Why Cows Become Hypocalcemic and Steps to Reduce the Impact?

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Iowa State University

College of Veterinary Medicine

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Jesse Goff

I have the following disclosures* related to my presentation:

I own a company, GlycoMyr, that produces vitamin supplements for baby pigs and is trying to patent novel vitamin D compounds for colon cancer and inflammatory bowel disease.

Grants/Research contracts: NIH R15 grant to examine vitamin D effects on colon cancer in mice

Consulting: West Central now Landus Farmer's Cooperative – I developed Soychlor for prevention of milk fever and continue to help them improve that product and do nutritional consults for them.

Investments: Sinking it all into GlycoMyr, TIAA-CREF and 40 acres of Iowa farmland

Wife, Sandra Goff, worked for Validus- a company that performed animal welfare audits of dairies.

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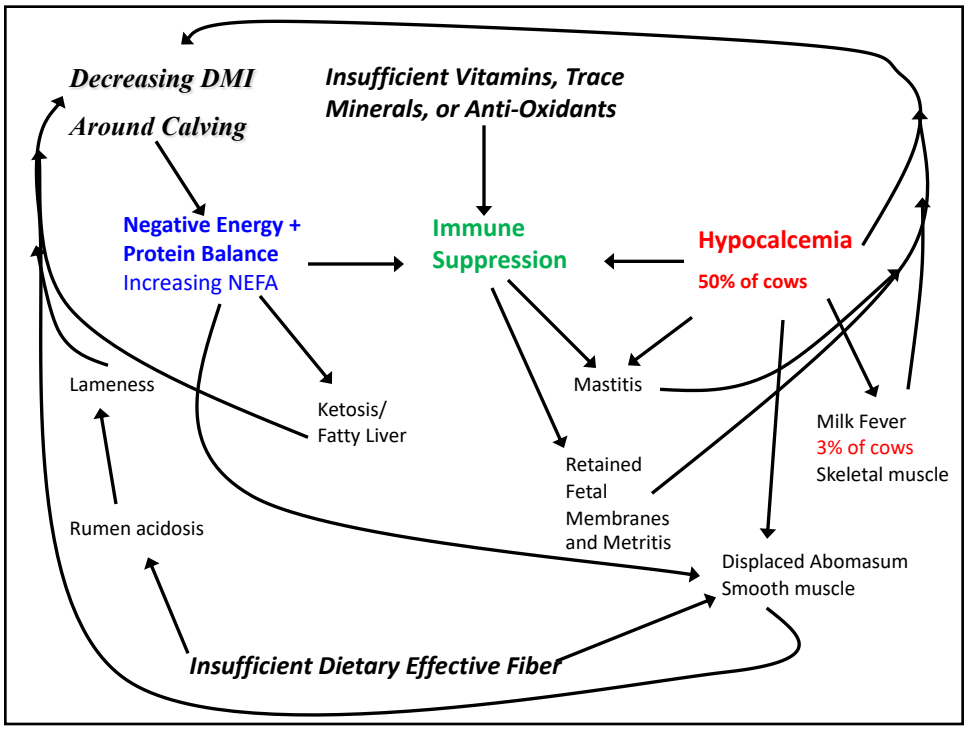
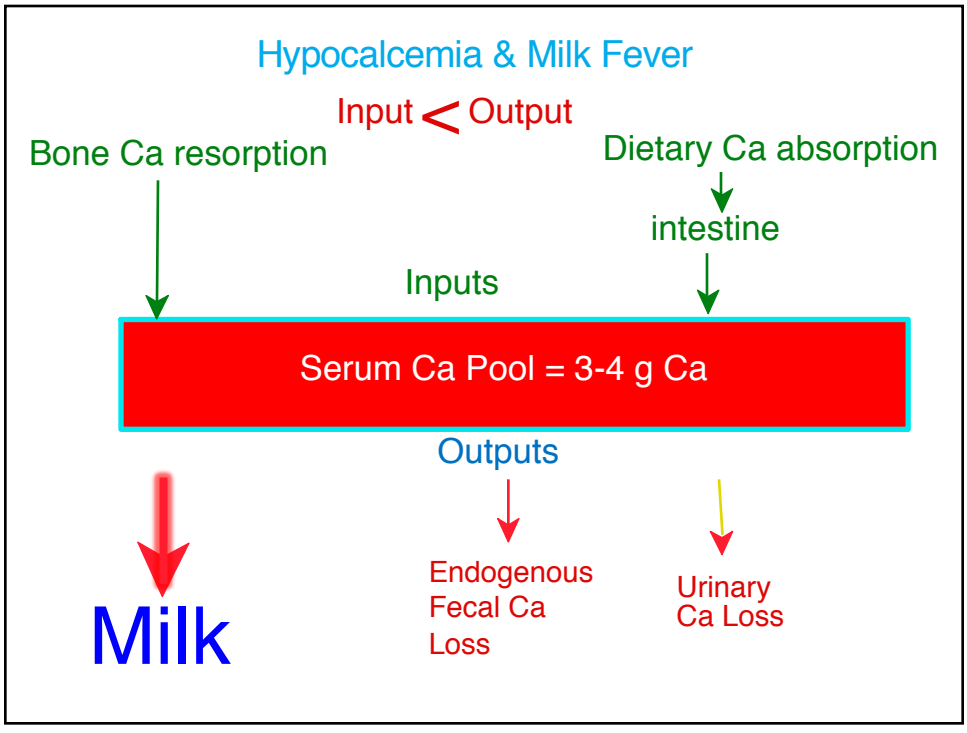

Decreasing DMI
Around Calving
Insufficient Vitamins, Trace Minerals, or Anti-Oxidants
Negative Energy + Protein Balance
Increasing NEFA
Immune Suppression
Hypocalcemia
50% of cows
Lameness
Ketosis/ Fatty Liver
Mastitis
Milk Fever
3% of cows
Skeletal muscle
Retained Fetal Membranes and Metritis
Rumen acidosis
Displaced Abomasum
Smooth muscle
Insufficient Dietary Effective Fiber

3


Hypocalcemia & Milk Fever
Input < Output
Bone Ca resorption
Dietary Ca absorption
intestine
Inputs
Serum Ca Pool = 3-4 g Ca
Outputs
Milk
Endogenous Fecal Ca Loss
Urinary Ca Loss

4

Ca Dynamics at Calving

1 Day Before Calving
Cow needs Ca for maintenance and calf skeletal development ~ 18 g / day.

1st Day of lactation
Cow needs Ca for Colostrum, 2nd milk, and maintenance ~ 50 -55 g / day

~ 32 g Extra Ca that must be brought into blood to avoid hypocalcemia on Day 1 of lactation!!!

Ramberg et al., Am J Phys 1984

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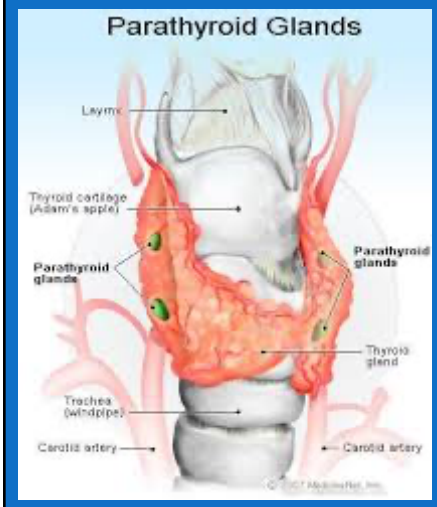

Parathyroid Glands located in neck

Monitor Ca concentration in branch of carotid artery.

Any decrease in Ca concentration causes rapid secretion of parathyroid hormone (PTH)

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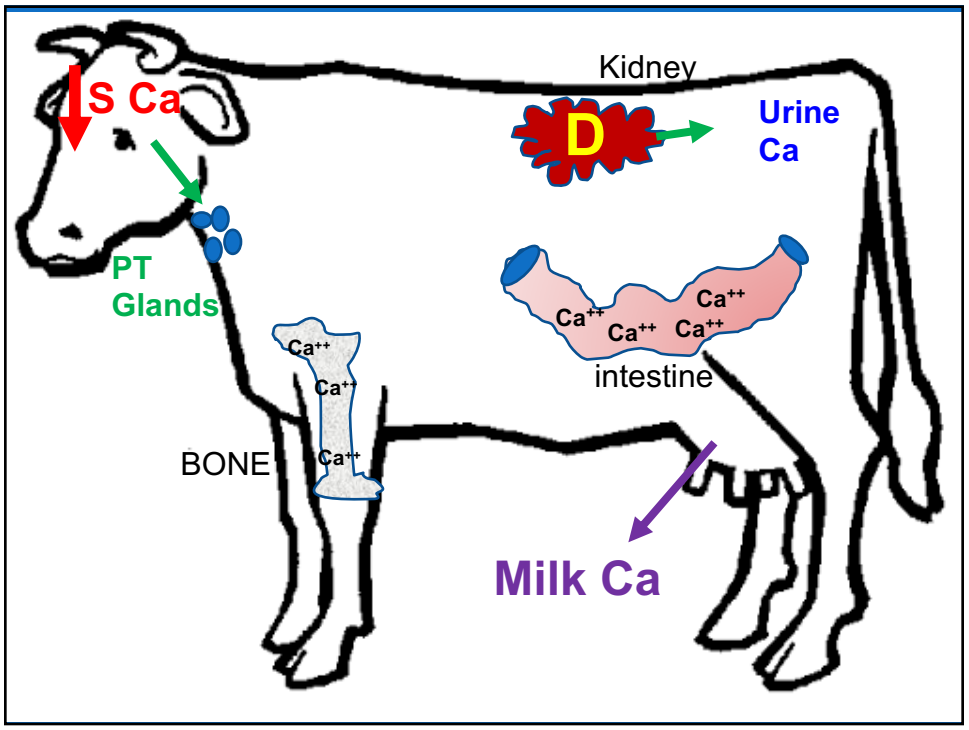
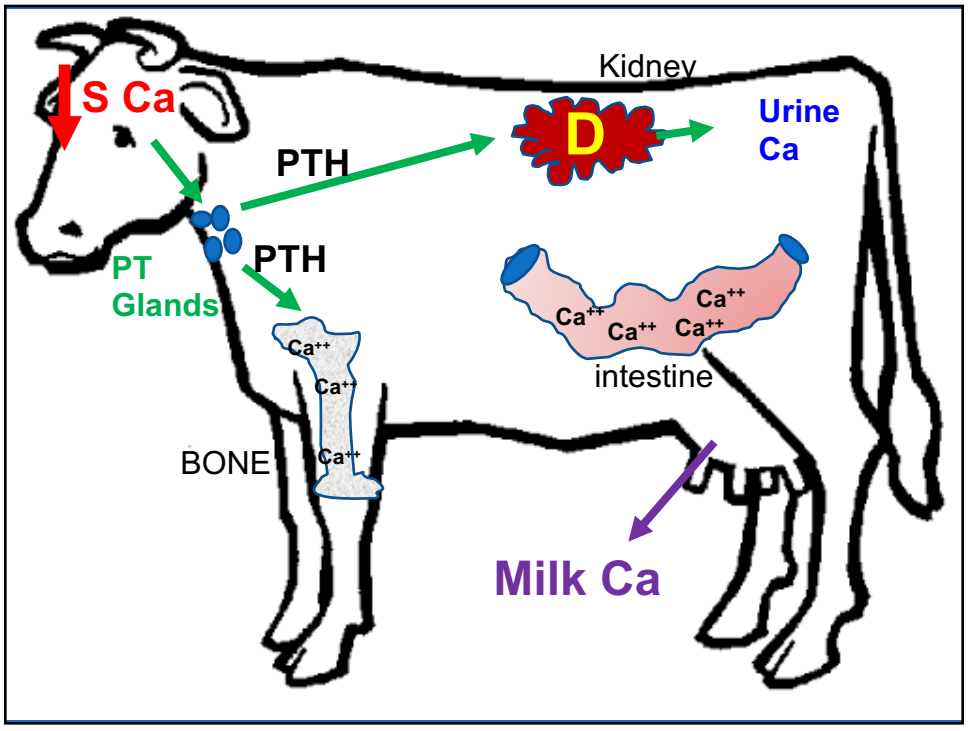

