Dietary Interventions for Prevention of Mineral Related Disorders Postpartum

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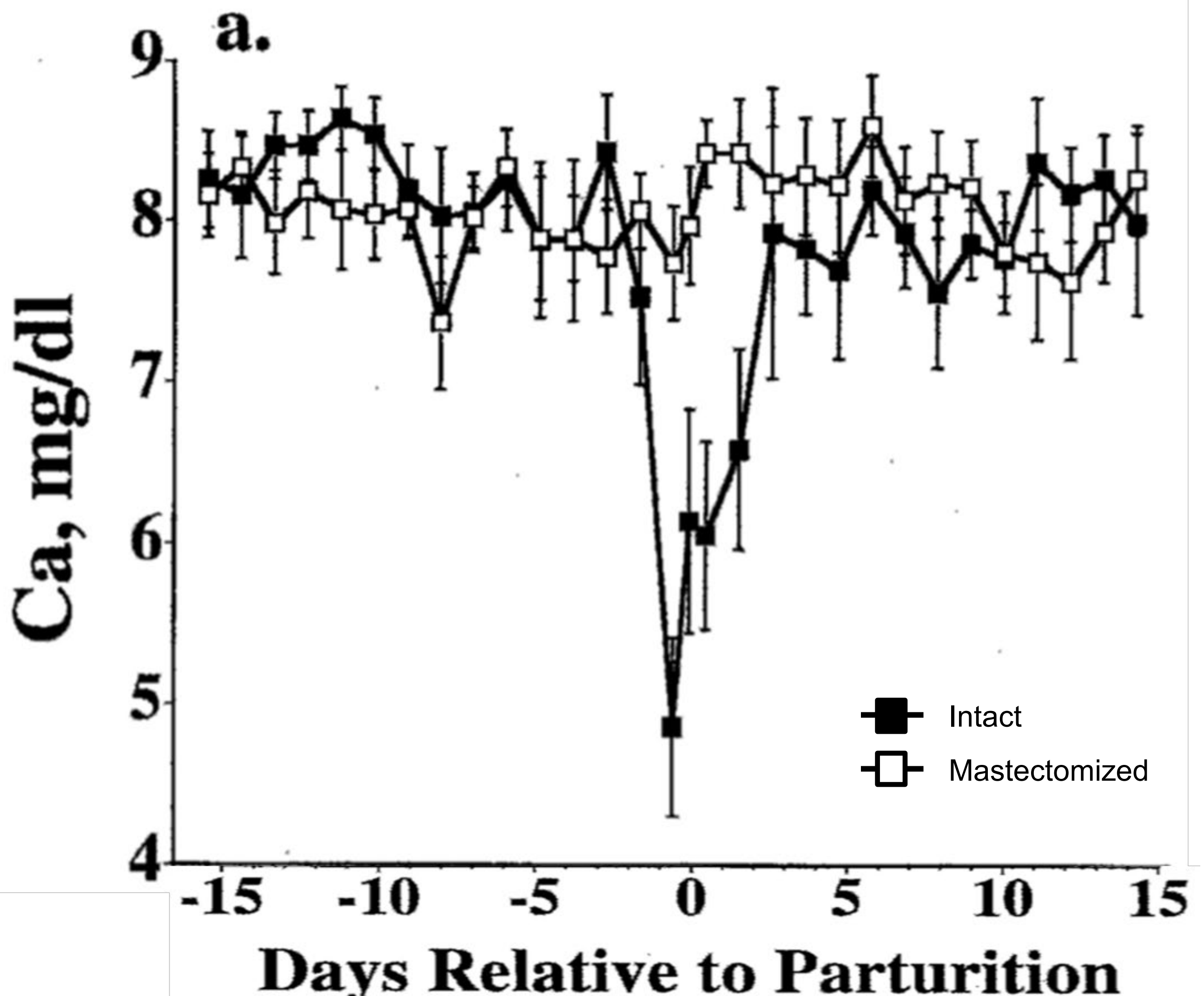
ANIMAL SCIENCES

Outline

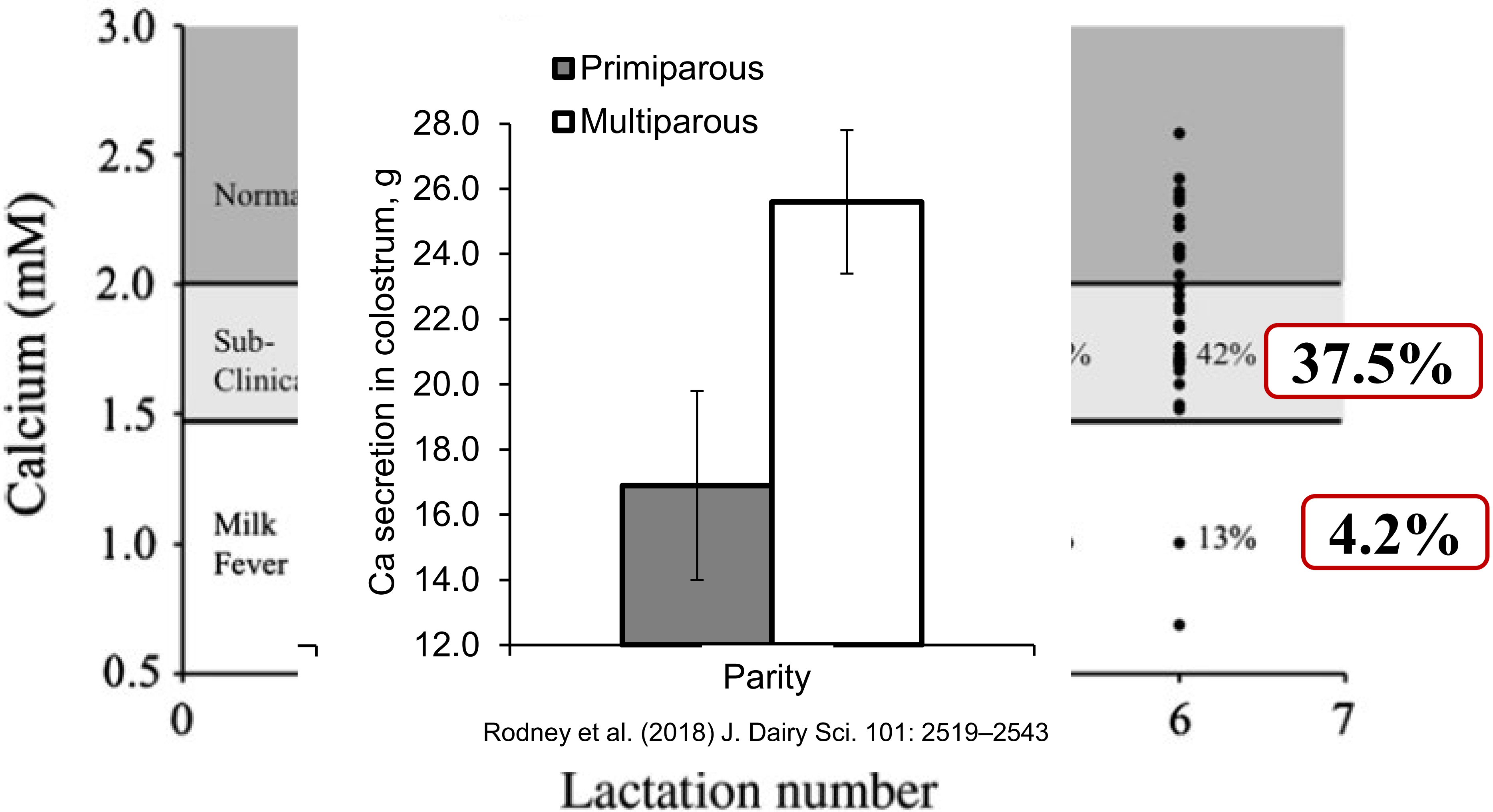
- ✓ Why dairy cows develop hypocalcemia
- ✓ Impacts of hypocalcemia on dairy cow health
- ✓ Methods of prevention of hypocalcemia
  - ✓ Restricted Ca absorption
  - ✓ Reduced P intake/absorption and blood phosphate concentrations
  - ✓ Induction of compensated metabolic acidosis
  - ✓ Oral Ca dosing

Why Dairy Cows Develop Hypocalcemia



Goff et al. (2002) J. Dairy Sci. 85:1427-1436

Why Dairy Cows Develop Hypocalcemia



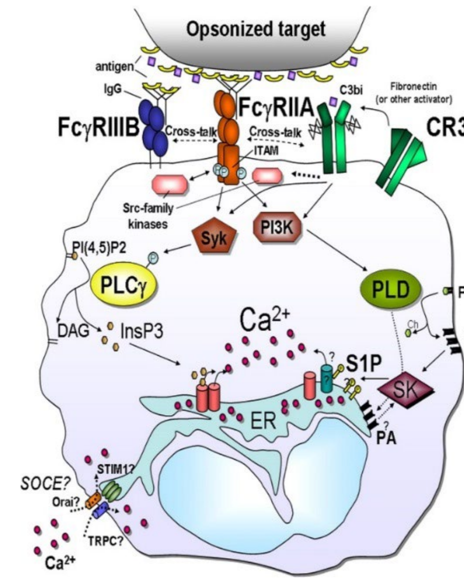
Rodney et al. (2018) J. Dairy Sci. 101: 2519–2543

Reinhardt et al. (2011) Vet. J. 188:122-124

Why Dairy Cows Develop Hypocalcemia

✓ Activation of immune cells?

Neutrophils		
1. Neutrophil no.	3,000,000	per mL
2. Diameter of neutrophil	15	µm
3. Cytosol vol./cell vol.	50%	
4. Blood [iCa]	1.2	mM
5. Neutrophil [iCa] at resting	85	nM
6. Neutrophil [iCa] at activation	400	nM
In 1 mL of blood		
Volume of 1 neutrophil	1,766	cubic µm
Total volume occupied by neutrophils	5,298,750,000	cubic µm
Total volume in 1 mL of blood	1,000,000,000,000	cubic µm
Neutrophils represent	0.53%	
Total iCa in 1 mL	48,000	ng
Increment in iCa upon activation	315.00	nM
iCa used upon activ. in 1 L of neu	12,600.00	ng
iCa used upon activ. in 1 mL of neu	12.60	ng
Cytosolic neutr. vol. in 1 mL	0.26%	
Adj. for cyto neutro vol present in 1 mL	0.033	ng
Absolute iCa in 1 mL	48,000.00	ng
iCa used by neutrophil activation in 1 mL	0.033	ng



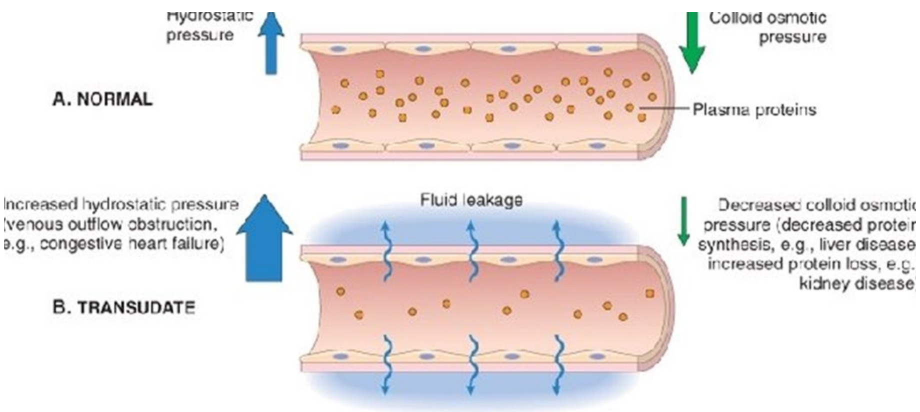
Nunes P , and Demaurex N J Leukoc Biol 2010;88:57-68

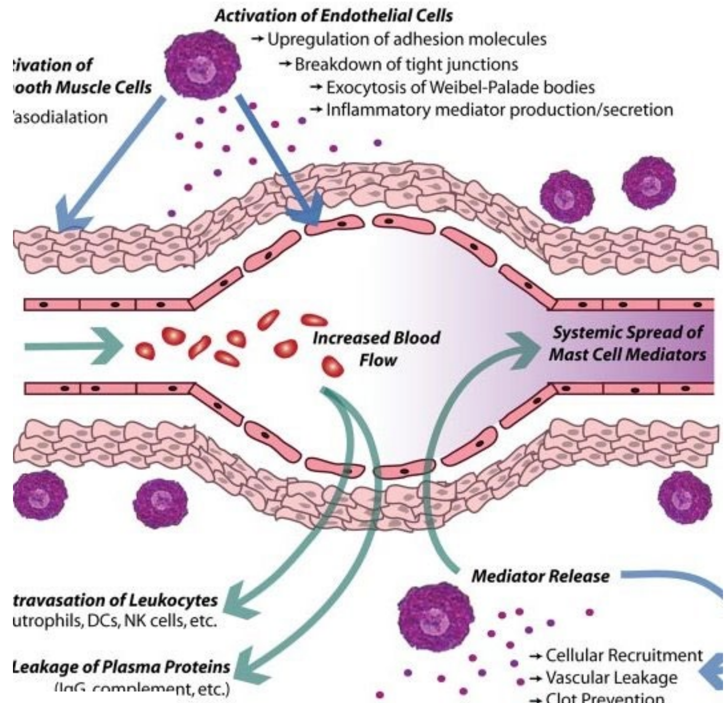
Proportion of iCa used upon activation of 50% of all neutrophils in blood

0.00007%

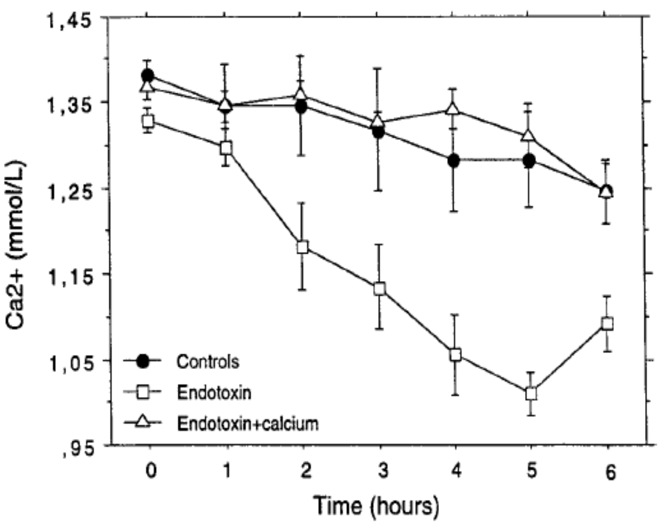
Vieira-Neto et al. (2024) Animals 14:1232. https://doi.org/10.3390/ani14081232

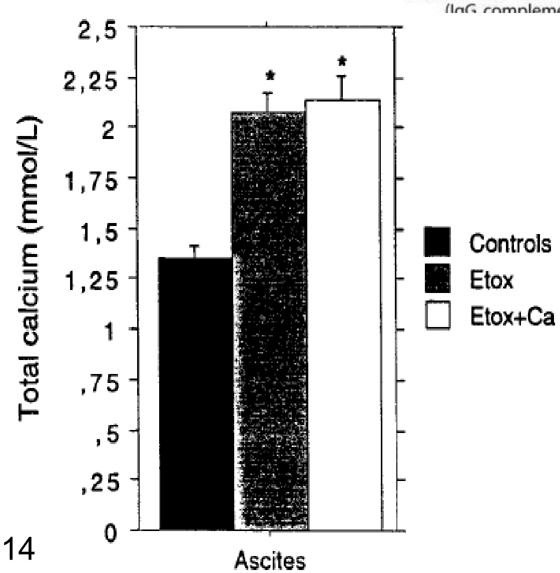
Inflammation Increases Vascular Permeability

