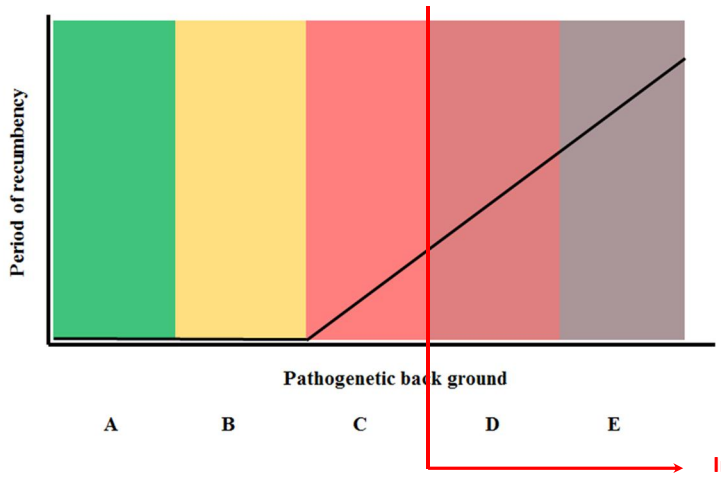
VEERkracht Dairy Congress 2019

Preventive advice on farms suffering from a high incidence of periparturient paresis

VEERkracht Dairy Congress 2019
Rik Hendriks
the Netherlands, January 31st

What are we discussing?



A: Normocalcemia

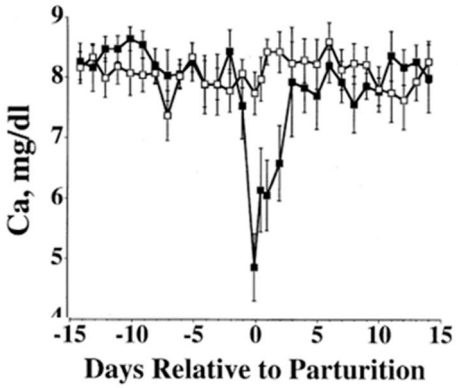
B: Subclinical hypocalcemia

C: Clinical (uncomplicated) hypocalcemia

D: Clinical complicated hypocalcemia

E: Downer cow

Hypocalcemia; a mammary gland problem



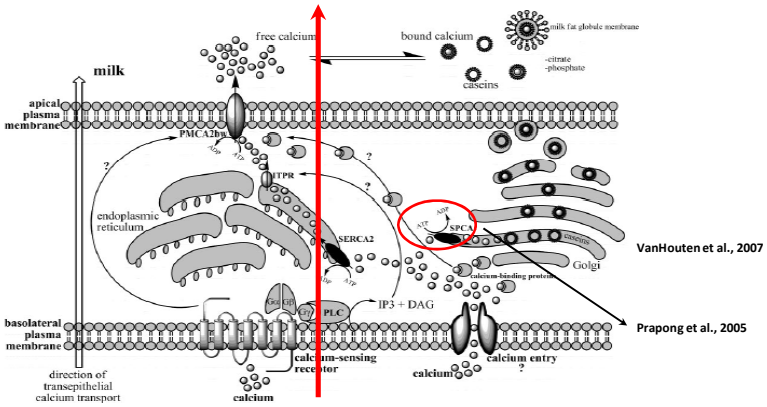
Concentrations of plasma calcium in intact (■) and mastectomized (□) cows around calving

Goff et al., 2002

Regulation of mammary calcium transport

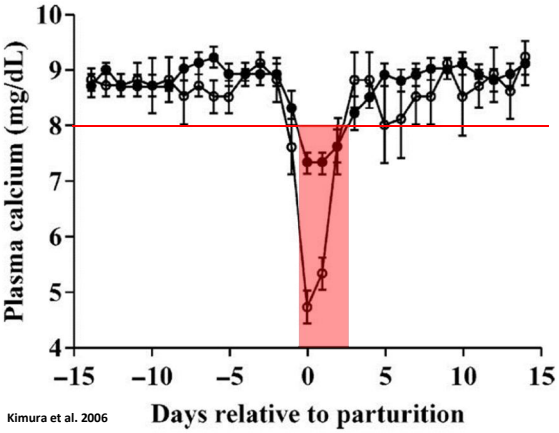
Colostrum: 170 -230 mg Ca/dL = 1,7 – 2,3 gr Ca/L (Goff, 2014)

Milk: 1,1 – 1,45 gr Ca/L (Hurtaud et al., 2011; Goff, 2014)

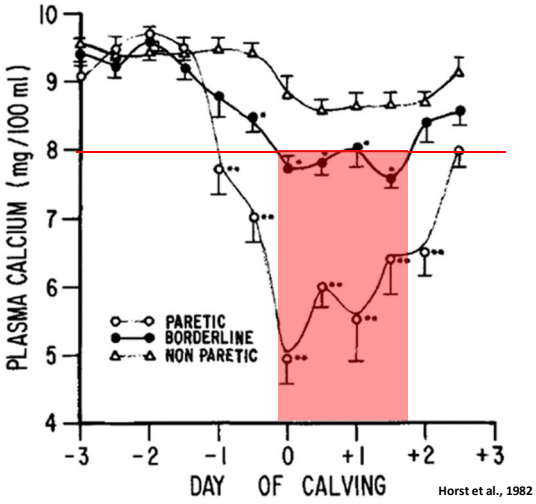


Blood: 8 – 10 mg Ca/dL

Hypocalcemia; should we worry?

