in an effort to prevent MF and fail, the resulting MF is often clinically more severe and prolonged than the naturally occurring MF. This suggests that vitamin D compounds and the hypercalcemia they produce are repressing the cow's endogenous adaptive homeostatic mechanisms rather than augmenting them.

Synthetic bovine PTH (1-34) has recently been used to prevent MF (Goff et al., 1986b; figure 8). Continuous, intravenous infusion of PTH before parturition stimulates both intestinal Ca absorption [via 1,25-(OH)2D production] and bone Ca resorption in the periparturient cow. Inhibition of endogenous adaptive homeostatic mechanisms does not seem to be a problem if severe hypercalcemia...
Figure 8. Changes in plasma calcium, magnesium, parathyroid hormone (PTH), total inorganic phosphate, 1,25-(OH)₂D and hydroxyproline in an aged Jersey cow intravenously infused (at two dose rates) with synthetic PTH-(1-34) bovine parathyroid hormone during the peripartal period. Arrow indicates time of parturition.

(>13 mg/dl) is avoided following administration of PTH. Once an effective practical delivery system is developed, exogenous administration of PTH could become a practical alternative to the low Ca diet as a tool for management of MF in dairy herds.

**Grass Tetany**

Figure 9a, b shows the changes associated with development of grass tetany (GT) in lactating beef cows grazing rye grass pastures during spring (Littledike and Cox, 1979). Cows not developing GT (data not shown) developed only mild hypomagnesemia during the grazing period, while the cow that developed GT had severe prolonged hypomagnesemia. The letter S represents the time of occurrence of clinical signs of GT; T + 10 and T + 20 indicate the time (min) after treatment with a commercial Ca + Mg solution. Clinical signs of grass tetany were evident only when the cow developed severe hypocalcemia. Plasma 1,25-(OH)₂D levels seemed appropriate for the degree of hypocalcemia that was present throughout the experimental period. In contrast, during the acute hypocalcemia period, PTH levels decreased and were inappropriate for the degree of hypocalcemia that was present. Plasma PTH levels were determined in cows with or without signs of GT in another study (Littledike et al., 1983). A reversal of the normal plasma Ca:PTH relationship was evident, indicating that, at least at the time of tetany, PTH secretion appeared inappropriate in cows with severe hypocalcemia and hypomagnesemia. This finding should be reevaluated with techniques, such as a bioassay for PTH, to quantify the amount of biologically active PTH present during the development of this disease. This reevaluation is needed to be certain that the radioimmunoassay technique is reflecting biologically active PTH and not inactive fragments of PTH.
Figure 9. Changes in plasma components (mean ± SE) of a lactating beef cow grazing a heavily fertilized rye grass pasture in Georgia. 0 time is the first day of the grazing period. S indicates when the cow developed the clinical signs of grass tetany. T + 10 and T + 20 indicate 10 and 20 min, respectively, following treatment with a Ca + Mg solution. PTH-(1-84) is the parathyroid hormone (PTH) concentrations quantified with a PTH antibody that detects primarily C-terminal PTH, and PTH-(1-34) is the PTH quantified with a PTH antibody that detects primarily the N-terminal PTH. The OH-PRO is the plasma-free hydroxyproline concentration (Littledike and Cox, 1979).

Figure 10 summarizes analyses from a number of normal cows, normal postpartum cows and cows with PPH, wheat pasture poisoning (WPP) and GT. Mean plasma levels of PTH and 1,25-(OH)2D are inversely proportional to plasma Ca concentrations in all cows except those with GT. In cows with GT, the plasma PTH secretion was inappropriately low. In cows with PPH, hypocalemia stimulated PTH secretion, which in turn caused Mg conservation by the kidney and resulted in a secondary hypermagnesemia. In WPP, and especially in GT, the forage is low in Mg; thus, PTH conservation of Mg is less significant because blood Mg is already below the renal threshold and conservation is already occurring.

**Wheat Pasture Poisoning**

Pregnant or lactating beef cows may develop signs of wheat pasture poisoning (WPP) when grazing winter wheat or other cereal grains during spring. Death loss may reach 20% on some pastures; however, 2 to 3% is common (Stewart et al., 1981). Figure 11 shows the
Figure 10. Mean plasma calcium concentration plotted against plasma 1,25-(OH)₂D and parathyroid hormone (PTH) concentrations of normal (n=8), normal postpartum (n=8), grass tetany (n=11), wheat pasture poisoning (n=5) and milk fever (postpartum hypocalcemia; n=10) cows. PTH was quantified with a N-terminal directed antibody.

severe hypocalcemia and moderate hypomagnesemia that accompany this disease (Bohman et al., 1983) (item 1). Development of clinical signs was associated with development of severe hypocalcemia. Plasma PTH (figure 11b) and 1,25-(OH)₂D (figure 11d) levels appeared appropriate for the degree of hypocalcemia that was present. Thus, moderate hypomagnesemia does not alter appropriate increases in the secretion of PTH as estimated by plasma PTH levels. Plasma PTH levels were determined by radioimmunoassay techniques. Most cows with WPP develop a more severe hypocalcemia than cows with GT, but the degree of hypomagnesemia is less severe (Littledike et al., 1983). The severity of the clinical signs of GT (excitement, convulsion, tetany) seems to be related to severity of the hypomagnesemia. The two most severely affected cows had clinical signs and plasma Ca and Mg levels similar to cows with classic GT (Bohman et al., 1983).