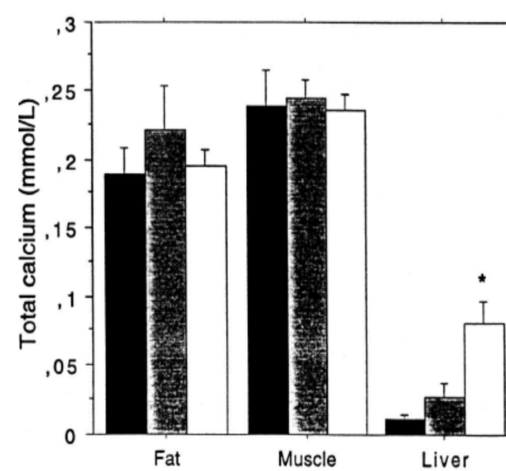




Kunder et al. (2011) Blood 118: 5383-5393





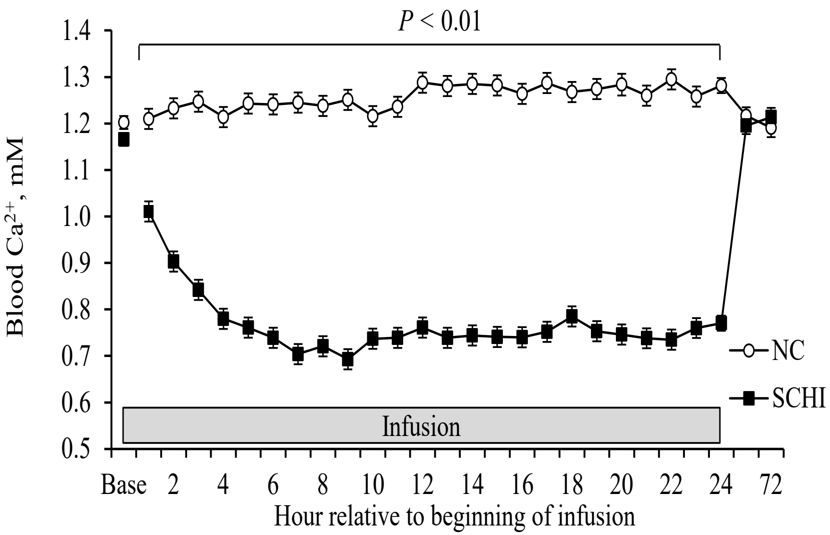


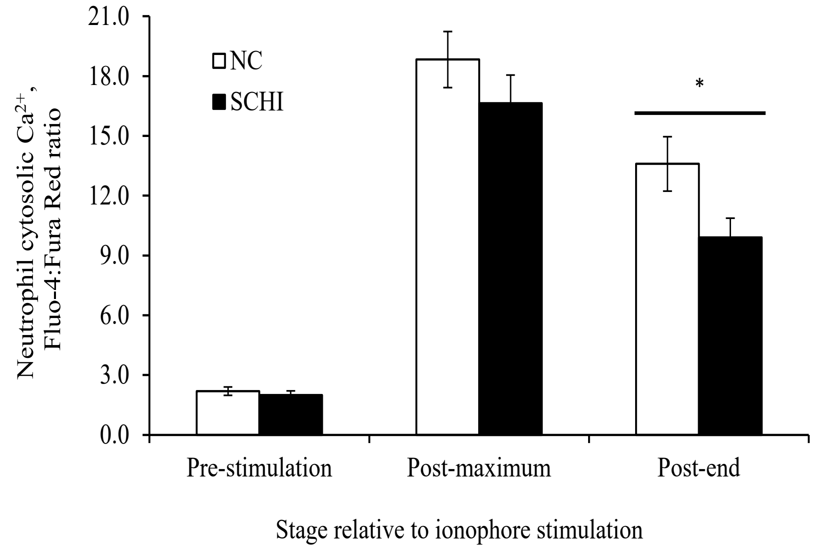
Calrstedt et al. (2000) Crit. Care Med. 28: 2909-2914

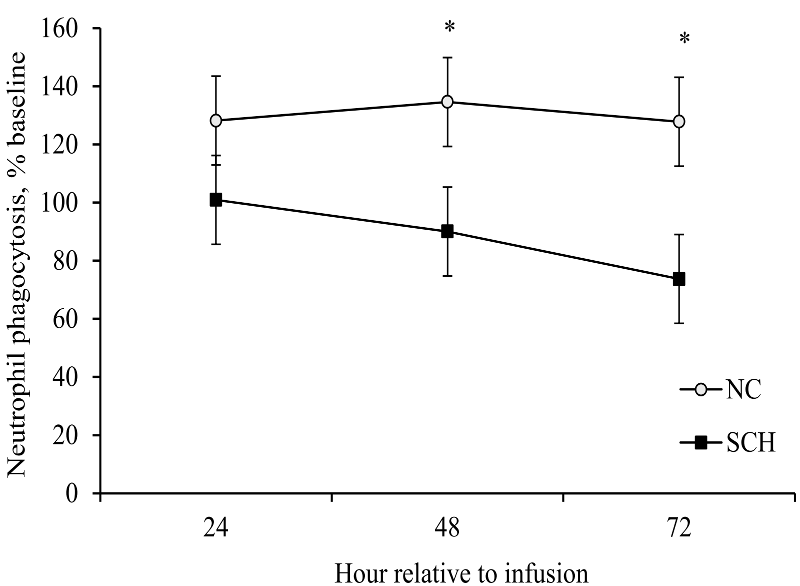
Prepartum Diet

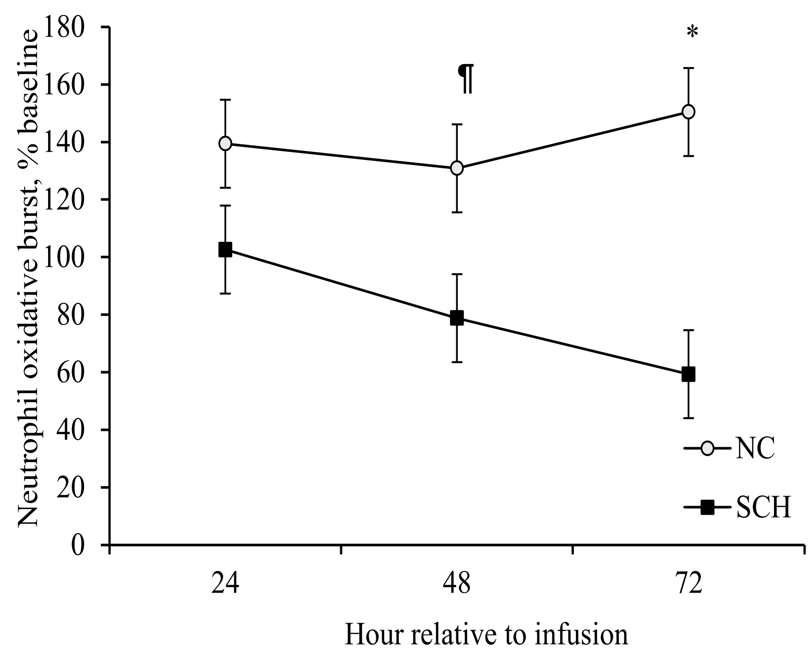
- ✓Alkalosis interferes with calciotropic hormones
  - ✓ Intake of K and Na
- ✓Dietary phosphorus
  - ✓Increased blood phosphate interferes with calciotropic hormones
- ✓Dietary magnesium
  - ✓Magnesium is required for proper activity of calciotropic hormones

