# hypercalcemia and chronic kidney disease- an overview of mineral metabolism and laboratory monitoring

**Dennis E. Jewell, PhD, Dipl. ACAN**

# What are the minerals of interest?

Phosphorus

Calcium

Sodium

# What is happening to mineral control?

- Idiopathic hypercalcemia
- During early and mid-stage CKD, total Calcium is high or normal iCA is normal or low
- Increased phosporus and reduced renal clearance results in complexes forming and explains reduced iCA
- Serum PTH is often elevated from the CKD related calcium and phosphorus concentrations

# What is the desired outcome?

- Control of circulating minerals
- Reduction of renal toxins
- Optimized renal function
- Reduced risk of CaOx stones

# Calcium control mechanism

→ calcitriol → Increase Ca and Phosphate Absorption

→ calcitriol → Increase Ca and Phosphate Reabsorption

→ Parathyroid Hormone → Increase Ca Reabsorption and Phosphate Ex

→ calcitonin → Decrease Ca Resorption

→ Parathyroid Hormone → Increase Ca Resorption

# Accurate Diagnosis of Hypercalcemia

1. Physical Exam
2. Measurement Complete Blood Count (CBC)
3. Measurement of Serum Biochemistry
4. Urinalysis
5. Measurement of iCa and PTH

# What do we look for in the laboratory monitoring?

- Total Ca >10.8 mg/dL
- Ionized Ca > 5.6 mg/dL
- Increasing Creatinine > 2.1 mg/dL
- Increasing SDMA > 14 ug/dL
- Urine protein/creatinine > 0.4
- Urine specific gravity < 1.035

# Calcium Oxalate Stone Formation

# Ca Ox stone formation

- Calcium based stones account for

  up to 75% of feline stones
- Caused by oversaturated with Ca and Ox
- Hypercalciuria appears to be more important than elevated oxalate
- Risk slightly reduced with increased pH
- Some breeds and genotypes are more prone to CaOx stones

# How do we reduce the incidence of Ca Ox stone formation?

- Increase water output (see my next talk!)
- Reduce Ca and Ox excretion
- Maintain neutral to slightly alkaline pH
- Promote and increase urolith inhibitors

# Food Effects on Hypercalcemia/Hypercalciuria and Risk of Calcium Oxalate Stone Formation in Cats

RESEARCH ARTICLE

## Increased dietary long-chain polyunsaturated fatty acids alter serum fatty acid concentr-ations and lower risk of urine stone formation in cats

Jean A. Hall[1]*, Jeff A. Brockman[2], Stephen J. Davidson[2], Jen M. MacLeay[2], Dennis E. Jewell[2]

PLoS ONE 12(10): e0187133. https://doi.org/10.1371/journal. pon

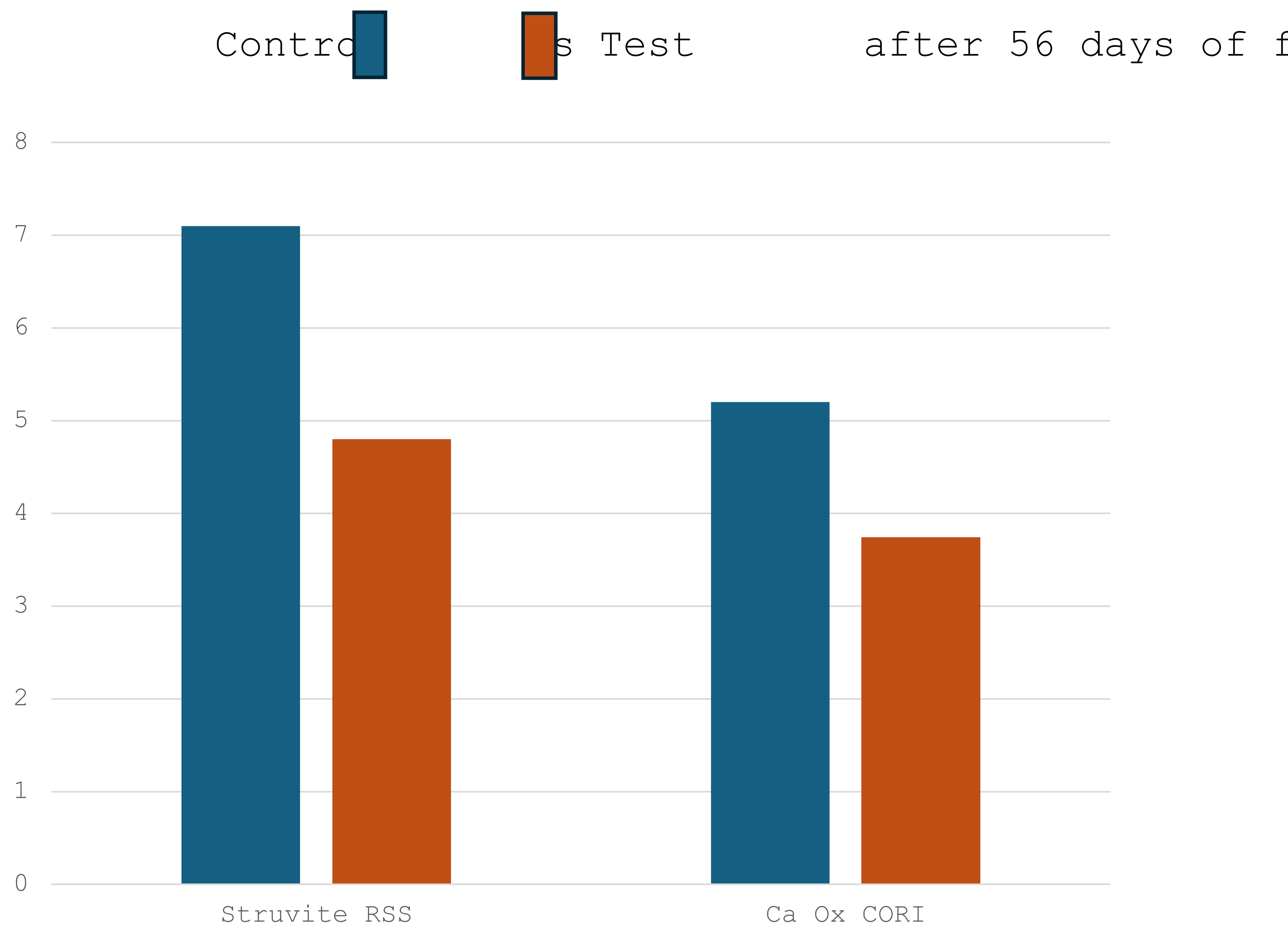
# Controlled Ca and Phos were the base Added PUFA were the treatment