S Ca
Kidney
D
Urine
Ca
PT
Glands
Ca++
Ca++
Ca++
Ca++
Ca++
Ca++
intestine
Ca++
Ca++
Ca++
BONE
Milk Ca

7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intestine
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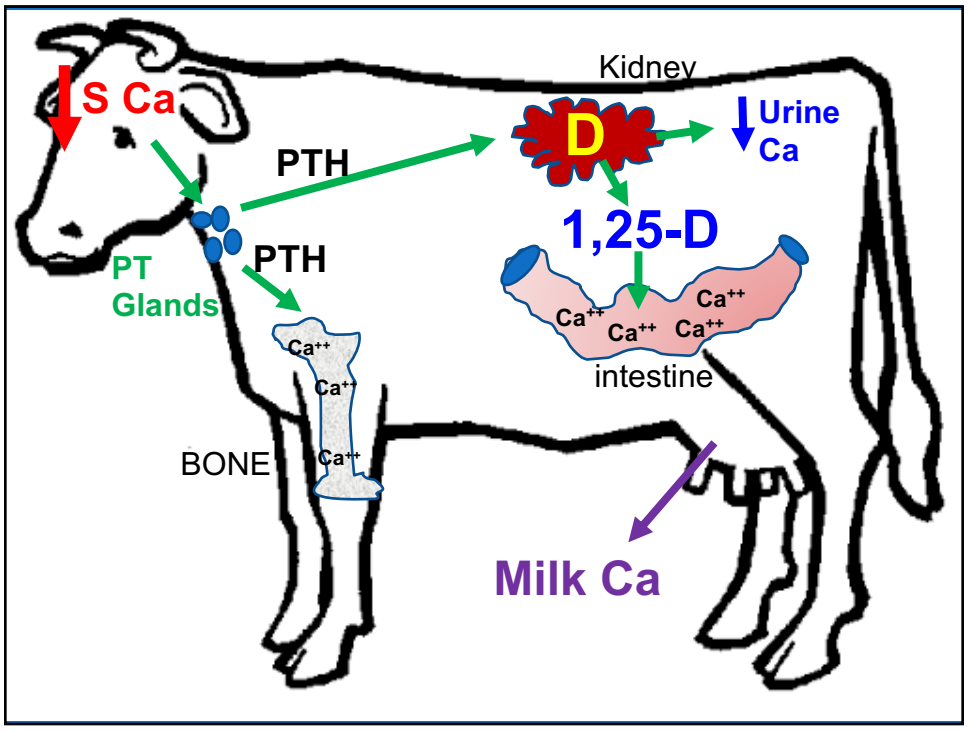
Ca++
Ca++
BONE
Milk Ca

8


S Ca
PTH
Kidney
D
Urine
Ca
1,25-D
PT
Glands
PTH
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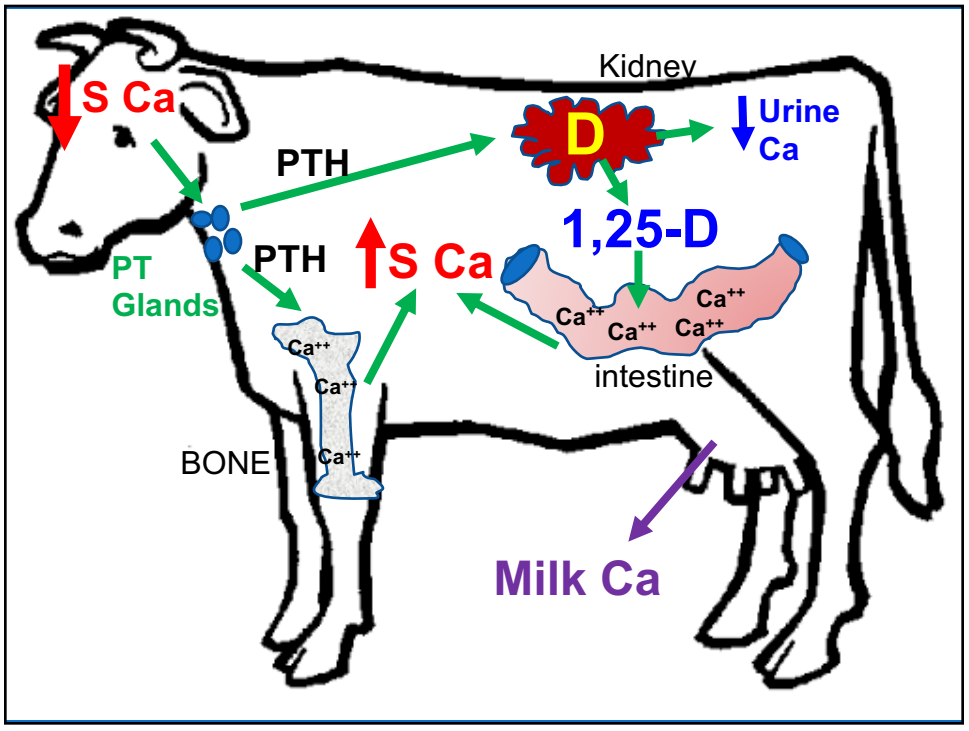
Ca++
Ca++
intestine
Ca++
Ca++
BONE
Ca++
Milk Ca

9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Ca++
Milk Ca

10

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!

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High DCAD diets cause Alkalosis & milk fever

DCAD ($_{mEq}$ Na + $_{mEq}$ K)- ($_{mEq}$ Cl + $_{mEq}$ SO_4)

K^+ absorbed from forages causes the blood and urine of the cow to become alkaline

High blood pH reduces ability of PTH to bind its receptor preventing recognition by bone and kidney cells.

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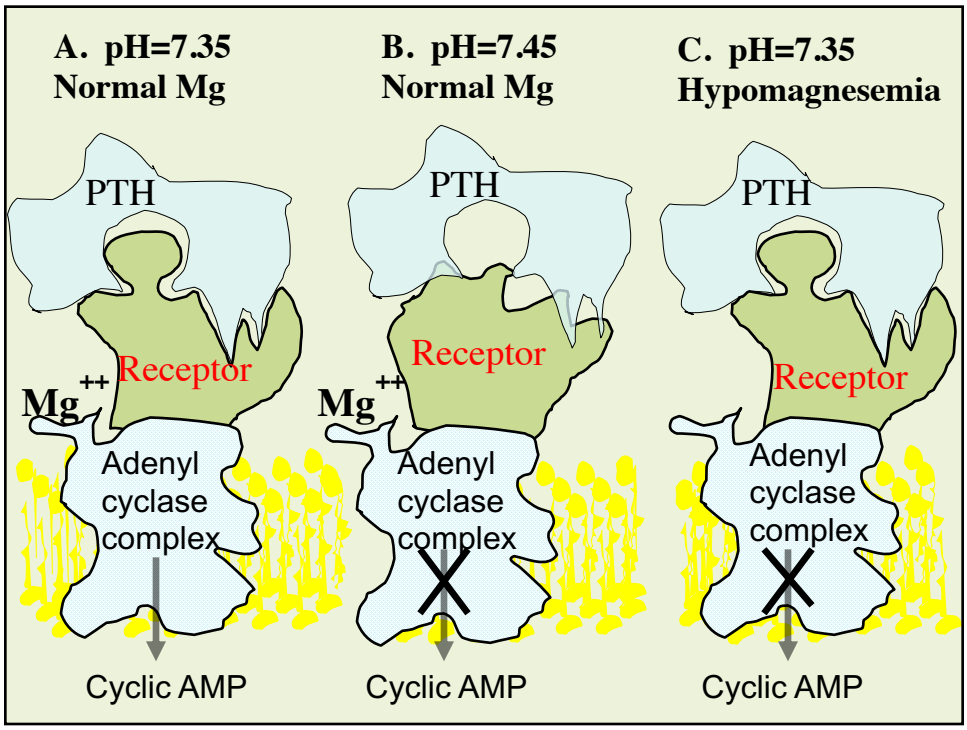
A. pH=7.35
Normal Mg
B. pH=7.45
Normal Mg
C. pH=7.35
Hypomagnesemia
PTH
PTH
PTH
Receptor
Receptor
Receptor
Mg++
Mg++
Adenyl cyclase complex
Adenyl cyclase complex
Adenyl cyclase complex
Cyclic AMP
Cyclic AMP
Cyclic AMP

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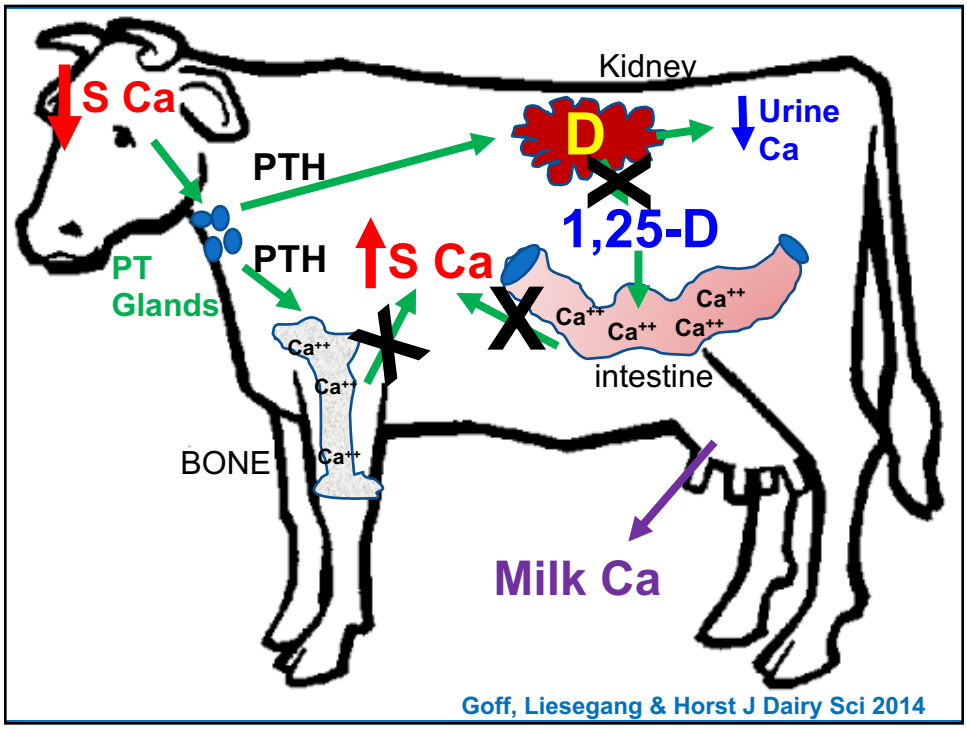
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1,25-D
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S Ca
PT Glands
Ca++
Ca++
Ca++
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Ca++
Ca++
Ca++
Ca++
intestine
BONE
Milk Ca
Goff, Liesegang & Horst J Dairy Sci 2014

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Kidney

A. PTH reduces urine Ca loss to ~ zero within minutes.
Brings <1 g Ca into blood.

B. Synthesis of 1,25-$(OH)_2$vitamin D increases within **10 hrs (acidic)** -20 hrs (alkaline)

Intestine

12-24 hr for 1,25-$(OH)_2$vitamin D to increase proteins involved in Ca absorption. Amount of Ca brought into blood??
Depends on diet Ca!