Induced Subclinical Hypocalcemia in Dairy Cows



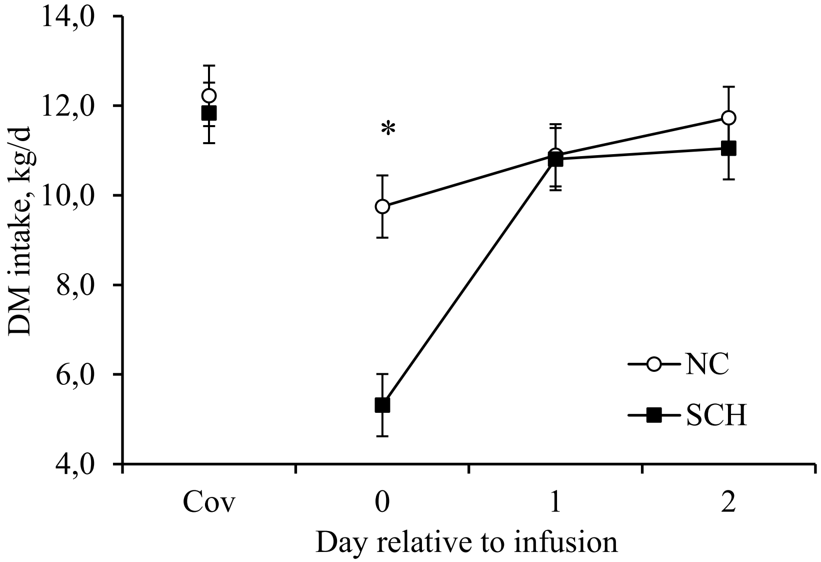




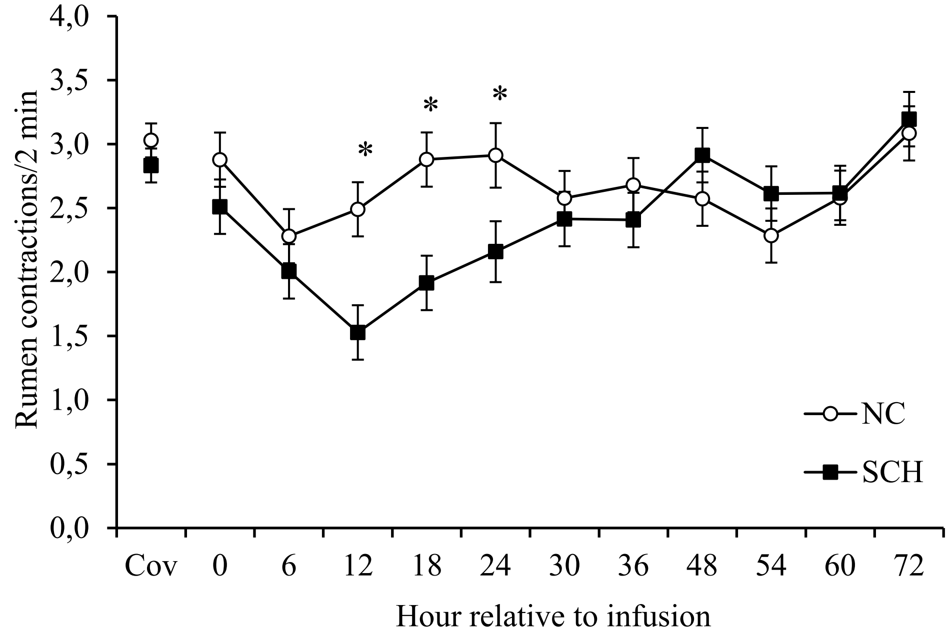


Martinez et al. (2014) J. Dairy Sci. 97 :874–887

Subclinical Hypocalcemia Reduces DM Intake and Rumen Motility in Dairy Cows



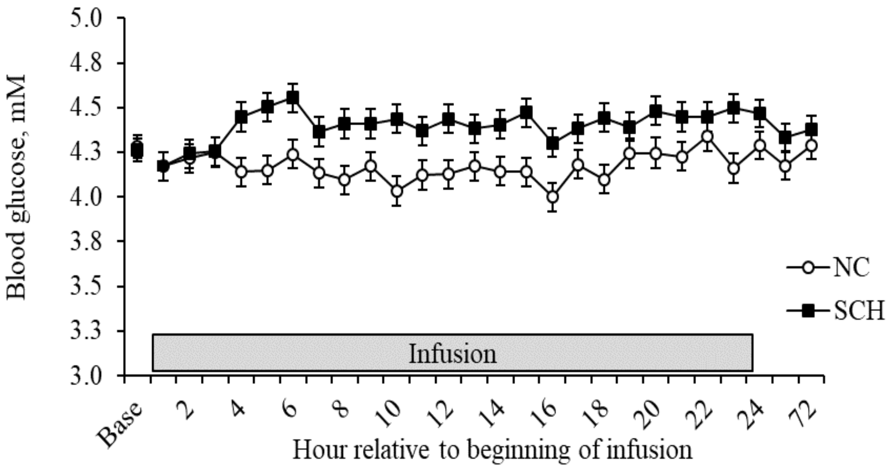
* P < 0.01



Martinez et al. (2014) J. Dairy Sci. 97 :874–887

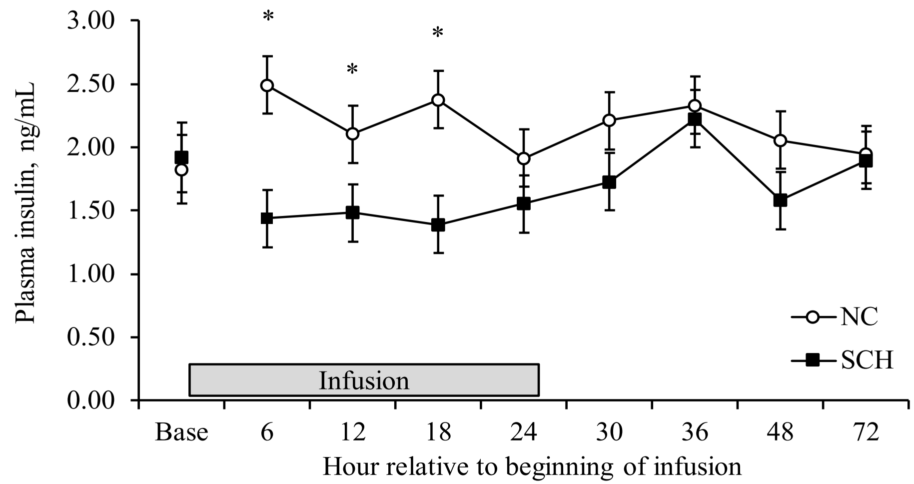
Glucose

Trt, $P = 0.01$
Hour, $P = 0.11$
Trt x Hour, $P = 0.25$



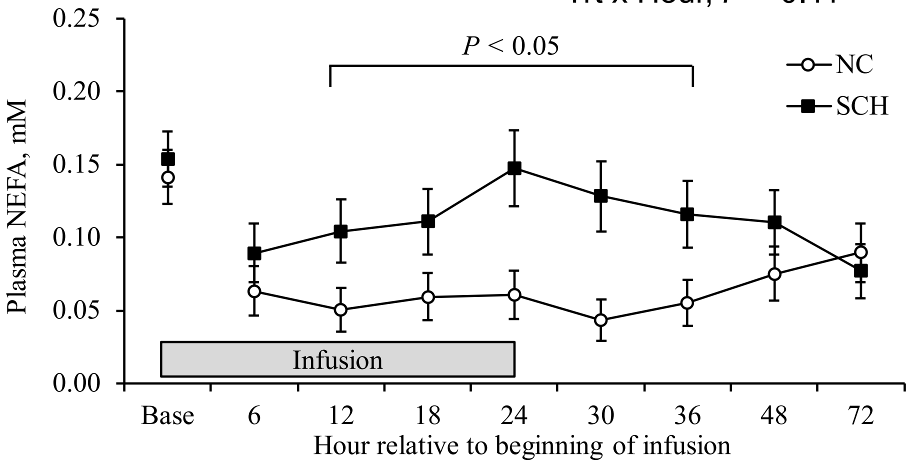
Insulin

Trt, $P = 0.07$
Hour, $P = 0.05$
Trt x Hour, $P = 0.02$



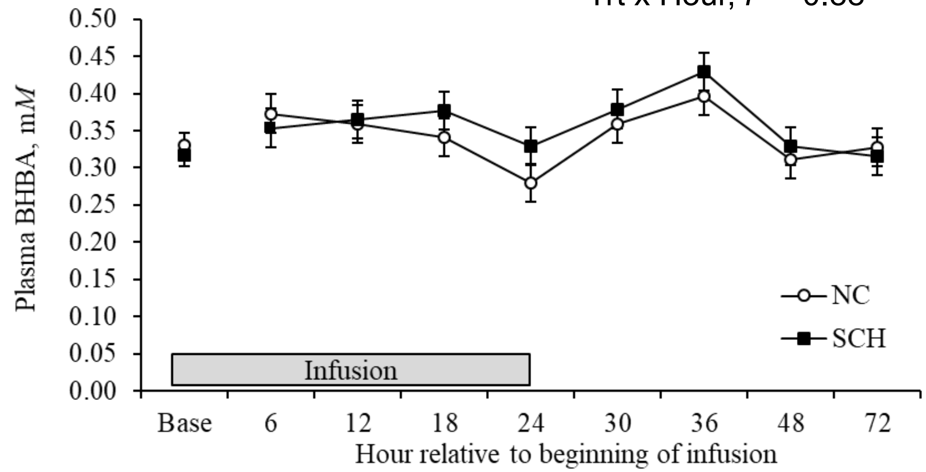
NEFA

Trt, $P = 0.02$
Hour, $P = 0.75$
Trt x Hour, $P = 0.11$

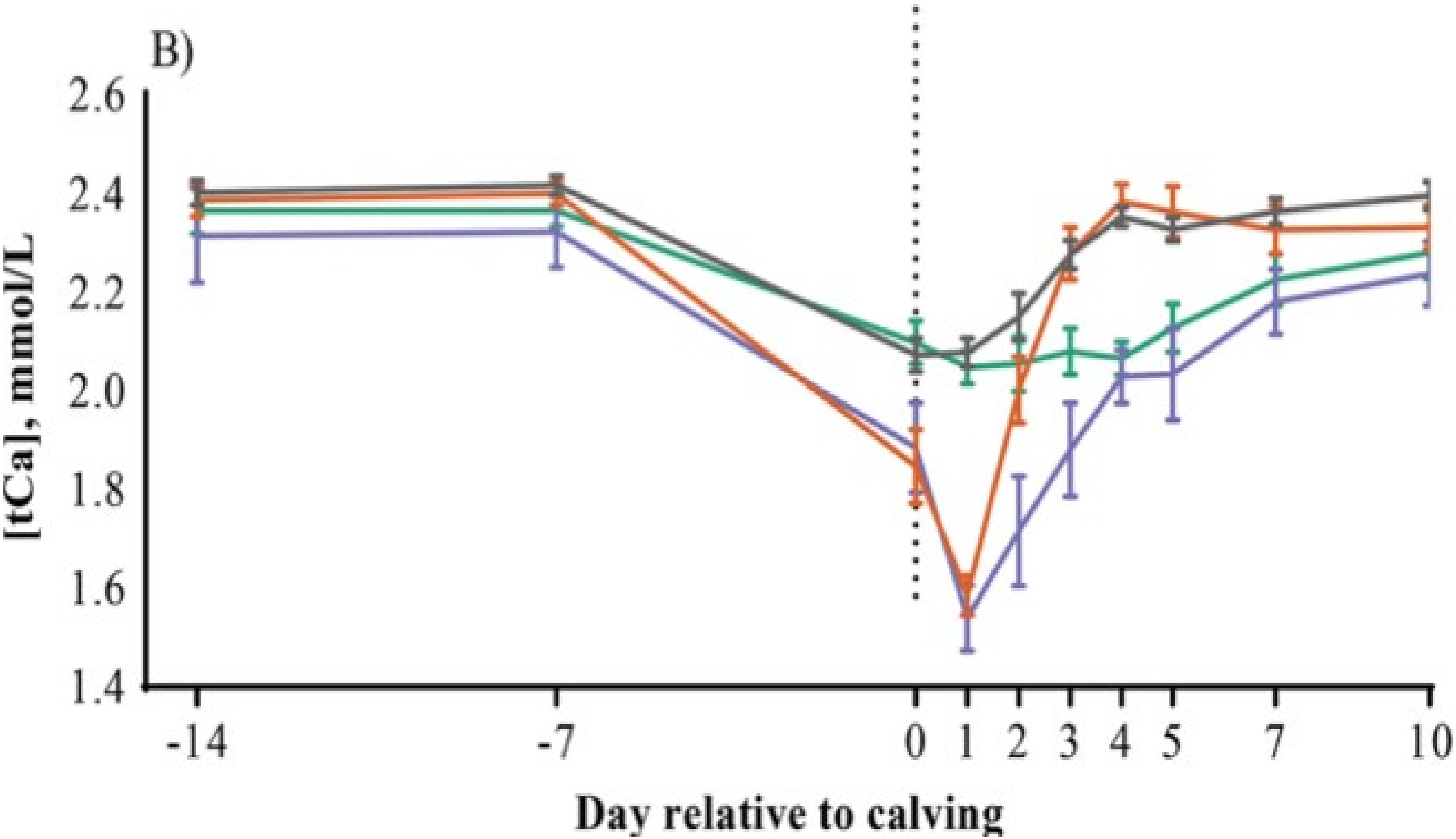


BHBA

Trt, $P = 0.39$
Hour, $P < 0.01$
Trt x Hour, $P = 0.88$



Martinez et al. (2014) J. Dairy Sci. 97 :874–887



McArt and Neves (2020) J. Dairy Sci. 103:690-701

Strategies Available to Reduce the Risk of Hypocalcemia

✓Prepartum diets with very low Ca content

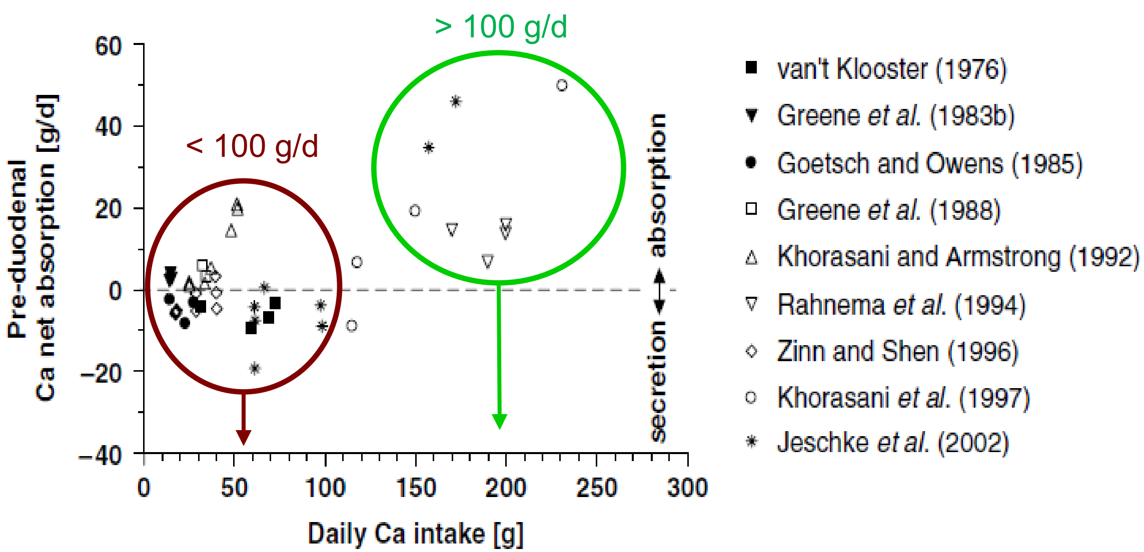
✓Reduced intestinal absorption of P and Ca

✓Altered acid-base status by dietary manipulation

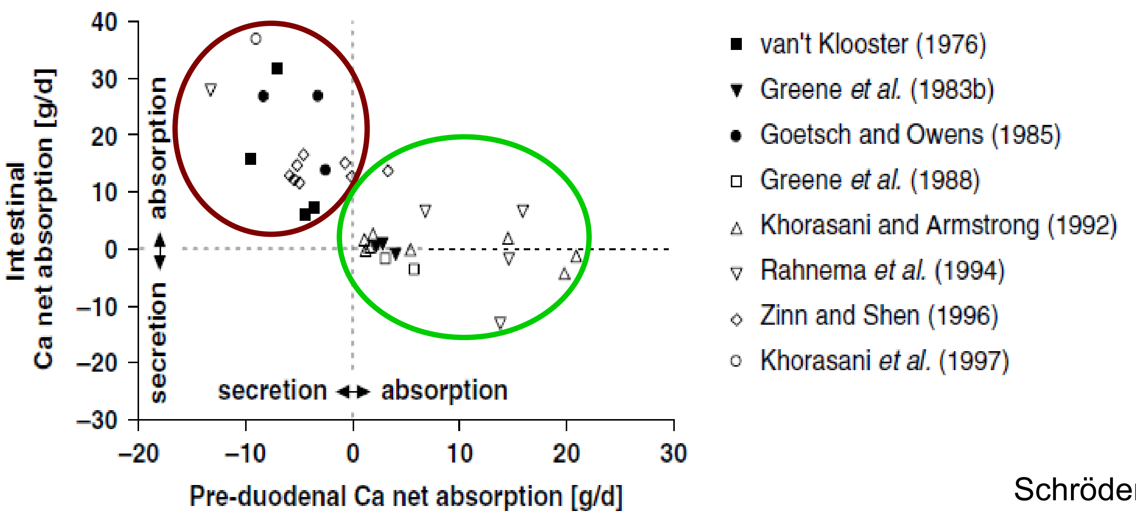
✓Administration of Ca at calving

Site of Ca Absorption in the GIT of Bovine

Pre-duodenum Ca absorption



Post-abomasum Ca absorption



Schröder and Breves (2007) Anim. Health Rev. 7(1/2):31–41

PCR Products for TRPV6 and PMCA1b in the Rumen and Duodenal Epithelium of Bovine

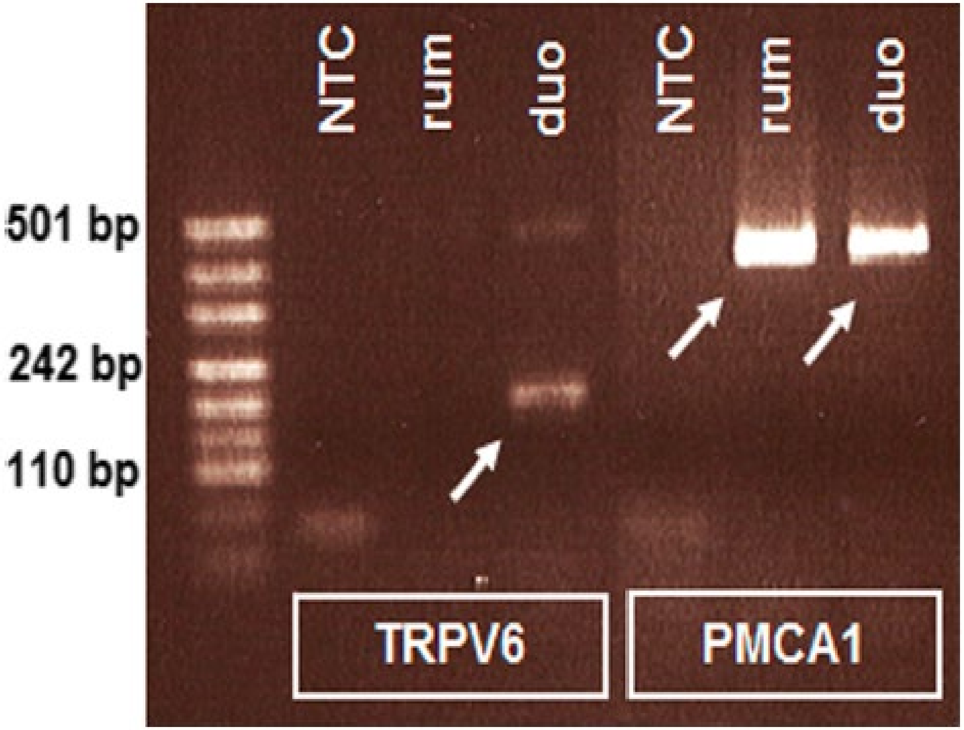
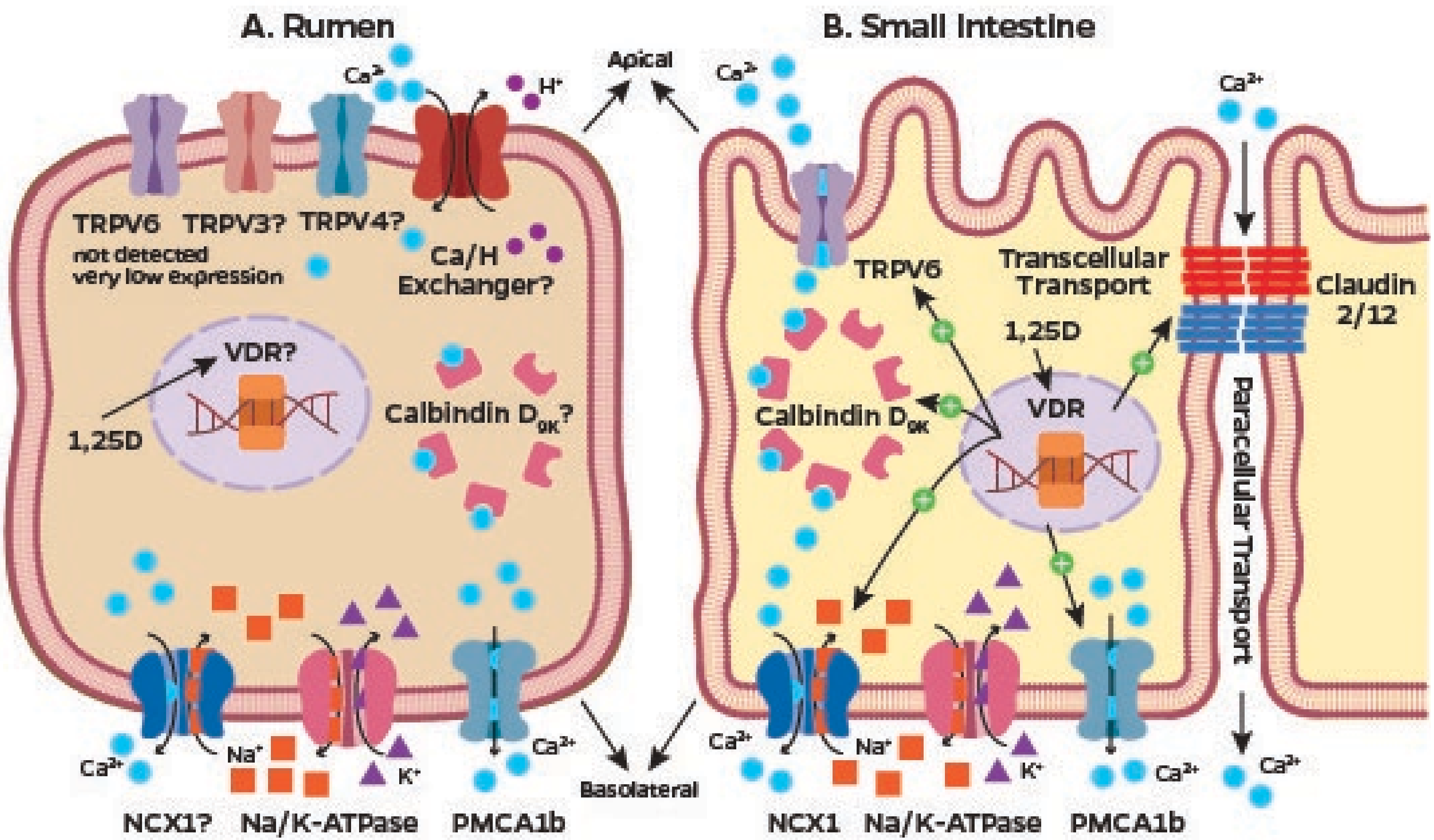


Figure 1. RT-PCR for the detection of products specific for TRPV6 and PMCA1. NTC, no template control; rum, rumen; duo, duodenum.

