Does Secondary Renal Osteopathy Exist in Companion Animals?

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KEYWORDS

• Dog • Cat • Mineral density • Quality • Bone • Hyperparathyroidism

KEY POINTS

- Renal secondary hyperparathyroidism is common in dogs and cats with chronic kidney disease.
- Renal osteodystrophy occurs in dogs and cats with chronic kidney disease and bone quality is reduced in these animals.
- In the cortical bone, material properties, bone geometry, and mechanical properties are affected.
- Bone mass is reduced in cancellous bone of animals with chronic kidney disease.

INTRODUCTION

Renal Secondary Hyperparathyroidism

Secondary hyperplasia of the parathyroid glands, resulting in increased parathyroid hormone (PTH) blood concentration, is an inevitable consequence of chronic kidney disease (CKD) in human and veterinary patients. The pathophysiology of this multifactorial syndrome, known as renal secondary hyperparathyroidism (SHPT), is complex. Progressive loss of functional nephrons leads to a decrease in the glomerular filtration rate, resulting in phosphorus retention, which promotes PTH secretion, by a direct stimulatory effect on the parathyroid gland, and more importantly, by binding free calcium, resulting in decreased ionized calcium concentration. PTH decreases phosphorus reabsorption in the renal tubules and restores normophosphatemia, but only to a certain point. As the disease progresses and glomerular filtration rate continues to decline, phosphorus retention becomes more severe and further triggers PTH secretion, which in turn promotes bone resorption and release of calcium and phosphorus to the circulation.[1,2] Vitamin D also plays a pivotal role in the pathophysiology of renal SHPT. Calcitriol, the active

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form of vitamin D, is formed by 1α-hydroxylation of 25-hydroxy-cholecalciferol in the kidney. Decreased functional renal mass and phosphorous retention result in decreased 1α-hydroxylase activity, hereby limiting calcitriol production. Calcitriol, in addition to promoting intestinal calcium absorption, is a major suppressor of PTH secretion. Therefore, reduced calcitriol levels contribute to the progression of renal SHPT, by promoting hypocalcemia and by decreasing the inhibitory effect of calcitriol on PTH secretion.[1,2] An additional, more recently identified key player in the development of renal SHPT, is fibroblast growth factor (FGF)-23, a hormone produced mainly by osteoblasts and osteocytes, which promotes renal phosphorous excretion. FGF-23 is secreted in response to hyperphosphatemia, early in the course of CKD. It downregulates 1α-hydroxylase activity, thus further decreasing calcitriol levels and worsening renal SHPT.[3,4] Increased serum FGF-23 concentration has been demonstrated as one of the earliest metabolic derangements in patients with CKD, often elevated while patients are still normophosphatemic and have normal PTH concentrations.[5]

Prevalence of renal secondary hyperparathyroidism in patients with chronic kidney disease

In humans, renal SHPT develops early in the course of CKD, and has been reported to affect 40% and 80% of patients with stage III and IV CKD, respectively.[6] Renal SHPT is also prevalent among cats and dogs with CKD. A 20-fold increase in PTH concentration was documented in a study of dogs with experimental CKD compared with healthy dogs.[7] A more recent study demonstrated SHPT is a common metabolic complication, documented in 76% and 84% of dogs and cats with naturally occurring CKD, respectively, and is present in all animals with International Renal Interest Society (IRIS) CKD stage IV disease.[8,9] In another survey, renal SHPT was documented in 47% of asymptomatic cats, being the only biochemical evidence of CKD.[9] PTH concentrations were higher in nonazotemic cats that subsequently developed azotemia within 12 months compared with cats that remained nonazotemic, and the increase in PTH occurred before changes in plasma calcium or phosphorous concentrations were detected.[10] FGF-23 blood concentration also increases in cats with CKD and were positively correlated with the IRIS stage.[11]

Bone Abnormalities Associated with Renal Secondary Hyperparathyroidism

Renal osteodystrophy

Persistently elevated PTH concentration increases bone resorption by activating osteoclasts, thereby leading to an imbalance in the bone remodeling process and consequently to decreased bone quality. This phenomenon is generally referred to as renal osteodystrophy (ROD), a complex disorder of bone, resulting from the individual and combined actions of metabolic and hormonal abnormalities that occur in CKD. ROD was defined by the National Kidney Foundation as a constellation of bone disorders, present or exacerbated by CKD, that lead to abnormal mineral metabolism, bone fragility, and fractures.[12] The definition was refined by the "Kidney Disease: Improving Global Outcomes Committee," and a new term, CKD–mineral and bone disorder was coined to refer more broadly to the skeletal and extraskeletal manifestations of the mineral disorders in CKD. The broader CKD–mineral and bone disorder is defined as a systemic disorder of mineral and bone metabolism caused by CKD and manifested by either one or a combination of (1) abnormalities of calcium, phosphorous, PTH, or vitamin D metabolism; (2) abnormalities of bone turnover, mineralization, linear growth, volume, or strength; or (3) vascular or other soft tissue calcification.[13,14]

