Calcium regulation + Hypercalcemia

<table>
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<tr>
<th>Parathyroid hormone (PTH)</th>
<th>Vitamin D</th>
<th>Calcitonin</th>
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<tbody>
<tr>
<td>Increase calcium (&amp; Mg)</td>
<td>Increase calcium (&amp; Mg)</td>
<td>Decrease calcium</td>
</tr>
<tr>
<td>Decrease phosphorous</td>
<td>Increase phosphorous</td>
<td>Decrease phosphorous</td>
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**Parathyroid hormone**
- **Made by:** Parathyroid gland chief cells
- **Regulated by:** Plasma concentrations of ionized calcium (Ca++)
- **Actions:**
  - GI: Promote intestinal absorption of calcium in presence of vitamin D
  - Kidney: Increase renal reabsorption of calcium, promote renal excretion of phosphorous, increase formation of active vitamin D by the kidney
  - Bone: Mobilize calcium and phosphorous from bone

**Vitamin D**
- **Sources:** Cholesterol via UV light to cholecalciferol (Vitamin D3); Vitamin D3 from diet; Vitamin D2 (ergocalciferol) from plants, Kidney activation to make calcitriol (active vitamin D) via cholecalciferol to liver (via 25-hydroxylase) to 25-HCC to kidneys (not horses) via 1-alpha-hydroxylase to active vitamin D (1,25-DHCC)
- **Regulated by:** Kidney formation of active vitamin D (increased by hypocalemia & hypophosphatemia); Hypocalcemia → increase PTH → increased formation of active vitamin D
- **Actions:**
  - GI: Promote intestinal absorption of calcium & phosphorous
  - Kidney: Promote renal reabsorption of calcium
  - Bone: Promote calcium & phosphorous release from bone

**Calcitonin**
- **Sources:** Thyroid parafollicular cells (C cells)
- **Regulated by:** Hypercalcemia
- **Actions:**
  - Kidney: Inhibit renal reabsorption of calcium (so increases renal excretion of calcium), Inhibit renal reabsorption of phosphorous (so increases its renal excretion)
  - Bone: Inhibit PTH-stimulated bone reabsorption of calcium

**Contributors to blood levels of calcium**

1. Total serum calcium (tCa) comprised of 3 major fractions:
   a. Free or ionized calcium (Ca++ or iCa) ~ 50% of total calcium
   b. Bound – anion-bound calcium ~ 40-45% of total calcium
      i. This is the part that is protein bound (mostly albumin), and influenced by plasma pH.
   c. Bound – non-protein anion-bound calcium ~ 5-10% of total calcium
2. Determinants of serum values:
   a. Age: higher total calcium in younger animals
   b. Albumin concentration: hypoalbuminemia can decrease total calcium (not iCa)
   c. GI absorption
      i. Requirements: vitamin D (induces mucosal epithelium to make Ca-binding proteins)
      ii. Mucosal integrity/GI function
         1. Horses: dependent on GI absorption of calcium as no renal activation
         2. Diffuse GI disease in small animals can result in hypocalemia, e.g. hypovitaminosis D, hypomagnesemia (pseudohypoparathyroidism)
   d. Bone: Reabsorption from bone vs. deposition into bone
      i. Impacted by dietary Ca:P, PTH, vitamin D, and calcitonin
   e. Kidneys
      i. Impacted by PTH, vitamin D, and calcitonin
      ii. Renal activation of vitamin D (non-equine)
   f. Calcium x phosphorous interaction
      i. Tissue mineralization with high Ca & P levels; Ca x P > 70, e.g. tissue, lungs
# Hypercalcemia differentials

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<thead>
<tr>
<th>Differential</th>
<th>Mechanism</th>
<th>Support</th>
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| G Granulomatous inflammation | Macrophages specific to this type of inflammation produce vitamin D-like substance due to fungal infection, higher order bacterial infections; dogs primarily | • Chronic inflammation on CBC, hyperglobulinemia  
• Geographic location  
• Lymphadenopathy, pulmonary disease, and/or granulomatous disease/mass-like lesions  
• Would expect decreased PTH |
| O Osteolytic disease | Osteolysis due to osteosarcoma (mild) or multiple myeloma (MM); dogs | • Lameness and/or lytic lesions  
• Hyperglobulinemia (multiple myeloma)  
• Increased ALP  
• Expect decreased PTH |
| S Spurious or idiopathic | Idiopathic – cats (must rule out other causes) | • Rule out other causes  
• Decreased PTH + low PTHrp |
| H Hyperparathyroidism (1°) | Parathyroid adenoma or carcinoma; Dogs primarily | • Elevated PTH or normal PTH (in face of hypercalcemia)  
• Non-detectable PTHrp  
• Hypophosphatemia (65%)  
• Elevated ALP (40%)  
• Variable USG (can be low due to nephrogenic DI from hypercalcemia)  
• UTI (29%) |
| D Vitamin D intoxication | Ingestion of cholecalciferol rodenticide or plants (ergocalciferol) | • Acute GI signs, e.g. hematochezia and hematemesis, diarrhea +  
• Acute renal failure  
• Marked increases in calcium and phosphorous due to vitamin D ingestion  
• Pulmonary distress (metastatic mineralization) |
| A Addison’s disease | Immune-mediated destruction of adrenal gland (~30% hypercalcemic)  
• Lack of cortisol decreases renal excretion of calcium | • Hypocortisolism – Absence of stress leukogram, hypoglycemia, hypocholesterolemia, GI distress  
• Hypoaldosteronism: Hyponatremia + hypochloridemia, dehydration, +/- azotemia, decreased USG |
| R Renal failure | Small animals - 10-15% with renal failure will have hypercalcemia | • Azotemia + low USG (isosthenuria often)  
• Hyperphosphatemia |
| N Neoplasia | PTHrp production by neoplasm (lymphoma, anal sac carcinoma, + others, e.g. squamous cell carcinoma) | • Decreased PTH  
• Increased PTHrp  
• Anal sac mass, lymphadenopathy, mass lesion (confirm with cytology +/- biopsy) |