Disorders of Calcium Metabolism

David Bruyette, DVM, DACVIM
Chief Medical Officer
Anivive Lifesciences
3750 Schaufele Ave, Suite 100
Long Beach, CA 90808
David@anivive.com

www.veterinarydiagnosticinvestigation.com

LABORATORY EVALUATION

Usually measuring total calcium

Methods for determining ionized Ca are available

Degree of protein binding affected by pH

Ionized Ca decreases by 0.15 mg/dl for every 0.1 unit increase in pH

DISTRIBUTION OF CALCIUM

Total calcium is divided into:

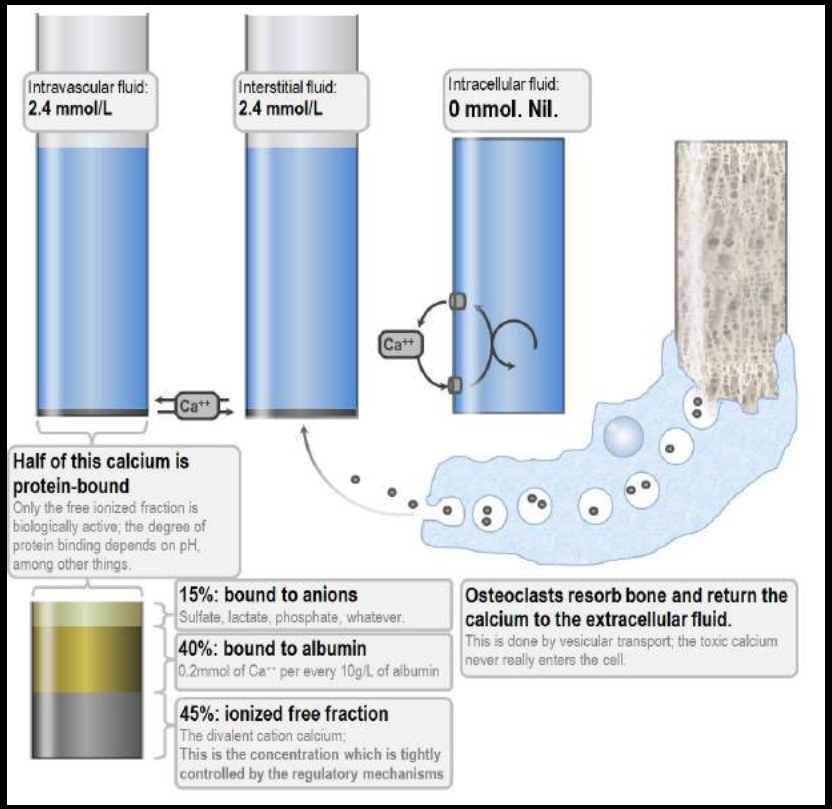
Protein bound (50%)

90% bound to albumin

Ultrafiltrable (50%)

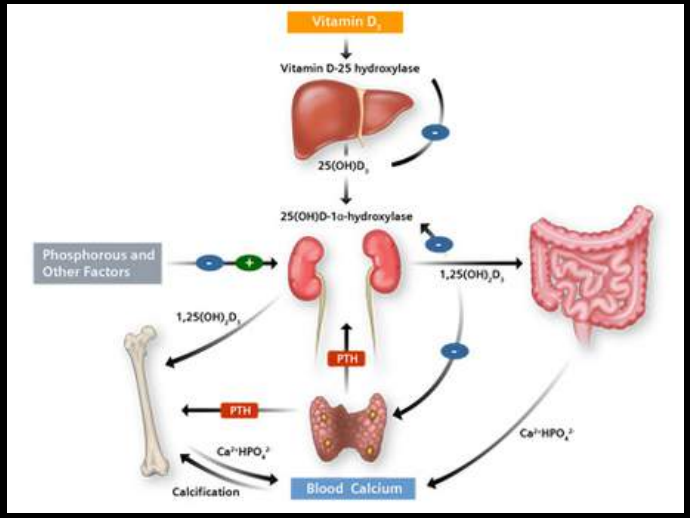
Complexed Ca (15%)