METHODS TO ASSESS BONE QUALITY

The overall mechanical behavior of whole bone is determined by its morphology and architecture (ie, the amount and spatial distribution of bone material), and by the intrinsic properties of the bone material itself. It may be inferred that bone fragility is reduced in at least three different ways: increase bone mass (larger bones are able to carry more load), effective distribution of bone mass (put more bone tissue where mechanical demands are higher), or improve the material properties of the bone (ie, bone is stronger at the tissue level).[15]

The ability of bone to resist fracture is the most important factor in defining bone quality, because a broken bone can fulfill but few, if any, of its functions. Fractures occur as a result of a catastrophic structural failure of the whole bone, which is initiated at the material level. Bones may fail because they are too weak, too flexible, do not absorb enough energy, and/or are not resistant enough to repetitive loading. Each one of these parameters (strength, stiffness, toughness) is evaluated by mechanical testing. The combination of these properties, rather than each independently, defines the resistance to fracture. Enhancing one property over the other might be detrimental to the overall mechanical performance of the bone. For example, increased mineralization increases stiffness of the bone but at the same time it decreases toughness.

There are numerous methods to assess bone quality including bone morphometry, assessment of bone mineral density (BMD) and porosity, and an array of mechanical testing of the bone. This article describes the most common methods to assess bone quality.

Bone Mineral Density

BMD is the amount of mineral present within the bone. It is considered the most important determinant of bone quality and is the current clinical standard to predict fracture risk.[16] BMD is measured by several methods, including dual-energy X-ray absorptiometry, which measures areal BMD (in grams per square centimeter) or quantitative computer tomography (CT)/high-resolution micro-CT analysis, which measure volumetric BMD (in grams per cubic centimeter). An exponential inverse correlation exists between BMD and probability of fracture, and even a small increase in BMD (5%–8%) can improve bone strength by more than 60%.[17] However, mounting evidence indicates that BMD alone cannot predict the risk of fracture in a given bone. Bone architecture and microarchitecture, bone turnover rate, and the amount of microdamage all affect bone quality and may play a role in the bone's ability to resist fracture.[18]

Porosity

Porosity is another major determinant of bone quality. It represents the sum of all voids within the bone, which includes osteocytic lacunae, canaliculi, blood vessels, and resorption cavities (**Fig. 1**). There is a nonlinear inverse correlation between the porosity and the stiffness of the bone.[19]

Mechanical Assessment of Bone Quality: Bending Tests

Bones can be tested mechanically in compression, tension, bending, or torsion. Bending tests are one of the most common methods to test the mechanical properties of bones.[20] In the bending test, the bone (whole bone or a prepared bone specimen) is loaded in bending until failure.

Bending tests are either three-point or four-point bending experiments. In three-point bending, a bone specimen is positioned on two supports, and a

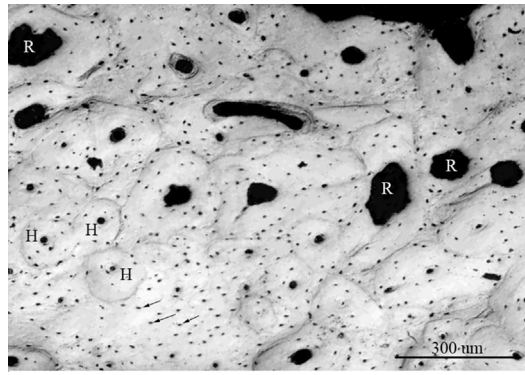

Fig. 1. Light microscopy of a feline bone depicting several secondary osteons with their central haversian canal (H). Resorptive lesions (R) are the largest cavities within the bone. Arrows indicate lacunae.

single-pronged loading device is applied to the opposite surface of the specimen, precisely in the middle of the two supports (**Fig. 2**). This central loading point is the point in which maximal load occurs, and at this location the bone ultimately fractures. Four-point bending tests use the same principles, but the load is applied by two loading prongs instead of one, located at an equal distance from either side of the midpoint. This configuration guarantees the specimen is loaded in pure bending with almost no shear stresses.[20,21]

The experimental procedure during a bending test involves induction of displacement of the loading prongs, which causes deformation of the specimen, while measuring the force required to induce this displacement yielding a load-deformation curve. This curve is subsequently converted to a stress-strain curve, from which inherent properties of the bone material are derived.[21] These properties include, for example, the Young's modulus, which is a measurement of the stiffness of a material (ie, the resistance to bending deformation), and energy to fracture, which represents the bone's toughness.