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Bone

Osteocytic Osteolysis : within 6-12 hours

Can bring ~ 9 g Ca (alkaline) – **15 g Ca (acidic)**

Osteoclastic Resorption : 16-96 hr to become fully active, depending on **age** of cow and **diet** .

Can bring 800 – 1200 g Ca into blood

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THE DCAD STRATEGY

#1. "REDUCE DIETARY POTASSIUM" so cow is not as alkaline

- **Use forage from fields with no manure application**
- **Warm season grasses (corn!) accumulate less K than cool season grasses**
- **As plants mature they contain lower K concentration (straw!)**

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THE DCAD STRATEGY

#1. "REDUCE DIETARY POTASSIUM" so cow is not as alkaline

#2. Add Anions (Cl, sulfate) to acidify the blood to improve bone and kidney response to Parathyroid Hormone

Choosing the right anion sources

Palatability Issues

Over and under acidification

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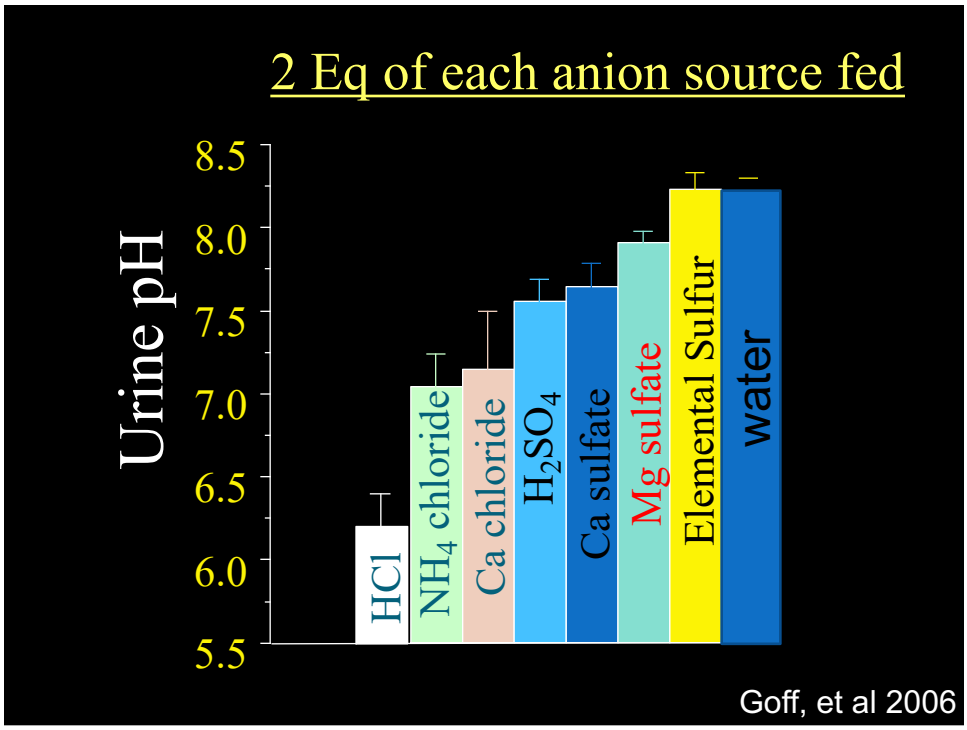

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THE DCAD STRATEGY

Anions added to the diet acidify the blood, improving tissue responsiveness to PTH!

Choosing the right anion sources

- sulfate salts acidify 60% as well as chloride salts
- proper DCAD equation should be

(mEq Na + mEq K) – (mEq Cl + 0.6 mEq S)

Palatability of Anions

Over and Under acidification

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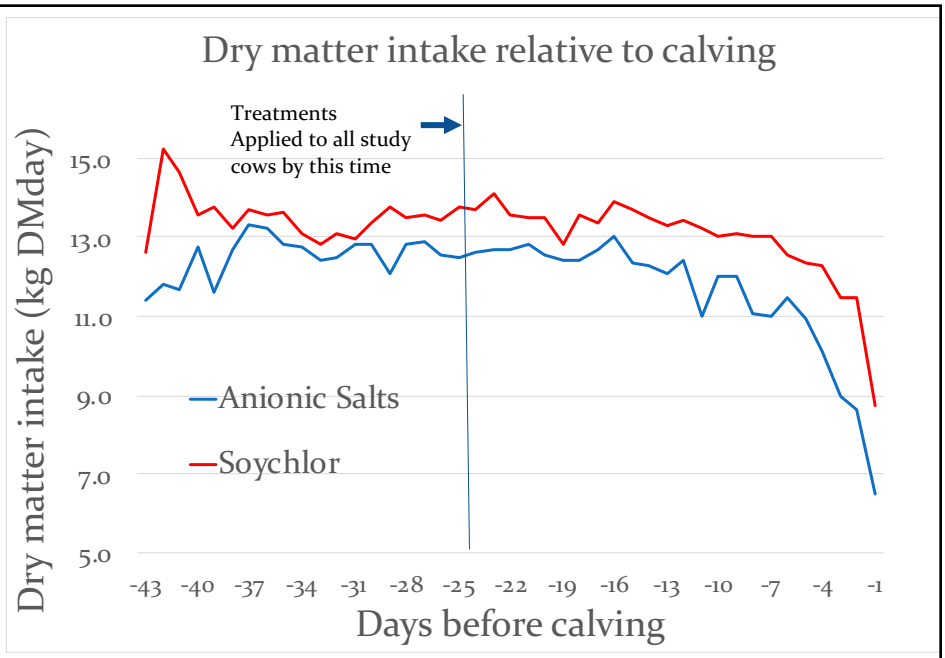

Strydom & Swiegart, 2016 ADSA

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THE DCAD STRATEGY

Anions can be added to the diet to acidify the blood and improve tissue responsiveness to Parathyroid Hormone

-Choosing the right anion sources

- Palatability of Anions

-Under- and Overacidification

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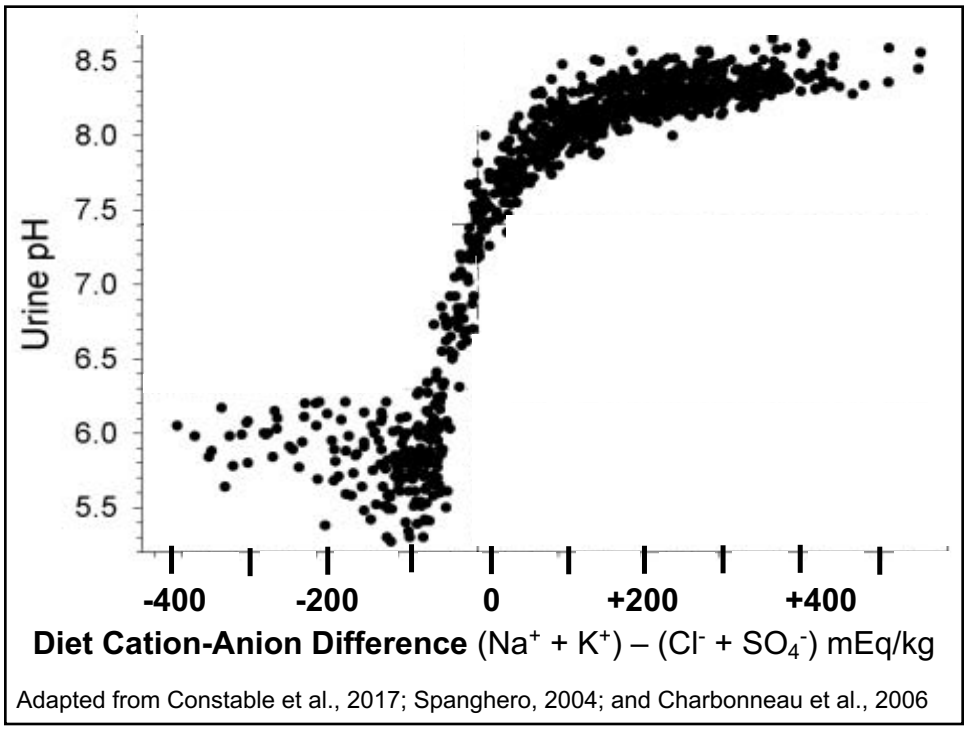

Adapted from Constable et al., 2017; Spanghero, 2004; and Charbonneau et al., 2006

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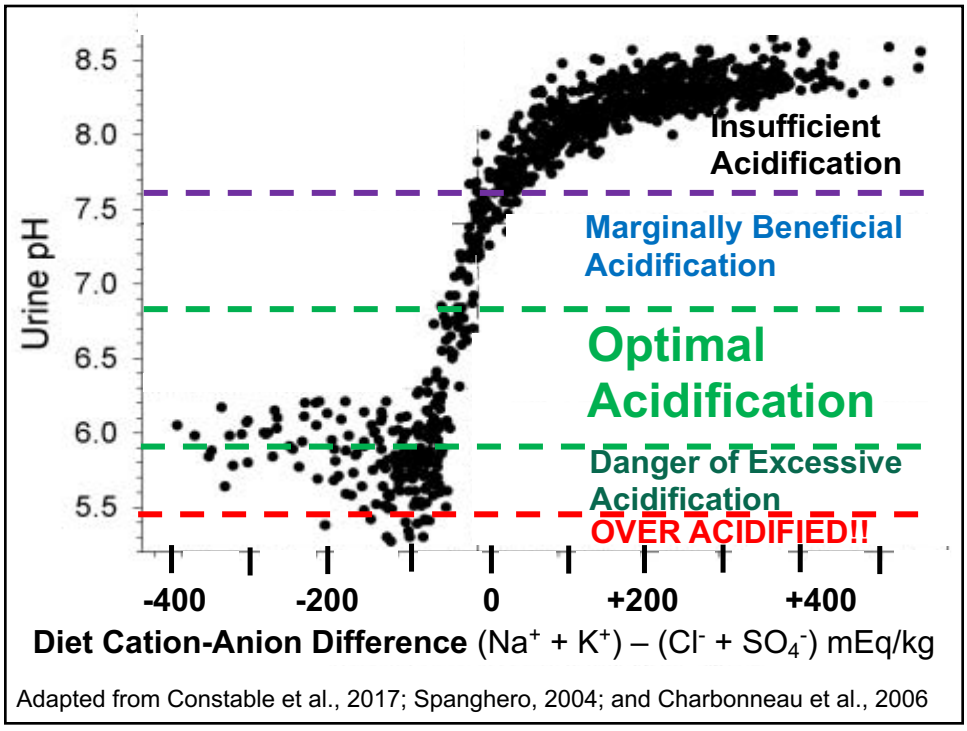