Ionized Ca (45%)



CALCIUM REGULATION

Vitamin D



Liver converts D_3 to 25-D_3

Kidney converts 25-D_3 to 1,25-D_3

Enhances GI absorption of Ca and PO_4

Mobilizes Ca and PO_4 release from bone

Enhances renal re-absorption of Ca and PO_4

Suppresses PTH release

CALCIUM REGULATION

Parathyroid hormone (PTH)

- 84 amino acid polypeptide
- Biologic effects mediated through amino terminus
- PTH acts through adenyl cyclase increasing cAMP
  - Results in phosphaturia and hypocalciuria

CALCIUM REGULATION

PTH Related Peptide (PTH-rp)

- Responsible for humoral hypercalcemia of malignancy (HHM)
  - Lymphoma, anal sac carcinoma, others
  - Binds to the PTH receptor
  - Actions similar to PTH
  - Results in hypercalcemia; PTH levels low to undetectable

DIAGNOSTIC APPROACH TO HYPOCALCEMIA

Clinical Signs

- Weakness; lethargy
- Focal trembling; twitching
- Generalized muscle fasiculations
- Ataxia; stiff gait
- Seizures
- Polyuria, polydipsia
- Cataracts

DIFFERENTIAL DIAGNOSIS OF HYPOCALCEMIA

Laboratory error

Hypoalbuminemia

Chronic or acute renal failure

Primary hypoparathyroidsim

Puerperal tetany

Hypomagnesemia

Malabsorption; enemas

Pseudo-hypoparathyroidism

TREATMENT OF HYPOCALCEMIA INITIAL MANAGEMENT

Ca gluconate 10% solution
- 0.5 - 1.5 ml/kg IV slowly
- Monitor EKG
- Do not use CaCl

After initial control
- Ca gluconate SQ every 6-8 hours
- Dilute 50% with saline

TREATMENT OF HYPOCALCEMIA

Daily monitoring of Ca

Calcitriol

25 - 40 ng/kg PO q 24 hours

DIFFERENTIAL DIAGNOSIS OF HYPERCALCEMIA

Laboratory error

Malignancy

- Lymphoma
- Anal sac carcinoma
- Multiple myeloma
- Bone tumors
- Others (mammary, prostate, SCC)

DIFFERENTIAL DIAGNOSIS OF HYPERCALCEMIA

- Primary hyperparathyroidism
- Chronic renal failure
- Hypoadrenocorticism
- Young animals
- Hypervitaminosis D
- Granulomatous disease
  - Blastomycosis
  - Granulomatous skin disease

FELINE HYPERCALCEMIA

- Neoplasia
  - SCC, LSA
- Renal Failure
- Primary Hyperparathyroidism
- Diet
  - Acidifying diets
    - Role of fiber
    - Role of prednisone
- Granulomatous disease
  - Cryptococcus

DIAGNOSTIC APPROACH TO HYPERCALCEMIA

Repeat Ca

Correction for albumin

Rule-out exposure to Vit D

Good physical examination

- Lymph node
- Anal sac

DIAGNOSTIC APPROACH TO HYPERCALCEMIA

- CBC/SMA
  - Rule-outs
  - Ca x PO_4 product
  - With PTH or PTH-rp
    - Hypercalcemia with low or low normal PO_4
- Urinalysis
  - Increased incidence of UTI
  - Specific gravity < 1.020

