My My Don’t You Have Squishy Bones!

Metabolic Bone Disease: Preventing and treating this syndrome in wildlife patients

Dave McRuer, Director of Wildlife Services, Wildlife Center of Virginia

Terminology

• Metabolic Bone Disease
  – A syndrome that refers to a suite of metabolic conditions of the bone that are most often caused by dietary or husbandry mismanagement
  – Characterized by metabolic defects affecting the morphology and functioning of bones.
  - May be found in all Classes of vertebrates that have a boney skeleton.

Molecular Structure

• Bone is made of a matrix of inorganic (mineral) and organic components. When portions of this matrix harden, what we know as “bone” is formed.
• Inorganic
  – Made from carbonated hydroxyapatite, a crystalline calcium and phosphate rich material that gives bone its strength
• Organic
  – Made from Type 1 collagen that gives bone its toughness or its the ability to “bend” slightly without shattering.

Purpose of Bone

• Protection – the skull protects the brain; the ribs protect internal organs in the chest.
• Structure – Provides a frame to support the body
• Movement – in combination with skeletal muscles, tendons, and ligaments, allow the body to move and be manipulated in 3-dimensional space.
• Sound transduction – small bones in the ear serve an important role in hearing.

More Terminology

• “Hyper….” – a prefix meaning more than or excessive amounts.
• “Hypo….” – a prefix meaning a deficiency or less than normal amounts
• “Osteo…” – a prefix meaning “bone”

• “Chondro…” - a prefix meaning “cartilage”

• **Rickets** – Inadequate mineralization of the organic matrix of growing bone – especially the growth plates at the end of the long bones.

• **Osteomalacia** – “softening” of the bone resulting from mineral loss from a previously mineralized bone, leaving an abundance of organic matrix. Usually refers to disorders in bone mineralization

• **Osteoporosis** – Severe losses of bone density that includes proportional losses of inorganic and organic matrix. As a result, the degree of mineralization remains relatively normal.

• **Fibrous Osteodystrophy** – Replacement of normal mineralized tissue by connective tissue making the bone feel “rubbery”.

### The Major Players

- **Sun** – UVB radiation (between 285 – 320nm) converts cholesterol in animals into vitamin D\textsubscript{3} in the skin or ergosterol into vitamin D\textsubscript{2} in plants.

- **Vitamin D** – after production in the skin (D\textsubscript{3}) or ingestion in food (D\textsubscript{2} or D\textsubscript{3}), vitamin D is changed into an active hormone known as 1,25 dihydroxycholecalciferol (1,25-DHCC) by way of the liver and kidneys.

- Active vitamin D is necessary for absorbing calcium in the intestine.

### The Major Players - Calcium

- 99% of the calcium in the body is found in bones and teeth and must ultimately come from the diet

- Much of the remainder exists in the plasma (blood). 48% of the total plasma calcium is ionized (free and unbound), 40% is bound to proteins (mostly albumin), and 12 % is bound to citrate and phosphate ions.

- Small amounts of calcium may be passively absorbed through the intestine however active vitamin D is used to actively transport the majority into the plasma from the GI tract.

- Ionized calcium is of particular physiological importance in the body (bone metabolism, cell signaling (constriction and relaxation of blood vessels, nerve impulse conduction, muscle contraction, and secretion of hormones), and co-factors in enzymes and proteins.

- Calcium is reabsorbed into the body by the kidneys.

### The Major Players - Phosphorus
• 85% of the body’s calcium is found in bones and teeth and must ultimately come from the diet

• the remainder exists in the blood (plasma) and soft tissues. Plasma inorganic phosphorus is 10% bound to protein, 35% bound to calcium, sodium, and magnesium, and the rest is ionized.

• Phosphorus is passively absorbed from the diet to the blood through the intestines and is not tightly regulated.

• Plasma phosphorus levels vary throughout the day and with diet, sex, age, and a variety of hormones

• Phosphorus is excreted from the bodies by the kidneys

The Major Players - Parathyroid Hormone

• Responsible for regulating ionized calcium levels in the blood.