Schröder et al. (2015) Physiol. Rep. 3:e12615

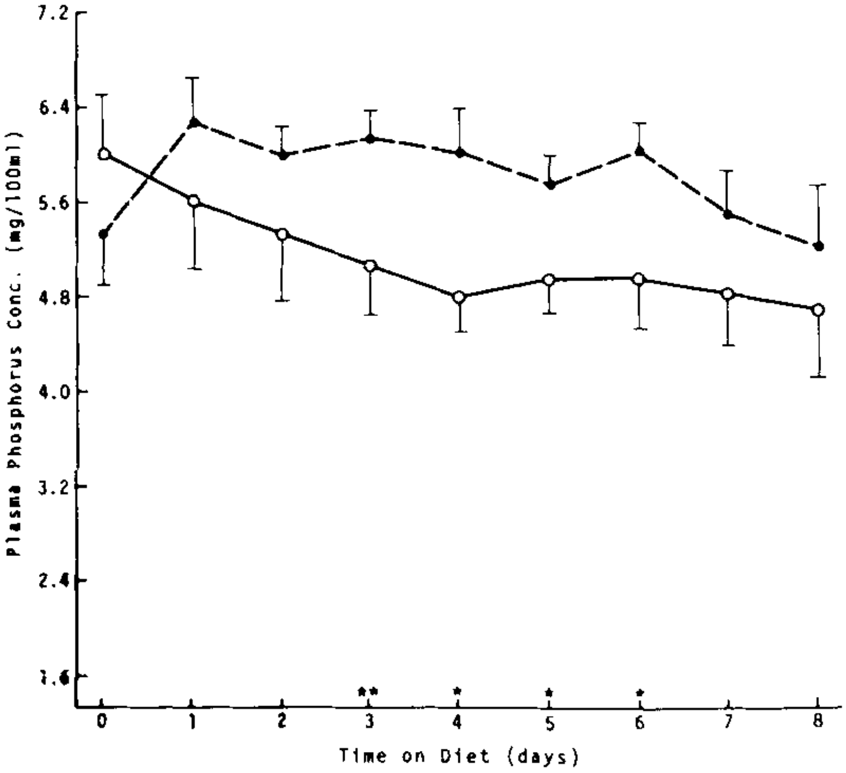
Mechanisms of Ca Absorption in the Bovine GIT (Ruminants)

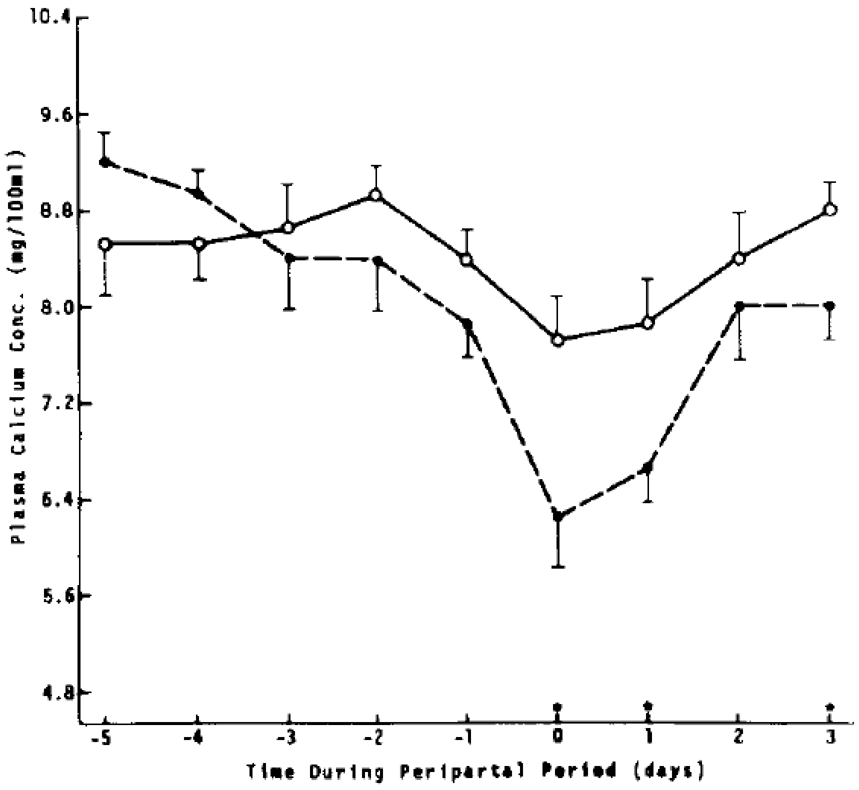


Vieira-Neto et al. (2024) Animals 14:1232. https://doi.org/10.3390/ani14081232

Ca-deficient diets prepartum prevent milk fever

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

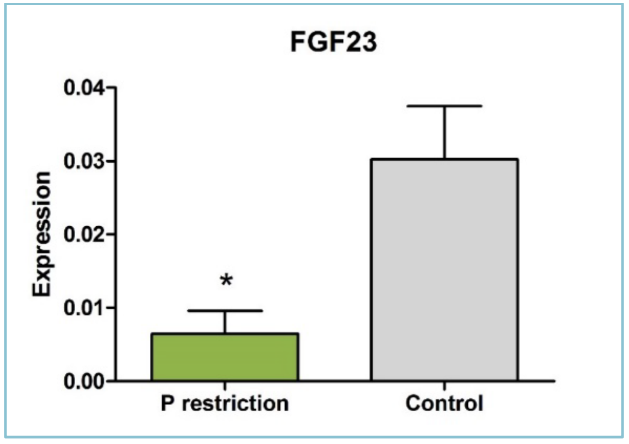




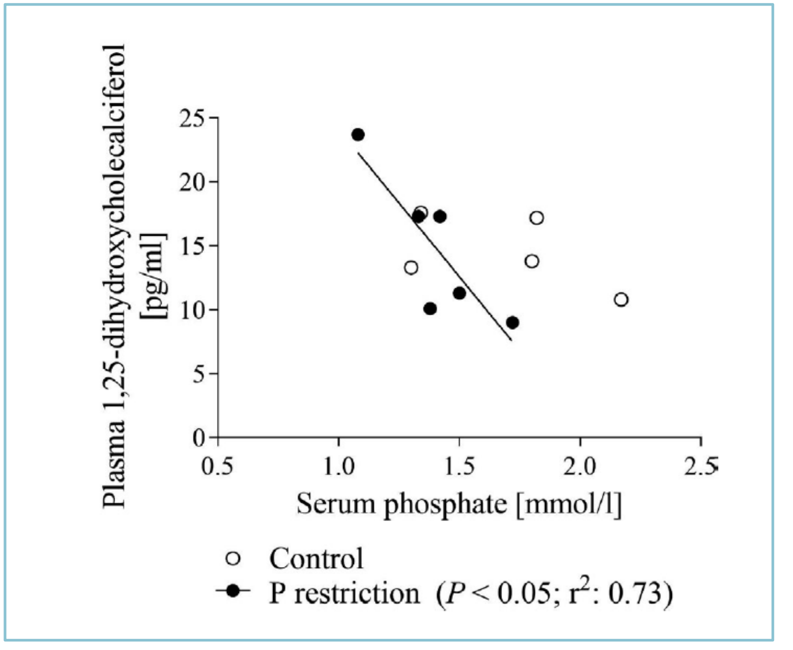
Green et al. (1981) 1981 J Dairy Sci 64:217-226

Dietary P and Ca Homeostasis – Lessons from Sheep

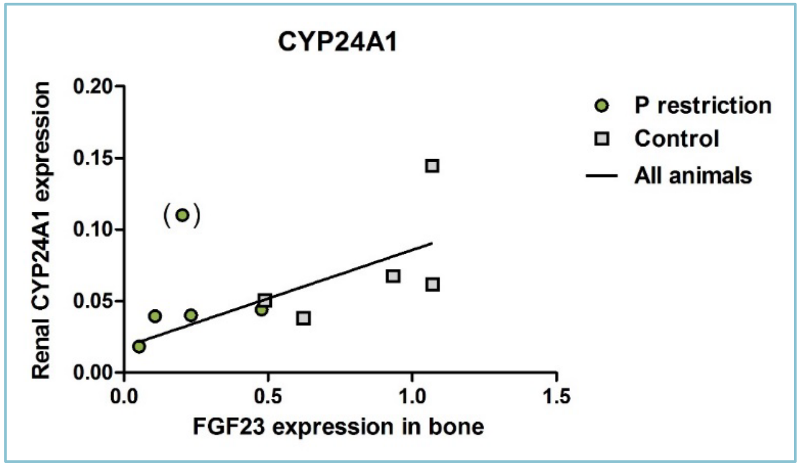
Dietary P restriction reduces FGF23



Plasma calcitriol is associated with serum P

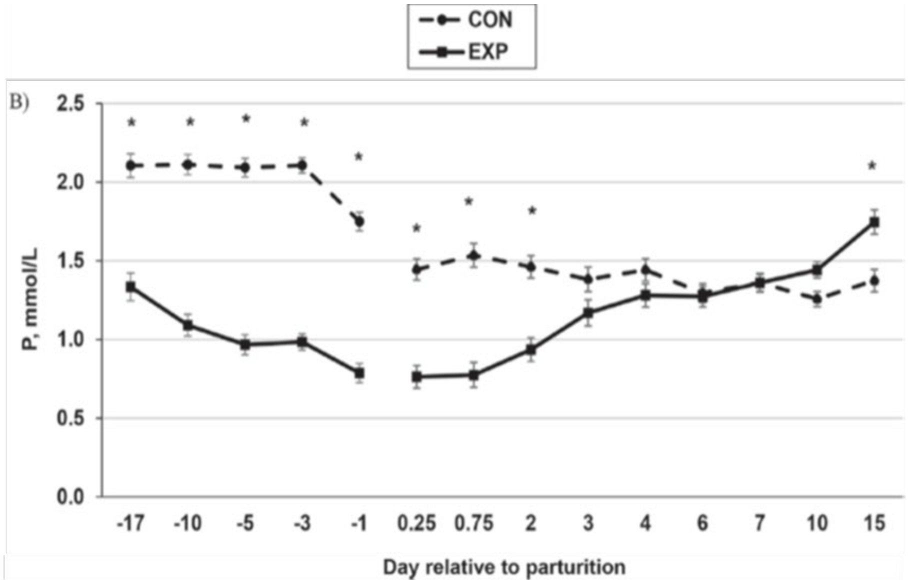


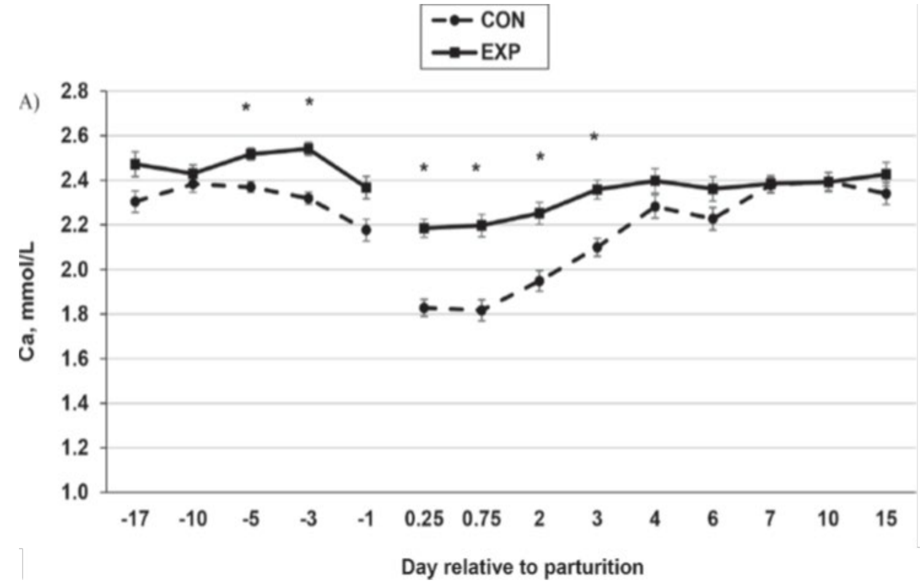
FGF23 is associated with CYP24A1 expression

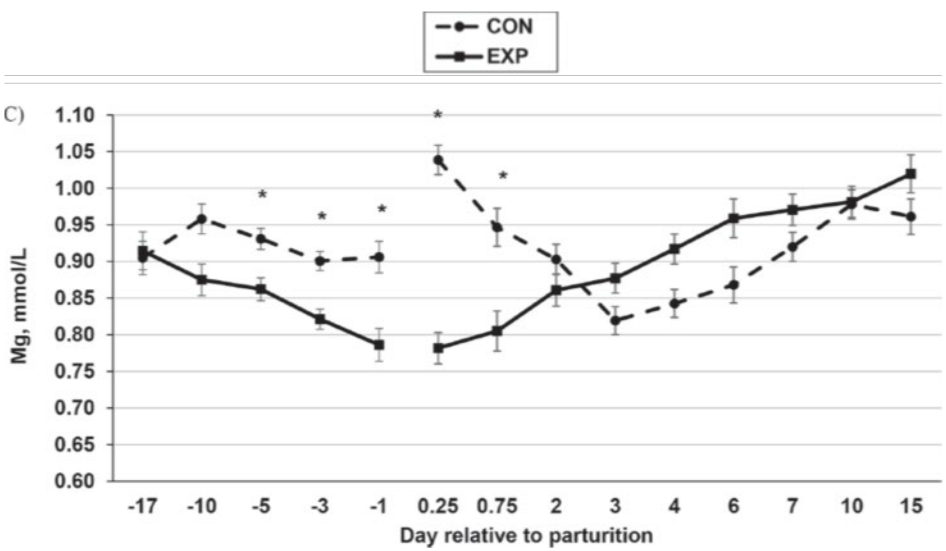


Köhler et al. (2021) J. Anim. Physiol. Anim. Nutr. 105:35-50

Feeding Zeolite Reduces Blood P and Improves Blood Ca

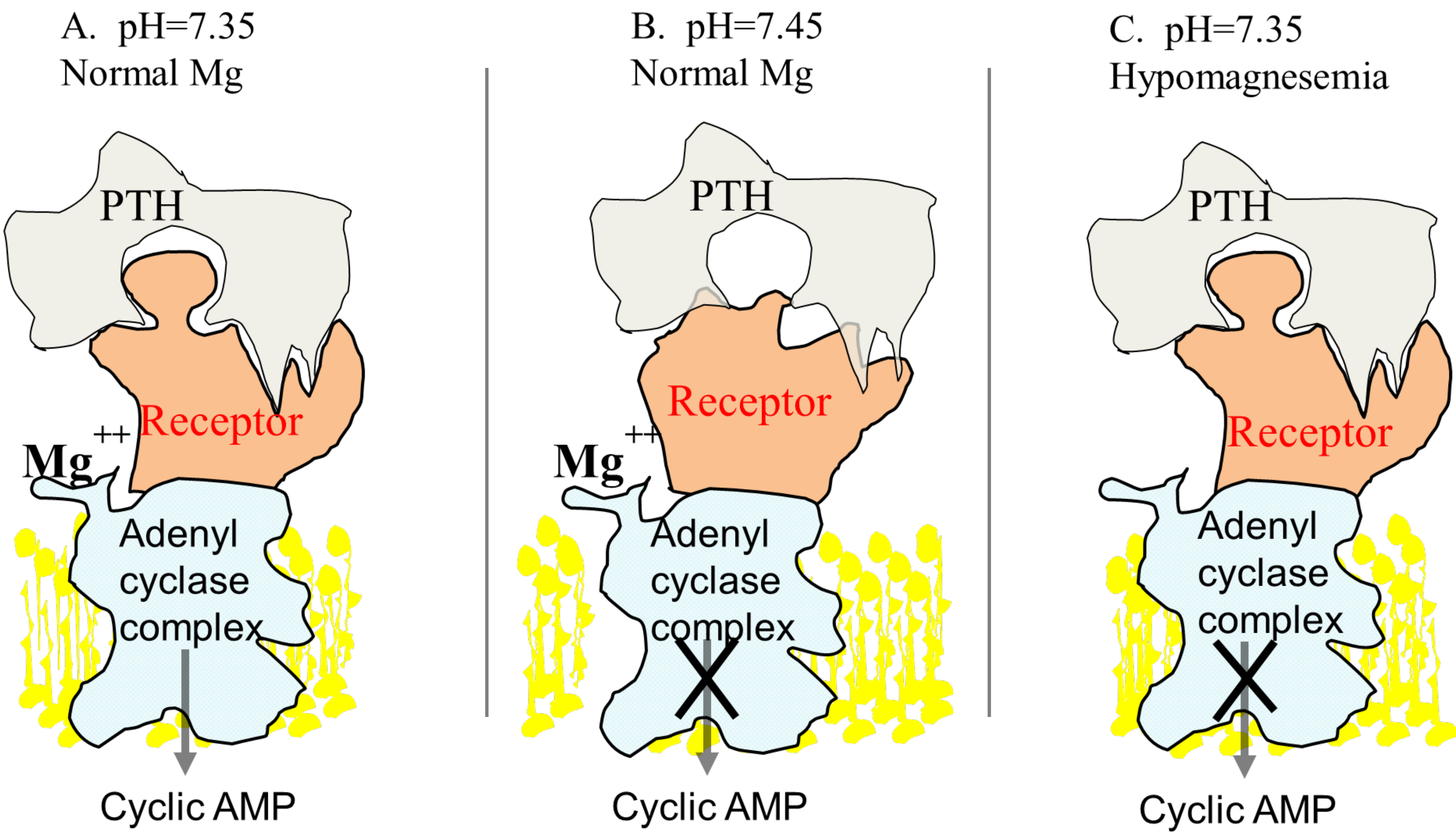






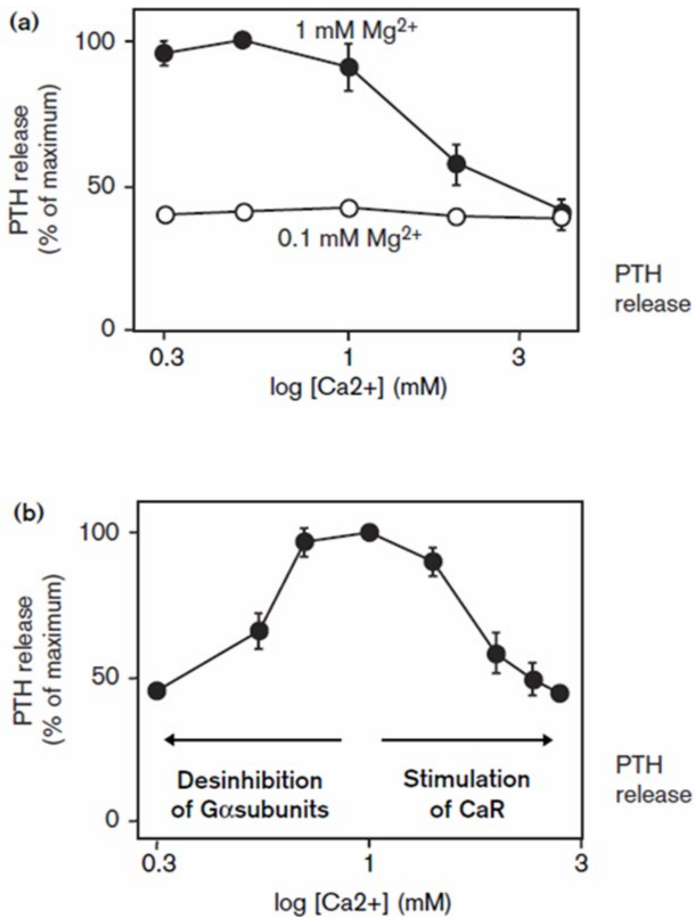
Kerwin et al. (2019) J. Dairy Sci. 102:5191–5207