DIAGNOSTIC APPROACH TO HYPERCALCEMIA

Thoracic radiographs

If animal is symptomatic

- Abdominal radiographs
- Bone marrow
- Abdominal US

If animal is asymptomatic

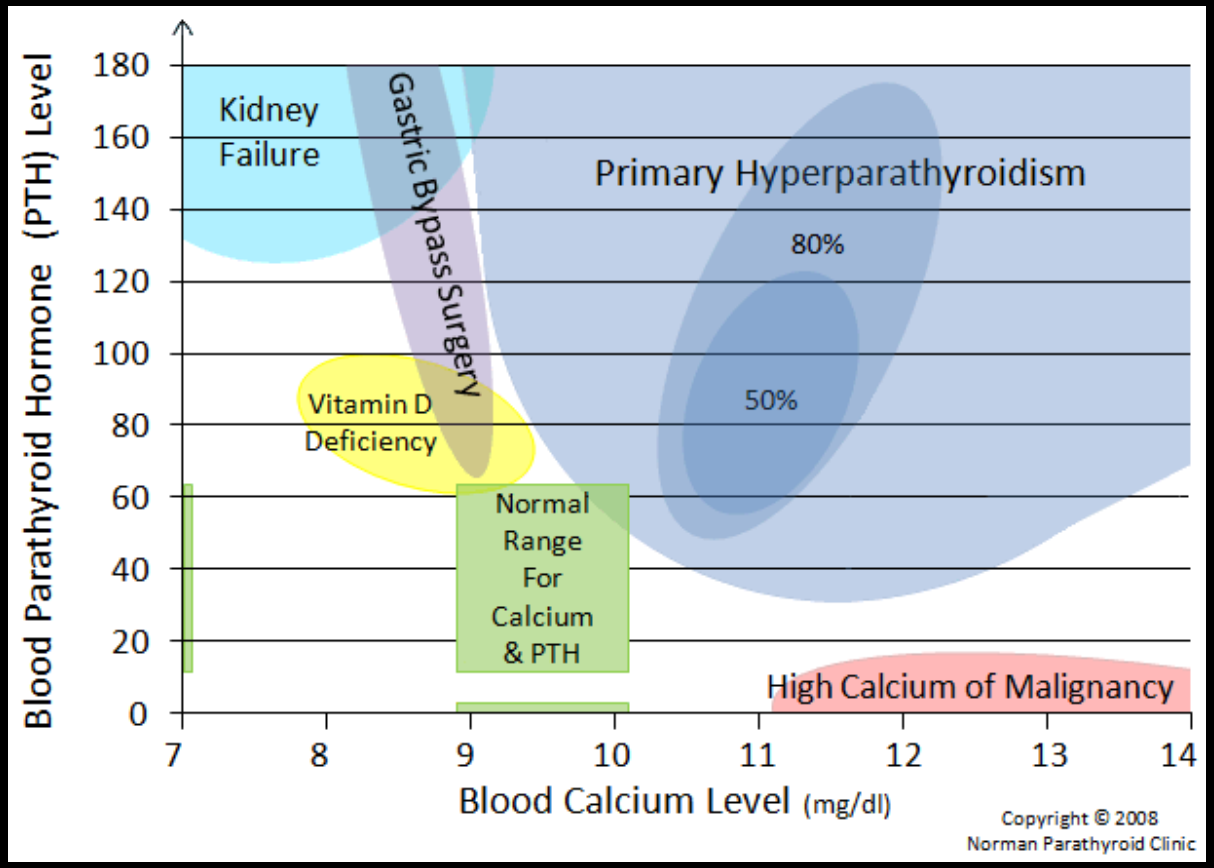
- PTH, ionized Ca, PTH-rp

DIAGNOSTIC APPROACH TO HYPERCALCEMIA

PTH and Ionized Ca

- PTH and iCa are elevated
  - Primary hyperparathyroidism
- PTH elevated, iCa low
  - Renal secondary hyperparathyroidism
- PTH low, iCa high
  - HHM

DIAGNOSTIC APPROACH TO HYPERCALCEMIA



TREATMENT OF HYPERCALCEMIA

Identify and treat the underlying disorder

Correct dehydration

- Saline diuresis
- Fluctuations in ionized Ca
- Lasix 2 - 4 mg/kg BID to TID

TREATMENT OF HYPERCALCEMIA

Glucocorticoids
- Cytotoxic
- Decrease GI Ca absorption
- Pros and cons
- 1 - 2 mg/kg/day

Salmon calcitonin
- 4 U/kg IV then 4 - 8 U/kg SC BID

TREATMENT OF HYPERCALCEMIA

When dietary modification and prednisolone are not successful, use of bisphosphonates should be considered. A number of cats have been successfully treated with 10 mg of alendronate (Fosamax) orally once weekly for up to one year. It's extremely important to give the drug on an empty stomach to increase GI absorption of the drug. Erosive esophagitis is a known side effect of oral bisphosphonates in humans, but has not been reported in cats. However, we recommend that the owner give 5–6 ml of water to their cat with a dosing syringe immediately after administration of alendronate; they then can apply a small amount of butter on the cat's lips to increase licking and salivation, which might further promote the transit of the pill to the stomach.