Table 1. Food composition.

| Nutrient[a] | Control food[b] | Test food[c] |
|---|---|---|
| Atwater Energy, kcal/kg | 3,902 | 3,899 |
| Calcium | 0.80 | 0.84 |
| Phosphorus | 0.74 | 0.75 |
| Sodium | 0.34 | 0.36 |
| Potassium | 0.93 | 0.95 |
| Magnesium | 0.07 | 0.08 |
| AA (20:4; n-6) | 0.07 | 0.17 |
| EPA (20:5; n-3) | <0.01 | 0.09 |
| DPA (22:5; n-3) | <0.01 | 0.02 |
| DHA (22:6; n-3) | <0.01 | 0.18 |

Calcium 0.210 gm/100 Kcal
Phosphorus 0.0.192 gm/100kcal

# Controlled Ca and Phos were the base, Added PUFA were the treatment




Both Struvite RSS and the Ca Ox Risk Index were reduced

# Gene Effects on Risk of Calcium Oxalate Stone Formation in Cats

*Article*

## Cats with Genetic Variants of AGXT2 Respond Differently to a Dietary Intervention Known to Reduce the Risk of Calcium Oxalate Stone Formation

Jean A. Hall [1,*], Kiran S. Panickar [2], Jeffrey A. Brockman [2] and Dennis E. Jewell [3]

Genes 2022, 13, 791. https://doi.org/ 10.3390/genes13050791`

# Gene Effects on Risk of Calcium Oxalate Stone Formation in Cats

A single allele was isolated from a genome wide association study of 445 ca showing a strong association with the where the AGXT2 gene is centered

| | AA | AG | GG |
|---|---|---|---|
| 2-oxoarginine | 0.45 ± 0.10 [c] | 0.92 ± 0.04 [b] | 1.27 ± 0.04 [a] |
| β-aminoisobutyrate | 6.53 ± 0.94 [a] | 3.05 ± 0.81 [b] | 1.53 ± 0.81 [b] |
| Dimethyl arginines(SDMA + ADMA) | 1.26 ± 0.05 [a] | 1.01 ± 0.05 [b] | 1.00 ± 0.05 [b] |

[a,b,c] Means with different superscripts within a row indicate significant differences between genotypes ($p < 0.05$).

# Gene Effects on Risk of Calcium Oxalate Stone Formation in Cats

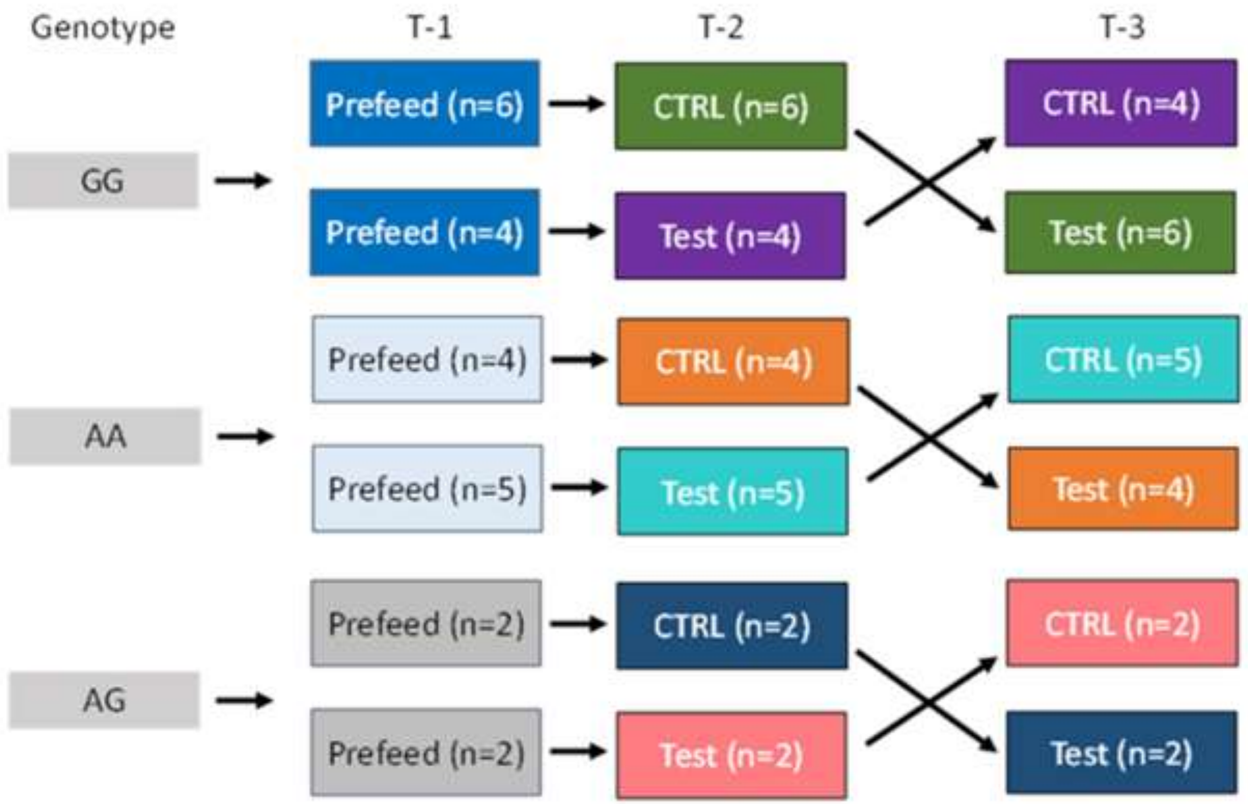



**Figure 1.** Cats with three alanine-glyoxylate aminotransferase 2 (AGXT2) single nucleotide polymorphisms (SNPs: GG, AG, and AA) were fed control food for 28 days (Prefeed; T-1). Cats within each genotype were then split into two groups and fed control (CTRL) or test food in a cross over study design for 28 days each (T-2 and T-3).