Illustration of the Role of Acid-Based Balance and Mg Status on PTH Action



Courtesy of Jesse P. Goff

Adequate Plasma Mg Improves Ca Resorption from Bones



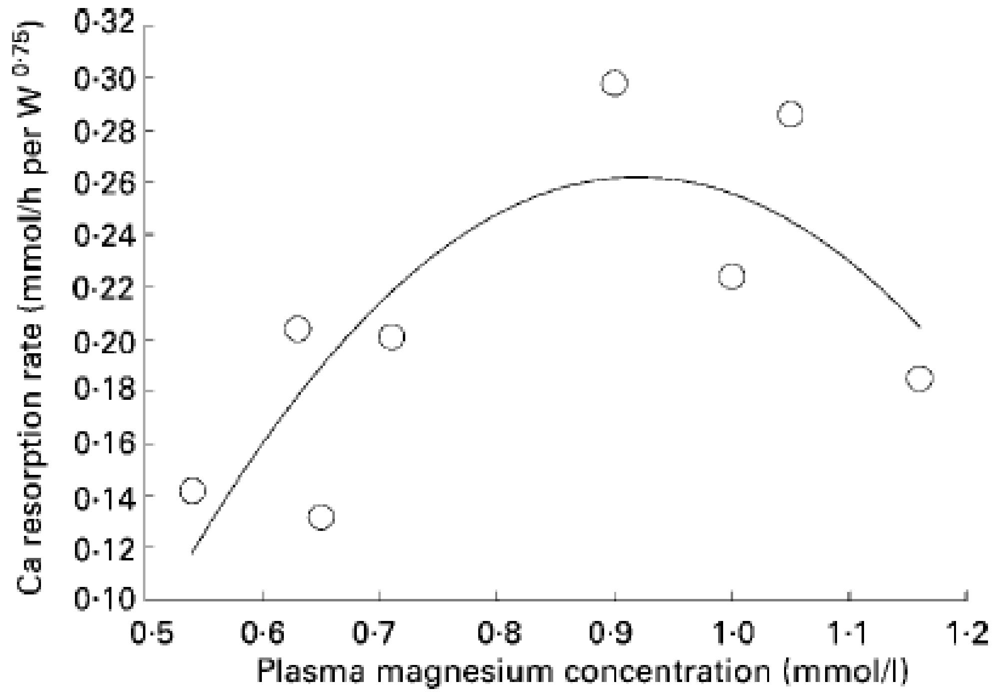


Fig. 4. Mean calcium resorption rate from bone corrected for metabolic live weight (R′, mmol/h per kg live weight $(W)^{0·75}$), as a function of plasma magnesium concentration (mmol/l). O, Data from Table 1; —, fitted quadratic equation.

Robson et al. (2004) Brit. J. Nutr. 91: 73-79

Vetter and Lohse (2002) Curr. Opin. Nephrol. Hypertens. 11:403-410

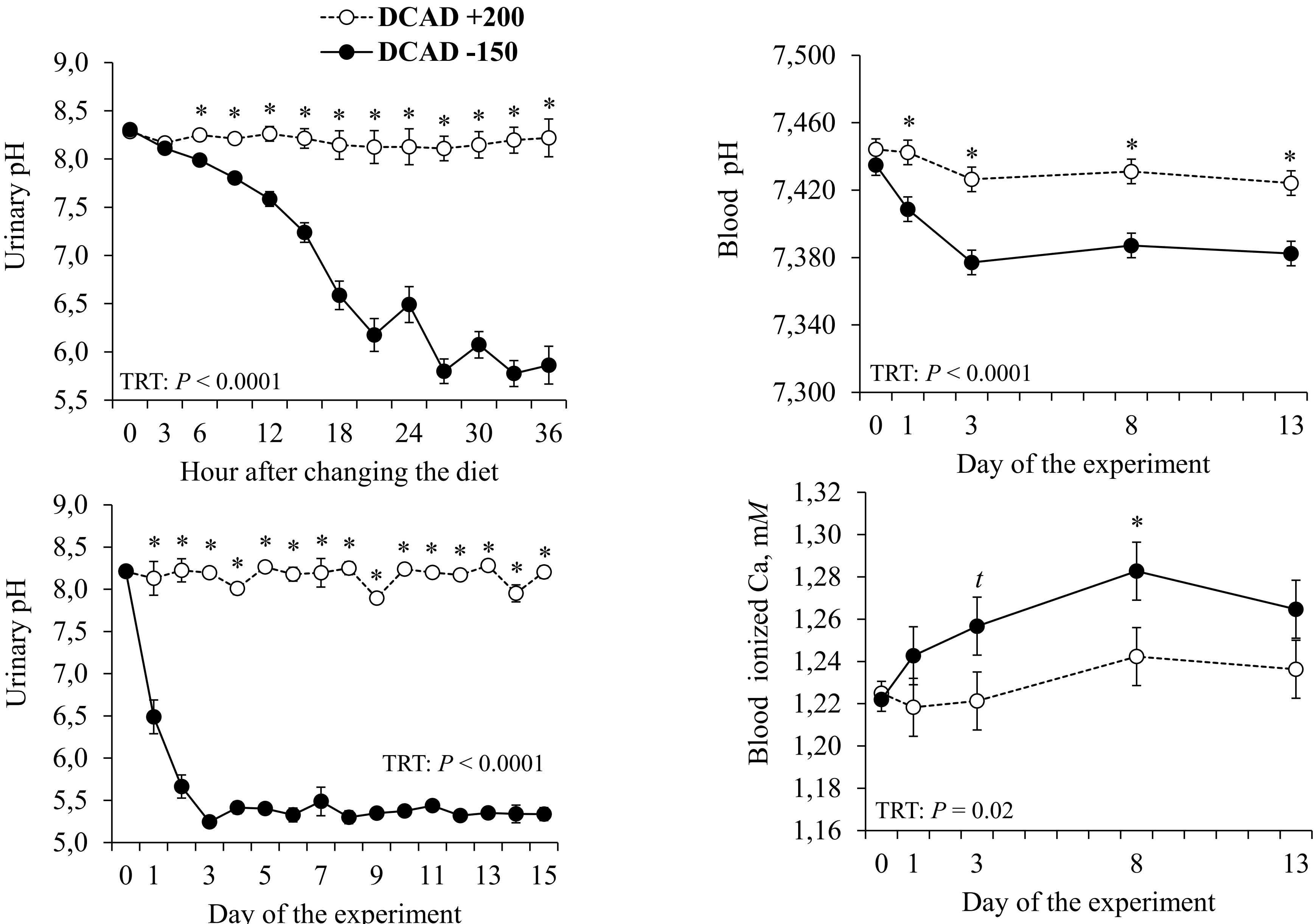
Peter Stewart's Strong Ion Difference

- ✓ Concept of Electroneutrality
  - ✓ In an aqueous solutions, the sum of all positively charged ions must equal to the sum of all negatively charged ions
- ✓ If a positive charge is added to this solution,
  - ✓ Na^+ or K^+,
  - ✓ then the positive charge necessitates loss of H^+ (a shift in the dissociation of water) making the solution alkaline.
- ✓ If a negative charge is added to the same solution,
  - ✓ such as Cl^-,
  - ✓ then the added negative change necessitates loss of HCO_3^- or gain of H^+
- ✓ Dietary cations or anions only affect blood pH if absorbed into the bloodstream in relatively large quantities and change the strong ion difference (**SID**) of blood

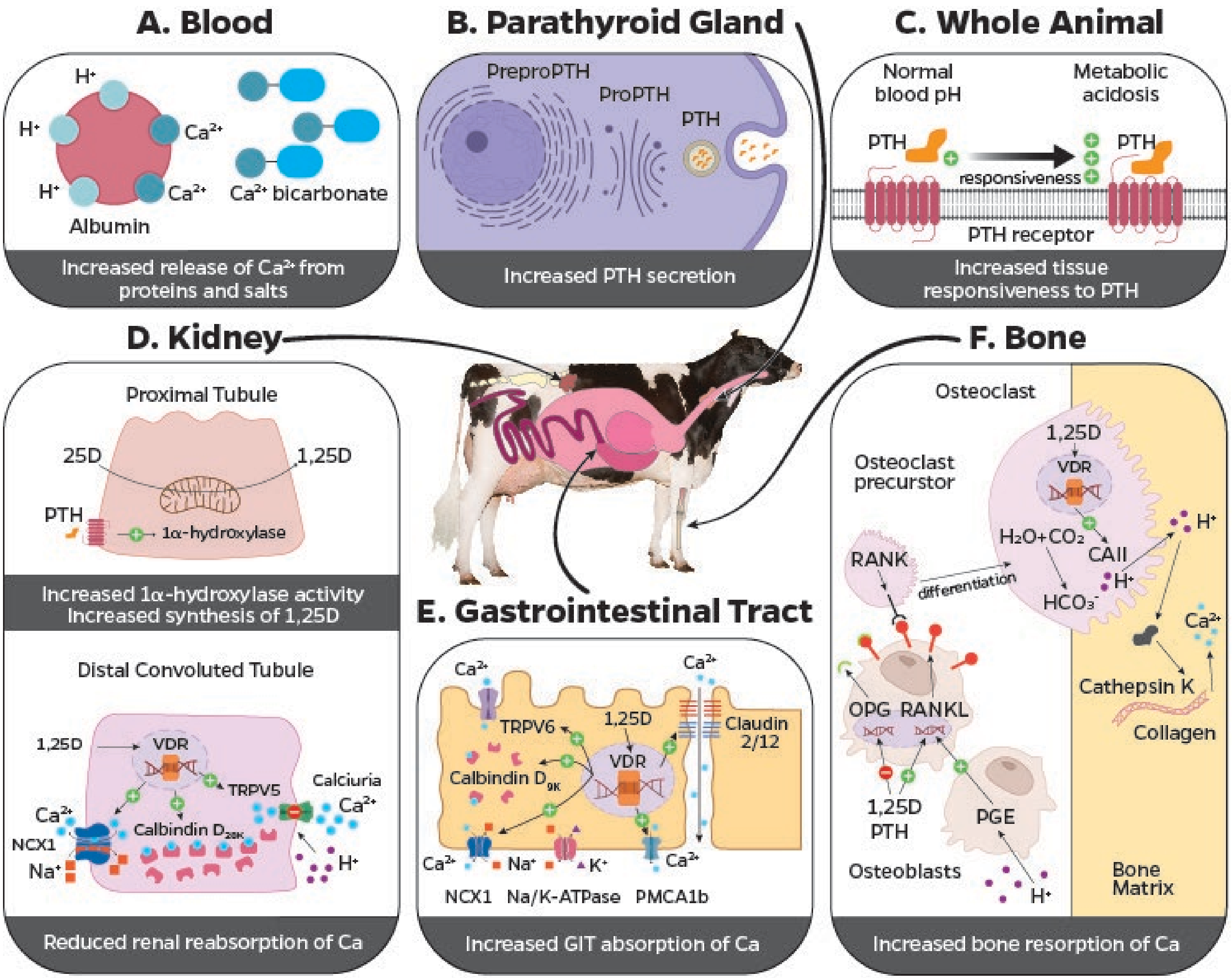
Stewart, PA. 1983. Modern quantitative acid-base chemistry. Can. J. Physiol. Pharmacol. 61:1444-1461

How DCAD Affects Blood Acid-Base Chemistry

Diet effects on acid-base status

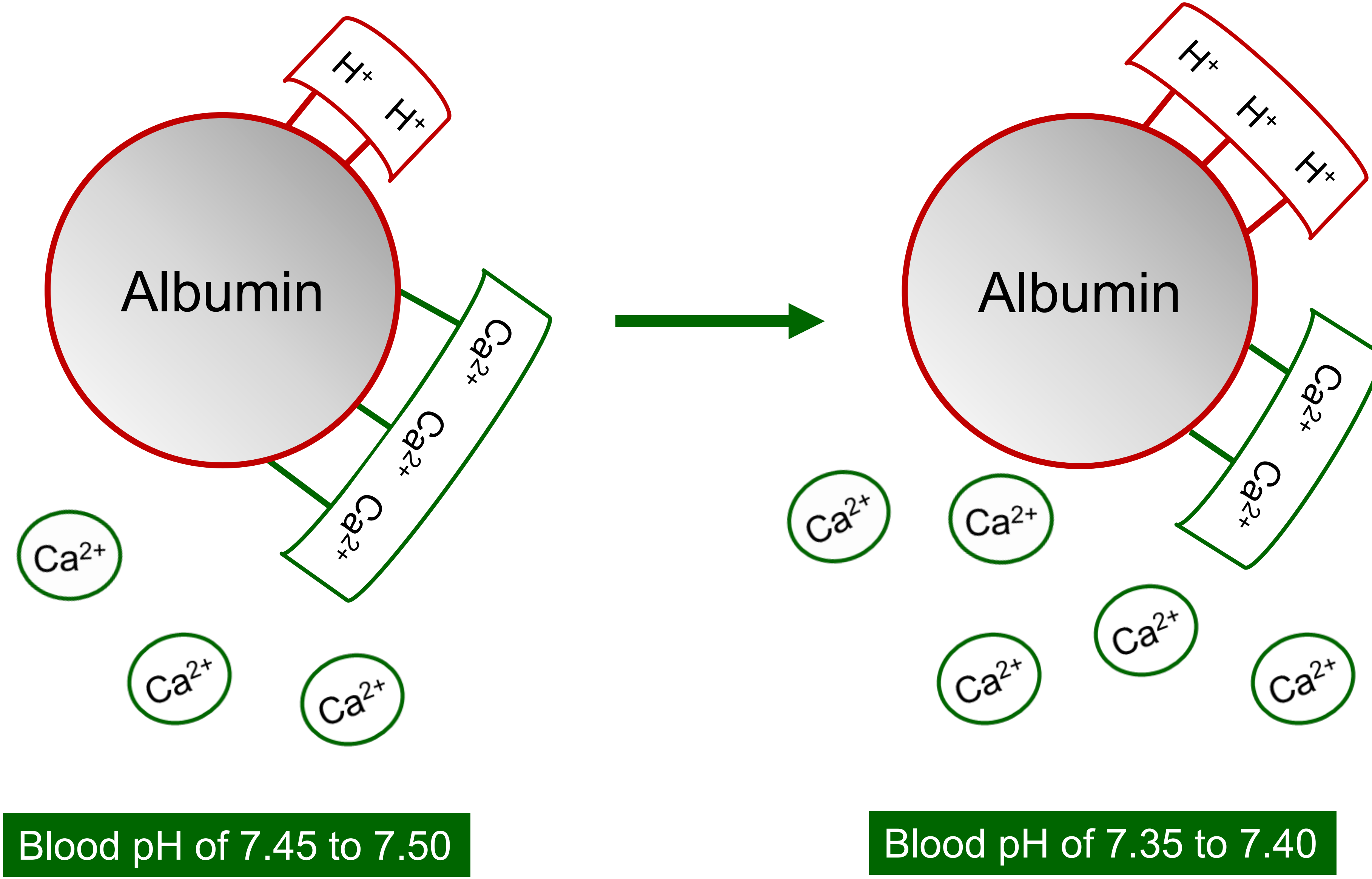


Vieira-Neto et al. (2021) J. Dairy Sci. 104:1018–1038



Vieira-Neto et al. (2024) Animals 14:1232. https://doi.org/10.3390/ani14081232

Acidemia Displaces Ca^{2+} from Albumin



Metabolic Acidosis Enhances PTH Release

22 dogs randomly assigned to treatments

Control (CO; 7)