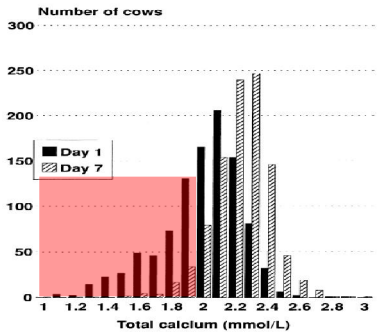


Kimura et al. 2006



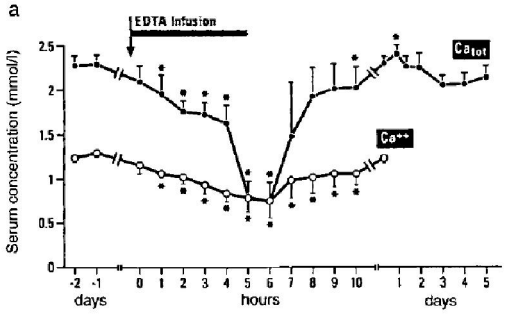
Horst et al., 1982

Subclinical and clinical hypocalcemia



Serum Ca_{tot} concentrations of non-paretic cows on D1 and D7 postpartum.

Bigras-Poulin and Tremblay, 1998



Effects of a 5 hour Na_2EDTA infusion on the serum concentrations of Ca_{tot} and iCa^{2+} six dairy cows. The arrow indicates the beginning of the infusion.
* $P < 0.05$

Riond et al., 1997

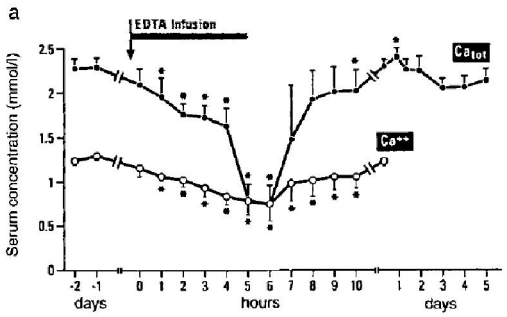
Subclinical and clinical hypocalcemia

If you want to measure

Think of *when* to measure

Don't measure just the outcome
(= blood calcium concentration)

Also measure the cause!
(= underlying mechanism)



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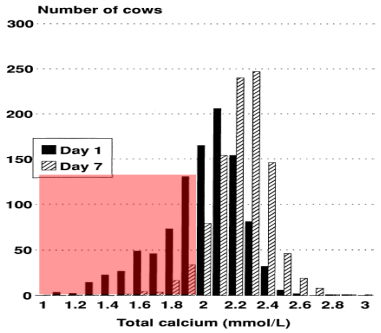
Subclinical and clinical hypocalcemia



Serum Ca_{tot} concentrations of non-paretic cows on D1 and D7 postpartum.

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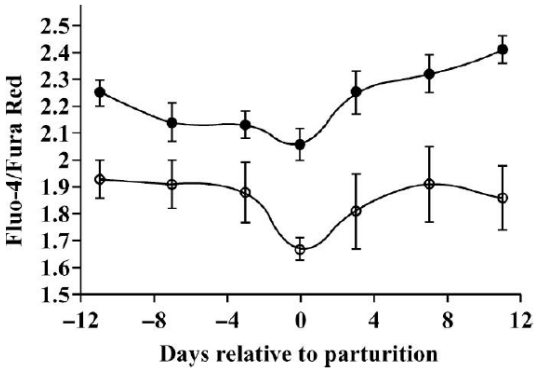
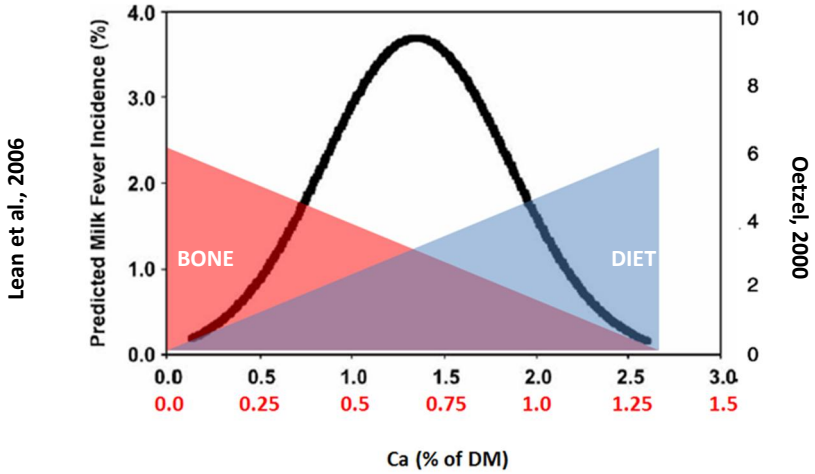


Flux of intracellular calcium in PMNC of cows with (●) and without (○) milkfever.