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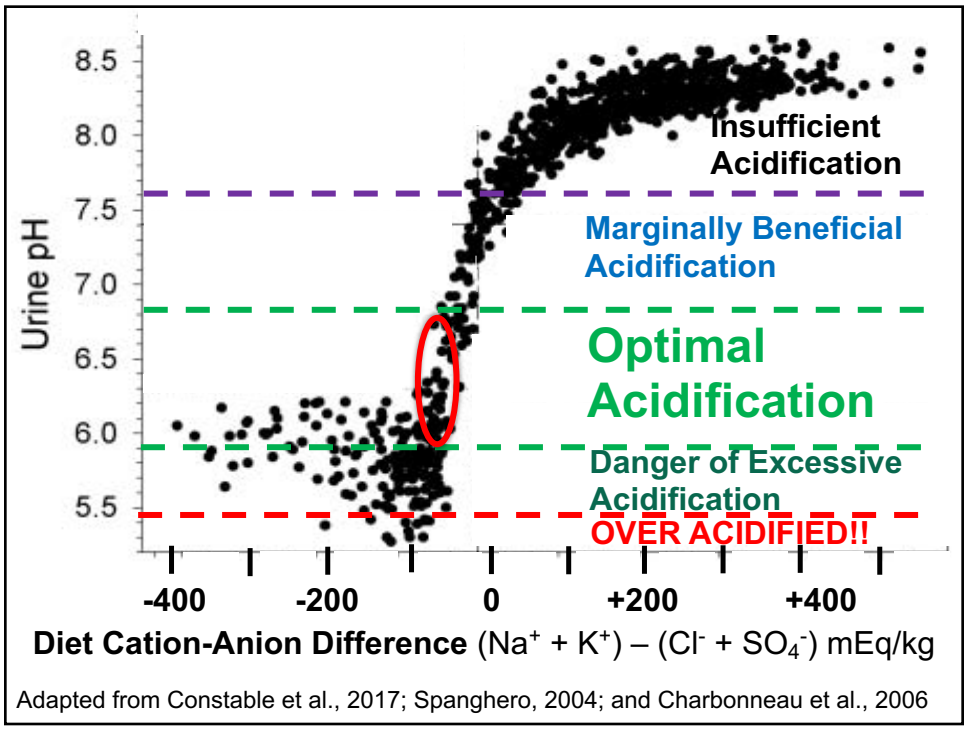

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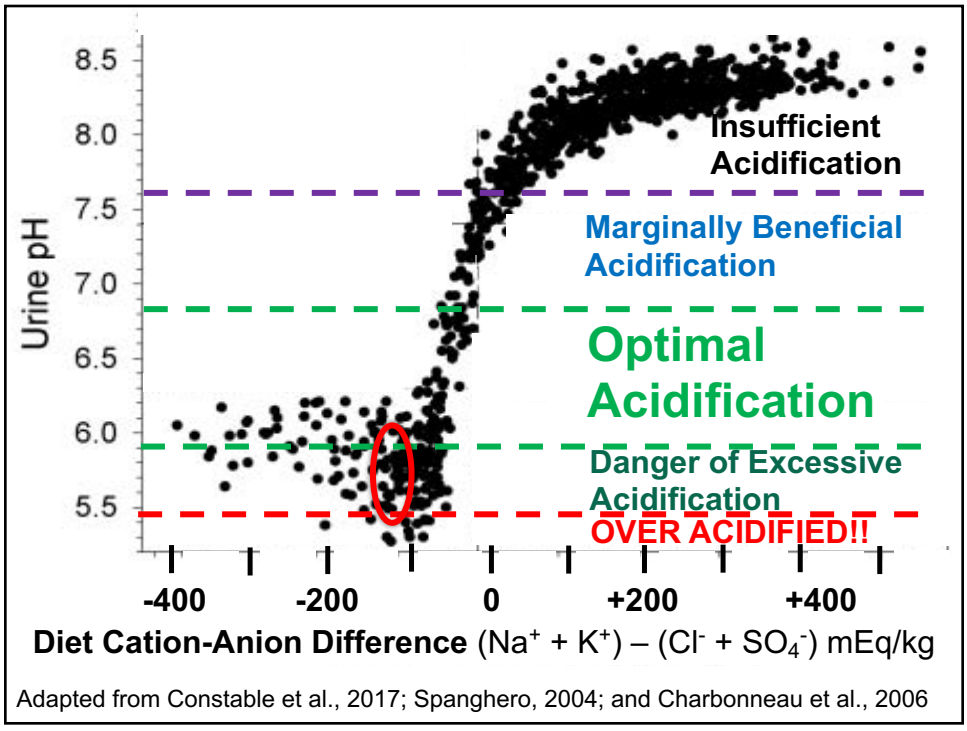

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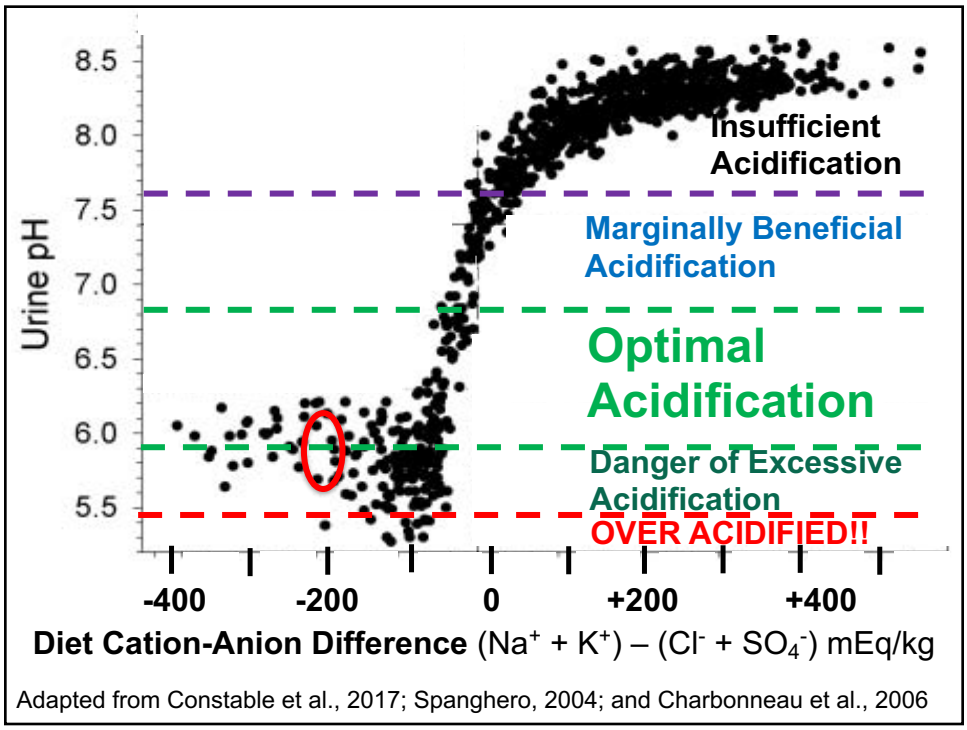

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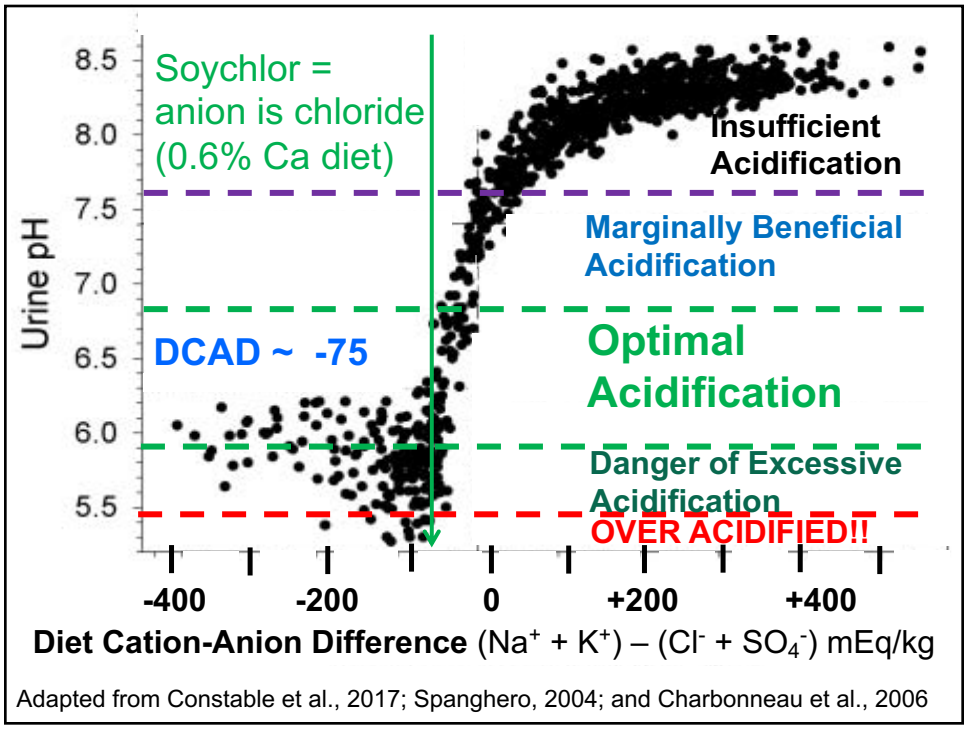

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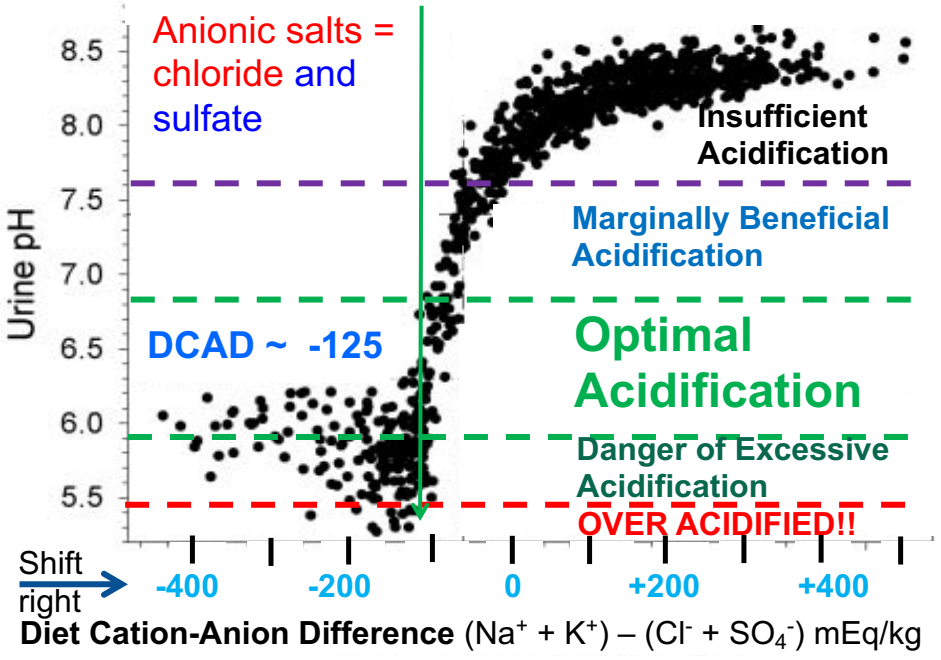

Adapted from Constable et al., 2017; Spanghero, 2004; and Charbonneau et al., 2006