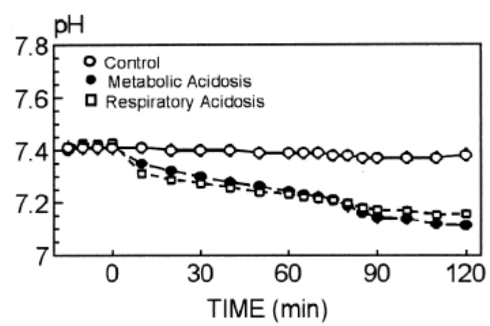
Metabolic Acidosis (MA; 8)

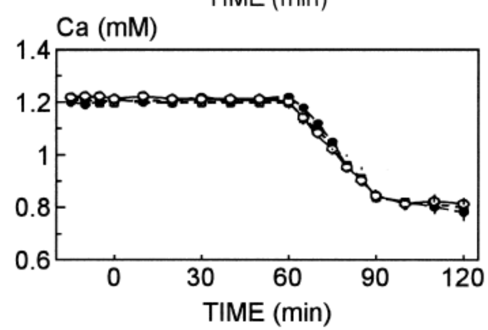
Respiratory Acidosis (RA; 7)

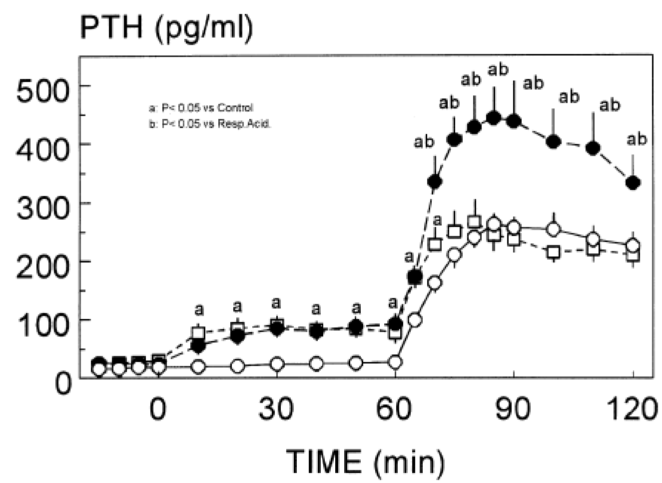
Baseline 20 min → Eucalcemia 60 min → Hypoalcemia 60 min

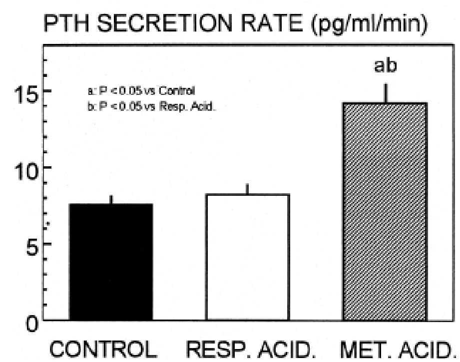
Eucalcemia: EDTA infusion in MA and RA to maintain [Ca^{2+}] equal to CO

Hypoalcemia: EDTA infusion to to induce hypocalcemia in all 3 treatments



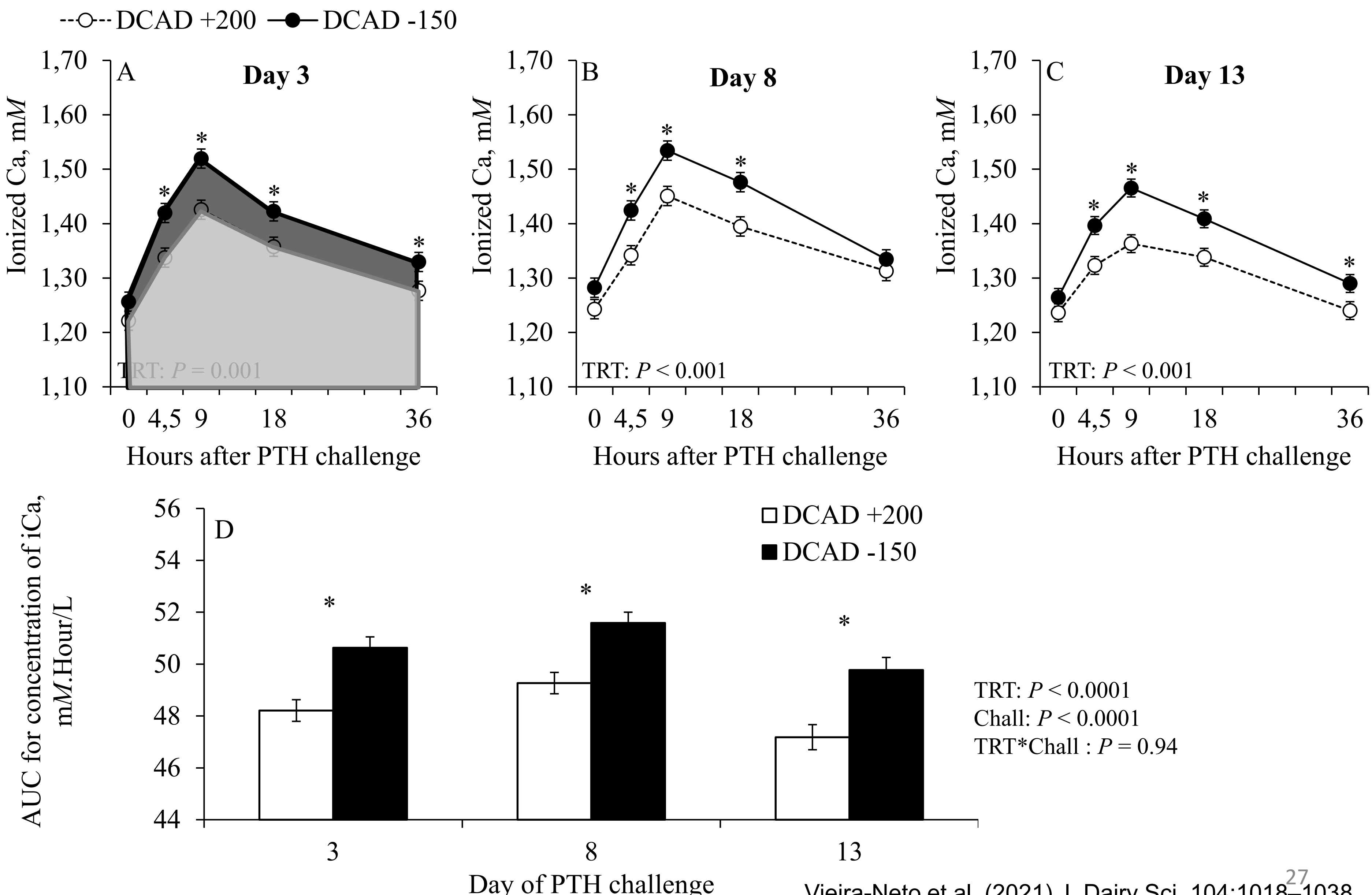






Lopez et al. (2002) J. Bone Min. Res. 17:1691-1700

Responses in iCa to PTH

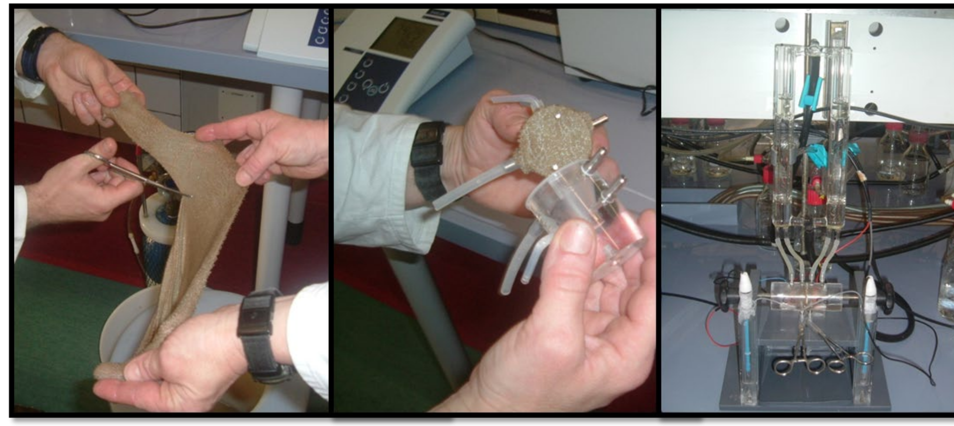


Vieira-Neto et al. (2021) J. Dairy Sci. 104:1018–1038

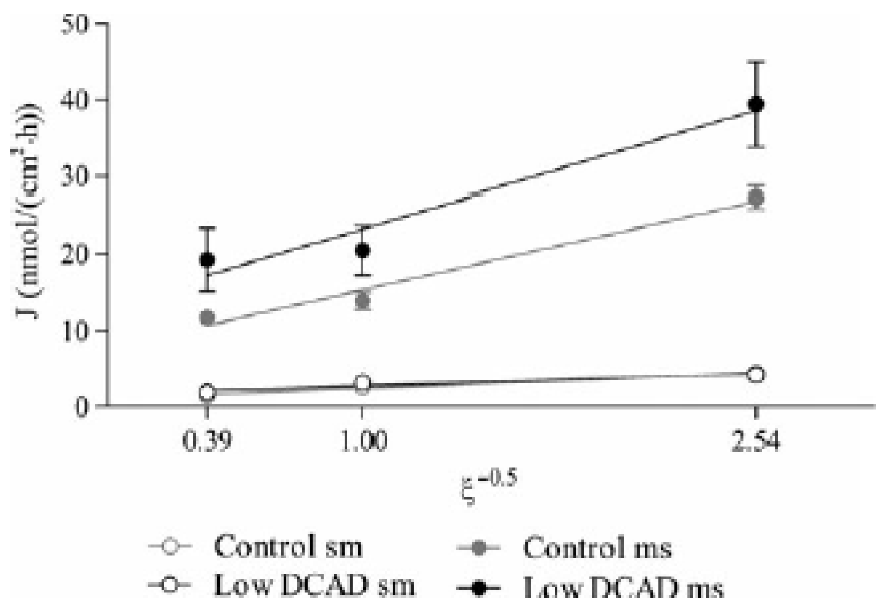
Acidogenic Diet Increases Gastrointestinal Ca Absorption in Sheep

Table 2 Composition of the rations as fed during the experimental period. DCAD values are calculated as [(meq Na^+/kg DM + meq K^+/kg DM)−(meq Cl^-/kg DM + meq SO_4^{2-}/kg DM)] (Oetzel 1993)

	Series A		Series B	
Intake [g]	Control	Low DCAD	Control	Low DCAD
Dry matter [kg]	1.7	1.7	1.4	1.4
Crude ash	125	134	105	113
Crude protein	191	206	169	182
Crude fat	35	36	30	31
ADF*	602	603	482	482
NDF*	967	967	776	776
Ca	8.8	8.6	7.5	7.3
Mg	4.5	6.7	4.0	5.9
Na	3.1	2.6	2.4	2.0
K	35.1	34.8	29.9	29.6
P	5.6	5.4	5.0	4.7
S	4.5	11.7	3.7	9.9
Cl	17.4	19.9	14.8	16.9
DCAD [meq/kg DM]	+154	−168	+160	−177

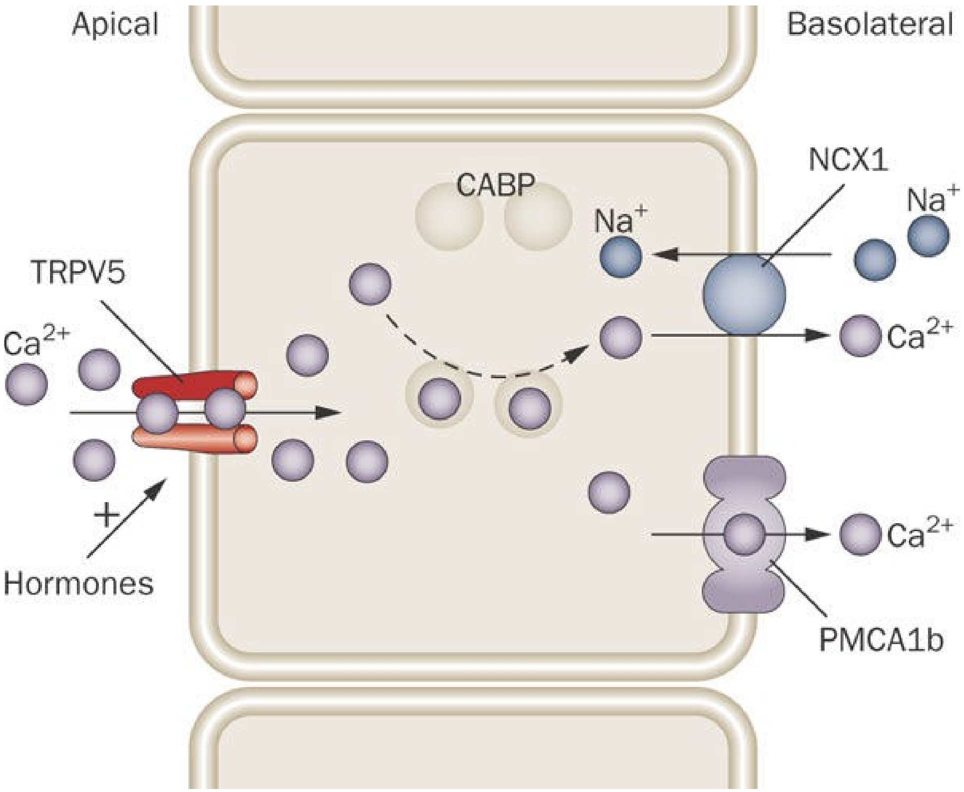


Unidirecional flux of Ca (JCa) from serosa to mucosa (SM) or mucosa to serosa (MS)



Wilkens et al. 2016) J. Anim. Physiol. Anim. Nutr. 100:156-166

Renal Ca Reabsorption is Mediated by Transient Receptor Potential V5, Ca Binding Protein, and Plasma Membrane Ca Pump

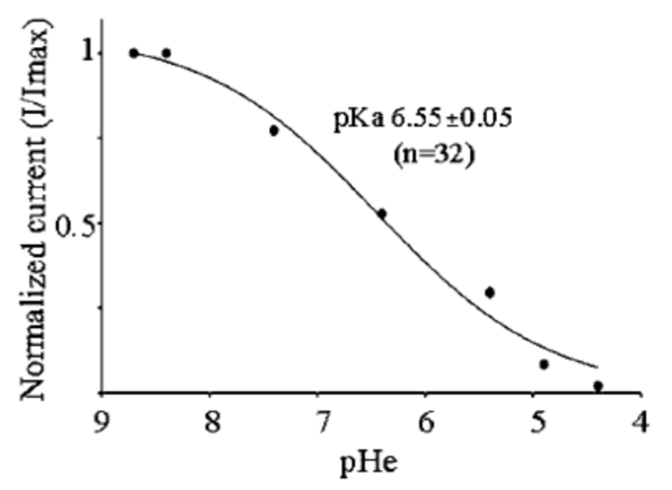


Woudenberg-Vrenken et al. (2009) Nature Rev. Nephrology 5: 441-449

TRPV5 in the apical membrane of the DCT is the rate-limiting step in Ca^{2+} re-absorption from the filtrate