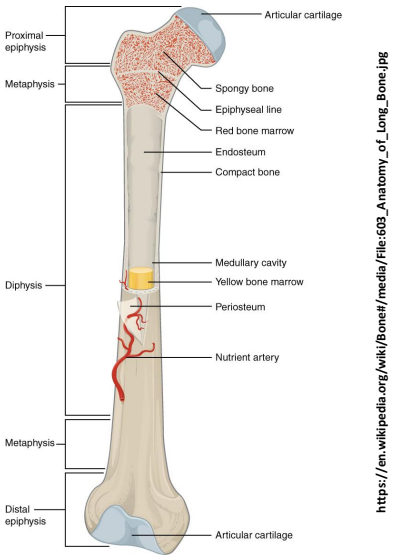
Kimura et al., 2006

Clinical (uncomplicated) hypocalcemia milk fever



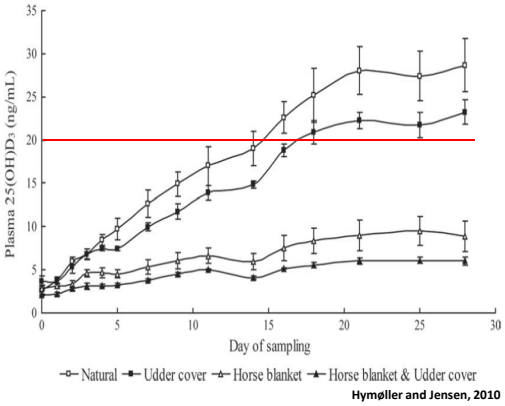
Calcium release from bone

- Bone:
  - PTH-dependent-system
  - Delay of 2-3 days
- Required:
  - Magnesium



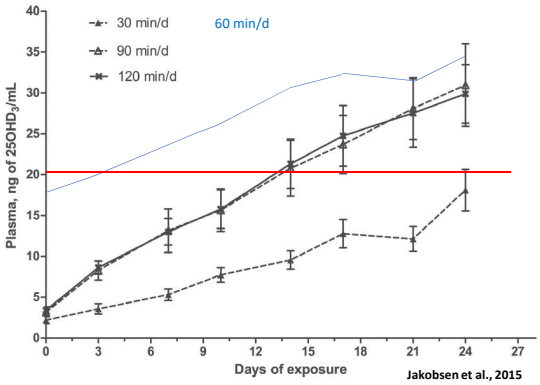
Calcium release from bone: vitamin D

- Meeting the requirement with sunlight



Hymøller and Jensen, 2010

- Meeting the requirement with artificial UV-B



Jakobsen et al., 2015

Calcium release from bone: magnesium

- Magnesium requirement:
  - Dietary requirement 0.35-0.40% on DM basis to circumvent impaired absorption by high (>2%) dietary K Goff, 2014
  - Magnesium absorption is stimulated by:
    - Enhanced rumen fermentation = *more protonated VFA* Gaebel et al., 1987; Leonhard-Marek et al., 2010
    - Increased Mg solubility at pH 5 (82%) 6 (53%) 7 (29%) Dalley et al., 1997

A proper close-up diet:

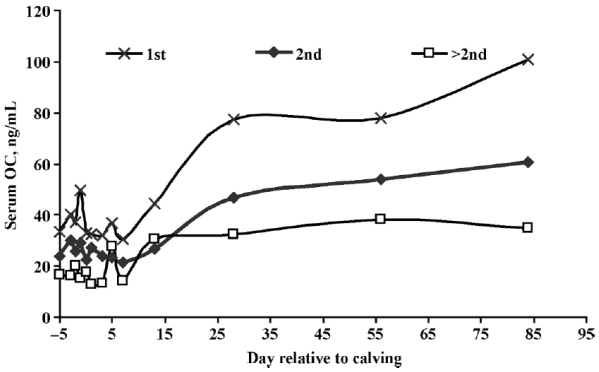
Enhancement of rumen fermentation!

Calcium release from bone: monitoring

- Magnesium:
  - Measured in the urine
  - Reference range:
    [Mg] > 2.5 mg/dL Schneider et al., 1985

Calcium release from bone: additional measures

- Exercise?! Gustafson, 1993
  - Stimulates bone turnover Harada and Rodan, 2003; Hiney et al, 2004



Effect of parity on serum osteocalcin (OC) concentration

Taylor et al., 2008

Calcium release from bone: additional measures

- Compensated metabolic acidosis (= low blood bicarbonate) → no more delay in Ca replenishment
  - Negative DCAD Escobosa et al., 1984; Tucker et al., 1988; Oetzel, 1991; Roche et al., 2003; Penner et al., 2008

Uncompensated metabolic acidosis when low DCAD combined with factors shown to decrease blood bicarbonate

- Heat stress Schneider et al., 1984; 1988a; 1988b
- Rumen acidosis Morgante et al., 2009; De Nardi et al., 2013

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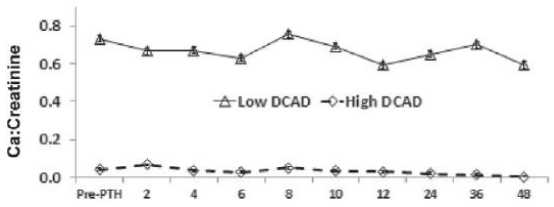
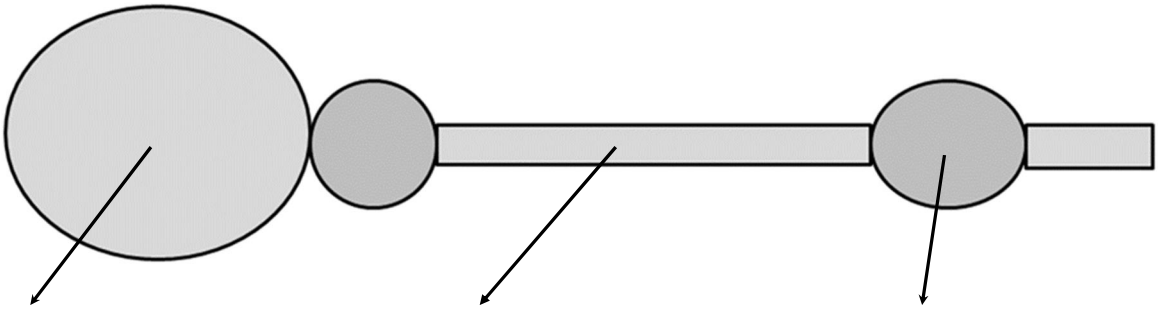