• Low blood Ca\(^{++}\) → increased secretion of parathyroid hormone → 1) increased production of active vitamin D → increased Ca\(^{++}\) absorption in the intestines to the blood 2) increased reabsorption of Ca\(^{++}\) in the kidneys and increased phosphorus excretion, 3) promotes the freeing of Ca\(^{++}\) from the bone to the blood.

• High blood Ca\(^{++}\) → decreased secretion of parathyroid hormone → decreased plasma Ca\(^{++}\) (decreased absorption in the intestines, decreased reabsorption in the kidneys, and decreased transfer of Ca\(^{++}\) from the bone to the blood).

The Major Players - Calcitonin

• Secreted by the thyroid gland in mammals and by the ultimobranchial gland in birds, reptiles, and amphibians.

• Responsible for reducing the amount of calcium in the blood by 1) decreasing the production of parathyroid hormone and 2) inhibiting the decreasing the transfer of calcium from the bone to the blood.

Causes of Metabolic Bone Disease

1) Feeding a diet with an unsuitable Ca:P ratio
2) Dietary deficiency of calcium
3) Dietary deficiency of suitable vitamin D
4) Lack of exposure to appropriate ultraviolet light
5) Disruption of vitamin D metabolism (renal, liver, intestinal, and parathyroid disease)
6) Temperature in reptiles and amphibians
7) Any condition that causes anorexia

1) Causes: Feeding a diet with an unsuitable Ca:P ratio

• The normal Ca:P ratio in the body is 2:1
• The Ca:P ratio in the diet should always be positive for healthy animals and is suggested between 1.1:1 – 2:1.

• Studies in reptiles indicate a wide species variation but generally need higher levels of calcium in the diet. One author recommends dietary levels between 3:1 – 6:1.

2) Causes: Dietary Deficiency of Calcium - General

• All calcium in the body needs to be ingested, therefore diets lacking suitable concentrations of calcium may cause deficiencies

• Dietary requirements for calcium vary with species and are likely increased in growing young animals and reproducitively active females

2a) Causes: Dietary Deficiency of Calcium - Carnivores

• Major problem – diets that contain predominantly skeletal muscle (all meat diet)

• Skeletal muscle is very low in calcium (0.02-0.03% dry matter) and the calcium-to-phosphorus ratios are greatly inverse (about 1:20)

• Skeletal muscle diets result in rickets and osteomalacia

• Decreased Ca++ and Vit D in the diet results in chronically stimulated parathyroid glands and bone demineralization. This results in fibrous osteodystrophy and reduced bone density and strength. This condition is called nutritional secondary hyperparathyroidism

• Whole prey diets are essential

• Can occur in the wild – example: Alaskan red fox kits

2b) Causes: Dietary Deficiency of Calcium - Herbivores

• The vegetative portions of plants, particularly the leaves, usually have adequate levels of calcium for maintenance and bone growth in herbivorous animals.

• Leaves of legumes have higher concentrations of calcium than grasses

• Some plants (ex: beet greens, kale, spinach) have high levels of calcium but they are bound to oxalate crystals making them physiologically unavailable. Feed in moderation only.

• Plant seeds contain very low levels of calcium and an inverse Ca:P ratio. Seed diets have resulted in rickets and folding fractures in a number of bird species.

2c) Causes: Dietary Deficiency of Calcium - Insectivores

• Mealworms, crickets, and wax worms are deficient in calcium and feeding them can result in MBD insectivorous animals

• Gut loading is recommended over dusting or dipping with calcium powder may be lost as the insect moves or grooms
• Insects fed a diet high in calcium (8%) represent a complete meal.

• Feeding insects a high calcium meal should only be done for 2-3 days, the time required to load the gut, otherwise excessive insect death may occur.

3) Causes: Dietary Deficiency of Suitable Vitamin D

• Humans, horses, pigs, rats, cattle, sheep and reptiles can synthesize vitamin D in their skin from solar exposure.

• Canid and felid species (and likely other obligate carnivores) have an obligatory requirement for dietary vitamin D; they cannot synthesize vit D in their skin

4) Causes: Lack of Exposure to UV Light

• Synthesis of vitamin D₃ in mammals is derived when UVB irradiation contacts the skin and converts cholesterol.

• Sunlight is the best and most suitable source

• Exposure to UVB is not fully understood in reptiles but is highly recommended.