Both Ca^{2+} and low pH suppress TRPV5

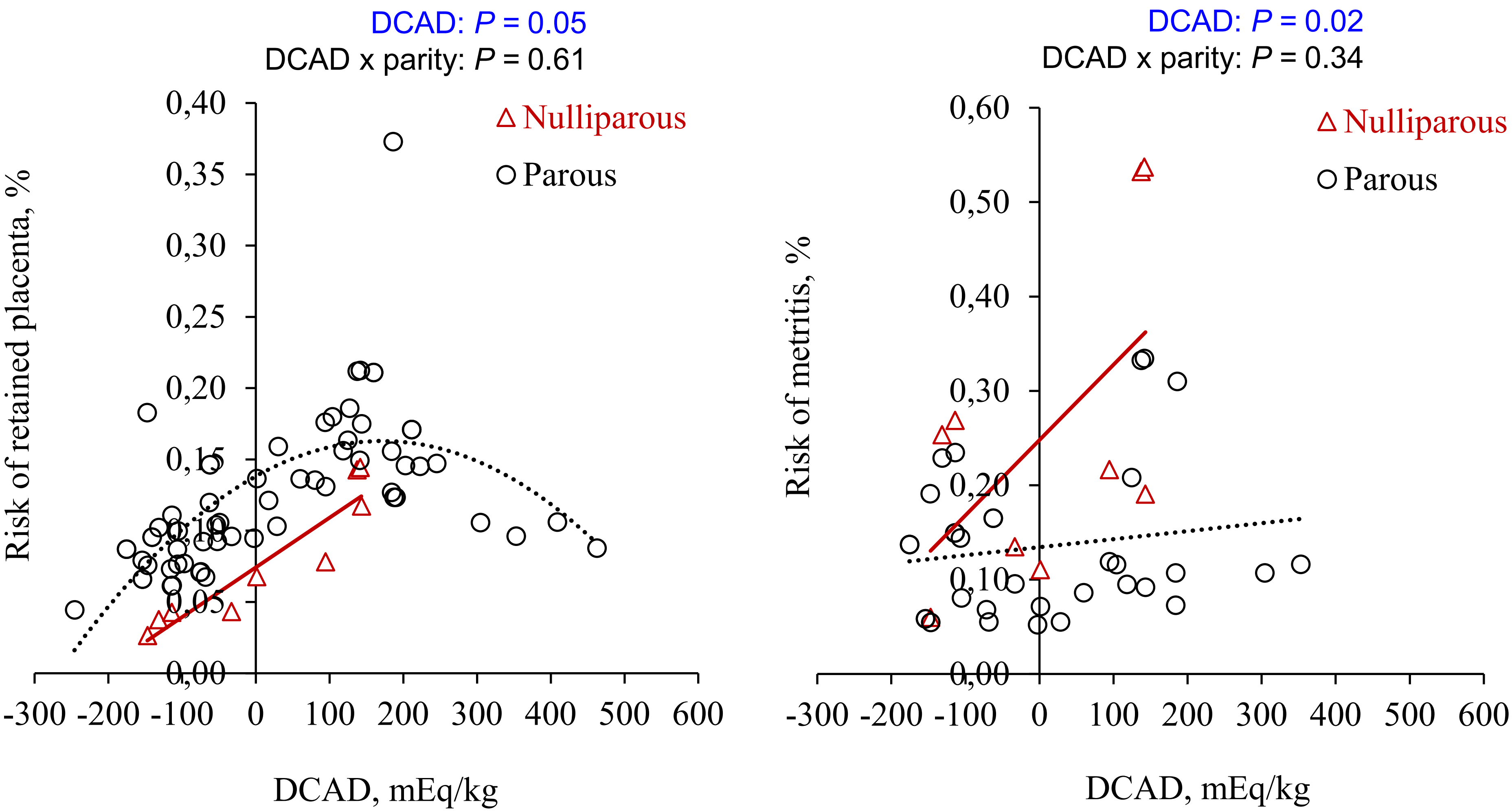
Acidogenic diets reduce filtrate pH and increase Ca^{2+} flux through the nephron because of increased blood $[Ca^{2+}]$



Low extracellular pH reduces current accross TRPV5

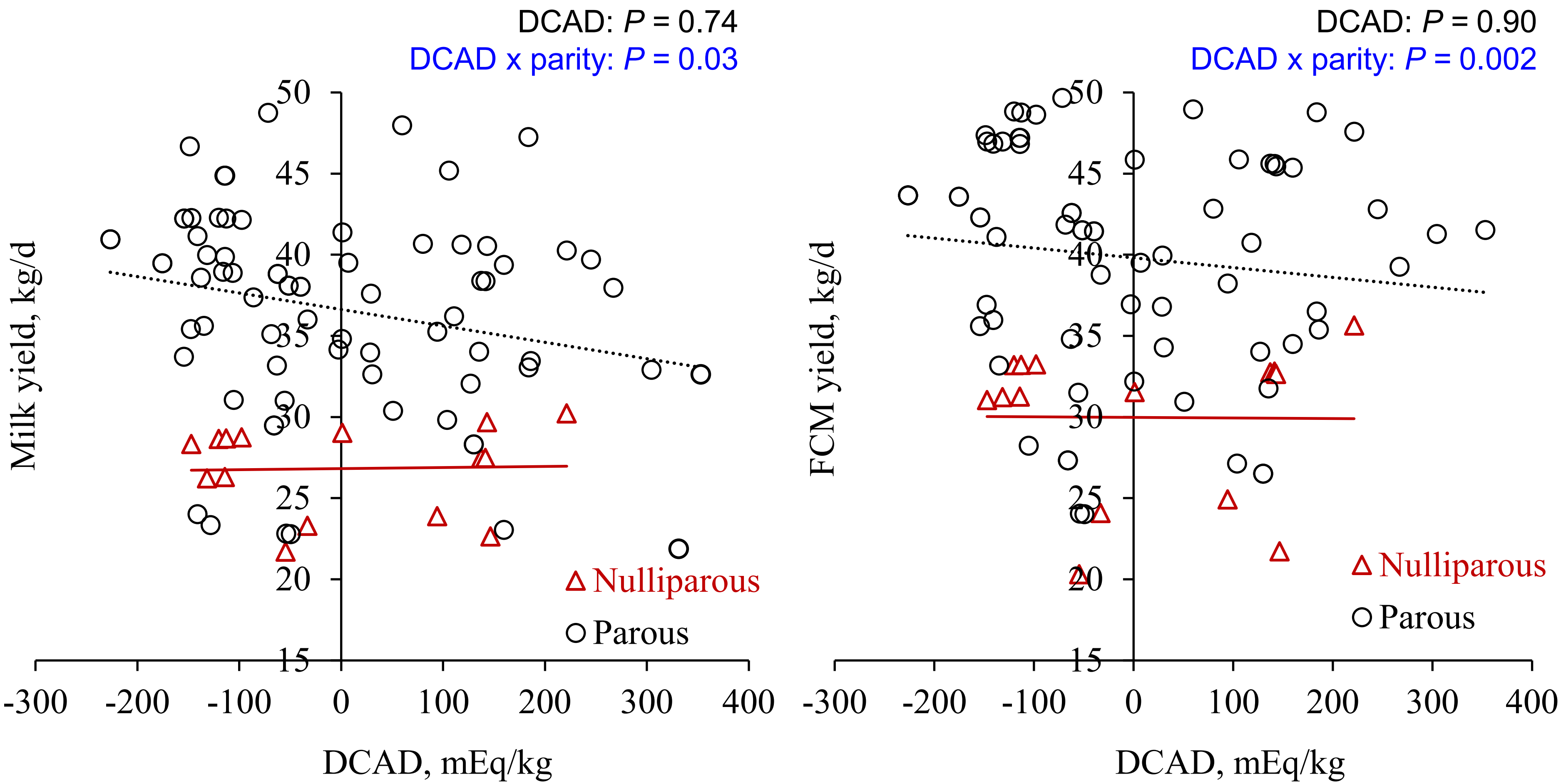
Yeh et al. (2003) J. Biol. Chem. 278:51044-51052

Effect of DCAD on Risk of Retained Placenta or Metritis



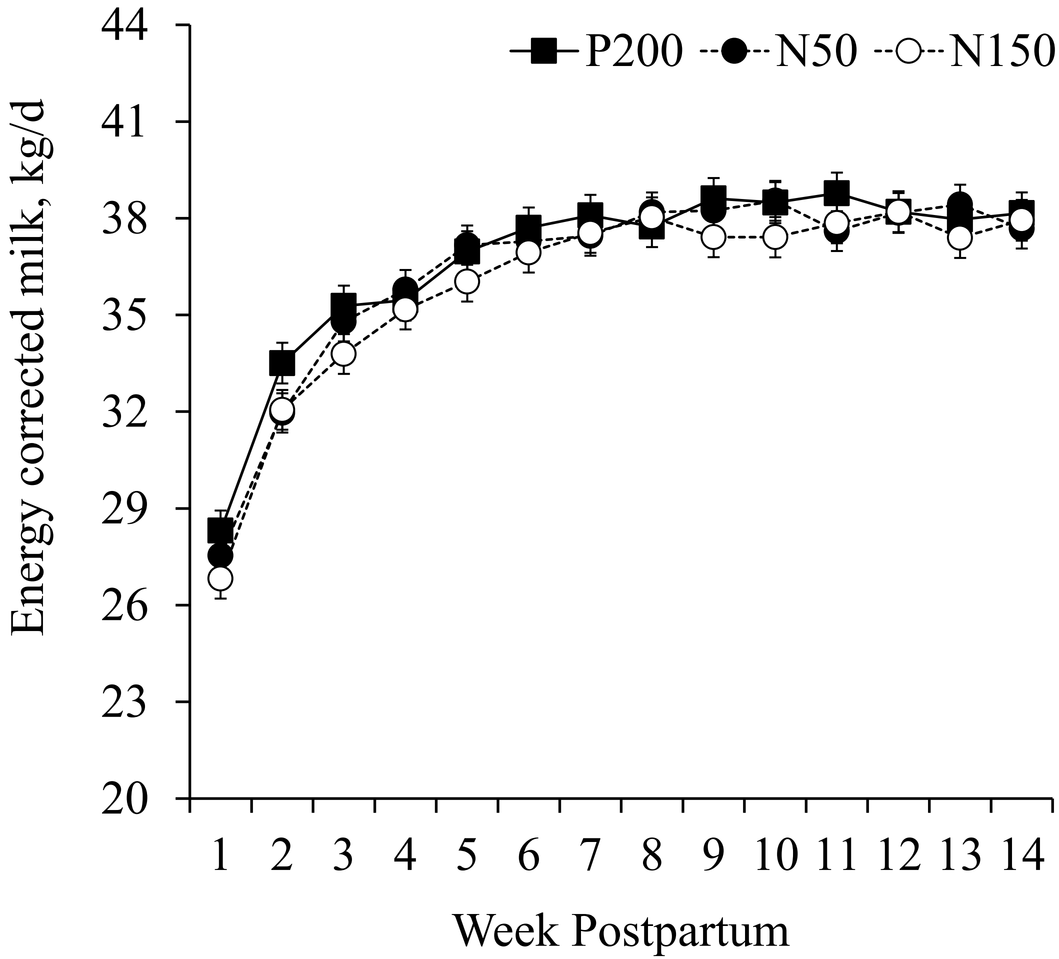
Santos et al. (2019) J. Dairy Sci. 102:2134–2154

Effect of DCAD on Yields of Milk and FCM According to Parity



Santos et al. (2019) J. Dairy Sci. 102:2134–2154

Effect of Manipulating the Prepartum DCAD fed to Nulliparous on Production



N = 132 nulliparous cows

+200 mEq/kg (P200; n = 43)
-50 mEq/kg (N50; n = 45)
-150 mEq/kg (N150; n = 44)

Zimpel et al. (2021) J. Dairy Sci. 104:12580–12599

On Farm Experiment – Effects on Production and Reproduction

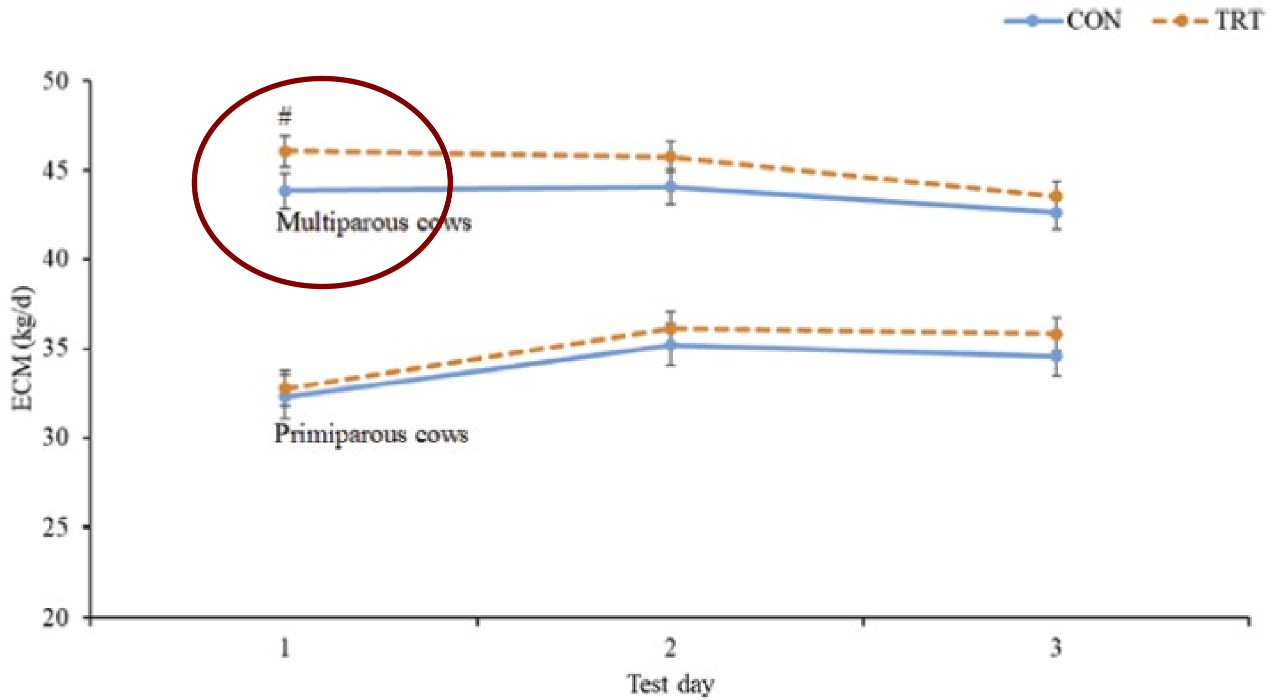


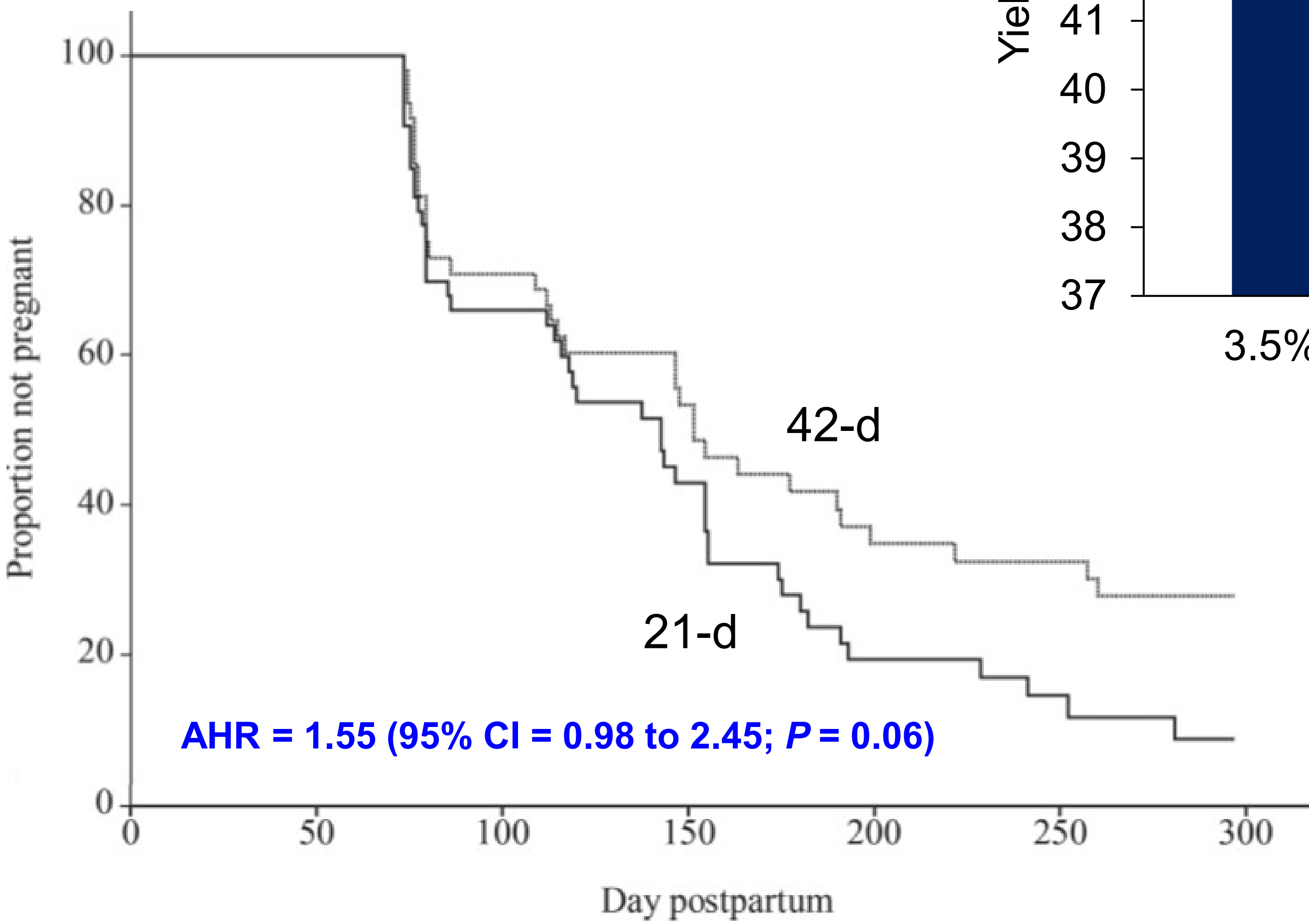
Table 1. Summary of multivariable survival analysis and logistic regression models of reproductive performance of Holstein cows in a blinded randomized controlled trial of a negative DCAD dry cow diet in the last 3 wk before calving (TRT; −108 mEq/kg of DCAD) or placebo control (CON; +105 mEq/kg of DM); there were 15 experimental units (8 pen treatments in TRT and 7 in CON)

