Nutritional secondary hyperparathyroidism in two cats
Evaluation of bone mineral density with dual-energy X-ray absorptiometry and computed tomography

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Keywords
All meat syndrome, feline, fibrous osteodystrophy, hyperparathyroidism

Summary
Two three-month-old, intact female Abyssinian cats were presented with a history of lameness, constipation and ataxia. The cats had been fed a diet composed almost exclusively of meat. Both showed severe osteopenia and multiple pathological fractures on radiography. Following euthanasia of the more severely affected cat, postmortem examination revealed changes consistent with nutritional secondary hyperparathyroidism and fibrous osteodystrophy, such as cortical thinning, massive connective tissue invasion in the diaphysis of long bones, and hypertrophy of the chief cells in both parathyroid glands. After introducing a balanced commercial diet to the surviving cat, bone mineralisation improved from the baseline value, and at subsequent examinations at three, six and 22 weeks later, as indicated by bone mineral density measurements obtained by dual-energy X-ray absorptiometry and computed tomography.

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Introduction
Nutritional secondary hyperparathyroidism (NSH) is a generalised metabolic bone disease characterised by osteopenia and caused by a diet providing inadequate calcium, excessive phosphorus, or a combination of both (1, 2). With the widespread availability of nutritionally balanced commercial pet food, nutritional disorders are currently rarely encountered. Although nutritional skeletal diseases were common in the past, veterinary literature on feline NSH is limited. The condition has been described in the cat in two case reports and its nutritional aetiology has been established by the experimental work of Scott in the late 1950s, and is further characterised by the work of Krook and of Rowland (3–8).

Dual-energy X-ray absorptiometry (DEXA) is widely used in human medicine for precise measurement of bone mineralisation. Its most significant clinical application is in identifying patients with osteoporosis and in estimating fracture risk, but it is also increasingly used to examine bone and body composition in longitudinal studies. The technique is based on measurements of tissue attenuation of two radiographic beams of different photon energies. An estimate of regional fat or mineral content can be made from the data (9). In veterinary medicine, DEXA has been most frequently used in a research setting for assessment of bone mineral density (BMD) (10–14). Clinical applications have been in the evaluation of fracture healing, and in measuring periprosthetic BMD and total body composition (9, 15).

Case reports
Two three-month-old, intact female Abyssinian littermate cats were referred to the Small Animal Hospital at the University of Copenhagen for evaluation. Both of the cats had a one week history of lameness, muscular twitching, constipation and...
stranguria. These signs were more severe in the first case than the second.

**Cat A**

The case history provided by the owner revealed that after weaning, this cat refused to eat commercially available cat food, and that its diet consisted mainly of fresh meat. Physical examination revealed abnormal gait and reluctance to ambulate on the hindlimbs. There were signs of pain on palpation of the pelvis and of both hindlegs. Occasional tremors and muscle twitching were observed. A distended, urine-filled bladder and a hard-packed colon were found on abdominal palpation. No abnormalities were detected on neurological examination. A complete blood cell count and urinalysis did not reveal any marked abnormalities. Biochemical analysis revealed elevated alkaline phosphatase activity and mild hyperphosphatemia. Total serum calcium concentration was normal (Table 1). Radiographically, marked generalised cortical thinning, osteopenia and multiple bilateral folding fractures of the femur, tibia and fibula were found (Fig. 1). There was lordosis of the lumbosacral spine, a compression fracture of the seventh caudal vertebra and marked narrowing of the pelvic canal caused by multiple pelvic fractures. Blood samples were collected to measure intact serum parathyroid hormone concentrations using a two-site immuno-radiometric assay validated for the cat (19). Parathyroid hormone concentration was markedly elevated (Table 1). Treatment consisted of strict cage rest, meloxicam (0.1 mg/kg PO sid), lactulose (1 ml PO bid) and laxatives. The diet was changed to a commercial diet for growing cats containing adequate and balanced

<table>
<thead>
<tr>
<th>Cat</th>
<th>Alkaline phosphate (u/l)</th>
<th>Calcium (mmol/l)</th>
<th>Phosphorus (mmol/l)</th>
<th>Parathyroid hormone (ng/l)</th>
<th>Ionized calcium (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>472</td>
<td>2.43</td>
<td>2.91</td>
<td>110.7</td>
<td>NA</td>
</tr>
<tr>
<td>B</td>
<td>172</td>
<td>2.85</td>
<td>2.35</td>
<td>32.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Reference range</td>
<td>10 - 90</td>
<td>2 - 2.95</td>
<td>1.45 - 2.6</td>
<td>3.3 - 22.5</td>
<td>1.0 - 1.4</td>
</tr>
</tbody>
</table>

NA: not applicable

**Postmortem Examination**

Macroskopically, the body condition score was below normal (2 out of 5) (20). There was marked femoral cortex thinning with cortices approximately 1 mm in thickness (Fig. 2, A and B). The trabecular bone of both femora was completely replaced by fibrous tissue and areas of microhaemorrhage. The cortex was thin, irregular and discontinuous in several areas, where it was replaced by fibrous tissue (Fig. 2, C and D). Microscopically, there was hypertrophy of the chief cells of the parathyroid glands and calcium deposits in the tubular epithelium of the kidneys, adjacent to blood vessels and stromal tissue (Fig. 2, E and F).