Urinary Ca:Creatinie ration in cows fed a low DCAD and a high DCAD

Goff et al., 2014

Calcium absorption from the GIT



Rumen:

transcellular vit D independent

Small intestines

transcellular vit D dependent
paracellular vit D dependent
vit D independent

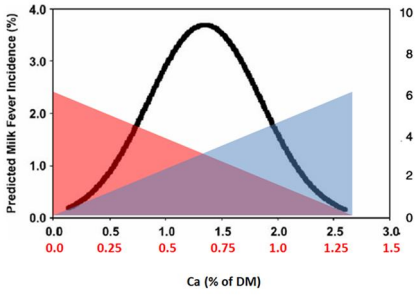
Large intestines

transcellular vit D dependent
paracellular vit D dependent
vit D independent

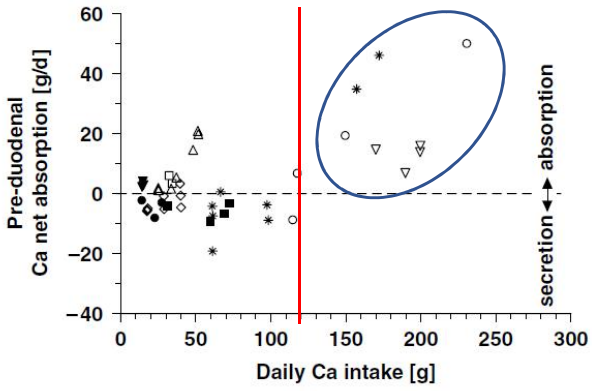
Rik Hendriks, VEERkracht Dairy Congress 2019, the Netherlands

Calcium absorption from the GIT: rumen

- Dietary Ca intake > 120 gr/day
  Schröder and Brevis, 2006
  - (at 10 kg daily DMI ≈ 1% Ca)



sorption as
intake



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Calcium absorption from the GIT: rumen

- Dietary chloride, possibly via the Cl^-/HCO_3^- exchanger in cooperation with the Ca^{2+}/H^+ exchanger Leonhard-Marek et al., 2007; Wilkens et al., 2016

(Partially?!) decreased DCAD

- Fermentation rate: increased VFA, especially *butyrate*, stimulates Ca absorption in the rumen Schröder et al., 1999

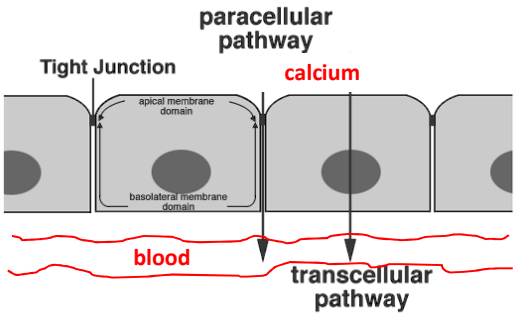
A proper close-up diet:

Enhancement of rumen fermentation

Dietary inclusion of sugars

Calcium absorption from the GIT: intestines

- PTH/VitD dependent (paracellularly AND transcellularly)



http://www3.mfour.med.kyoto-u.ac.jp/~htsukita/new-pub/NatBox1.html

Calcium release from the GIT: vitamin D dependent

- Requirement:
  - Feed: 20.000 – 30.000 IU/day **Goff, 2004**
  - UV-B:
    - Artificial **Jakobsen et al., 2015**
      - > 14 days, minimal 90 minutes/day
    - Sun **Hymøller et al. 2009, Hymøller and Jensen, 2010, 2012**
      - Summer (Denmark) > 14 days, 5 hrs sun/day
    - Days of exposure needed to reach reference value also depend on basal level

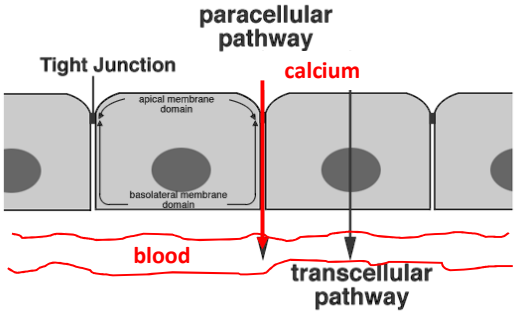
Hymøller and Jensen, 2010

Calcium release from GIT: vitamin D dependent

- Vitamin D:
  - Measured in the blood as [25(OH)D_3]
  - Reference range:
    [25(OH)D_3] 20 – 50 ng/mL **Horst et al. 1994**

Calcium absorption from the GIT: intestines

- PTH/vitD *in*dependent (paracellularly)
  - Ca-gradient
  - "Open" tight junctions; Claudin 2, 12 or 15 Chirayat et al., 1998; Amsheh et al., 2000; Fujita et al., 2008; Diaz de Barboza et al., 2015