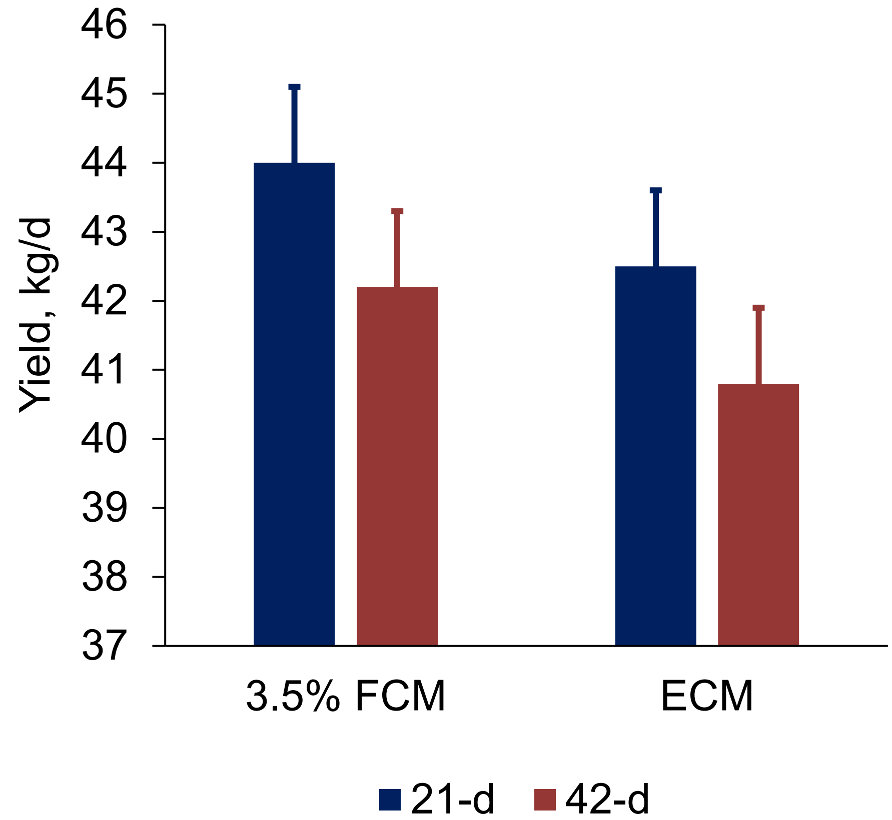
	Multiparous cows TRT (n = 455) vs. CON (n = 271)					Primiparous cows TRT (n = 226) vs. CON (n = 134)				
	Relative measures			LSM ± SE		Relative measures			LSM ± SE	
Outcome	Estimate[1]	95% CI	*P*	CON	TRT	Estimate	95% CI	*P*	CON	TRT
Time to first AI	HR = 0.96	0.54–1.71	0.89			HR = 0.66	0.27–1.62	0.36		
First-service pregnancy risk (%)	OR = 1.53	1.07–2.21	0.02	32 ± 4	42 ± 3	OR = 0.74	0.47–1.17	0.20	52 ± 5	45 ± 4
Relative pregnancy rate	HR = 1.20	0.96–1.49	0.11			HR = 0.76	0.59–0.99	0.04		

[1]HR = hazard ratio; OR = odds ratio.

Couto Serrenho et al. (2021) J. Dairy Sci. 104:6919–6928

N = 114 cows





Lopera et al. (2018) J. Dairy Sci. 101:7907–7929

Treatments

Item	T1	T3	T4
Forage %	65.0	65.0	65.0
Concentrate %	34.6	24.8	27.3
Acidogenic product %	-	7.5	7.5
Magnesium oxide, %	0.4	0.2	0.2
Sodium chloride, %	-	-	-
Potassium chloride, %	-	-	-
Na sesquicarbonate, %	-	1.5	-
Potassium carbonate, %	-	1.0	-
K, %	1.42 ± 0.09	1.71 ± 0.04	1.29 ± 0.05
S, %	0.18 ± 0.03	0.37 ± 0.04	0.39 ± 0.03
Na, %	0.04 ± 0.02	0.54 ± 0.10	0.13 ± 0.02
Cl, %	0.26 ± 0.01	0.89 ± 0.07	0.91 ± 0.05
DCAD, mEq/kg	**196 ± 20**	**192 ± 27**	**-114 ± 26**
Acid-base status	**Alkalosis**	**Alkalosis**	**Acidosis**

N = 10/treatment

Zimpel et al. (2018) J. Dairy Sci. 101:8461-8475

Depression in Intake is Mediated by Acid-Base Status

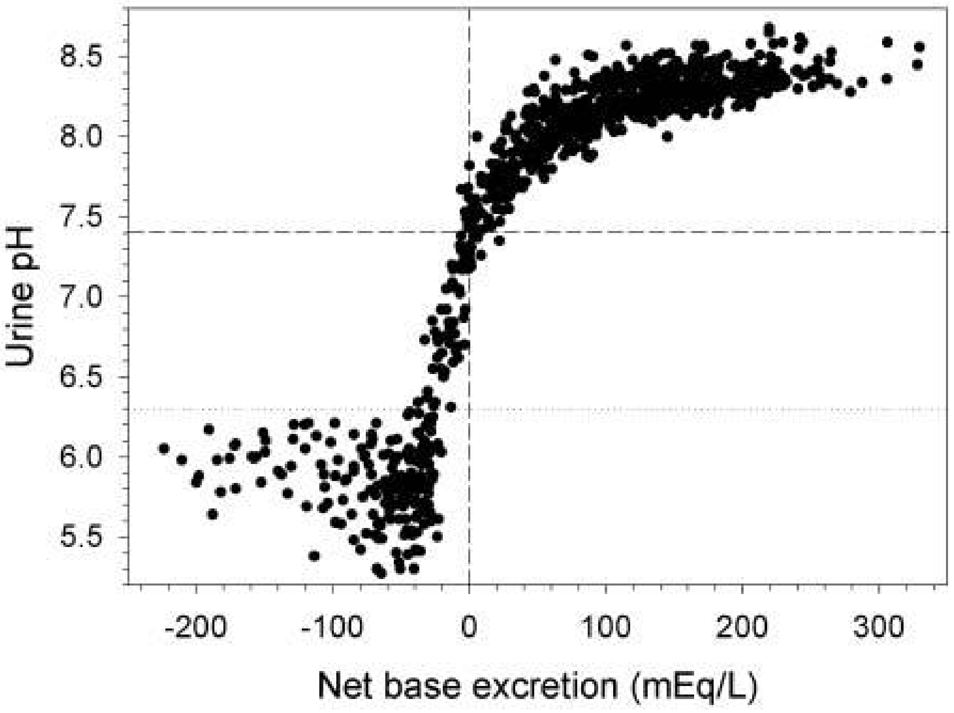
	Treatment				*P*-value	
Item	**T1**	**T3**	**T4**	**SE**	**AP**	**AB**
Urine pH	8.12	7.92	5.65	0.07	< 0.001	< 0.001
Blood pH	7.450	7.435	7.420	0.005	< 0.001	< 0.001
HCO_3^-, mM	25.9	25.8	24.3	0.3	0.003	< 0.001
Base excess, mM	1.85	1.45	-0.20	0.32	< 0.001	< 0.001
DM intake, kg/d	10.3	10.2	9.7	0.2	0.02	0.003
DM intake, % BW	1.76	1.74	**1.68**	0.03	0.03	0.003

AP (effect of the acidogenic product)= T1 vs. T4

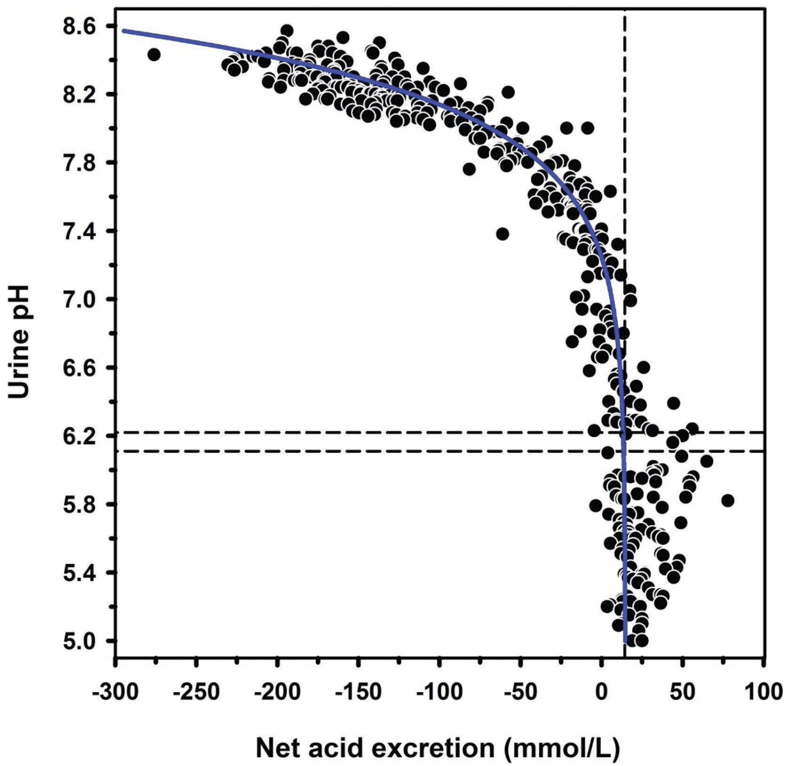
AB (effect of acid-base balance) = T3 vs. T4

Zimpel et al. (2018) J. Dairy Sci. 101:8461-8475

Monitor Urinary pH and Avoid Metabolic Over-Acidification

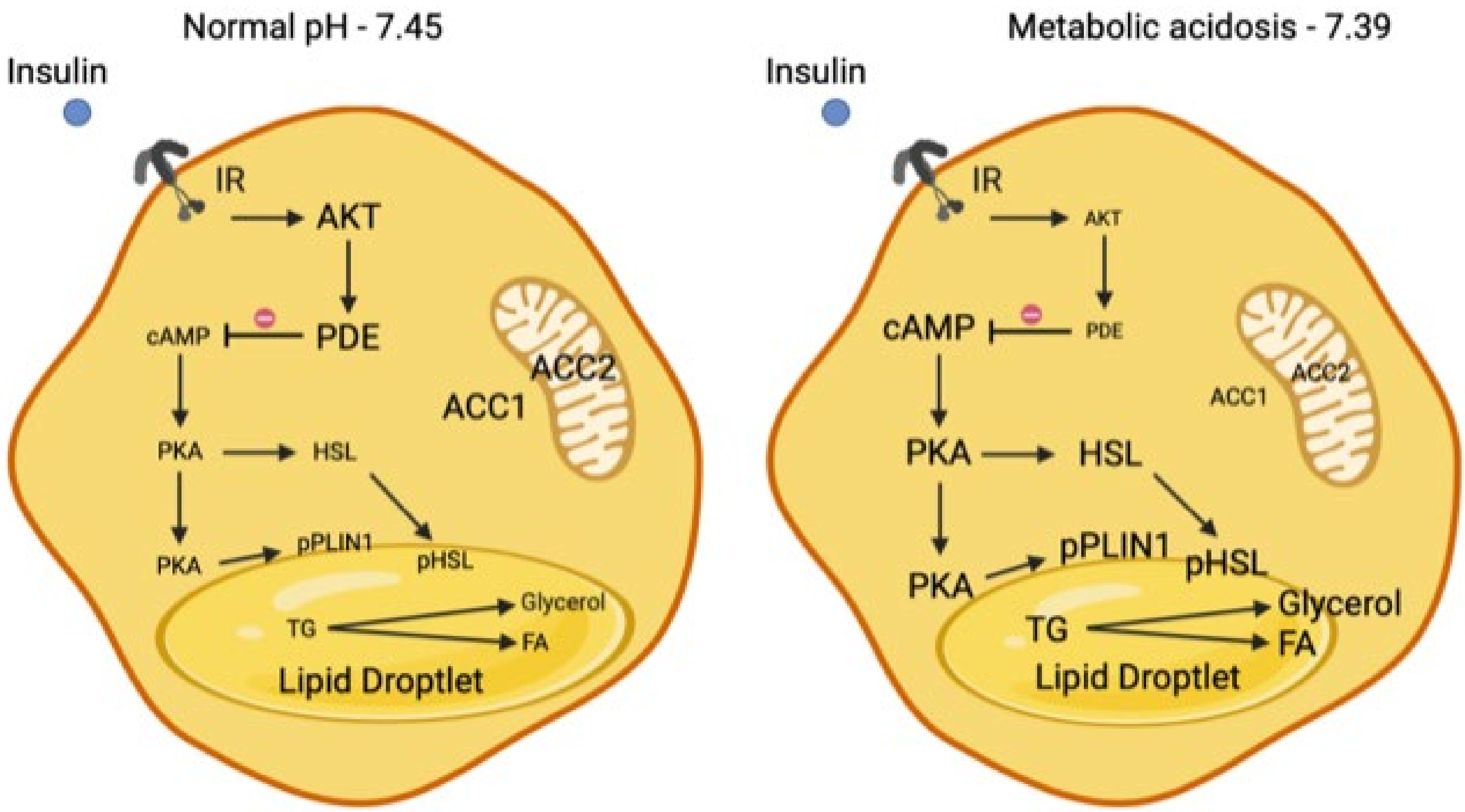


Constable et al. (2009) Am. J. Vet. Res. 70:915–925



Constable et al. (2019) J. Dairy Sci. 102:11370–11383

Avoid Diets that Cause Excessive Metabolic Acidosis



Vieira-Neto et al. (2021) J. Dairy Sci. 104:1660–1679

Oral Ca Boluses

- ✓ Sufficient evidence from multiple experiments
  - ✓ 40 to 80 g of Ca as salts dosed orally increases plasma Ca 2 to 6 h
  - ✓ Prevents milk fever
  - ✓ Transient effect on subclinical hypocalcemia
  - ✓ Mixed effects according to cohort of cows
    - ✓ Benefits to multiparous, high-risk cows, those with history of high milk production
    - ✓ **Detrimental** effects on primiparous cows
    - ✓ **Detrimental** effects on multiparous cows without calving problems or those with a history of below average milk production within the herd

University of Wisconsin; University of Florida; University of Guelph; Cornell University; University of California Davis

Recommendations

- ✓ Select ingredients with low concentration of K and Na
  - ✓ Analyze feedstuffs and use ICP-MS methods for minerals. Do not use NIR values!!
  - ✓ Dietary K < 1.2% and Na = 0.10 to 0.15%
- ✓ Restrict dietary P to < 0.30%
- ✓ Supplement Mg (~ 0.40%)
  - ✓ $MgCl_2 \cdot 6H_2O$ or $MgSO_4 \cdot 7H_2O$ are better sources of Mg than MgO (problem: they only contain 10 to 11% Mg)
- ✓ Add Cl^- to reduce the DCAD to ~ -100 mEq/kg
  - ✓ Keep dietary S at < 0.40%
  - ✓ Keep moderate dietary Ca content (0.60 to 0.80%)
- ✓ Monitor urinary pH twice weekly
  - ✓ Target a mean urine pH of ~6.2 to 6.4 (range of 5.8 to 7.0)
- ✓ Feed from 250 d of gestation to calving
- ✓ If you cannot manage acidogenic diets, then use aluminosilicates (Zeolite) to sequester P combined with a low Ca diet prepartum
  - ✓ Make sure to keep Mg at least 0.40%

Thank you

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