On the basis of the history, as well as the biochemical, radiographic and postmortem findings, the diagnosis of NSH with consequent fibrous osteodystrophy was made.

**Cat B**

Cat B was fed the same diet as cat A, but occasionally ate small portions of dry commercially available cat food. Physical examination revealed lameness on the left hindlimb and a distended urinary bladder. The results of a complete blood cell count, urinalysis, and biochemistry analysis were unremarkable, except for elevated alkaline phosphatase activity (Table 1). Radiographs revealed a generalised decrease in bone opacity and cortical thinning. There were folding fractures of the left femur, thoracolumbar kyphosis (Fig. 3) and narrowing of the pelvic canal on the ventrodorsal radiographic view. Serum parathyroid hormone concentration was increased. Serum ionised calcium was first measured 10 days after initial presentation and was found to be within normal limits (Table 1). The cat was treated with strict cage rest, meloxicam (0.1 mg/kg PO sid first day, followed by 0.05 mg/kg sid) lactulose (1 ml PO bid) and laxatives. The diet was changed to a commercial diet for growing cats containing adequate and balanced.

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Table 1 Results of selected biochemical parameters and serum parathyroid hormone in two cats with nutritional secondary hyperparathyroidism.

Fig. 1 Lateral radiograph of cat A. Marked generalised osteopenia, multiple femoral, tibial and fibula fractures and lordosis of the lumbosacral spine.

Fig. 2 A and B. The trabecular bone of both femora was completely replaced by fibrous tissue and areas of microhaemorrhage. The cortex was thin, irregular and discontinuous in several areas, where it was replaced by fibrous tissue.

Fig. 3 Thoracolumbar kyphosis and narrowing of the pelvic canal on the ventrodorsal radiographic view.

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amounts of calcium and phosphorus, and fed to meet the cat’s daily energy requirement. Within the next 24 hours, the cat was able to urinate and defecate normally. Lameness resolved within three weeks. The cat continued to do well during a six-month observation period, and no further abnormalities were observed.

Quantitative bone analysis

Quantitative bone analysis was performed using DEXA and CT five days after initial presentation, and repeated after three, six and 22 weeks. Computed Tomography and DEXA were performed during the same day, and in order to avoid motion artefacts, the cat was examined under general anaesthesia. A mixture of diazepam® (0.4 mg/kg IM), ketamine® (5 mg/kg IM) and buprenorfine® (0.01 mg/kg IM) was used for premedication, and anaesthesia was induced with propofol® (4mg/kg IV) and maintained with isoflurane® and oxygen after intubation. All DEXA measurements were performed by radiologist A (DHN), and radiologist B (LB) assessed all CT examinations. For critical assessment of DEXA results, measurements at six weeks were compared with DEXA measurements of an age-matched, healthy cat.

Computed tomography

Full body CT scans were performed on a single slice helical CT scanner®. The cat was examined in a prone spread-eagle position. Transverse slices were obtained in a cranio-caudal direction with a slice thickness of 3 mm. Data analysis was performed on a dedicated workstation®. Multiplanar reconstructions of the examined volume were performed and regions of interest (ROI) were manually applied after visual inspection. The ROI were created to include the diaphyses of both femora and tibiae. These included both cortical and trabecular bone. Although every effort for standardising patient positioning and ROI application was made, the tibial region measurements sometimes included parts of the fibula. The mean CT number in Hounsfield units was recorded from each ROI. Measurements were repeated four times and the mean value was recorded as the result. This value increased for each ROI with every consecutive analysis (Table 2).

Fig. 2  (A) Femur (non-decalcified), von Kossa stain. Scanned picture of histological section of the femoral bone. Mineralised bone is dark brown. Scale bar = 2 mm. (B) Histological picture of image A. The cortical bone is thin, irregular and discontinuous (asterisk marks the bone surface). Scale bar = 200 μm. (C) Femur, van Gieson stain. The cortical bone and medullary cavity are infiltrated by fibrous tissue (light pink) (asterisk marks the bone surface). Scale bar = 40 μm. (D) Femur, Masson trichrome stain. The cortical bone and medullary cavity are infiltrated by fibrous tissue (light blue) (asterisk marks the bone surface). Scale bar = 40 μm. (E) Kidney, von Kossa stain. Calcium deposits (arrow) in tubular epithelium. Kidney tubule (t) and blood vessel (v). Scale bar = 15 μm. (F) Parathyroid glands, Hematoxylin and eosin stain. Diffuse hypertrophy of Chief cells (arrow), containing increased amounts of eosinophilic cytoplasm. Scale bar = 15 μm.