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DCAD Equations

1. Traditional equation (Na + K) – (Cl + S)

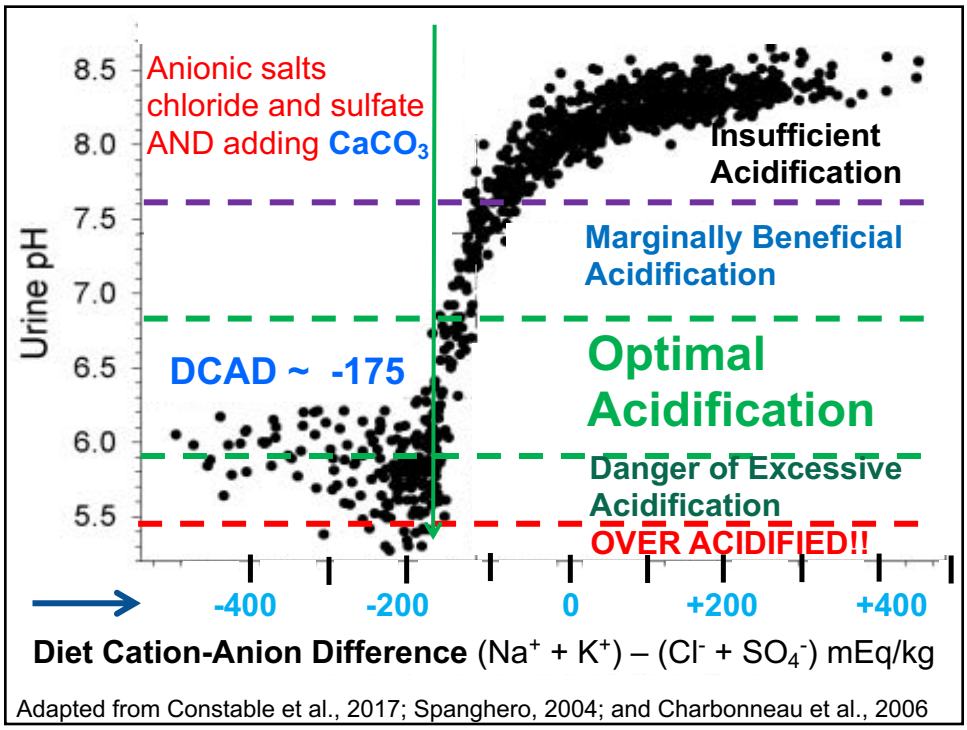
   Does not account for fact S is not as acidifying as Cl

2. Better !! (Na + K) – (Cl + 0.6 S)
   - but does not account for alkalinizing effect of diet Ca coming from calcium carbonate, or Mg coming from MgO, or acidifying effect of Phos

3. Goff proposes

$(Na + K + 0.25\ Ca + 0.15\ Mg + 0.2\ NH_4^+) – (Cl + 0.6\ S + 0.5\ P)$

30



Adapted from Constable et al., 2017; Spanghero, 2004; and Charbonneau et al., 2006

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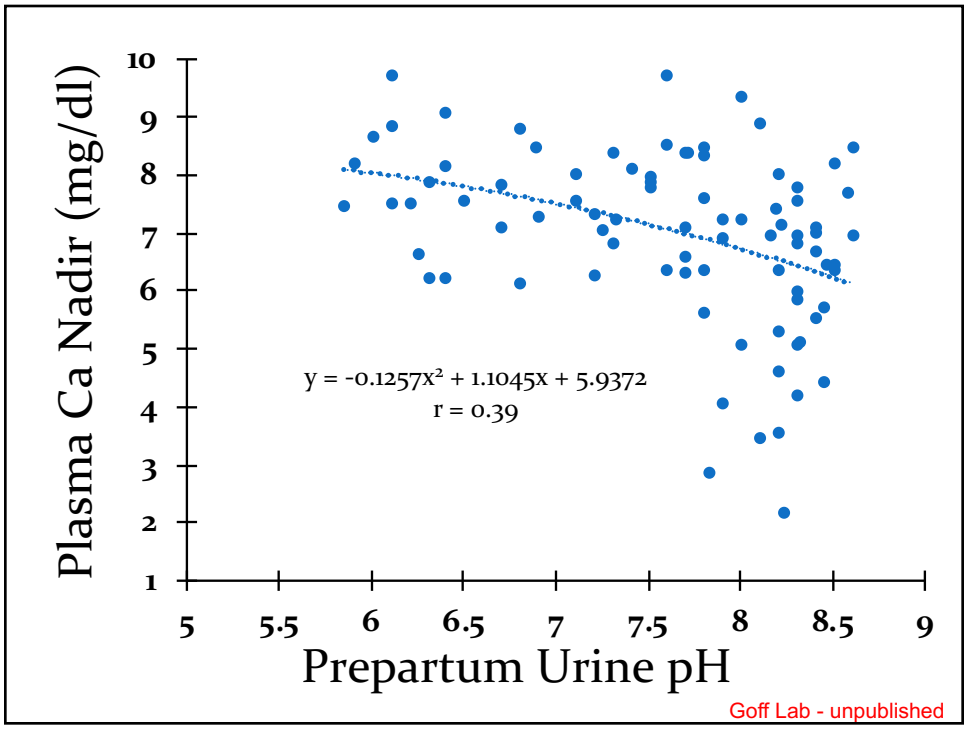
pH 4.5-9.0
TEST STRIPS
100 Strips
RUNBO
50 in Bottle . 50 Refills in Sealed Foil Bag
for Better Preservation.
15 Second Results
pH ion Balance
Diagnostic pH Test Strips
Practitioner Preferred
Over 10 Million
Medical pH Test Strips Sold...
90 Wide Range 4.5 - 9.0 pH Test Strips

33


Plasma Ca Nadir (mg/dl)
10
9
8
7
6
5
4
3
2
1
y = -0.1257x² + 1.1045x + 5.9372
r = 0.39
5
5.5
6
6.5
7
7.5
8
8.5
9
Prepartum Urine pH
Goff Lab - unpublished

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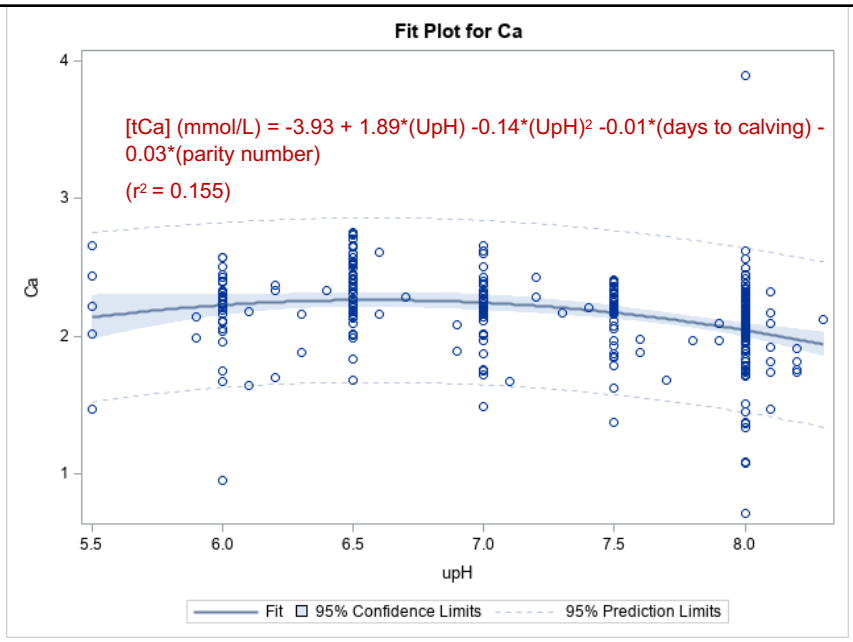

Melendez et al., ADSA 2020 abstr # 81659

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Mecitoglu et al., 2016

Fed 115 cows anionic salts and had 13 cows (11%) develop LDA. Found cows with LDA had had lower urine pH than non-LDA cows.

Concluded that urine pH below 6 increased likelihood of a cow developing a LDA.

Table-1. Mean (± SE) urine pH, serum ionized Calcium (mmol/L) and blood pH for LDA and healthy groups

	LDA Group	Healthy Group	*P* value
Urine pH	6.11 ± 0.2	6.65± 0.1	$P < 0.05$
Serum iCa^{++}	1.39 ± 0.01	1.36 ± 0.01	Not significant
Blood pH	7.27 ± 0.01	7.32 ± 0.01	$P < 0.05$

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Minerals/DCAD for Close-up Diets

- Phos at .25-.31%
- Mg at .4% to use passive absorption!!
- S between .22 and .4%
- Ca at .85-1.3% ??
- Na at .1-.15%
- K as close to 1% as possible
- Enough Chloride to ↓ urine pH.

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In addition to stimulating intestinal Ca transport
1,25-$(OH)_2$Vitamin D also stimulates transport of phosphate!!!

Now we know there is a phosphate homeostasis mechanism relying on a bone hormone called FGF23.

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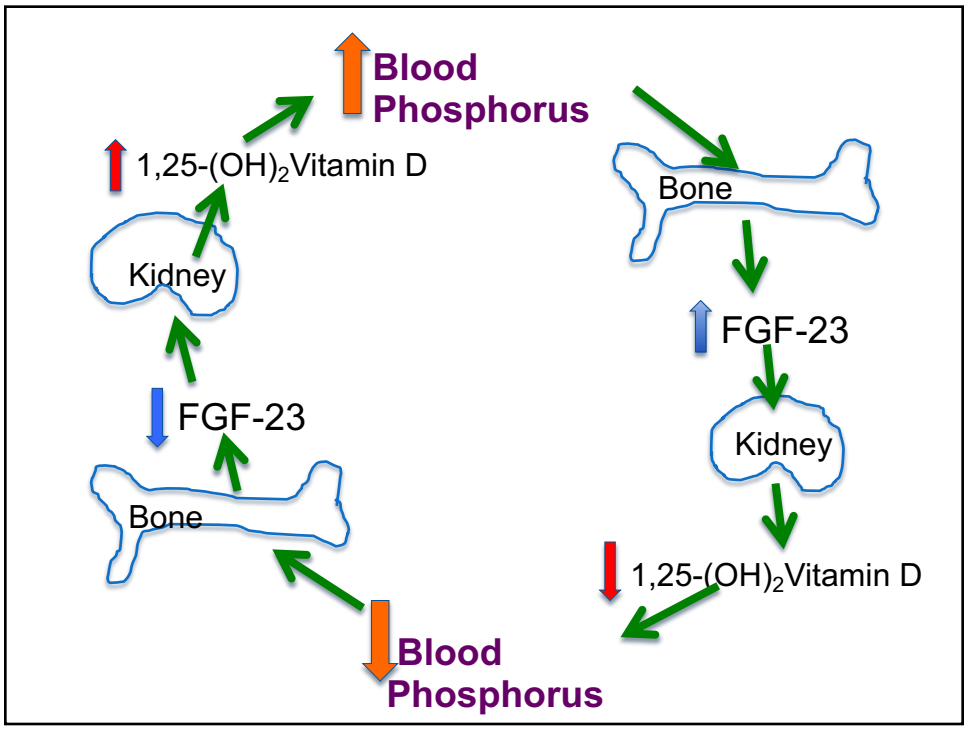
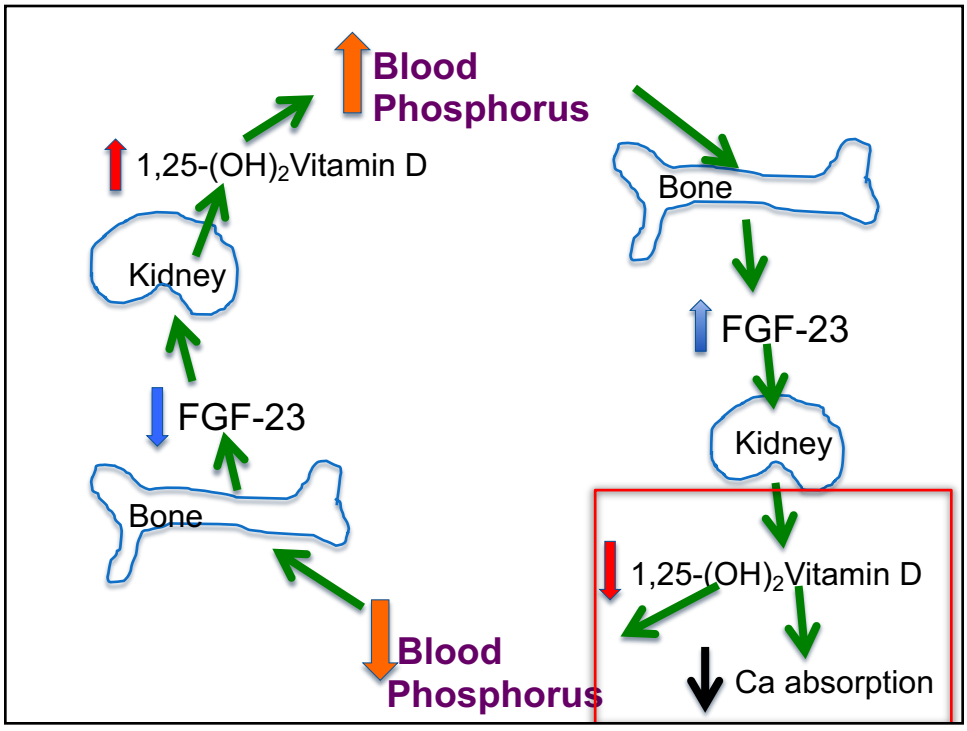