TREATMENT OF HYPERCALCEMIA

Pamidronate is the most commonly used parenteral drug.

The recommended dosage in dogs is 1.0–2.0 mg/kg administered intravenously mixed in 0.9 % saline over 2 hours. Adequate hydration is essential when treating with bisphosphonates since these drugs may cause nephrotoxicity, especially at higher doses.

The drug can be repeated in 3–4 weeks if needed.

PRIMARY HYPERPARATHYROIDISM

Etiology:

Adenomas >>> carcinomas
Hyperplasia (< 8%)

Pathogenesis:

Inappropriate secretion of parathyroid hormone (PTH) by autonomously functioning neoplastic or hyperplastic parathyroid "chief" cells.

Signalment:

>/= 7 yo (1), 11.2yrs (2)
Keeshonds over represented

Few reported cases in the cat.
Siamese overrepresented

CLINICAL SIGNS OF HYPERPARATHYROIDISM

PU/PD

Listlessness, Muscle weakness

Development of renal insufficiency is rare

Gastrointestinal Signs

LUTS attributed to urolithiasis or UTI (stranguria, pollakiuria, hematuria)

PE generally unremarkable

Seizures: one case report

In general, signs are mild to moderate.

DIAGNOSIS

Clinical Signs

CBC

Chemistry Panel

- Calcium [hypercalcemia, elevated iCa]
- Phosphorus [hypophosphatemia]
- Chloride [mild hyperchloremia]
- ALP [possibly mild elevation]

Urinalysis

- Low USG
- UTI

DIAGNOSIS- LOCALIZATION PROCEDURES

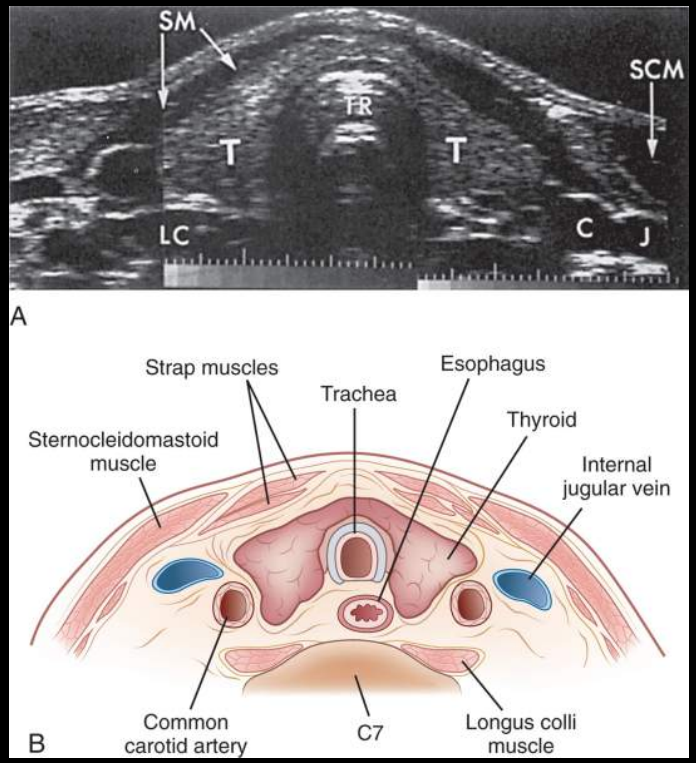
Approximately 10 % of parathyroid tissue is ectopic in location, and furthermore, approximately two thirds of "missed" adenomas are within the thyroid bed.