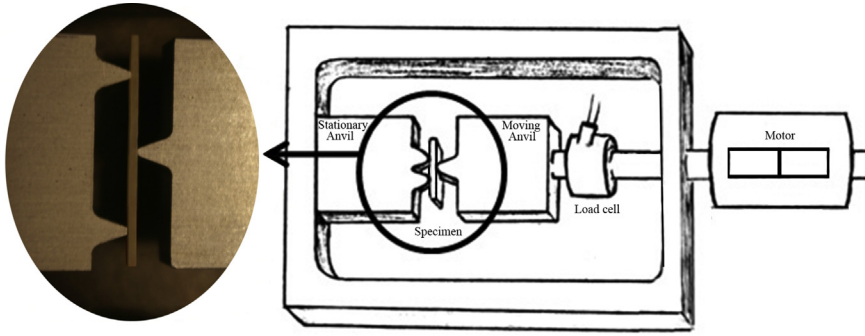

Fig. 2. Mechanical testing (three-point bending test). A bone specimen is held between two anvils. A moving anvil (with one prong) is attached to a motor that advances the anvil toward the stationary anvil (with two prongs) resulting in deformation of the tested specimen. The load required to advance the anvil is measured by a load cell.

RENAL OSTEODYSTROPHY IN HUMAN AND ANIMALS WITH CHRONIC KIDNEY DISEASE

Renal Osteodystrophy in Human Patients with Chronic Kidney Disease

Analysis of bone biopsy from the iliac crest is currently the gold standard for diagnosing and classifying ROD.[12] Because studies in humans are restricted to noninvasive or minimally invasive procedures, the precise microstructural, compositional, and mechanical bone changes that occur during ROD are not entirely known. Mild manifestations of ROD are usually observed early in the course of the disease (as early as stage II), and worsen as kidney function deteriorates. The type and nature of ROD may vary from one patient to another and encompasses a spectrum from severely suppressed to markedly elevated bone turnover. The two major types of ROD recognized in human patients are high-turnover bone disease (osteitis fibrosa) and low-turnover bone disease (adynamic bone disease), both of which are associated with increased bone fragility. Some patients suffer from one of these types predominantly, whereas others have a mixed type of bone disease. Osteomalacia also may be present.[22]

In high-turnover bone disease, increased PTH concentration enhances osteoclast activity, leading to increased bone resorption. Bone abnormalities include increased number of resorption cavities, enlarged haversian canals, and marked fibrosis involving the bone marrow.[22] Additional osteoporotic alterations include endocortical resorption, trabecular perforation, cortical thinning, and increased cortical porosity.[12]

The mechanisms underlying the development of low-turnover bone disease are not fully understood, but it generally is not associated with high PTH levels (ie, not mediated by renal SHPT). Adynamic bone disease is characterized by a defect in bone matrix formation and mineralization and a decrease in the number of osteoclasts and osteoblasts on bone surfaces. These changes are associated with an increased risk of overt fractures and microfractures. The reported prevalence of adynamic bone disease in dialysis-dependent patients with CKD varies between 15% and 60%.[22]

Bone abnormalities in all types of ROD greatly increase the risk of pathologic fractures, which are associated with excess morbidity, mortality, and health care costs. The United States Renal Data reveals that the risk for hip fracture is about four-fold higher among human hemodialysis patients compared with the general population, with the risk correlated to the duration on renal-replacement therapy.[23] Moderate-to-severe kidney disease is associated with more than a two-fold increase in hip fracture, demonstrating that patients with CKD who do not yet require renal-replacement therapy are also at an increased risk of fragility fractures.[12] Furthermore, outcomes of fractures are significantly worse in the CKD population compared with the general population, with a two- to three-fold increase in mortality following hip fractures.[14] The risk of fracture in patients with CKD has been linked directly to the severity of renal SHPT, and is reported to increase by 9% with each 200-pg/mL increase in PTH concentration and by 72% with PTH concentrations greater than 900 pg/mL.[24]