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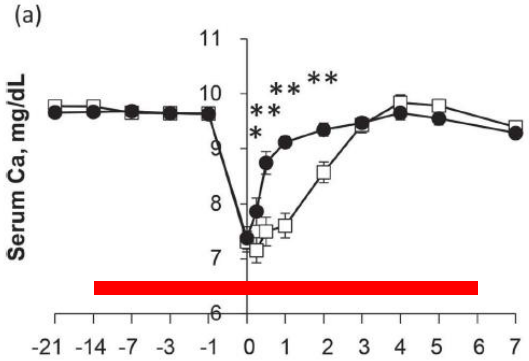
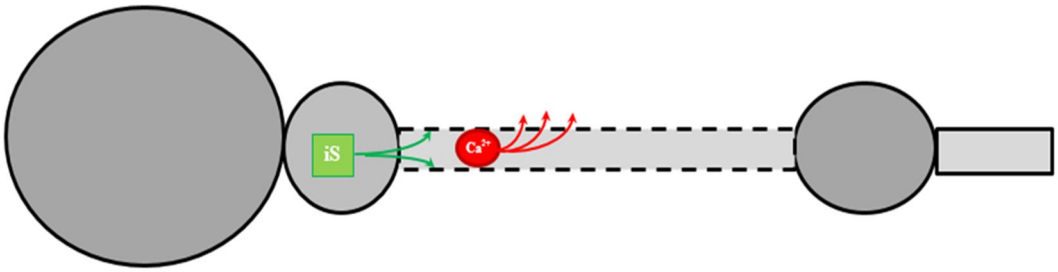
Calcium absorption from the GIT: intestines

- PTH/vitD *in*dependent (paracellularly)
  - Role of oligofructose and difructose anhydrides (DFA)? Mineo et al., 2001; Sato et al., 2007 Abstr.; Teramura et al., 2015a,b
  - In combination with dietary Ca!!



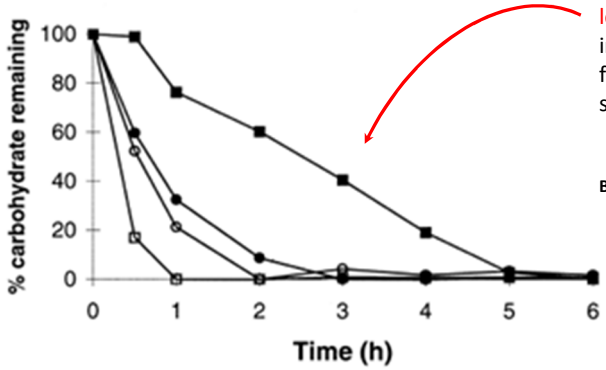
Serum concentrations of Ca in transition cows supplemented without (□) and with (●) 40 gr DFA-III/cow/day (red bar: DFA-feeding) Teramura et al. 2015b

Calcium absorption from the GIT: intestines



iS: indigestible saccharides

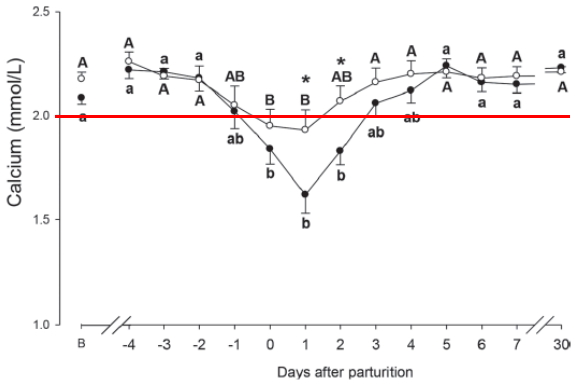
Calcium absorption from the GIT: intestines



% of fructose remaining in rumen fluid of a cow ;
levan (■)
inulin (●)
fructose(□)
sucrose (○)

Biggs et al., 1998

Calcium absorption from the GIT: serotonin-effect



Serum Ca concentrations in peripartal cows administered saline (●) or 5-hydroxy-tryptophan (○)

Hernandez-Castellano et al., 2017

Calcium absorption from the GIT: serotonin-effect

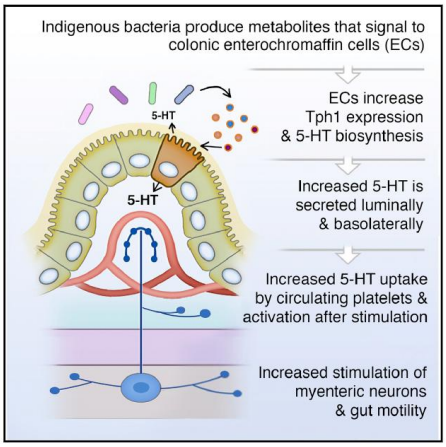
- Do we see serotonin-effect in the Netherlands??
  - Predominantly produced in the Entero Chromaffine cells in the GIT, by
    - Duodenal fructose and colonic glucose **Zelkas et al., 2015; Martin et al., 2017**
  - Cows with high blood serotonin produce less colostrum **Kessler et al., 2018**

Clinical (uncomplicated) hypocalcemia

- Prevention:
  - Aim at more than 1 (sub)system
    - Bone:
      - Exercise
      - Magnesium
      - Negative DCAD (in the Netherlands?!)
    - Diet
      - Magnesium
      - Vitamin D → diet / light
      - Calcium
      - Fructose?
      - Enhancement of fermentation in close-up period