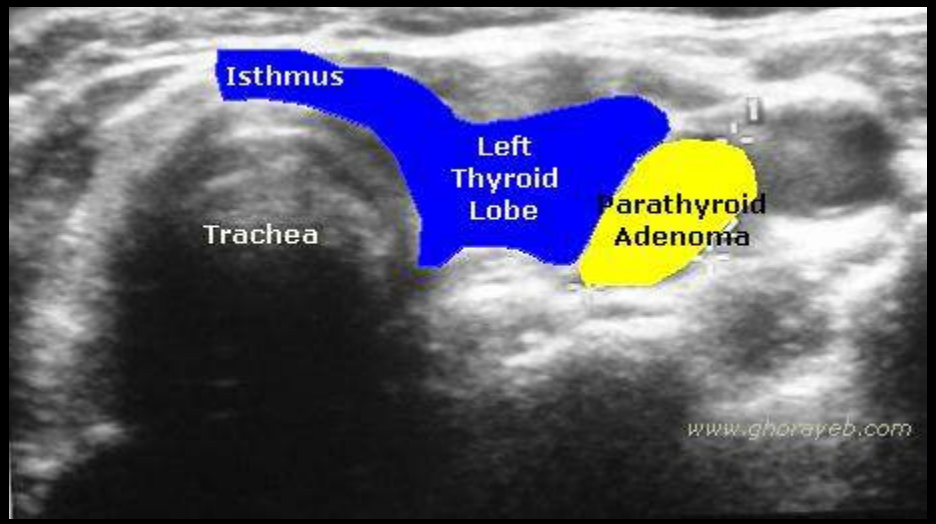
Historically CT, MRI, and US- these modalities are very insensitive for ectopic and mediastinal glands

Angiography and venography with venous sampling for parathormone are cumbersome and invasive

Scintigraphy - Technetium-99m Sestamibi

CERVICAL ULTRASOUND

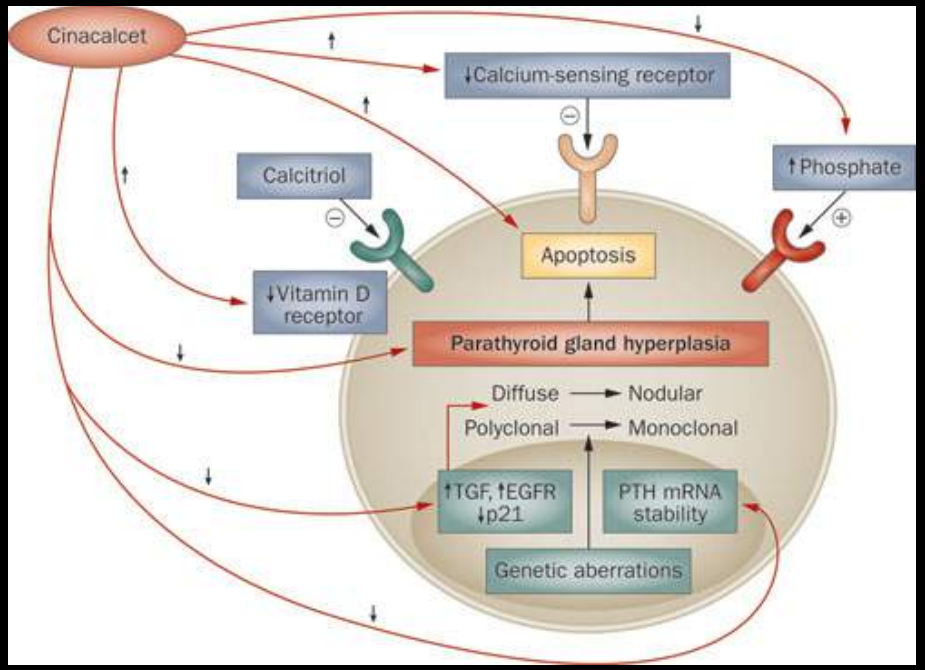




TREATMENT

Medical Options:

To treat or not treat: Discuss the reasons why we treat and reasons why we might tell an owner we don't have to treat.