# Gene Effects on Risk of Calcium Oxalate Stone Formation in Cats

**Table 1.** Composition of pre-trial (control food) [1] and test food [2].

| Nutrient [3] | Pre-Trial & Control Food | Test Food |
|---|---|---|
| Atwater Energy, [4] kcal/kg | 3815 | 3816 |
| ARA [20:4 (n-6)] | 0.09 | 0.10 |
| EPA [20:5 (n-3)] | 0.15 | 0.16 |
| DHA [22:6 (n-3)] | 0.11 | 0.12 |
| Betaine (mg/kg) | 344 | 5210 |

# Gene Effects on Risk of Calcium Oxalate Stone Formation in Cats

## Body Weight and Food Intake Were Unchange

| | Initial | Control Food | Test Food |
|---|---|---|---|
| Body weight (kg) | $5.0 \pm 0.7$ | $5.0 \pm 0.7$ | $5.0 \pm 0.8$ |
| Food intake (grams) | $44.4 \pm 17.6$ | $47.4 \pm 1.7$ | $45.9 \pm 1.7$ |

# Gene Effects on Risk of Calcium Oxalate Stone Formation in Cats

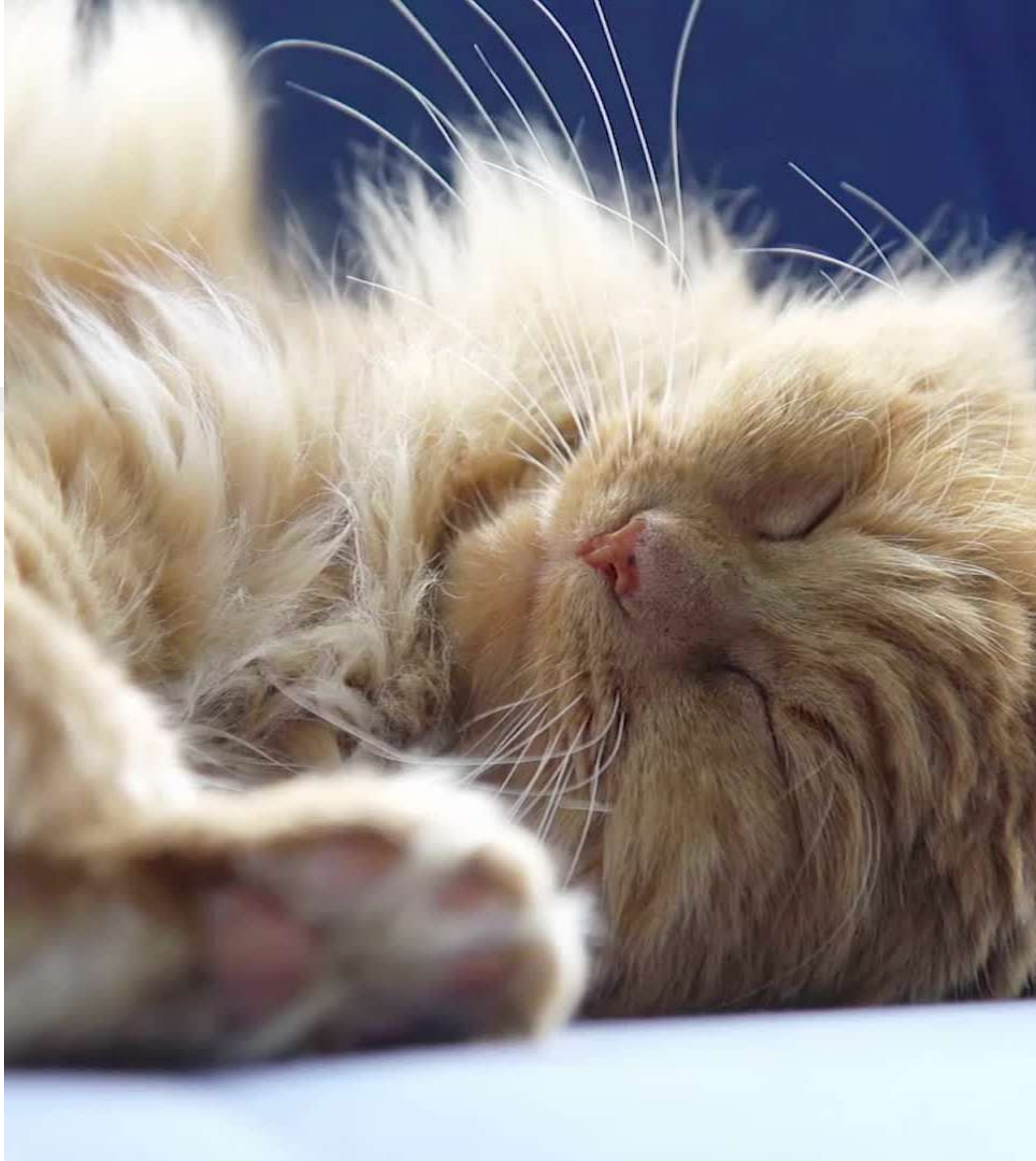
Struvite RSS remained below one
CaOx RSS
was significantly improved in the GG genotype

| Urine Parameters | AA | AG | GG |
|---|---|---|---|
| Struvite relative super saturation (ln) | | | |
| Initial | −1.42 ± 0.40 | −0.46 ± 0.36 | −0.27 ± 0.40 |
| Control Food | −0.97 ± 0.38 | −1.03 ± 0.54 | −0.04 ± 0.38 |
| Test Food | −1.10 ± 0.38 | −0.96 ± 0.54 | 0.06 ± 0.38 |
| Calcium oxalate titration test (ln 1/L) | | | |
| Initial | 2.55 ± 0.25 | 2.15 ± 0.61 | 2.58 ± 0.21 |
| Control Food | 2.67 ± 0.29 | 2.56 ± 0.40 | 2.74 ± 0.28 [a] |
| Test Food | 2.94 ± 0.29 [c] | 2.18 ± 0.40 [c,d] | 2.12 ± 0.28 [b,d] |

[a,b] Means with different superscripts within a column indicate significant pairwise differences ($p < 0.05$).
[c,d] Means with different superscripts within a row indicate significant differences between genotypes ($p < 0.05$).
NA = not available.