Calcium absorption from the GIT: serotonin-effect

- Do we see serotonin-effect in the Netherlands??
  - The GIT microbiome ultimately regulates serotonin synthesis Yano et al., 2015
  - Predominantly produced in the EC cells in the GIT, by
    - Luminal glucose Zelkas et al., 2015
    - Duodenal fructose and colonic glucose Martin et al., 2017
    - Mechanical strain Chin et al., 2012
  - Higher serotonin levels after calcitriol injection Vieira-Nieto et al., 2017
  - Cows with high blood serotonin produce less colostrum Kessler et al., 2018



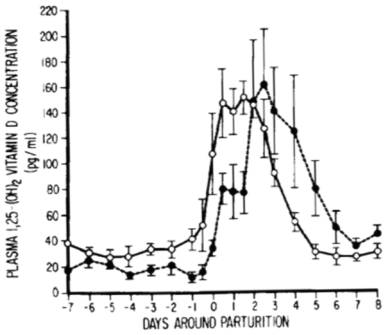
Yano et al., 2015

Complicated hypocalcemia

- Definition?
  - Multiple treatments necessary?
  - Younger animals: 2nd & 3rd parity?
  - Occurrence > 3 days in lactation?
  - Sustained drain of calcium??
  - Altered setpoint for restoring hypocalcemia ??

Complicated hypocalcemia

- Definition?
  - Relapsing cases?
  - Multiple treatments necessary?
  - Younger animals: 2nd & 3rd parity?
  - Occurrence > 2-3 days in lactation?
  - Sustained drain of calcium??
  - Altered setpoint for hypocalcemia ??

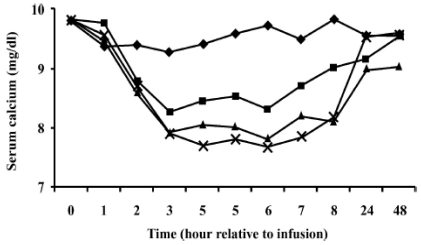


Plasma calcitriol in cows with relapsing and non-relapsing milkfever.

Goff et al., 1989

Complicated hypocalcemia: calcium drain

- Pro-inflammatory cytokines are causative
  - I.v. LPS administration decreases Ca_{tot} Griel et al., 1975; Waldron et al., 2003
  - I.v. LPS administration decreases iCa^{2+} Elsasser et al., 1996; Kvidera et al., 2016
  - Milk fever cows with LPS in the peripheral blood Aiumlamai et al., 1992
  - Cows with *E. coli* mastitis have decreased Ca_{tot} Griel et al., 1975
  - Cows with rumen acidosis have decreased iCa^{2+} Danscher et al., 2015; Aditya et al., 2018
  - Horses with enterocolitis have decreased iCa^{2+} Toribio et al., 2001
  - Sheep with septic shock have decreased Ca_{tot} Cumming, 1994

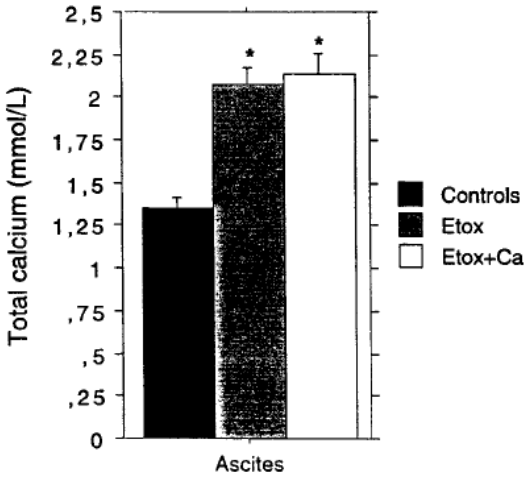


I.v. LPS administration decreases serum Ca_{tot} in a dose dependent way

Waldron et al., 2003

Complicated hypocalcemia; calcium drain

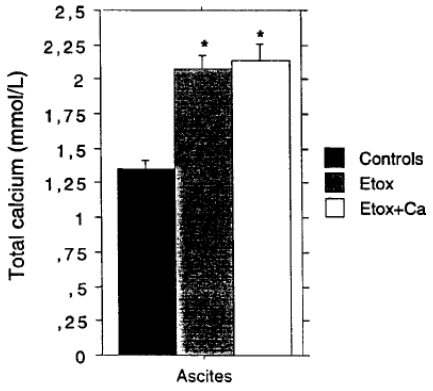
- Shift of blood calcium
  - to interstitial fluid Carlstedt et al. 2000



Ca_{tot} in ascites of pigs treated with saline, endotoxin, or endotoxin with calcium
Carlstedt et al., 2000

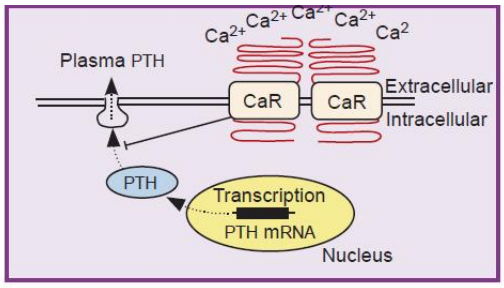
Complicated hypocalcemia; calcium drain

- Shift of blood calcium
  - to interstitial fluid Carlstedt et al. 2000
  - to intracellular Sayeed, 1986
    - → cell apoptosis ?!
    - → e.g. in cardiomyosites?!
  - In Downer cows:
    - Arrythmia Yamagishi et al., 1999; Peek et al., 2000
    - Myocardial necrosis Yamagishi and Naito, 1997; Yamagishi et al., 1999
    - Tachicardia Yamagishi et al., 1999; Labontée et al., 2018
    - Increased cardiac troponin I Serra et al., 2000; Labontée et al., 2018



Ca_{tot} in ascites of pigs treated with saline, endotoxin, or endotoxin with calcium
Carlstedt et al., 2000

Complicated hypocalcemia; altered setpoint



Ionized calcium occupies the CaSR which acts inhibitory on PTH secretion.