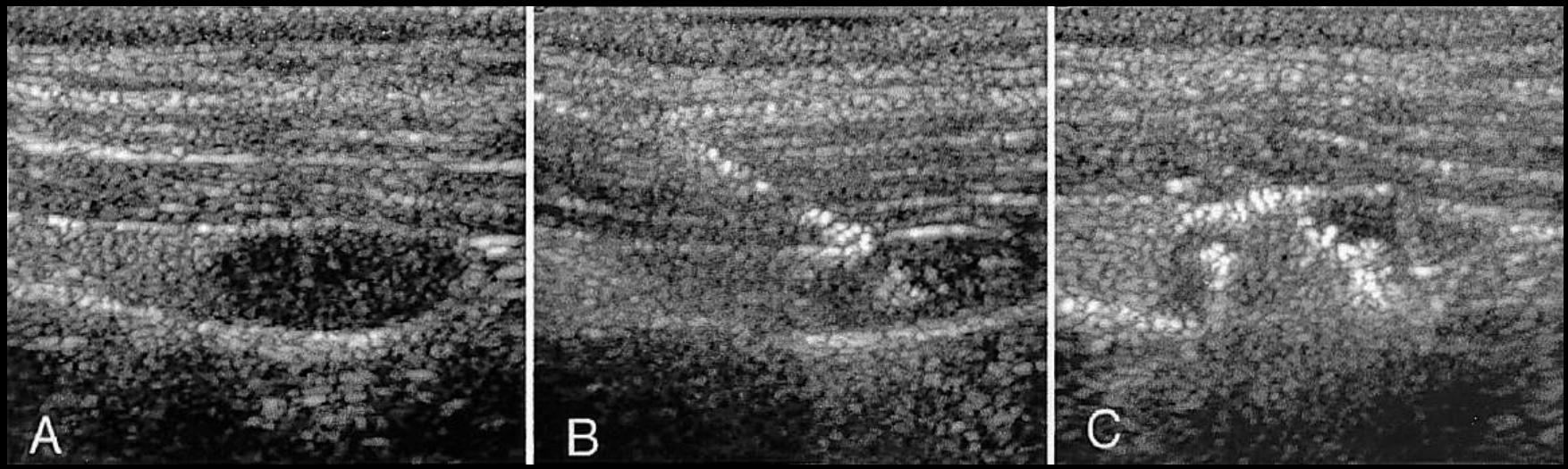


TREATMENT

Surgery -In experienced hands, surgical removal of an adenoma within the thyroid bed cures the hyperparathyroidism 90% to 95% of the time

Chemical or ethanol ablation

Heat Ablation



COMPLICATIONS OF TREATMENT

Hypocalcemia - Muscle fasiculations, tetany, and seizures, behavior and gait abnormalities

Trauma to recurrent laryngeal nerve

Hemorrhage

Recurrence

RETROSPECTIVE EVALUATION OF THREE TREATMENT METHODS FOR PRIMARY HYPERPARATHYROIDISM IN DOGS

The medical records of 110 dogs treated for primary hyperparathyroidism were reviewed. Dogs were treated via parathyroidectomy (n=47), percutaneous ultrasound-guided ethanol ablation (n=15), or percutaneous ultrasound-guided heat ablation (n=48). Forty-five of 48 (94%) parathyroidectomies resulted in control of hypercalcemia for a median of 561 days. Thirteen of 18 (72%) ethanol ablation procedures resulted in control of hypercalcemia for a median of 540 days. Forty-four of 49 (90%) heat-ablation treatments resulted in control of hypercalcemia for a median of 581 days.

SUMMARY

Think about primary hyperparathyroidism as a differential for hypercalcemia particularly in patients with…