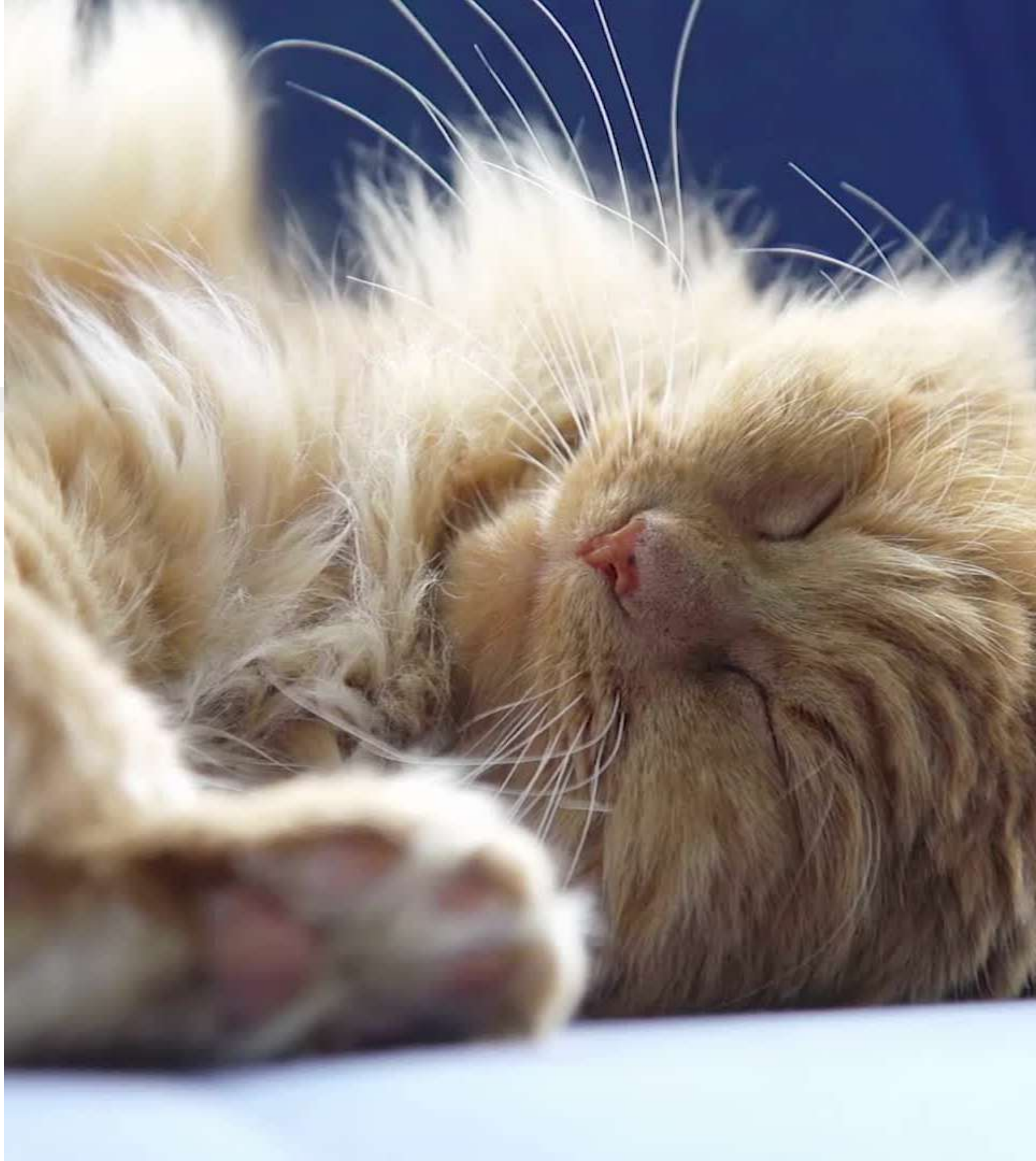
# What happens as health declines?

- Circulating mineral concentrations may change
- Glomerular Filtration declines
- 1α-hydroxylase enzyme declines
- calcitriol production



# What marks this renal decline?

- SDMA and creatinine increase resulting from GFR decline
- Increased serum phosphate
- Increased FGF-23
- Decreasing calcitriol
- Changing iCa



# What was first done to aid in the managemen t of kidney disease?

- Controlled phosphorus
- Balanced calcium
- Controlled protein

# Was this effective?

**Clinical evaluation of dietary modification for treatment of spontaneous chronic kidney disease in cats**

Sheri J. Ross, DVM, PhD, DACVIM; Carl A. Osborne, DVM, PhD, DACVIM; Claudia A. Kirk, DVM, PhD, DACVN, DACVIM; Stephen R. Lowry, PhD; Lori A. Koehler; David J. Polzin, DVM, PhD, DACVIM

Phosphorus restriction is at the heart of mineral nutrition to aid in the management of renal disease

| | Dry | |
|---|---|---|
| Nutrient | Renal diet | Maintenance diet |
| Protein (% [% ME]) | 29 (23) | 46 (35) |
| NFE (% [% ME]) | 45 (36) | 22 (17) |
| Fat (% [% ME]) | 21 (41) | 26 (48) |
| ME (kcal/g) | 4.3 | 5.0 |
| Calcium (%) | 0.7 | 1.1 |
| Phosphorus (%) | 0.5 | 0.9 |
| Sodium (%) | 0.2 | 0.4 |

Calcium g/100 kcal 0.163 0.220

Phos g/100 kcal 0.116 0.180

Was this effective?