Murray et al. 2008

- Impaired calcium homeostasis:
  - CaSR in parathyriod gland:
    - mRNA upregulation after 48 hrs IL-1β *in vitro* Nielsen et al., 1997
    - mRNA upregulation and increased expression of CaSR in chief cells after burn injury *ex vivo* in sheep Murphey et al., 2000
  - PTH secretion from <u>*bovine*</u> parathyroid glands is:
    - decreased *in vitro* after 24 hrs IL-6 Carlstedt et al., 1999
    - decreased *in vitro* after 48 hrs IL-1β Nielsen et al., 1997
- Setpoint for hypocalcemia is changed?

Downer Cow Syndrome (DCS)

- Definition Menard and Thompson, 2007
  - Cows recumbent for > 24 hours
  - Cows recumbent after > 3 treatments

  plus

  - No skeletal of muscular damage

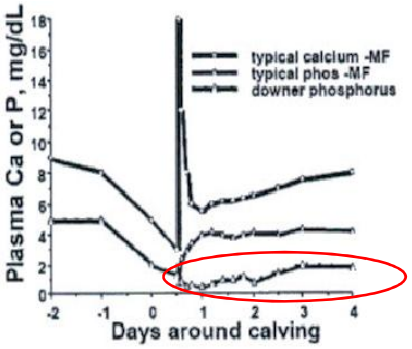
- Known associations:
  - Hypophosphatemia = association!
  - Hypokalemia = association!
  - Others = associations!

Downer Cow Syndrome (DCS)

- Known associations with:
  - Hypophosphatemia + hypocalcemia

    Yamagishi and Naito, 1997; Menard and Thompson, 2007; Kalaitzakis et al. 2010
  - Hypophosphatemia and normocalcemia

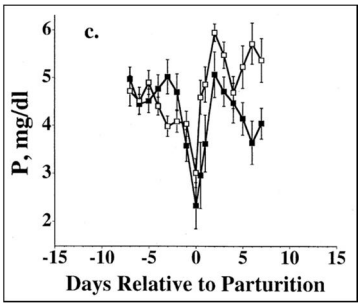
    Oikawa and Katoh, 2002



Source: Anonymous

DCS and hypophosphatemia

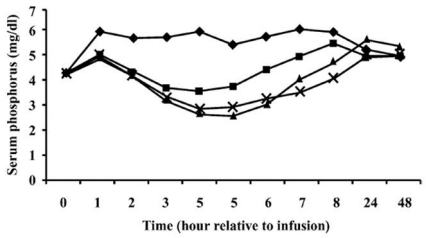
- Peripartal hypophosphatemia is physiological



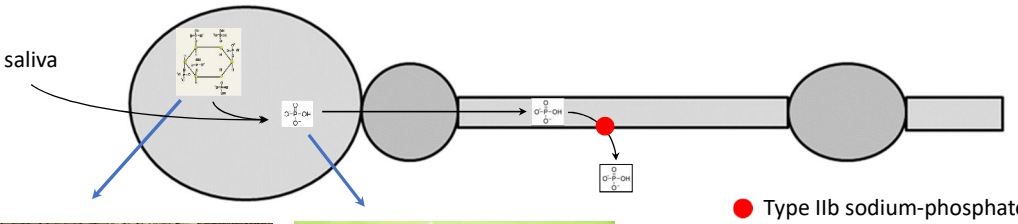
Serum P in intact (■) and mastectomized (□) periparturient cows

Goff et al., 2002

- Blood Pi declines after LPS administration in a dose dependent way Waldron et al., 2003

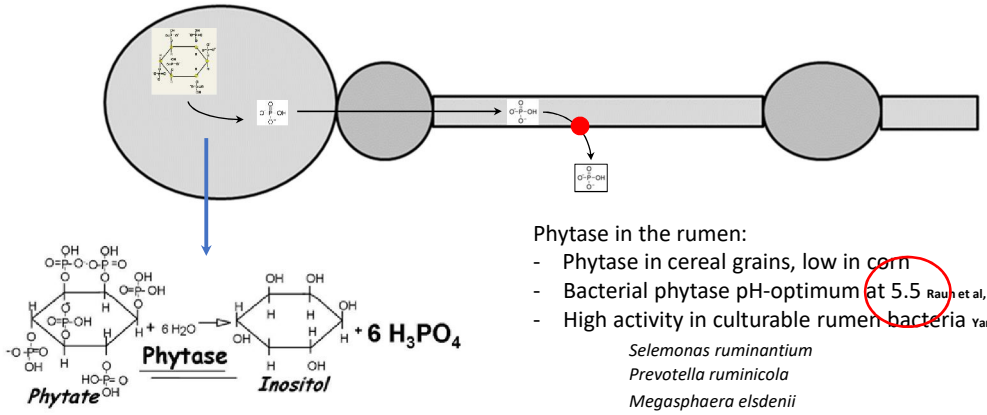


DCS and hypophosphatemia



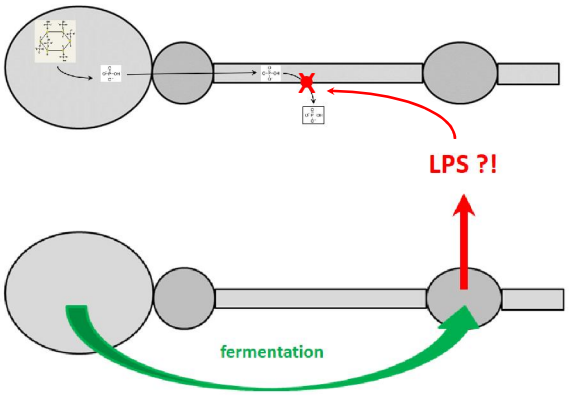
● Type IIb sodium-phosphate co-transporter NaPi-IIb