Blood Phosphorus
1,25-(OH)2Vitamin D
Kidney
FGF-23
Bone
Bone
FGF-23
Kidney
1,25-(OH)2Vitamin D
Blood Phosphorus

39


Blood Phosphorus
1,25-(OH)2Vitamin D
Kidney
FGF-23
Bone
Bone
FGF-23
Kidney
1,25-(OH)2Vitamin D
Ca absorption
Blood Phosphorus

40

Peterson et al., 2005

Pre-partum diet of cows was either 0.21, 0.31, or 0.44 % Phosphorus

Cows fed 0.44% P diets had lower blood Ca around the time of calving than did cows in lower P treatments.

Cows fed 0.21% P had blood P within the normal range (4-6 mg/dl) and showed no adverse effects in milk production

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Cohrs et al., 2018

Cows fed 0.15% P prepartum diets had better blood Ca (mM) on day 1 and 3 after calving than cows fed prepartum diet with 0.28% P.

	Day 1	Day 3
0.15% P	2.46 ± 0.11	2.61 ± 0.13
0.28% P	2.27 ± 0.41	2.35 ± 0.25

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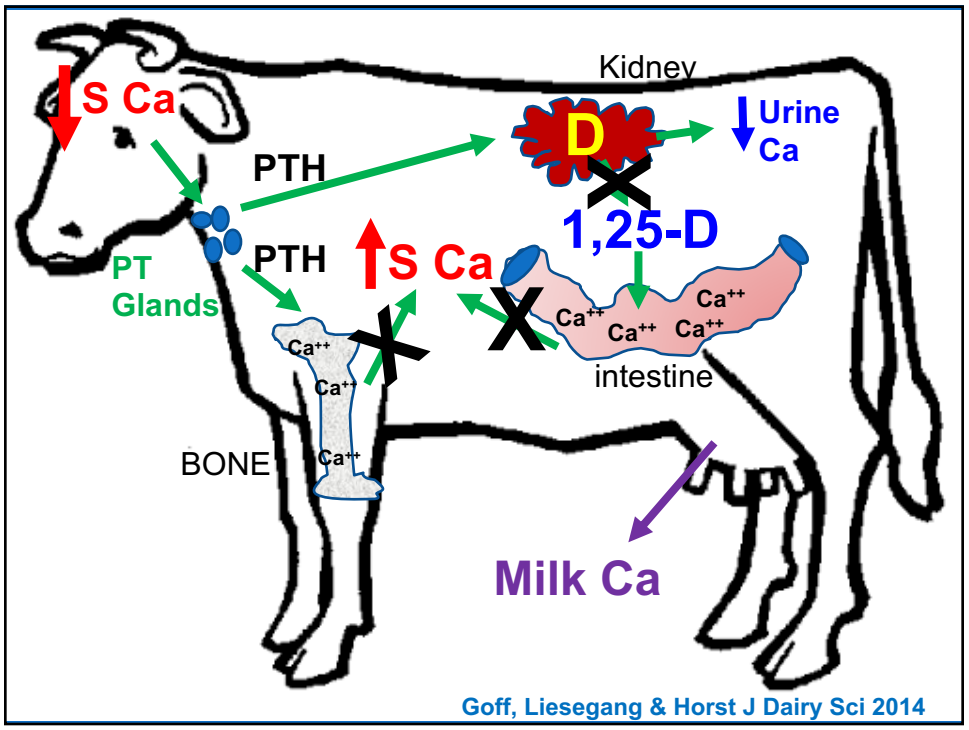
Kidney
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Goff, Liesegang & Horst J Dairy Sci 2014

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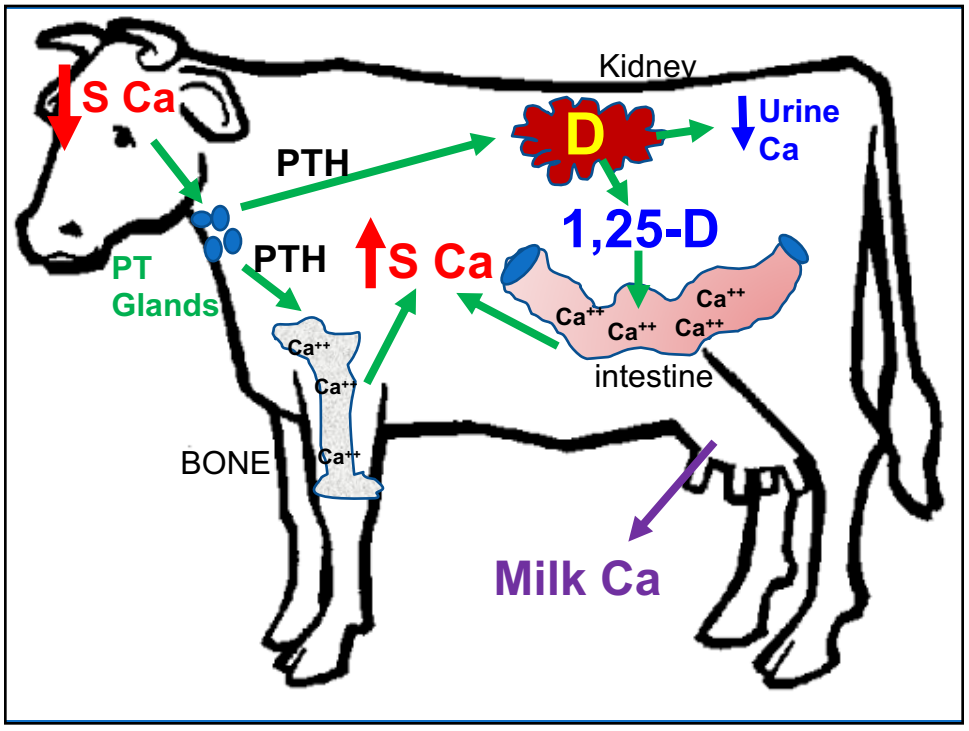
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- **Mg at .4% to use passive absorption!!**
- **S between .22 and .4%**
- **Ca at .85-1.3% ??**
- **Na at .1-.15%**
- **K as close to 1% as possible**
- **Enough Chloride to ↓ urine pH.**

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Magnesium

Adult Ruminants absorb diet Mg across rumen wall only! Mg insoluble at rumen pH is NOT available.

- ***Main Transport*** process efficient at low diet Mg BUT EASILY POISONED BY DIET high in K or 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!

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Hypomagnesemia

Blood Mg < 1.9 mg/dl within 12 hrs of calving indicates inadequate dietary absorption of Mg.

-secondary hypocalcemia (common cause of mid-lactation "milk fevers"

-Depressed feed intake, depressed rumen fermentation (Ammerman, et.al., 1971)

-Tetany in grazing dairy (below 1.2 mg/dl).

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Magnesium sources

Pre-calving
- using $MgSO_4$ or $MgCl_2$ 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 – supplies Mg and acts as rumen alkalinizer.

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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 and let sit 30 minutes. Check the pH.

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.

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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% , Diet P <0.35%!
4. ***Reduce diet Ca to stimulate parathyroid hormone release well before calving.***
5. Vitamin D administration
6. Oral calcium therapies (IV Ca?)

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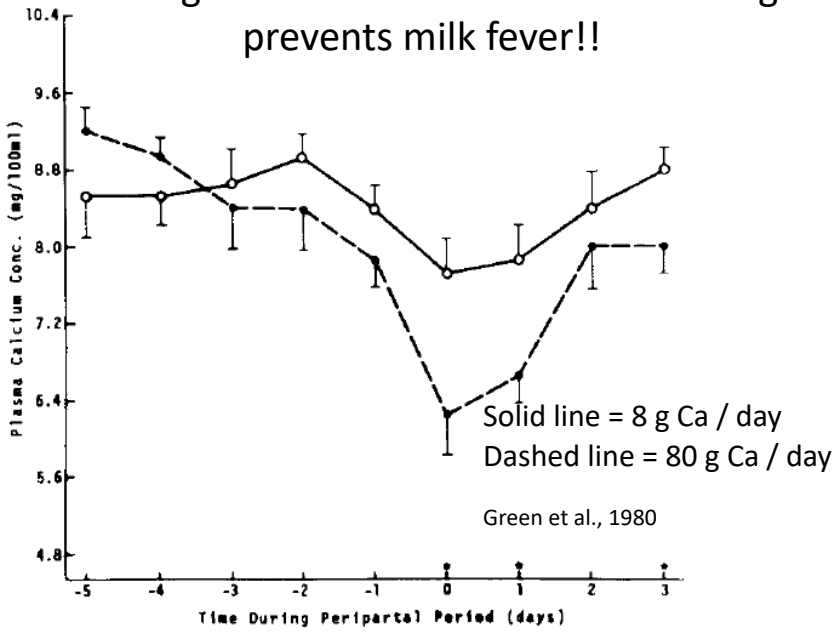
Feeding a Ca-deficient diet before calving prevents milk fever!!



Solid line = 8 g Ca / day
Dashed line = 80 g Ca / day

Green et al., 1980

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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
4. ***Reduce diet Ca to stimulate parathyroid hormone release well before calving.***

   Zeolite may make it realistic to achieve
5. Oral calcium therapies (IV Ca?)

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Zeolite A

In a test tube the sodium aluminosilicate can bind 1 g of Ca for every 10 g zeolite.

Seems to bind phosphate and magnesium as well. Transient reduction blood Mg and Phos.