Rickets and Osteomalacia

Rickets and osteomalacia are bone diseases associated with deficiency of either Ca, P or vitamin D. Rickets is a disease of young, growing animals, in which the cartilaginous matrix at the growth plate and the osteoid matrix formed during bone remodeling fail to mineralize. In adults (no active growth plates), the term osteomalacia is used to describe the failure of osteoid matrix to mineralize. In animals that are vitamin D-deficient, fibrous osteodystrophy secondary to hyperparathyroidism can also develop (Jubb et al., 1985). The hyperparathyroidism is associated with the hypocalcemia that usually accompanies severe vitamin D deficiency.

The role of vitamin D in bone formation is unclear. Vitamin D may only be important for maintenance of normal blood Ca and P concentration, because histologically normal bone can be attained during vitamin D deficiency if Ca and P are administered intravenously to overcome the deficit in intestinal absorption due to vitamin D deficiency (Underwood and DeLuca, 1984; Balsan et al., 1986). However, although treatment of vitamin D-deficient animals with 1,25-(OH)₂D corrects the hypocalcemia and hypophosphatemia, the bone is not completely normal, implying a role for other metabolites of vitamin D in bone formation (Rasmussen and Bordier, 1978). Phosphorus seems to be necessary for initiation of the mineralization process (Glimcher and Krane, 1968).

Overt rickets is readily diagnosed by clinical signs and radiographic examination of the skeleton. Elevated serum alkaline phosphatase and low serum P concentrations are also indicative of rickets. Low serum concentration of 25-(OH)D is an excellent indicator of vitamin D deficiency rickets in sheep (<20 ng/ml; Hidiroglou et al., 1979), cow and pig (<10 ng/ml; Horst and Littledike, 1982; Engstrom et al., 1984).

Newborn pigs are able to adapt to very low 25-(OH)D present at birth and for the first few weeks of life. Marked increases in renal 1α-hydroxylase activities occur, with large reduction in all plasma vitamin D metabolites except 1,25-(OH)₂D. Plasma 1,25-(OH)₂D can be maintained at a near normal level until plasma 25-(OH)D concentration falls below 1 ng/ml. Vitamin D deficiency rickets is uncommon in animals housed outside because, in all but the higher latitudes, sunlight stimulates sufficient
Figure 11. Mean (± SE) plasma calcium, magnesium, parathyroid hormone (PTH), phosphorus and 1,25-(OH)2D concentrations of non-tetany (n=27) and tetany cattle (n=5) from a study of wheat pasture poisoning. 1,25-(OH)2D values represent only tetany cattle (n=5; Bohman et al., 1983).
endogenous production of vitamin D₃ to prevent rickets. Total confinement of animals is becoming increasingly more common and necessitates that adequate vitamin D be supplied via the diet to prevent clinical or subclinical rickets. Of the common farm animals, the piglet is born with the lowest plasma concentrations of 25-(OH)D (Horst and Littledike, 1982). In confinement operations, the piglet receives little vitamin D until it begins eating a starter ration. Thus, vitamin D status of the piglet for the first few months after birth is highly dependent on vitamin D status of the sow, as shown in figure 12. Treatment of sows with vitamin D before parturition can be an effective method of supplementing young piglets with vitamin D (via the sow’s milk) and 25-(OH)D (via placental transport) during the time period between birth and weaning (Goff et al., 1984).

**Vitamin D Toxicity**

As vitamin D deficiency syndromes become less common, errors in supplementation and overzealous use of injectable preparations of vitamin D increase the incidence of vitamin D intoxicification. Excessive vitamin D causes prolonged hypercalcemia and hyperphosphatemia, resulting in metastatic calcification of soft tissues, especially blood vasculature and kidneys. Vitamin D intoxication results in greatly elevated plasma concentrations of 25-(OH)D and most of the other vitamin D metabolites. Plasma levels of 25-(OH)D can be very useful in diagnosis of suspected toxicity (Littledike and Horst, 1982; Harrington and Page, 1983).

Several species of plants, such as Solanum malacoxylan, Cestrum diurnum and Trisetum flavescens contain a glycoside of 1,25-(OH)₂D. Following ingestion, the glycoside linkage is broken and the 1,25-(OH)₂D is absorbed. 1,25-(OH)₂D causes rapid hypercalcemia and widespread metastatic calcification. The result may be a wasting syndrome in cattle grazing pastures containing these plants (Haussler et al., 1976).

**Literature Cited**