Causes: Lack of Exposure to UV Light - Artificial Lights

• Artificial UVB sources (lights) should have a wavelength between 285-320nm.

• Recommended brands – Powersun®, Zoomed, Reptisun 5.0®, Zoomed

• Lights should be set to seasonal patterns

• Glass and most plastics will filter UVB. No material should be placed between the light and the animal

• UVB coating will degrade with time. Recommend light replacement every 6 months.

• Blacklights emit UVB but with no visible light. Have been linked to conjunctivitis and cataract formation in reptiles which may have to do with UVC emissions.

5) Causes: Disruption of vitamin D metabolism

• Excessive Dietary Protein
  – In mammals, excessive dietary protein is associated with increased excretion of Ca in the kidneys
  – In birds, weakened tendons during heavy growth periods when young may lead to slipped tendons → Angel Wing.
  – Turtles – may lead to differential growth in the scutes leading to a condition known as pyramiding.

Causes: Disruption of vitamin D metabolism
• Diseases of the kidney, liver, and intestine
  – Diseases of the kidney will interfere with phosphate excretion, calcium retention, and formation of active vitamin D
  – Diseases of the liver may interfere with formation of active vitamin D and production of bile salts needed for Ca absorption in the intestines.
  – Diseases of the intestines interfere with Ca absorption

6) Causes: Temperature in reptiles and amphibians
• Reptiles have a Preferred Optimal temperature Zone (POTZ) needed for homeostasis
• In suboptimal temperatures, blood flow is directed away from the GI tract causing stasis
• A decreased supply of calcium in the ingesta and decreased active transfer of Ca across the intestinal mucous membranes lead to lower plasma calcium levels
• Especially important in growing animals and reproductive females

7) Causes: Any condition that causes anorexia
• Conditions that prevent an animal from obtaining, manipulating, ingesting, or assimilating nutrients may limit the body’s access to calcium and phosphorus.
• Examples include:
  – Poor husbandry conditions
  – Ongoing injuries – beak and skull fractures, metabolic imbalances
  – Infectious and non-infectious diseases
  – Inappropriate diet
  – Conditions that cause ongoing stress
  – Etc.

Clinical Signs
• Depend on the species, age, duration of deficiency, degree of deficiency, and potentially the type of deficiency

Clinical Signs - Mammals
• Lameness caused by fractures, mechanical joint deformity of the bones, or painful joints
• Reluctance to move so to pain of doing so
• Anorexia associated with poor ability to chew. Teeth tend to loosen causing pain when eating, gingivitis is common.
• With fibrous osteodystrophy, jaws may thicken, become rubbery, fail to close properly, and lead to abnormal teeth eruptions.

• Skeletal deformities: Bowing of the weight-bearing limbs, folding or complete pathological fractures, spinal fractures with deviations, collapsed pelvis, young quadrupedal animals may have narrow chest and prominent sternum from softened ribs and vertebrae.

• Cataract formation and cross-eye (especially in cat species)

Clinical Signs - Birds

• Rare in the wild (e.g. acid rain soaked environments, vultures mistaking bone)

• At Risk:
  – Captive juvenile carnivorous birds fed a skeletal meat diet (beef, chicken breast, etc.)
  – Birds receiving and all seed diets.
  – Handfed altricial nestlings. This group grows at 5x the rate of similar sized mammals. Need to increase dietary calcium accordingly.

• Drowsiness, feather picking, regurgitation, increased drinking and loose stool.

• Skeletal deformities: Folding or complete pathological fractures, spinal fractures with deviations, beak deviations, curves in the line of the sternum.

• Involuntary muscle contractions (tetany). Birds may sway and fall of their perch, flutter their wings, or have complete seizures during which time limbs may fracture.

Clinical Reptiles

• Most common in lizards, crocodilians, and turtles

• Not common in snakes as they are usually fed a whole prey diet. Can occur in young animals fed day-old pinkies

• In lizards, muscle tetany and impaired muscle and nerve function to the limbs are common signs. Lizards may fall from perches and fracture vertebrae, pelvis, or a limb.