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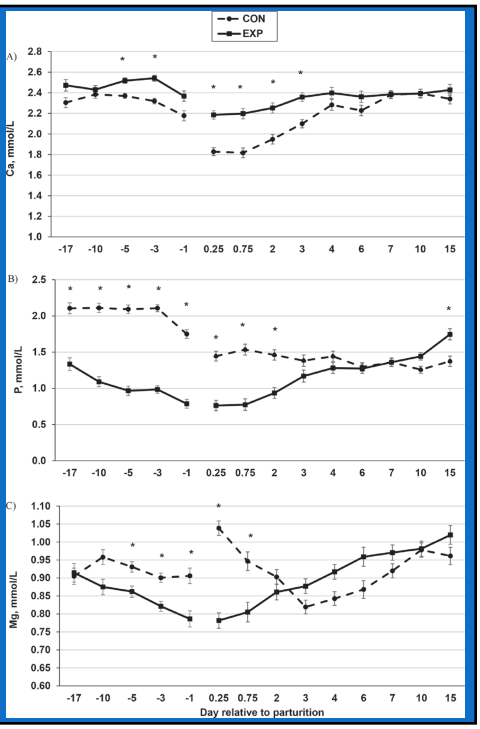
Kerwin et al., 2019

Added 0.5 kg zeolite to a diet that was 0.65 % Ca , 0.39% Phos, and 0.42% Mg with DCAD of + 268 mEq/kg



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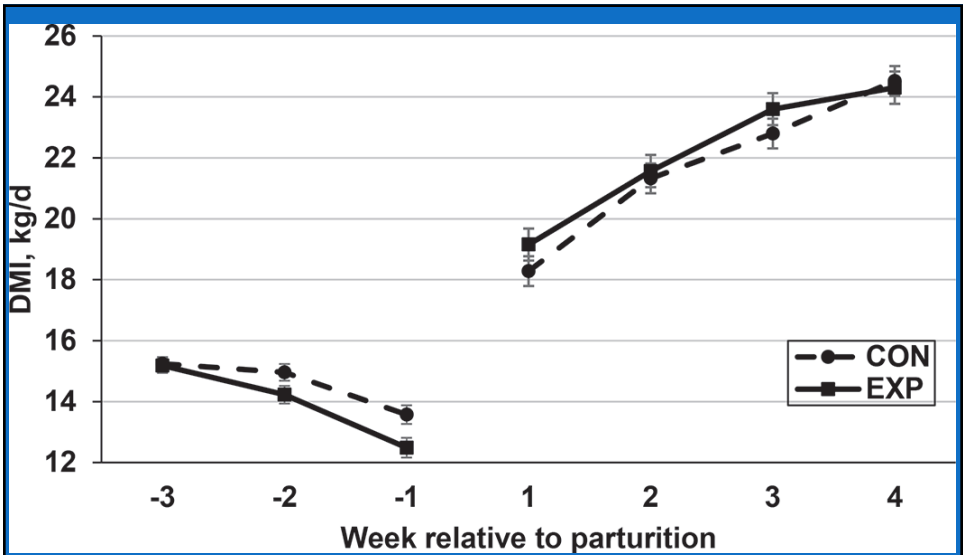

DMI Treatment X week P= 0.04
Rumination rate significantly decreased with zeolite prepartum.P=0.03

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Milk Fever Prevention

1. Avoid very high potassium forages for close-up cows; practiced by most dairies in US.
2. Add anions (Cl or Sulfate) to diet to reduce blood and urine pH; various forms practiced.
3. Diet Mg ~ 0.4% , Diet P < 0.35%
4. Reduce diet Ca to stimulate parathyroid hormone release well before calving. Zeolite?
5. Vitamin D administration – too dangerous at effective doses
6. Oral Calcium drench, bolus, gels.
7. IV calcium to each cow??

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Milk Fever Prevention

1. Avoid very high potassium forages for close-up cows; practiced by most dairies in US.
2. Add anions (Cl or Sulfate) to diet to reduce blood and urine pH; various forms practiced.
3. Diet Mg = 0.4% and available
4. Reduce diet Ca to stimulate parathyroid hormone release well before calving. Zeolite?
5. Vitamin D administration – too dangerous at effective doses
6. Oral Calcium drench, bolus, gels.
7. IV calcium to each cow??

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Without 1,25-dihydroxyvitamin D stimulation, intestinal cells may only absorb 10-25% of dietary Calcium

Under special circumstances, such as **oral Ca boluses and drenches**, small amounts of Ca can be absorbed without the need for vitamin D.

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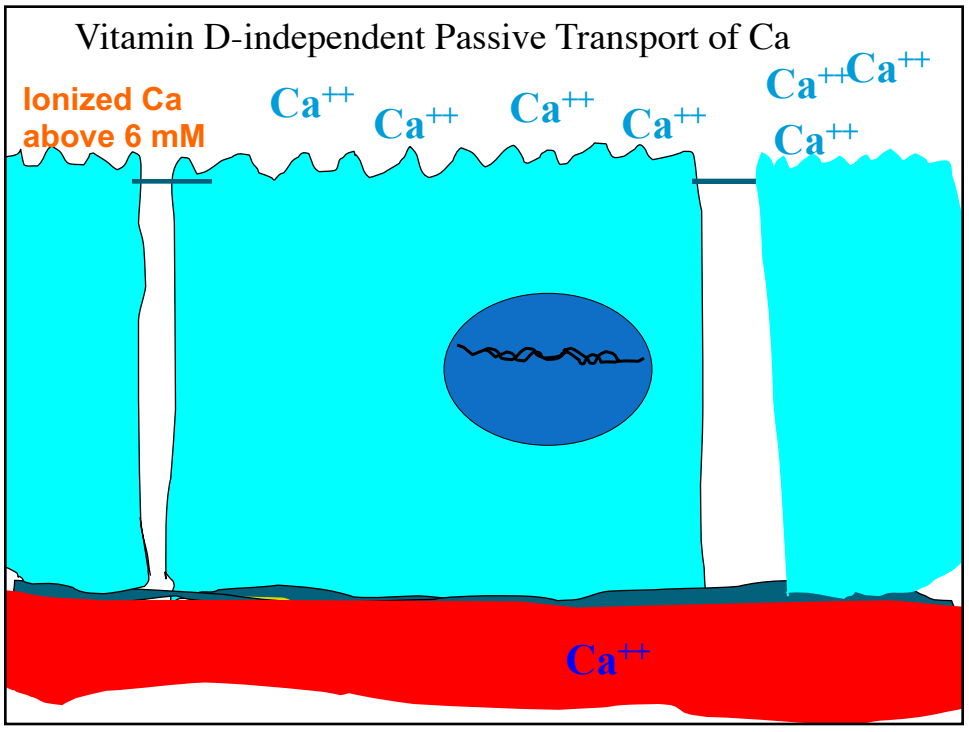
Vitamin D-independent Passive Transport of Ca
Ionized Ca
above 6 mM
Ca++
Ca++
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Ca++Ca++
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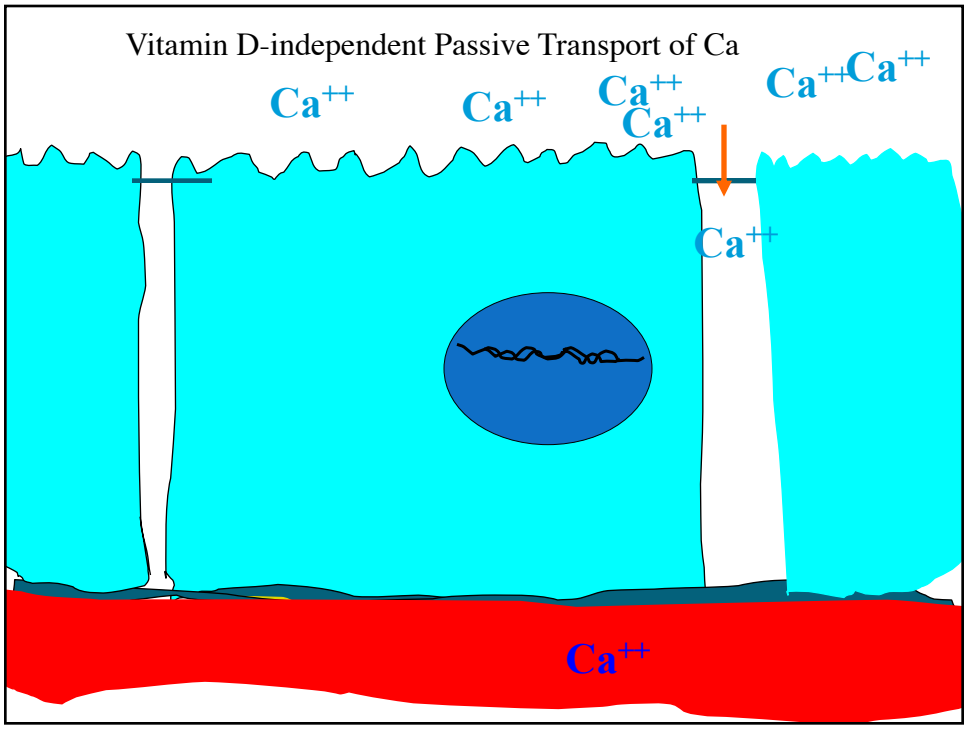
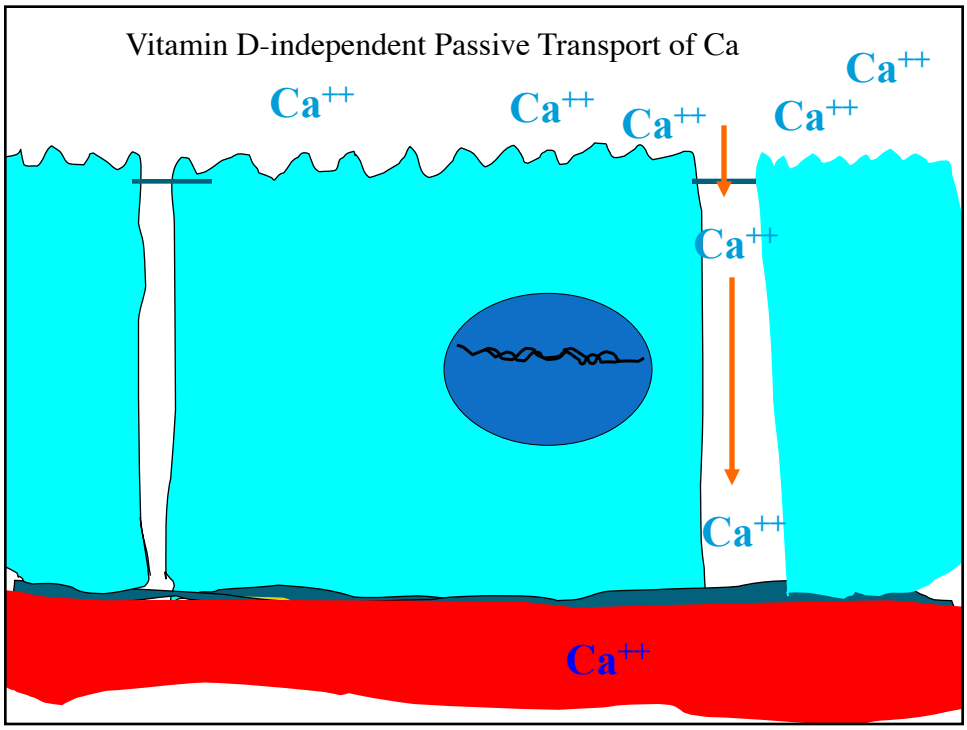
Ca++

