Mechanisms of calcium metabolism in the dairy cow; relation to hypocalcemia.

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Incidence of hypocalcemia in USA confinement herds

<table>
<thead>
<tr>
<th>Ca (mM)</th>
<th>Lactation #</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>1.0</td>
<td>2</td>
</tr>
<tr>
<td>1.5</td>
<td>≥3</td>
</tr>
<tr>
<td>2.0</td>
<td>25%</td>
</tr>
<tr>
<td>2.5</td>
<td>54%</td>
</tr>
<tr>
<td>3.0</td>
<td>53%</td>
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Normal, Sub-clinical, Milk Fever
EFFECTS OF HYPOCALCEMIA AND MILK FEVER ON DISEASE RESISTANCE

1. Reduced feed intake ➔ worsens negative energy balance

2. Lack of muscle contraction
   - impairs teat sphincter closure
   - failure to expel contents of uterus after calving

3. Reduction in Immune Cell Response to Stimuli
   - Calcium is the “second messenger” of immune cells
Normal Lymphocyte activation

Cytokine, antigen, or bacterial cell wall

Endoplasmic reticulum

Ca^{++} Ca^{++} Ca^{++} Ca^{++} Ca^{++} Ca^{++} Ca^{++} Ca^{++} Ca^{++} Ca^{++} Ca^{++} Ca^{++} Ca^{++} Ca^{++}
Normal Lymphocyte activation

Cytokine, antigen, or bacterial cell wall

Antibody, Antibacterial peptide production, etc.
After Ca infusion (n=5)
Pretreat (n=5)

Fold increase in Fluo-4/Fura red

Lymphocyte activation during Hypocalcemia
Cytokine, antigen, or bacterial cell wall

Endoplasmic reticulum
Lymphocyte activation during Hypocalcemia

Cytokine, antigen, or bacterial cell wall

IP₃

Endoplasmic reticulum

Ca²⁺

Ca²⁺

Ca²⁺
Lymphocyte activation during Hypocalcemia

Cytokine, antigen, or bacterial cell wall
Ca Dynamics in the Periparturient Cow

**Late Gestation**

650 kg dairy cow needs to absorb:

7-8 g Ca to support daily maintenance requirement

= Endogenous fecal loss, urine loss

9-10 g Ca to support fetal skeleton development.

Total = 16-18 g Ca that must be restored to blood to maintain normal blood Ca concentrations

**Primarily met by absorbing dietary Ca!**
Ca Dynamics The Day of Calving

Maintenance – 7-8 g Ca

First Colostrum – 7.5 Kg X 2.3 g Ca / kg = 17.25 g Ca

Within 45 min of colostrum removal - Ca uptake by mammary = ¾ of 17.25 = 10-12 g Ca

2nd milking removal at 12 hrs – mammary sequestered 11 g Ca plus additional 3 g Ca (8.7 kg X 1.7 g Ca / kg= 14.8 g Ca)

Within 45 min of second milk removal - Ca uptake by mammary for next milk is another 8-10 g Ca.

Total Ca loss from blood between calving and 14 hrs after calving can be 50 g Ca.

Increase in Ca Demand the first half day after calving

50 g Ca (post-calving ½ day) – 18 g Ca (precalving) = ~ 32 g Extra Ca that must be brought into blood to avoid hypocalcemia
Ca Homeostasis Begins With The Parathyroid Gland

Parathyroid cells have a Ca-Sensing G-Protein Coupled receptor on their surface.