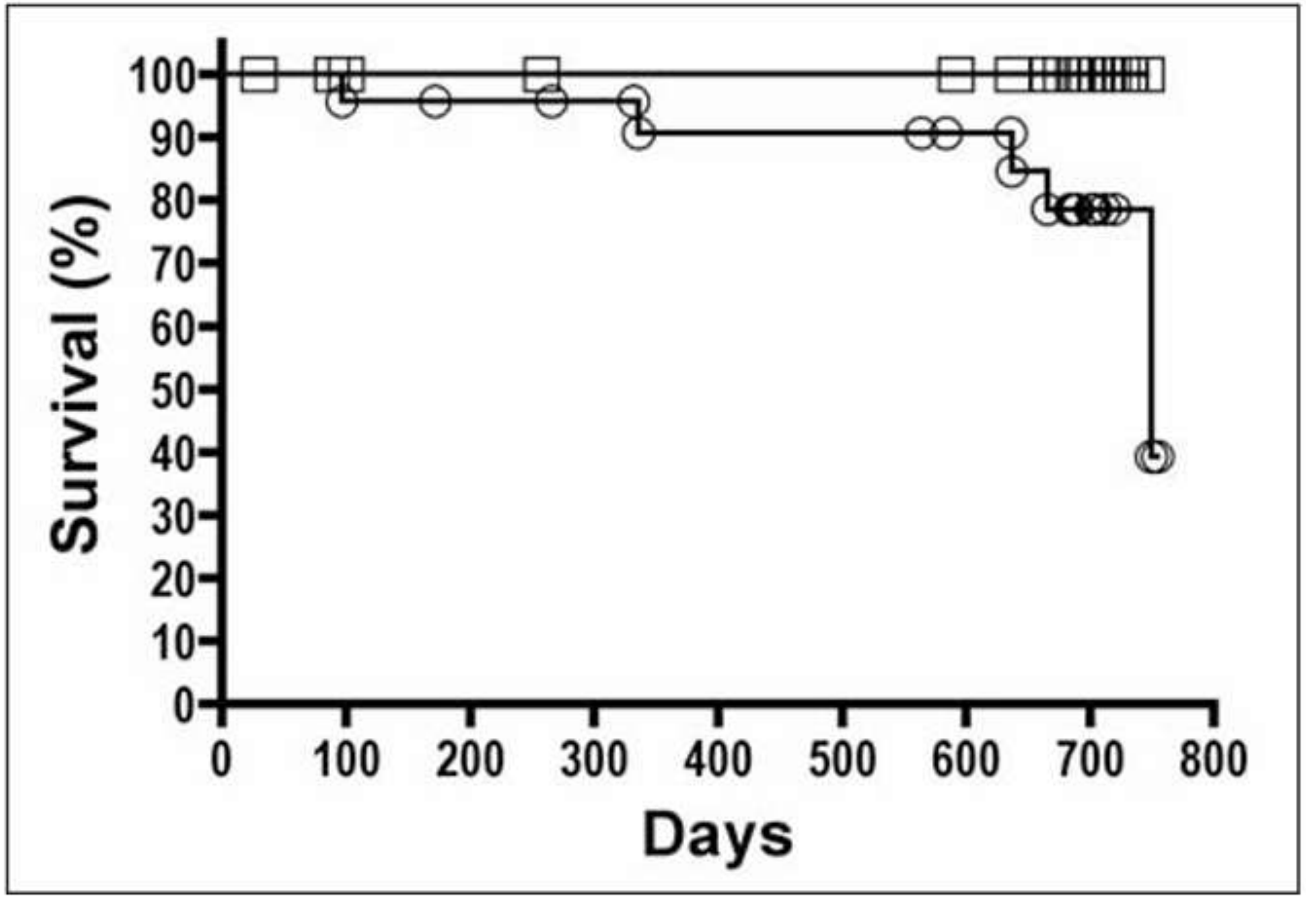



Figure 2—Kaplan-Meier analysis of death from renal causes in cats with spontaneous CKD fed a renal diet (squares; n = 22) or a maintenance diet (circles; 23).

# What laboratory monitoring has been added to follow the progress of renal decline?

- Estimates of GFR through SDMA
- Calcium and ionized calcium
- FGF-23 as a P balance indicator
- Urinalysis
- Measurments of renal toxins

## What has followed to improve the aid in the management of kidney disease?

- Early Intervention
- Other Nutrients
- Focused Dietary Protein, Calcium and Phosphorus

Early intervention reduces SDMA and creatinine, enhancing glomerular filtration rate

RESEARCH ARTICLE

# Positive Impact of Nutritional Interventions on Serum Symmetric Dimethylarginine and Creatinine Concentrations in Client-Owned Geriatric Cats

Jean A. Hall[1]*, Jennifer MacLeay[2], Maha Yerramilli[3], Edward Obare[3], Murthy Yerramilli[3], Heidi Schiefelbein[2], Inke Paetau-Robinson[2], Dennis E. Jewell[2]

| | |
|---|---|
| Calcium | 0.217 g/100 Kcal |
| Phosphorus | 0.203 g/100 Kcal |
| Energy | 409 kcal/100 gm DMB |

DHA&EPA, antioxidants and carnitine can enhance the aid in the management of renal disease

| | Owner's- Choice Foods | Test Food |
|---|---|---|
| **Number of Animals, N** | **47** | **33** |
| **Renal function markers:** | | |
| *Urea Nitrogen (mg/dL)* | | |
| Initial | 27.96 ± 0.86 | 28.62 ± 1.04[a] |
| 3 months | 28.15 ± 0.89 | 25.52 ± 1.06[b] |
| 6 months | 27.99 ± 0.81 | 25.35 ± 0.96[b] |
| *Serum Creatinine (mg/dL)* | | |
| Initial | 1.45 ± 0.04 | 1.41 ± 0.05[a] |
| 3 months | 1.44 ± 0.04 | 1.26 ± 0.05[b] |
| 6 months | 1.42 ± 0.04 | 1.23 ± 0.05[b] |
| *Serum SDMA (µg/dL)* | | |
| Initial | 10.32 ± 0.43[a] | 10.29 ± 0.52 |
| 3 months | 11.19 ± 0.53[b] | 9.98 ± 0.63 |
| 6 months | 11.39 ± 0.53[b] | 9.74 ± 0.63 |

Betane and fiber can enhance the aid in the management of renal disease

RESEARCH ARTICLE

# Feeding cats with chronic kidney disease food supplemented with betaine and prebiotics increases total body mass and reduces uremic toxins

Jean A. Hall[1]*, Dennis E. Jewell[2], Eden Ephraim[3]

Betane and fiber can enhance the aid in the management of renal disease

| Nutrient | Pre-trial & Control Food | Test Food |
|---|---|---|
| Atwater Energy,[3] kcal/kg | 4083 | 4077 |
| Calcium | 0.73 | 0.72 |
| Phosphorus | 0.52 | 0.51 |
| Sodium | 0.22 | 0.22 |
| ARA [20:4 (n-6)] | 0.09 | 0.09 |
| EPA [20:5 (n-3)] | 0.02 | 0.02 |
| DHA [22:6 (n-3)] | 0.03 | 0.03 |

Calcium 0.217 g/100 Kcal
Phosphorus 0.203 g/100 Kcal

Test food had added betaine at 0.500%
prebiotics: oat beta-glucan (0.586%)
short-chain fructooligosaccharides (0.407%).

Betane and fiber can enhance the aid in the management of renal disease

| Cat group | Total body Mass (g) | Total fat Mass (g) | Food Intake (g/day) | Food Intake (kcal/day) |
|---|---|---|---|---|
| CKD cats | | | | |
| Baseline | 5399.5 ± 410.4 | 1699.9 ± 234.8 | 41.8 ± 0.9[b] | 169.1 ± 3.6[b] |
| Control food | 5175.8 ± 410.3[b] | 1516.6 ± 211 | 45.7 ± 0.6[a] | 184.9 ± 2.4[a] |
| Test food | 5346.9 ± 412.2[a] | 1584.4 ± 214.3 | 46.6 ± 0.7[a] | 188.1 ± 2.7[a] |

Betane and fiber can enhance the aid in the management of renal disease

| Urine Metabolites | Mean Values[1] | |
|---|---|---|
| | Control Food | Test Food |
| **Tryptophan Metabolism** | | |
| 3-indoxyl sulfate | 1.25 | 0.90 |
| 5-hydroxyindole sulfate | 0.99 | 0.62 |
| 6-hydroxyindole sulfate | 1.06 | 0.64 |
| 7-hydroxyindole sulfate | 1.14 | 0.73 |

Control food resulted in increased uremic toxins as compared to test food

For each metabolite, mean value is the group mean of re-scaled data to have median equal to 1

# How has controlled protein advanced to better aid in the management of kidney disease?

Protein value is like a barre
each stave is an amino acid
and the value is defined by
the amount of water the barre

How has controlled protein advanced to better aid in the management of kidney disease?