Bone Abnormalities in Veterinary Patients with Chronic Kidney Disease

Although renal SHPT is highly prevalent among cats and dogs with CKD, its effects on their bone metabolism have not been thoroughly studied. There are several case reports of cats and dogs with CKD suffering from bone abnormalities. Most reports are of young growing dogs with renal dysplasia. This is most likely because bones of young animals are more sensitive to the effects of PTH. Findings include thinning of the cortices and severe bone demineralization, with the skull and mandible most severely affected. These abnormalities often lead to pathologic jaw fractures and teeth

loosening.[25,26] A case report of a cat with CKD and parathyroid hyperplasia demonstrated cortical bone lysis and cystic bone lesions, most severe in the femoral diaphysis.[27] Despite these few anecdotal reports, clinical signs associated with ROD are generally considered uncommon in dogs and cats with CKD.[25] It is possible that veterinary patients with CKD do not live long enough for skeletal changes to become clinically evident. However, with the advancement of medical management and growing availability of hemodialysis for veterinary patients, the effects of CKD on bone might become more clinically important.

Recently, two case-control studies were designed to evaluate the effect of CKD on bone quality of dogs and cats.[28,29] In the first study, 13 cats with IRIS CKD stage III and IV were compared with cats that died or were euthanized because of reasons unrelated to the urinary system (control animals). Similarly, nine dogs diagnosed with IRIS CKD stage III and IV were compared with age, sex, and body weight matched control animals. Both the cortical and the cancellous bone were evaluated.

Material Properties of the Cortical Bone

The two main determinants of bone strength (porosity and BMD)[19] were found to be altered in animals with CKD compared with control animals. The BMD of cats with CKD was lower by 4.8% compared with control animals. BMD is a major determinant of bone quality and the current clinical standard to predict fracture risk in patients with osteoporosis.[16] Even a small decrease in BMD substantially decreases the stiffness of the bone and increases fracture risk,[30] because the relationship between these two bone characterizes is exponential.[31,32] Indeed, there is an inverse correlation between low BMD and fracture risk in human dialysis patients.[16]

BMD in human patients with CKD varies, depending on the type of ROD; it may be normal or even high in adynamic bone disease, whereas it is generally low in high-turnover disease.[12] The BMD is 4.2% lower in predialysis patients with CKD compared with control subjects,[33] and 17.5% lower in patients beginning hemodialysis.[34] A recent longitudinal study that tracked changes in cortical bone in 53 human patients with CKD, found a significant decrease in BMD over time,[35] implying the length of the disease plays a role in the expected decrease in BMD. The shorter disease length might account for the more subtle changes documented in animals with CKD.

Porosity, another major determinant of bone quality, is the sum of all voids within the bone, including osteocytic lacunae, blood vessels, and resorption cavities. The overall porosity was significantly higher in dogs with CKD compared with control animals, but only tended to be higher in cats with CKD. Both dogs and cats affected with CKD had a significantly higher density of resorption cavities compared with healthy control animals (**Fig. 3**). Resorption cavities represent the largest pores in the bone, and when present in high density, bone strength is decreased because these cavities are a defect in the bone causing weakening and deterioration of bone quality.[36] Resorptive cavities are formed normally by osteoclasts as part of the remodeling process to remove damaged bone and replace it with new bone. The remodeling process is carried out by a multicentric unit, which is a group of cells comprised of osteoclasts that erode bone and form the resorption cavities, and osteoblasts that fill the bone defect with new bone matrix. Under normal conditions bone resorption and formation are approximately equal, and bone mass is maintained. SHPT leads to an imbalance of the remodeling process, causing more bone to be resorbed and less bone to be formed, leaving part of the resorption cavities not filled with new bone. Models indicate that resorption cavity size and location are important factors in determining bone quality, and the effect of cavities is larger than can be expected from simple bone loss.[37] This effect could be caused by stress concentrating effects of these cavities,

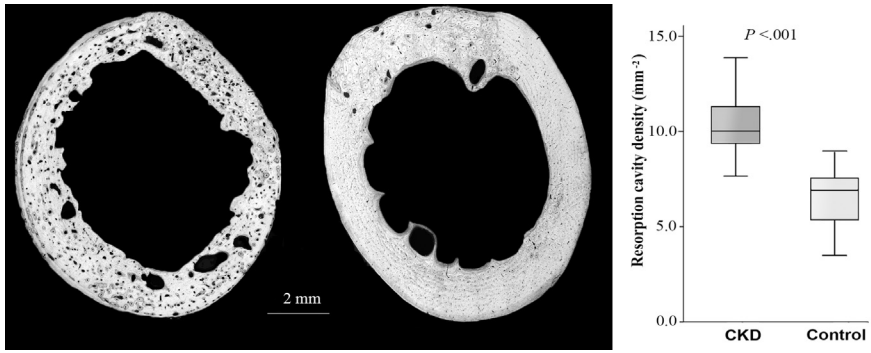

Fig. 3. Two cross-sections of bone; the left is from a cat with chronic kidney disease and the right is from a control cat. Note the increased number and size of resorption cavities in the bone of the chronic kidney disease affected cat. The box plot on the right depicts the density of resorptive cavities of cats with chronic kidney disease compared with control cats.