Lack of extracellular ionized Ca++ bound to the Ca-Sensing receptor elicits Parathyroid Hormone Secretion

**Parathyroid Hormone Targets**

- Kidney tubule cells
- Bone osteocytes and osteoblasts
- Salivary glands

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**Extracellular Ca Pool ~11 g**

**Serum Ca pool ~ 3.5 g**

- **Urine Ca**
  - 0.2 g
- **Lactation**
  - 20-30 g increase in Ca demand!
  - Colostrum ~2.3 g Ca/L
  - Milk ~ 1.1 g Ca/L

- **Endogenous Fecal Loss**
  - 5-8 g Ca

- **25-OH vit D**
  - 1,25(OH)₂D

**PTH**

**Diet Ca**

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**PTH**
Figure 50.5

Parathyroid Hormone

Bone
~ 8 Kg Ca
Osteoclast recruitment & activation

Bone Fluid
~ 9 g Ca

Diet Ca = 45-150 g

Passive Ca Transport

Active Ca Transport

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Parathyroid Hormone

Kidney
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1,25(OH)₂D

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Endogenous Fecal Loss
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Osteocytic Osteolysis
Ca within fluid surrounding each osteocyte and within canaliculi is pumped into blood under control of PTH

Endosteal surface of a single spicule of trabecular bone in the resting state. Note the small microfracture within the bone matrix.
Activation – osteoblasts retract from the surface of the area of bone to be remodeled. Osteoclasts move toward the site of exposed bone.

Resorption – osteoclasts develop a ruffled border and form a tight seal with the exposed bone. Secretion of acids and enzymes causes dissolution of the organic matrix freeing the minerals which enter extracellular fluid.
Resorption – osteoclasts “scoop” out bone matrix and mineral to a depth of approximately 50 µ.

Reversal – osteoclasts leave the area and become inactive. Osteoblasts from among the endosteal bone lining cells at the edge of the resorption site now enter the depths of the resorption cavity.
Osteoblasts begin producing new bone matrix to fill in the resorption cavity. Some become trapped within the matrix to give rise to new osteocytes.

The area of remodeled bone re-enters a resting state. However there is now approximately 50µ of new bone formed to replace the microfracture with new bone.
Normal Bone Remodeling – “Old” bone resorbed is replaced by New
Lactational osteoporosis

The need for calcium to support lactation causes a “disconnect” between the resorptive and reversal phases of the remodeling process. Mediated by PTH and perhaps PTH-rP (beyond first week of lactation??)

This occurs to some extent in all mammals even if diet calcium is adequate. PTH-rP made by mammary gland!!

This resorbed bone is not replaced until some later point when dietary calcium absorption is sufficient to sustain calcium requirements of milk production, growth etc. About 5 weeks in a cow. By that point 10-13% of skeletal Ca will have been removed.

The resorbed bone can be successfully replaced in late lactation??

Lactational Osteoporosis

Osteoclasts dig down 50 μ but osteoblasts fail to replace matrix leaving 50 μ divots
Lactational Osteoporosis

Later when Ca balance is better or lactation ceases - bone resorbed is replaced with New bone as improved Ca status triggers osteoblast activity

Lactational osteoporosis is reversible
Parathyroid Hormone

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Osteoclast recruitment & activation

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 Passive Ca Transport
 Active Ca Transport

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25-OH vit D
1,25(OH)2D

Urine Ca
0.2 g

Endogenous Fecal Loss
5-8 g Ca

Lactation- 20-30 g increase in Ca demand!
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PTH

Target Tissues
Bone, Intestine

1,25-Dihydroxyvitamin D3

25-Hydroxyvitamin D3

KIDNEYS

Diet

Liver

7-Dehydrocholesterol

Diet

Vitamin D3

HO

OH

HO

OH

HO

OH

HO

OH

UV Light
Heat

Target Tissues
Bone, Intestine

1,25-Dihydroxyvitamin D3

25-Hydroxyvitamin D3

KIDNEYS
Vitamin D-dependent Active Transport of Ca

Ca++  Ca++  Ca++

VDR

Ca++  1,25-vitD

VDR-1,25-vitD

VDR
Vitamin D-dependent Active Transport of Ca

Ca++  Ca++  Ca++

TRPV6  CaBP  VDR-1,25-vitD  VDR-1,25-vitD

Ca-ATPase pump

Ca++
Vitamin D-dependent Active Transport of Ca

Ca\textsuperscript{++} \rightarrow CaBP

Ca - ATPase Pump

TRPV6
Vitamin D-independent Passive Transport of Ca

Ionized Ca above 6 mM

Vitamin D-independent Passive Transport of Ca
Vitamin D-independent Passive Transport of Ca++

Ca++ Ca++ Ca++ Ca++

Ca++ Ca++

Ca++ Ca++

Ca++
Ca Homeostasis – How long does it take to react?