Veterinary Record (2018) doi: 10.1136/vr.104865

# Cats with IRIS stage 1 and 2 chronic kidney disease maintain body weight and lean muscle mass when fed food having increased caloric density, and enhanced concentrations of carnitine and essential amino acids

Jean A Hall,[1] Dale A Fritsch,[2] Dennis E Jewell,[2] Patricia A Burris,[2] Kathy L Gross[2]

# How has controlled protein advanced to better aid in the management of kidney disease?

**Table 1** Analysed chemical composition* of control and test foods, with AAFCO minimum recommendations

| Nutrient† | Control food‡ | Test food§ | AAFCO minimum¶ |
|---|---|---|---|
| Protein | 6.650 | 6.693 | 6.5 |
| Lysine | 0.240 | 0.361 | 0.208 |
| Methionine | 0.216 | 0.153 | 0.05 |
| Phenylalanine | 0.294 | 0.346 | 0.105 |
| Threonine | 0.206 | 0.274 | 0.183 |
| Tryptophan | 0.064 | 0.068 | 0.04 |
| Calcium | 0.226 | 0.201 | 0.15 |
| Phosphorus | 0.118 | 0.105 | 0.125 |
| Potassium | 0.250 | 0.223 | 0.15 |
| Sodium | 0.086 | 0.077 | 0.05 |
| Chloride | 0.174 | 0.155 | 0.05 |

Values are grams/100 kcals

# How has controlled protein advanced to better aid in the management of kidney disease?

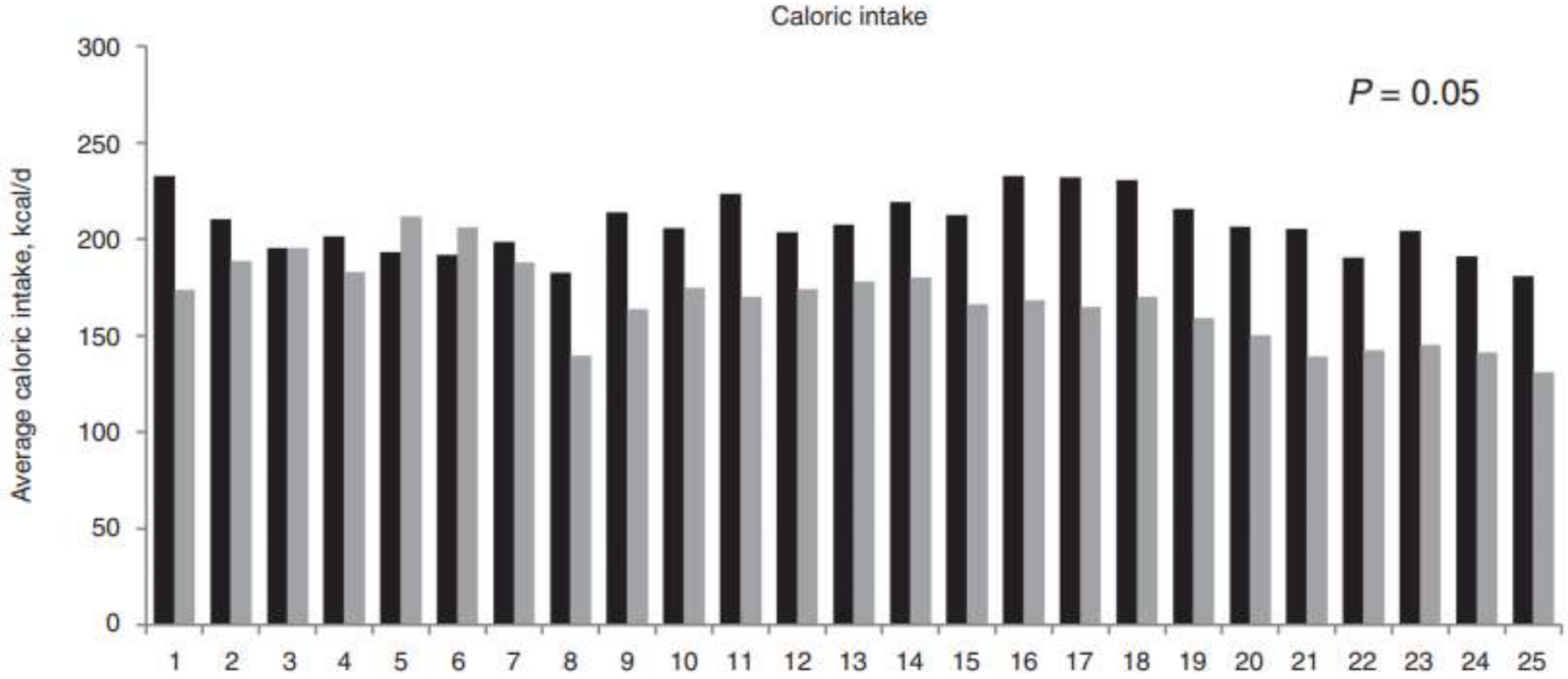
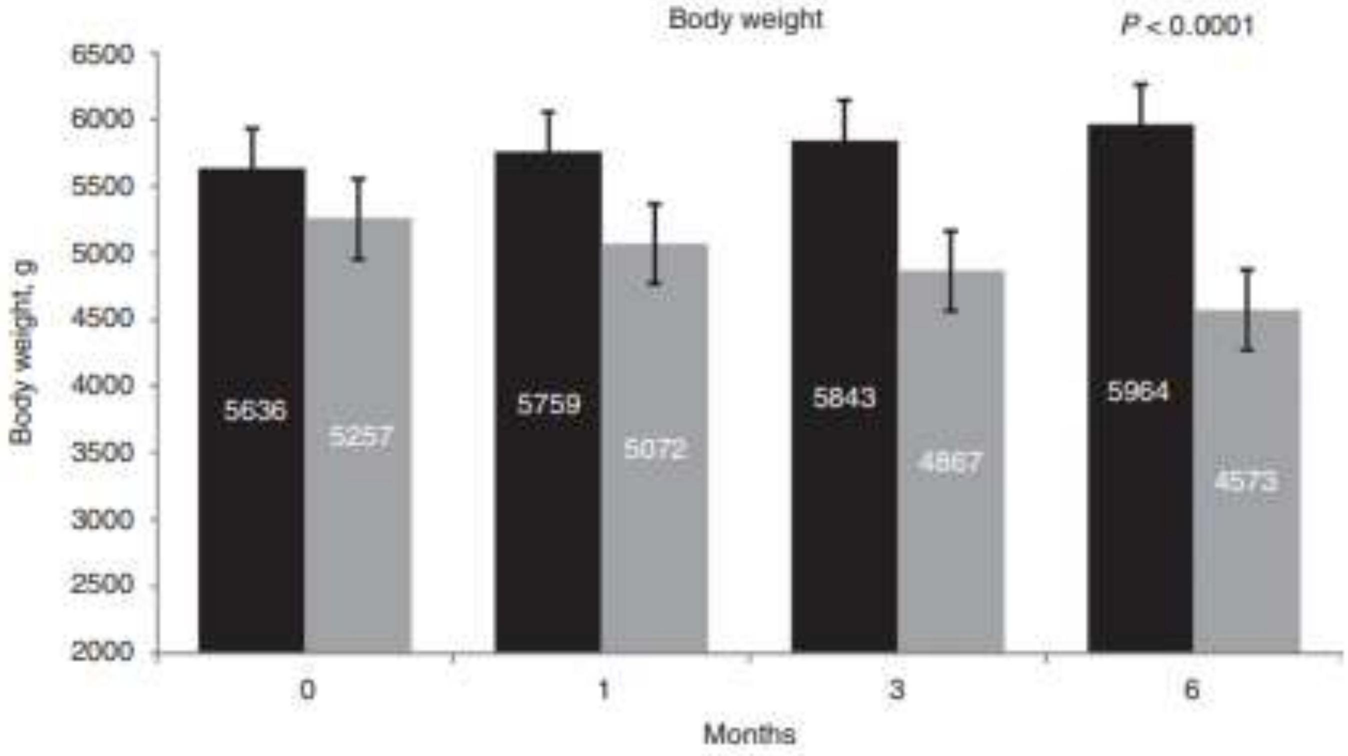