DCS and hypophosphatemia



Phytase in the rumen:
- Phytase in cereal grains, low in corn
- Bacterial phytase pH-optimum at 5.5 Raun et al, 1956
- High activity in culturable rumen bacteria Yanke et al., 1998
  - *Selemonas ruminantium*
  - *Prevotella ruminicola*
  - *Megasphaera elsdenii*

DCS: inflammation and hypophosphatemia



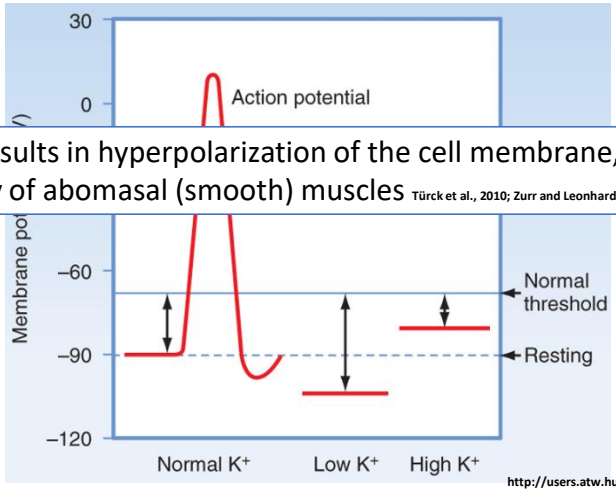
Limited data on effect of inflammation on intestinal Pi absorption Chen et al. 2009
- in mice: induction of colitis reduces small intestinal Pi absorption
- in mice and rats: induction of colitis reduces NaPi-IIb protein and NaPi-IIb mRNA in small intestines
- in Caco-2 cells: TNFα reduces Pi absorption, NaPi-IIb protein and NaPi-IIb mRNA

Dry cow: diets low in CP/RDNB:
- Fermentation shifts from rumen to the hindgut Jost et al. 2013
- Reduces fecal pH Aschemann et al., 2012; Jost et al., 2013

- Hindgut dysbiosis?! → LPS-translocation?! → proinflammatory cytokines?!

Fresh cows: sudden transition to lactation diet → rumen dysbiosis

DCS and hypokalemia



Hypokalemia results in hyperpolarization of the cell membrane, and reduces the contractility of abomasal (smooth) muscles Türck et al., 2010; Zurr and Leonhard-Marek, 2012

http://users.atw.hu/blp6/BLP6/HTML/C0359780323045827.htm

DCS and hypokalemia

- All cases: recumbend or severely weak cows
  - Correa et al. 1993: hypocalcemia, dystocia, still birth, retained placenta
  - Sielman et al. 1997: Iatrogenic DC: treated with *isoflupredone acetate*. Fever, metritis, diarrhea, LDA
  - Sattler et al. 1998: all cases with protracted, often infectious disease

Hypokalemia is the result of another disturbance resulting in decreased DMI
Hypokalemia is no cause of DCS

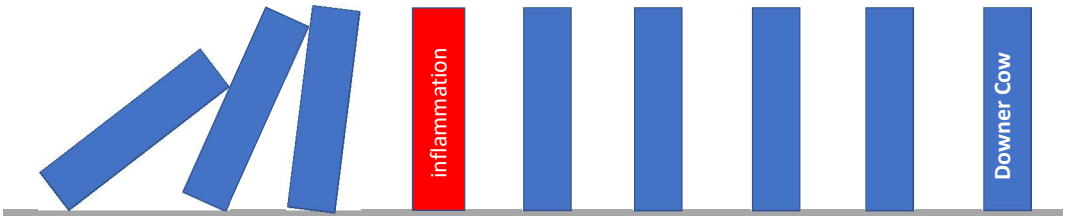
- Seyrek-Intas et al. 2013: mild and temporal hypokalemia in cows with dystocia, normakalemia in cows with eutocia
- Schneider et al. 2016: Healthy periparturient (D1-3) cows: no hypokalemia.

DCS and other associated disturbances

- Decreased insulin sensitivity Guyot et al., 2017
- Fatty liver Kalaitzakis et al., 2010
- Prepartum indications of an APR Zebeli and Ametaj, 2011

DCS is the result of a preceeding inflammation in a cascade of events

DCS; domino effect



Complicated hypocalcemia and DCS

- First: prevention of inflammation
  - Antepartum : prevention of rumen dysbiosis and hindgut dysbiosis
  - Partum: prevention of lacerations of the birth canal
  - Early postpartum : prevention of
    - Rumen dysbiosis and hindgut dysbiosis
    - Mastitis
    - RFM and metritis (roots lay antepartum)
- Second: prevention of hypocalcemia

Rik Hendriks, VEERkracht Dairy Congress 2019, the Netherlands

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