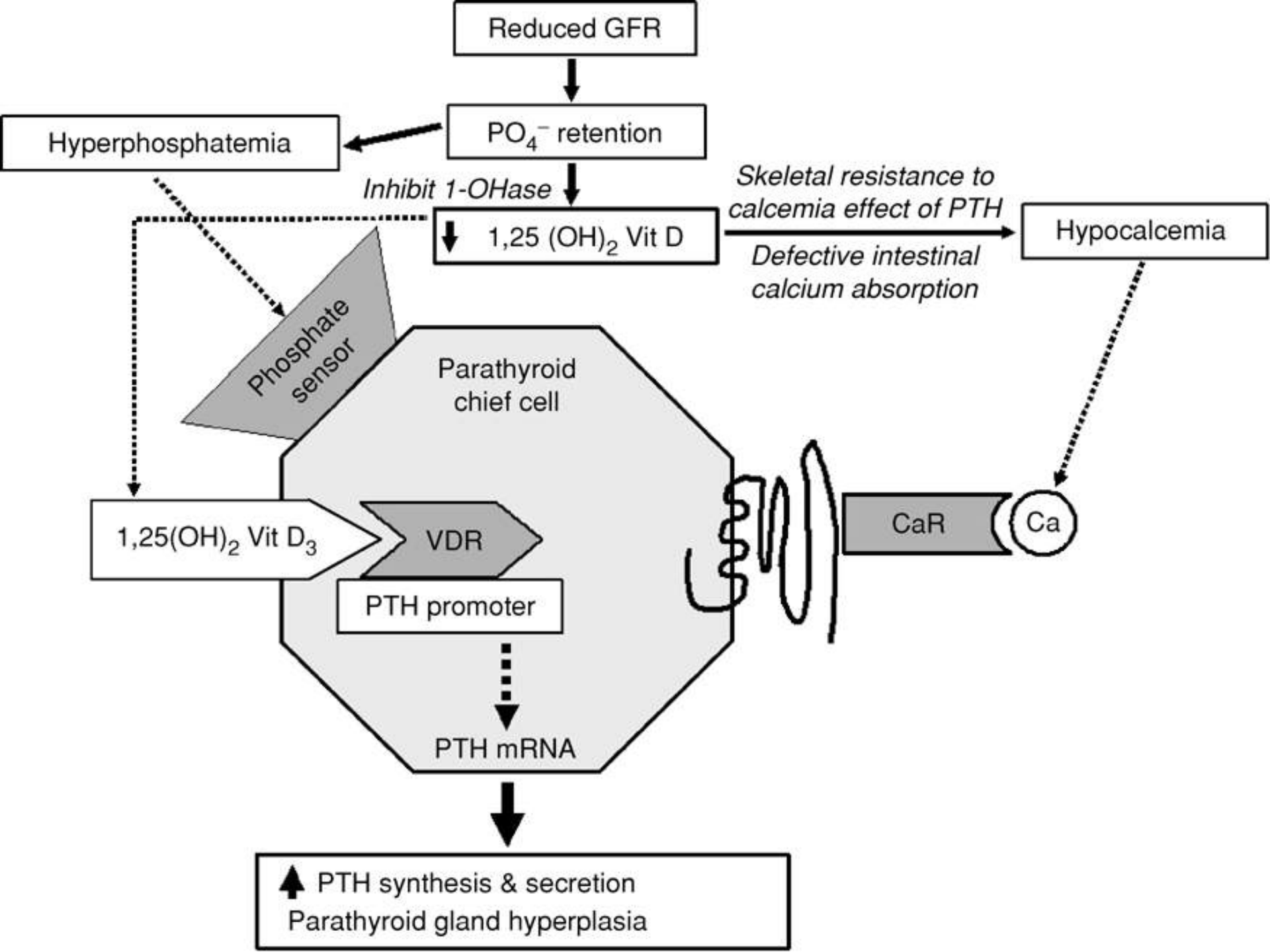
Mild to mod clinical signs

- High Ca, low Phos
- Older dogs, Keeshonds

Diagnosis is based on clinical signs, laboratory data, and imaging of the parathyroid nodule

Treatment options include surgical parathyroidectomy and heat ablation

The most common complication post-procedure is hypocalcemia


Reduced GFR
PO_4^- retention
Hyperphosphatemia
Inhibit 1-OHase
1,25 $(OH)_2$ Vit D
Skeletal resistance to calcemia effect of PTH
Defective intestinal calcium absorption
Hypocalcemia
Phosphate sensor
Parathyroid chief cell
1,25$(OH)_2$ Vit D_3
VDR
PTH promoter
PTH mRNA
CaR
Ca
PTH synthesis & secretion
Parathyroid gland hyperplasia