**Figure 1** Caloric intake (means) for each week are plotted for all cats (n=28) at all time points for which data were available. A similar number of calories was offered to cats fed test food (black bars; 261.6 kcal/day) and control food (grey bars; 263.2 kcal/day) during the 6-month feeding period (P=0.93). Cats voluntarily consumed 23 per cent more calories when offered test food (mean, 207.1 kcal/day) compared with cats offered control food (mean, 168.0 kcal/day) during the 6-month feeding period (P=0.05).

Control food is grey
Test food is black

# How has controlled protein advanced to better aid in the management of kidney disease?

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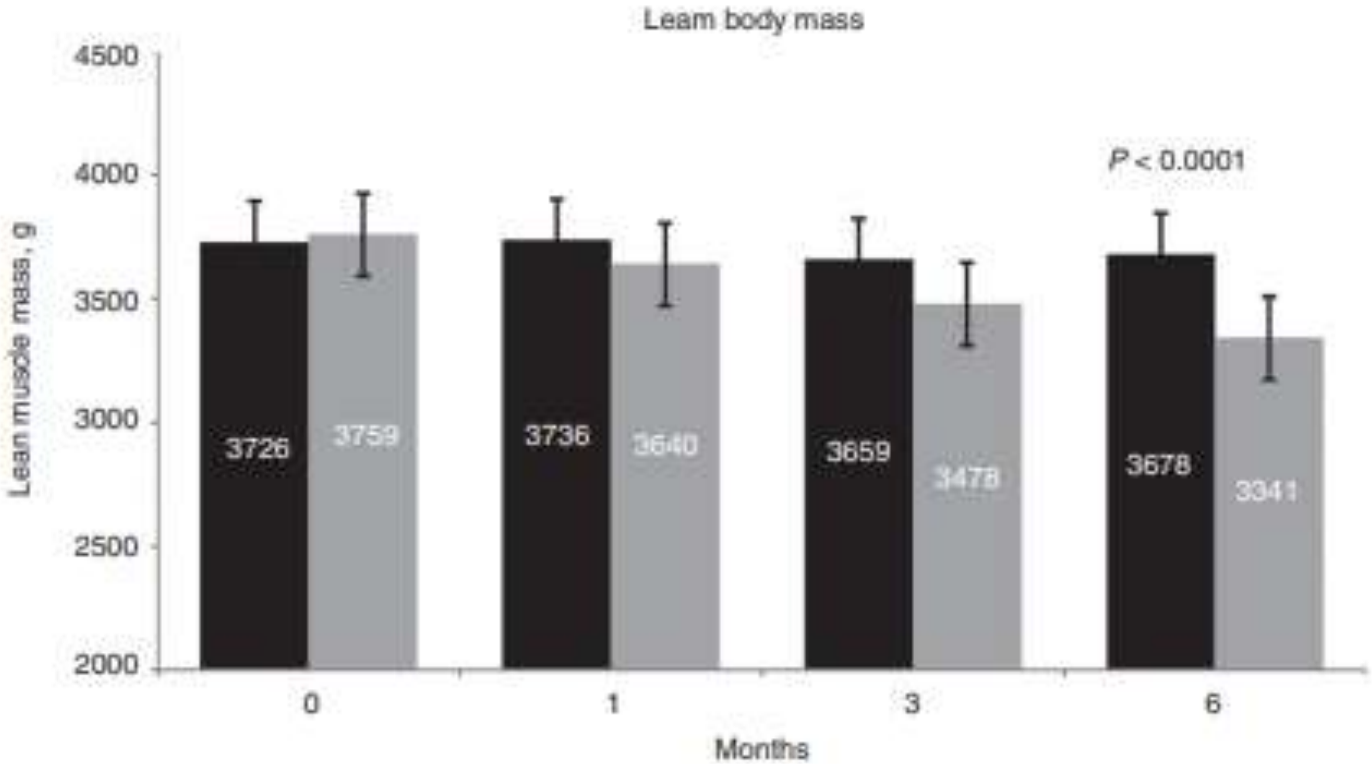
# How has controlled protein advanced to better aid in the management of kidney disease?