60


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

61


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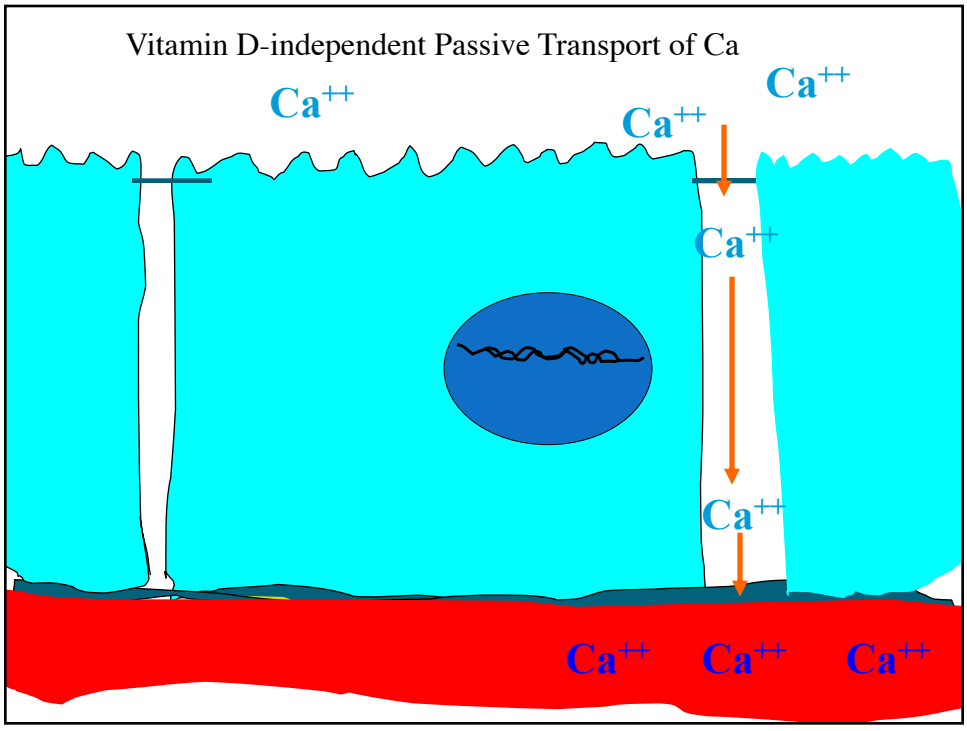
Ca++
Ca++

62


Vitamin D-independent Passive Transport of Ca
Ca++
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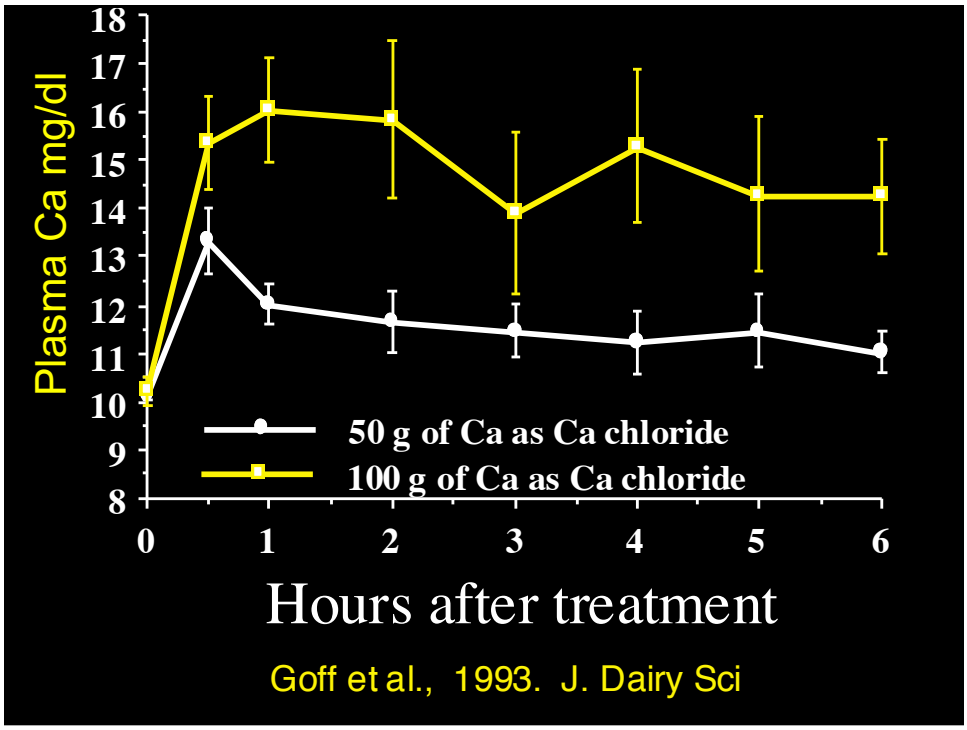
63



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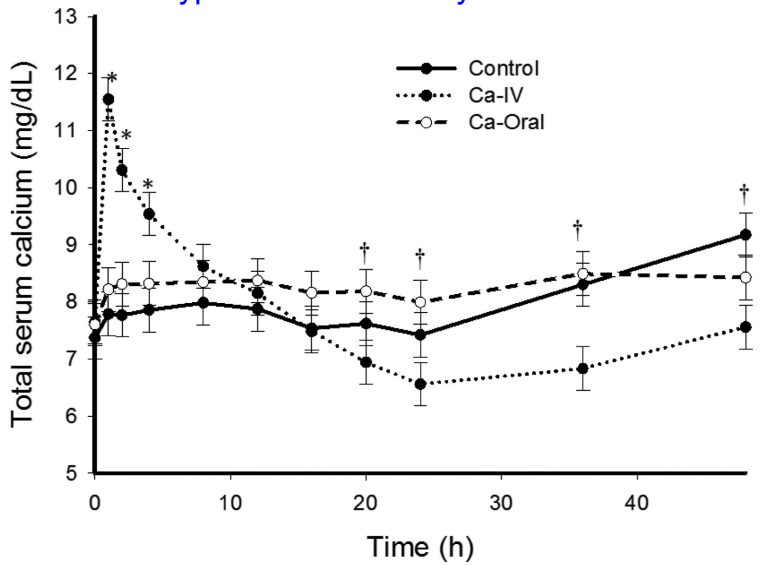
Routine use of IV Calcium at calving may cause more subclinical hypocalcemia 1-2 days after treatment



Blanc et al., JDS 2014

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Oral bolus, gel , drench minerals – which ones to use?

To raise blood Ca quickly by providing rapidly ionized Ca:

Calcium chloride – also acidifying
Calcium propionate – also gluconeogenic
Calcium formate, acetate, or lactate

To supply Mg soluble in rumen to raise blood Mg:

Mg sulfate.7 H_2O – also acidifying
Mg chloride.2 H_2O – also acidifying
Celtic sea Mg carbonate **
Mg oxide **

To supply Ca or Mg after passage thru abomasum

Ca sulfate- also acidifying
Ca carbonate
Mg carbonate

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Roberts, et. al. N Zeal Vet J 2018

First Ca bolus (41 g Ca) at 1st milking
12 hours after calving 5/13 (41%) treated cows had urine pH <7

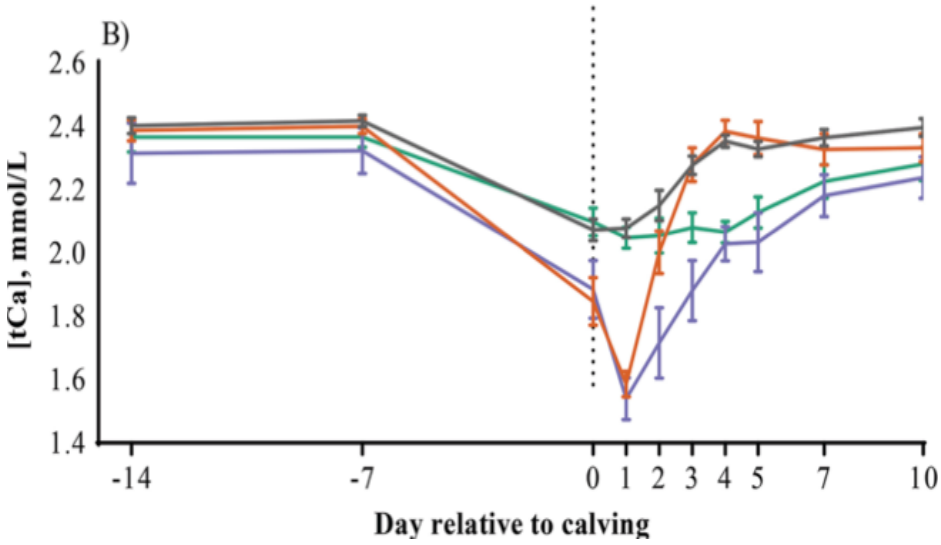
0/12 (0%) control cows ($p<0.001$)

Second bolus given ~12 hrs after calving

24 hours 13/13 (100%) treated cows had urine pH <7

0/12 (0%) control cows ($p<0.001$).

67



McArt et al., 2020 J Dairy Science

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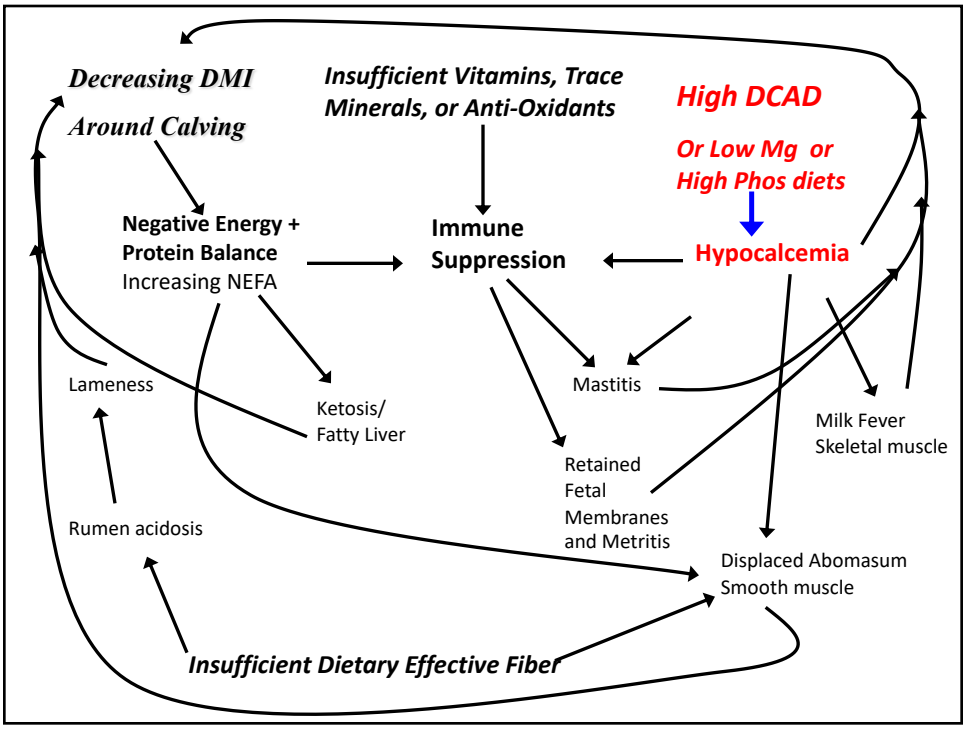

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