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Dual-energy X-ray absorptiometry

Dual-energy X-ray absorptiometry scans were performed using a LUNAR DXP-a Dual-Energy Bone Densitometer running the appendicular scan type on the Small Animal software program, version 4.7e. The whole body was scanned. The cats were placed on the scanning table in a prone spread-eagle position, with legs extended from the body. From the total body scans, five ROI were analysed: the diaphyses of both femora, the diaphyses of both tibiae, and the pelvis. Bone mineral content (BMC; g), and bone mineral density (BMD; g/cm²) were measured from each of these ROI at each scan. Increasing BMD was observed for every ROI in each consecutive analysis as shown in Figure 4. This figure also shows BMD values for Cat B at six weeks compared to those of a healthy, age-matched cat.

Discussion

Nutritional secondary hyperparathyroidism

With the advent of commercial, nutritionally balanced pet food, NSH has become a rare disease. Nevertheless, many cats and dogs are still fed all-meat diets, probably due to a lingering false belief that these correspond to the pets’ natural prey in a feral state.

The pathophysiology of NSH has been reviewed (2, 7, 8, 21). In short, chronic dietary calcium deficiency results in hypocalcaemia, which in turn triggers an increase in parathyroid hormone secretion. Parathyroid hormone stimulates increased bone resorption, increased renal calcium reabsorption and phosphorus excretion, and increased renal hydroxylation of 5-hy-
droxycholecalciferol (25(OH)D) to calcitriol, (1,25-(OH)₂D). Calcitriol acts to enhance active intestinal calcium and phosphorus uptake and to accelerate bone resorption. The actions of both hormones result in restoration of normocalcaemia at the expense of the growing skeleton, thus resulting in skeletal calcium depletion and osteopenia (2, 21). Pathologic greenstick fractures of the appendicular skeleton, compression fractures of cancellous bones and pelvic canal narrowing can be seen in severe cases.

The cats in our study were fed an almost exclusive meat diet with milk and yoghurt supplementation. Meat has low calcium content, and a calcium to phosphorus ratio ranging from 1:10 to 1:50. The optimal calcium:phosphorus ratio of 1.1:1 recommended for growing cats (22) was therefore not met. The calcium content of milk and milk products is insufficient to correct the calcium:phosphorus imbalance induced by an otherwise, all-meat diet. Although the daily calcium intake of the animals was not calculated, it is likely that cat B maintained a higher calcium intake. This might explain the less severe clinical signs and the lower parathyroid hormone activity this cat showed compared to cat A. Radiographic and postmortem findings in our two cases were typical of NSH, and in accordance with previous reports (7, 8). Ultimately in the present cases the final diagnosis of NSH was made based on the typical nutritional history, radiographic findings, elevated parathyroid hormone activity, postmortem findings, and the fast recovery observed after introducing cat B to a balanced commercial diet.

**Dual energy X-ray absorptiometry and computed tomography**

Bone mineral density, as measured by DEXA, has been found to correlate strongly with histomorphometric studies of the feline skeleton, providing a non-invasive and objective tool for measurement of areal BMD (g/m²) in cats with metabolic bone disease (23). The results of DEXA measurements in the current study showed an increase in BMD with every consecutive determination of bone mineral status in cats with clinical bone disease. The authors suggest that these techniques have the potential to become important clinical and research tools for studying nutritional, metabolic and endocrine conditions affecting the feline skeleton, such as NSH, rickets, osteogenesis imperfecta, mucopolysaccharidosis V1 and renal secondary hyperparathyroidism. Future studies to determine normal reference ranges would allow a more valid comparison of BMD measurements.

In conclusion, DEXA and CT are useful, non-invasive diagnostic tools that can be used in the clinical setting for precise quantification of bone mineral status. Although CT has not been used as extensively as DEXA to assess BMD and fracture risk, it has the potential of providing true volumetric density values, separate measurements of cortical and trabecular bone, and might be more accurate in assessing bone strength and fracture risk. This is explained by the fact that compared to DEXA, CT reflects both changes in bone mineralisation and in bone architecture and porosity (25, 26). Another advantage of CT is its more widespread availability in veterinary practices compared to the DEXA. Disadvantages are that the procedure is expensive, and uses a radiation dose that is 30-times higher than DEXA (9). Whereas both DEXA and CT are sensitive to positioning errors, and require exact patient positioning to obtain accurate serial measurements, the CT is the less sensitive of the two.

Although BMD measurements were not essential for the diagnosis and management of NSH in the cats in our study, this study shows that CT and DEXA can be used to provide precise, quantifiable assessment of bone mineral status in cats with clinical bone disease. The authors suggest that these techniques have the potential to become important clinical and research tools for studying nutritional, metabolic and endocrine conditions affecting the feline skeleton, such as NSH, rickets, osteogenesis imperfecta, mucopolysaccharidosis V1 and renal secondary hyperparathyroidism. Future studies to determine normal reference ranges would allow a more valid comparison of BMD measurements.
tification of bone mineral density in cats with diseases associated with altered bone metabolism. Nutritional secondary hyperparathyroidism is still an important clinical diagnosis that should be considered in cases of growing animals with spontaneous fractures.

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References