Control food is grey
Test food is black

Phosphorus restriction is at the heart of mineral nutrition to aid in the management of renal disease

| | Dry | |
|---|---|---|
| Nutrient | Renal diet | Maintenance diet |
| Protein (% [% ME]) | 29 (23) | 46 (35) |
| NFE (% [% ME]) | 45 (36) | 22 (17) |
| Fat (% [% ME]) | 21 (41) | 26 (48) |
| ME (kcal/g) | 4.3 | 5.0 |
| Calcium (%) | 0.7 | 1.1 |
| Phosphorus (%) | 0.5 | 0.9 |
| Sodium (%) | 0.2 | 0.4 |

Calcium g/100 kcal 0.163 0.220

Phos g/100 kcal 0.116 0.180

Excessive phosphorus restriction in the presence of excess calcium is detrimental

## Effect of Two Therapeutic Renal Diets on Hormonal and Regulatory Pathways Affecting Calcium Homeostasis in Cats With Early-Stage Chronic Kidney Disease

Jean A. Hall[1] | Elizabeth M. Morris[2] | Dale A. Fritsch[2] | John J. Brejda[3] | Kim M. Wilson[2]

| | g per 1000 kcal | |
|---|---|---|
| Analyte | M-PR | H-PR |
| Calcium, % | 1.79 | 2.27 |
| Phosphorus, % | 1.53 | 1.13 |
| Sodium, % | 0.77 | 0.88 |

# Excessive phosphorus restriction in the presence of excess calcium is detrimental

| Variable | Normal reference range | Day 140 M-PR | Day 140 H-PR | SEM | Diet |
|---|---|---|---|---|---|
| Ionized calcium, mmol/L | 1.10–1.30 | 1.238[b] | 1.416[a] | 0.033 | < 0.001 |
| Total calcium, mg/dL | 8.80–10.00 | 9.51[b] | 11.49[a] | 0.27 | < 0.001 |
| Phosphorus, mg/dL | 3.70–6.60 | 4.57 | 4.54 | 0.17 | 0.254 |
| PTH, pmol/L | 0.7–3.4 | 3.1 | † | 5.42 | 0.918‡ |
| Calcitriol, pmol/L | 90–342 | 186 | 94 | 40 | 0.021 |
| Calcifediol, nmol/L | 127–335 | 126 | 116 | 12 | 0.632 |
| FGF-23, pg/mL | ≤ 299 | † | 1325 | 395 | 0.003 |
| Calcium fractional excretion, % | | 0.19[b] | 1.18[a] | 0.22 | < 0.001 |
| Phosphorus fractional excretion, % | | 16.8 | 15.9 | 5.4 | 0.303 |

†Only one cat had a quantifiable PTH concentration

†Only one or two cats had a quantifiable FGF-23 concentration

# Excessive phosphorus restriction in the presence of excess calcium is detrimental

**The effect of attenuating dietary phosphate restriction on blood ionized calcium concentrations in cats with chronic kidney disease and ionized hypercalcemia**

Rebecca F. Geddes[1] | D. Hendrik N. van den Broek[1] | Yu-Mei Chang[2] | Vincent Biourge[3] | Jonathan Elliott[4] | Rosanne E. Jepson[1]

Similar results were reported with the highly phosphate restricted food resulting in increased ionized calcium which was resolved by a lower phosphate restricted food with lower Ca:P ratio.

# Excessive phosphorus restriction in the presence of excess calcium is detrimental

**Objectives:** To describe the effect of feeding a moderately phosphate-restricted diet (MP; 1.5 g/Mcal phosphorus; Ca : P ratio, 1.3) to cats with concurrent azotemic CKD and ionized hypercalcemia.

**Animals:** Client-owned cats with ionized hypercalcemia (ionized calcium [iCa] concentration >1.4 mmol/L) at diagnosis of CKD (n = 11; baseline hypercalcemics) or after CKD diagnosis while eating a phosphate-restricted clinical renal diet (0.8 g/Mcal phosphorus; Ca : P ratio, 1.9; n = 10; RD hypercalcemics).

# Excessive phosphorus restriction in the presence of excess calcium is detrimental

| Nutrient | Low Protein and phosphate restricted | Moderate Protein ar phosphate restricte |
|---|---|---|
| Energy (Kcal/kg) | 3925 | 3789 |
| Minerals (g/Mcal) | 15 | 15 |
| Calcium (g/Mcal) | 1.5 | 2.0 |
| Phosphate (g/Mcal) | 0.8 | 1.5 |
| Calcium : phosphate ratio | 1.9 | 1.3 |
| Sodium (g/Mcal)[a] | 1.0 | 1.1 |

# Excessive phosphorus restriction in the presence of excess calcium is detrimental

In conclusion, cats that appear to have ionized hypercalcemia induced by feeding a highly phosphate-restricted and high Ca : P ratio experience resolution of their hypercalcemia after transition onto a less phosphate-restricted diet with a lower Ca : P ratio.

# What measurements do we follow?

- **Serum Creatinine:** A classic marker does change with lean body mass
- **SDMA (Symmetric Dimethylarginine):** Has the value of changing earlier than creatinine and not influnenced by LBM
- **Urinalysis:** Foundational for assessing kidney function and for identifying secondary issues:
  - **Urine Specific Gravity (USG):** A USG below 1.035 may indicate renal dysfunction.
  - **Urine Protein:Creatinine (UPC) Ratio:** Measures protein loss in the urine. Persistent elevation (UPC >0.4) is a marker for CKD (and intervention!).
  - **Urine Culture:** urinary tract infections are common in cats with CKD.
- **Blood Chemistry (Electrolytes & Phosphorus):** Especially monitoring for high calcium or phosphorus levels which again require intervention.
- **Complete Blood Count (CBC):** Used to monitor for anemia which may result from reduced erythropoietin production by failing kidneys.

# What is recommended?

- **Know your cat:** Hypercalcemia can be a diagnostic challenge!
- **This review concentrated on hypercalcemia from CaOx stones or renal disease.** The optimum nutrients matter.

- **CaOx stone formation:** Desired outcome is reduced incidence and recurrence (estimated by RSS or CORI). Suggestions not complete specs.
  - Controlled calcium (0.150 to 0.250 g/100kcal)
  - Controlled phosphorus (0.125 to 0.225 g/100kcal)
  - Controlled urine pH (basically neutral (6.6 to 7.4)
  - Added long chain PUFA (DHA > 0.4, EPA > 0.5 mg/100 kcal)
  - Added citrate (to establish pH, reduce RSS and CORI)
  - Added Betaine (0.125 g/100 kcals or more)

# What is recommended?

- **Chronic Kidney Disease:**
Desired outcome is enhanced length and quality of life (suggestions not complete specs)
  - Calcium (0.18 to 0.23 g/100 kcal)
  - Phosphorus (0.10 to 0.16 g/100 kcal)
  - Controlled ratio (> 1.0 and < 1.5)
  - Controlled sodium (> 0.06 and < 0.10 g/100 kcal)
  - Controlled high quality protein
    - Protein >0.65 g/100 kcal
    - Lysine > 0.35 g/100 kcal
    - Methionine > 0.13 g/100 kcal
    - Threonine > 0.25 g/100 kcal
    - Arginine > 0.35 g/100 kcal
  - Added long chain PUFA
    - Combined EPA&DHA > 0.1 g/100 kcal
  - Added antioxidants
    - Vitamin E > 12.5 IU/100 kcal
    - Vitamin C > 3.0 mg/100 kcal
  - Added betaine > 125 mg/100 kcal
  - Added Fiber ? > 0.5 insoluble 0.15 soluble

# Questions?