• Most common in young turtles and proper nutrition is especially important for the first 8 weeks of life. Signs include soft-shell, overgrown beak, distorted shell with pyramid scute growth, splayed legs and abnormal gait resulting from a flattened pelvis, alterations in carapace shade from pelvic and pectoral muscles pulling on weak shell.

• Adult turtles are less prone as they have large calcium reserves in their shell
• Adult turtles more prone to non-specific diseases such as shell erosions in aquatic turtles, anorexia, difficulty laying eggs, cloacal organ prolapse, abnormal digestion/constipation, muscle weakness

• Adult turtles with chronic MBD can suffer from skeletal abnormalities, fractures.

Diagnosis

• History
  – Unsuitable dietary provisions. Perform a diet evaluation including a full analysis of the type and quantity of the diet for estimating daily energy, calcium, phosphorus and nutrients obtained.
  – Lengthy stay of a wild animal in captivity
  – Lack of exposure to adequate UVB, natural, or artificial lights
  – Possible filtration of useful UVB by plastic or glass screening

• Clinical Appearance – discussed

• Blood biochemistry
  – Hypocalcaemia, especially with respect to ionized (physiological) calcium
  – Normals are often not available in wildlife species. Compare to “normal” patients of the same species and life stage.
  – High levels of alkaline phosphate (released during active bone remodelling)

• Radiographs

Radiographic findings

• Lesions are not apparent until late in the disease process when at least 40% of the mineral in bone has been resorbed.

• Typical findings include:
  – Decreased cortical density
  – Thinning of the cortices
  – Increased trabecular pattern
  – Folding Fractures or bowing in weight-bearing long bones
  – Failing of callous material around fractures
Pelvic abnormalities: twisted ilia, narrowed pelvic bones, compressed pubic bones by medial displacement of the hip socket (acetabula)

Spinal abnormalities (compression fractures of vertebrae, twisting of spine)

Abnormal shape and bone density of mandibles and facial bones with fibrous osteodystrophy in mammals and lizards

Mammal Case - Opposum

Prevention

• Preparation of a well balanced diet is essential in preventing MBD

• Provide access to natural sunlight or artificial UVB lightsource.

• Easier to prevent than treat

• Essential to know the dietary requirement for the species, life stage, season, and health status when determining an adequate diet

• Difficult because nutritional requirements are generally not known for wildlife

• For windows or covers, use acrylic polymers that allow the passage of UVB (Solacryl SUVT)

Treatment- When Prevention Has Failed

• Prognosis
  
  – Mild cases caused by dietary imbalances of deficiencies (no underlying disease) respond well if corrected
  
  – Mild limb deformities in growing animals may heal with corrective splinting
  
  – In severe cases (multiple pathological fractures, permanent abnormal bone healing, conditions leading to a non-releasable state) euthanasia is indicated.

Treatment

• Initial treatment: treat life-threatening disorders first – hypoglycemic tetany (calcium gluconate), splint pathologic fractures.

• In mild cases, provide appropriate diet (correct Ca:P ratio), husbandry changes (improve artificial UVB lighting or increase exposure to natural sunlight)

• In severe/chronic cases, parathyroid hypertropy (increase in size) may occur and the production of parathyroid hormone is no longer negatively influenced by the affect of high calcium in the blood.

• This results in increased freeing of calcium from the bone and even higher levels of calcium in the blood.
• More severe cases:
  – Provide diet/husbandry changes and supportive care.
  – Restore blood calcium levels using oral calcium gluconate or calcium glubionate.
  – Supplement with oral vitamin D₃ (1 drop/kg daily for 3 days, switch to EOD for no more than 20 days).
  – Stop bone loss and promoting new bone formation using salmon calcitonin (50 IU/kg, IM; two doses 1 week apart).
  – Calcitonin works by:
    • decreasing the production of parathyroid hormone (irrespective of calcium levels)
    • decreasing the activity of the cells that break down bone
    • increasing urinary calcium excretion.
    • Patent MUST have normal calcium levels in the blood (ionized) before administering calcitonin as this drug may cause hypocalcemia. **Vitamin D₃ and supplemental calcium should be given for at least 3 days before calcitonin is administered.**

References

- Food nutrient database: http://www.nal.usda.gov/fnic/foodcomp/search/
- UVB windows: http://www.spartech.com/polycast/solacryl.html