Kidney

*PTH* promotes Ca reabsorption from tubular fluid within minutes (but normally brings <1 g Ca into blood).

Renal production of 1,25-dihydroxyvitamin D. Plasma 1,25-dihydroxyvitamin D can increase within 8*-16 hrs, and requires another 12-24 hrs for significant increase in proteins involved in Ca absorption to be produced.

Bone

Osteocytic Osteolysis – minutes to a few hours (~ 9 g Ca***)

Osteoclastic Resorption – 36-96 hr, depending on age of cow and diet. Can bring 800 – 1200 g Ca into blood

Why doesn’t Ca Homeostasis work for all cows???

Aged cows lose vitamin D receptors in intestine

Aged cows have fewer sites of active bone resorption (fewer osteoclasts) capable of responding to PTH rapidly

**BLOOD pH AFFECTS TISSUE RESPONSIVENESS TO PTH!**
Cows fed high DCAD diets become alkalotic and fail to respond to PTH stimulation by increasing blood Ca and 1,25-(OH)2 Vit D production. THIS CAUSES SEVERE HYPOCALCEMIA

A. pH=7.35
Normal Mg

B. pH=7.45
Normal Mg

C. pH=7.35
Hypomagnesemia

PTH Receptor
Adenyl cyclase complex
Mg
Cyclic AMP

PTH Receptor
Adenyl cyclase complex
Mg
Cyclic AMP

PTH Receptor
Adenyl cyclase complex
×
Cyclic AMP
Acid-Base Physiology & Strong Ions

All solutions must be electrically neutral., ie.

The number of + charges in a solution must equal the number of - charges in a solution.

Neutral solutions have an equal number of H⁺ and OH⁻ particles in them. This results in a pH of 7.0

If K⁺ ions are added to the solution it necessitates a loss of H⁺ ions and a simultaneous increase in OH⁻ in the solution to achieve electroneutrality. The pH increases.

Diet Cation-Anion Difference (DCAD) & Acid-Base Status

Diet Cations (Na⁺, K⁺, Ca++, Mg++, NH₄⁺) absorbed into the blood will alkalinize the blood

Diet Anions (Cl⁻, SO₄⁻, PO₄⁻) absorbed into the blood will acidify the blood.
NaCl has equal numbers of + and - charges

Both Na\(^+\) and the Cl\(^-\) are absorbed into the blood with nearly 100% efficiency. The blood gains an equal number of + and - charges. NO CHANGE in Electrical charge = NO CHANGE in pH!!!

Ca Cl\(_2\) also has an equal number of + and – charges

The Cl\(^-\) is absorbed with nearly 100% efficiency into the blood. Less than 20% of the Ca in the salt is absorbed into the blood.

More – charges enter the blood than do + charges. The blood becomes more negative necessitating a rise in H\(^+\) = lower pH = More acidic blood

Milk Fever Prevention Strategies

1. Avoid high potassium forages for close-up cows so cows are less alkaline
2. Add anions (Cl or Sulfate) to diet to reduce blood (and urine) pH.
3. Diet Mg = 0.4% must be available to cow
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2 Eq of each anion source fed

- HCl
- NH₄Cl
- Ca chloride
- H₂SO₄
- Ca sulfate
- Mg sulfate
- Elemental Sulfur
- Water

Urine pH
Parathyroid Hormone

Bone
~ 8 Kg Ca
Osteoclast recruitment & activation

Bone Fluid
~ 9 - 15 g Ca *

Extracellular Ca Pool ~11 g
Serum Ca pool ~ 3.5 g

Diet Ca = 45-150 g **
Passive Ca Transport
Active Ca Transport

Urine Ca
0.2 - 6 g *

Endogenous Fecal Loss
5-8 g Ca

DCAD Equations

Most Commonly Used Equation

(mEq Na + mEq K) – (mEq Cl + mEq S)

Corrected for lower sulfate absorption

(mEq Na + mEq K) – (mEq Cl + 0.6 mEq S)
Minerals/DCAD for Close-up Diets

- Phos at .30-.35%, or lower??
- Mg at .4% to use passive absorption!!
- S between .22 and .4%
- Ca at .85-1.3% ??
- Na at .1-.12%
- K as close to 1% as possible
- Enough Chloride to \( \downarrow \) urine pH.

Blood Phosphorus

1,25\((\text{OH})_2\) Vitamin D

FGF-23

Bone

Kidney

Blood Phosphorus

1,25\((\text{OH})_2\) Vitamin D

FGF-23

Bone

Kidney
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- S between .22 and .4%
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- K as close to 1% as possible
- Enough Chloride to ↓ urine pH.

HOW MUCH Chloride do I add to the diet?

Enough to bring urine pH between 6.2 and 6.8 the week before calving. (Jersey target= 5.8-6.2)

When urine pH is below 5.3 in the cows you may have caused an uncompensated metabolic acidosis = trouble!!!!!!

Thumbrule To Get Started with Anions

% Chloride needed = % K - 0.5

Example -If diet K is 1.3% then bring diet to 0.8 % Cl and check urine pH to fine tune diet
Adapted from Constable et al., 2017 and Charbonneau et al., 2006
Magnesium

Adult Ruminants absorb Mg across rumen wall! Mg insoluble at rumen pH is NOT available.
- **Active transport** process efficient with low diet Mg BUT EASILY POISONED BY DIET K AND NITROGEN
- Second **passive transport** system exists, but requires high concentration of ionized Mg in rumen fluid to work

Keep diet Mg at 0.4% prepartum and early post-partum to take advantage of passive transport of Mg across rumen wall
MAKE SURE Mg Source is AVAILABLE to the cow. Finely ground, not overly calcined!

Magnesium sources

Pre-calving
- using MgSO₄ or MgCl₂ as “anions” also supplies readily available, soluble Mg.

- The better anion supplements on the market include Mg in this form to remove Mg worries pre-calving.

Post-calving
Magnesium Oxide – supply Mg and act as rumen alkalizer.
* my experience; Low Mg = primary cause of mid-lactation milk fevers
Testing Magnesium Oxide Availability

Weigh out 3 g MgO into large vessel.
Add 40 ml of 5% acetic acid (white vinegar) slowly!!
Cap container and shake well, shake again at 15 min. Check the pH at 30 min mark.
Vinegar will be pH 2.6-2.8!
The best MgO will bring the pH up to 8.2.
The worst to just 3.8.
pH is a log scale so this represents >10,000 fold difference in buffering action.

Lean, et al 2014 Meta-Analysis

Studies contrasted use of anion supplements vs controls. Anions had to be fed at least 21 days pre-calving for inclusion in study.
Utilized 15 published studies with 34 diet comparisons.
Cows fed anions produced an average of 1.13 kg more Fat corrected milk / day for first 65 days in milk (or 73 kg 1st 65 days).
Anions cost $12 to $22 / cow

\[
\text{Milk price} = 0.33 \text{ USD/liter} \times 73 \text{ kg in 65 days} = 24.11 \text{ USD}
\]

Over whole lactation – use 318 kg figure (Beede)
\[
0.33 \text{ dollars/liter} \times 318 \text{ kg in 305 days} = 104.94 \text{ USD}
\]

Relative risk Milk Fever has on other Disease Development in that lactation (Curtis et al 1985)

**Ketosis** – 23 fold increased risk (16 fold for RP)
**All Mastitis** – 5 fold increased risk
**Coliform Mastitis** - 11 fold increased risk
**Retained Placenta** – 4 fold increased risk

Reduced retained placenta, improved uterine health, less displaced abomasum, less mastitis? How many $$$$$????