increasing the risk of bone failure at that point. Thus, higher resorption cavity density in the bone of patients with CKD is expected to negatively affect bone ability to resist fracture by increasing the porosity and by serving as stress risers. The higher porosity and higher density of resorptive lesions found in animals with CKD should be taken into consideration when traumatic or pathologic fractures occur in these animals.

Additional structural features that have been shown to affect cortical bone quality include osteon size and density, haversian canal size, and several other microarchitechture changes.[38] Light microscopy of bones from dogs with CKD revealed smaller lacunae.[29] It is accepted that osteocytes play a crucial role in maintaining material properties of bone by regulating the modeling and remodeling processes.[39] The morphologic changes documented may affect the osteocyte-canalicular system and impair cell-to-cell communication. This change can reduce the effectiveness of the osteocytes' role in mechanosensing and damage repair and could perhaps point to one of the mechanisms leading to cortical bone deterioration.

Bone Geometry

The geometry of the bone has been evaluated only in cats, because there is a large variability in bone size among different dog breeds. Micro-CT analysis of cortical bone of the femoral diaphysis of cats with CKD showed significantly lower cortical cross-sectional area (ie, smaller cortical area) and a 17% decrease in cortical thickness.[28] These findings suggest not only are the material properties of the bone in cats with CKD reduced, but also its mass is decreased, as reflected by smaller and narrower cortexes. Intuitively, narrower cortices and bones with lower cortical area have reduced flexural stiffness and are expected to fail (break) at lower loads.

Mechanical Properties of the Cortical Bone

The mechanical performance of whole bones depends on their geometry and the material properties of the bone matter. The most commonly assessed property of the bone material is the Young's modulus, which reflects the stiffness of the bone (the bones' ability to resist bending forces). Bones of cats with CKD had inferior mechanical properties compared with control animals; in particular they demonstrated a lower Young's modulus (by 13%), lower yield stress, and lower ultimate stress (ie, the bones were able to withstand smaller stresses before yielding and breaking). These

differences were not apparent in bones from dogs with CKD. Similar to cats, human patients with CKD also have inferior mechanical bone properties compared with healthy patients, as reflected by a decreased Young's modulus (by 11.9%) in patients with high-turnover ROD.[40]

PROPERTIES OF CANCELLOUS BONE

Cancellous bone represents approximately 20% of the skeletal mass and is found in the epiphyseal regions of long bones and in flat and irregular bones. It is made of the same constituents as cortical bone but has a different spatial distribution and considerably higher porosity. In some bones, like the vertebrae, the proportion of cancellous bone is very high compared with the cortical bone.

The contribution of cancellous bone to overall mechanical properties of the whole bone is controversial[41–43]; however, it is believed it improves the bones' structural strength and assists in load distribution (energy dissipation). The lumbar vertebrae are a common place for cancellous bone analysis because of the high proportion of cancellous bone and because pathologic fractures are common in this site. Cancellous bone is assessed mainly by evaluating its bone volume (ie, the proportion of the bone volume compared with the overall volume) and trabecular thickness. Analysis of cancellous bone in cats with CKD revealed deterioration in cancellous bone quality as reflected by significantly lower trabecular thickness and bone volume (bone volume/total volume) (**Fig. 4**). Furthermore, the effect on cancellous bone was multisited and shown to occur in the vertebral bodies and in the long bones (distal femur). These findings in cats (reduced trabecular thickness and bone volume/total volume) negatively affect bone quality and were shown to be associated with increased risk for fracture.[44]

Species Differences

These studies of dogs and cats revealed similarities between the two species; however, some differences were also documented. Bone abnormalities of cats were demonstrated in all levels tested (material properties, geometry, and mechanical properties). In dogs, abnormalities were more subtle and were not documented in all aspects tested. Some of the differences between dogs and cats are likely related to the progression rate of the disease. Because SHPT is one of the early consequences of CKD, it is likely that cats, as humans, are exposed to the metabolic derangements associated with the disease for years, as opposed to dogs in which CKD often

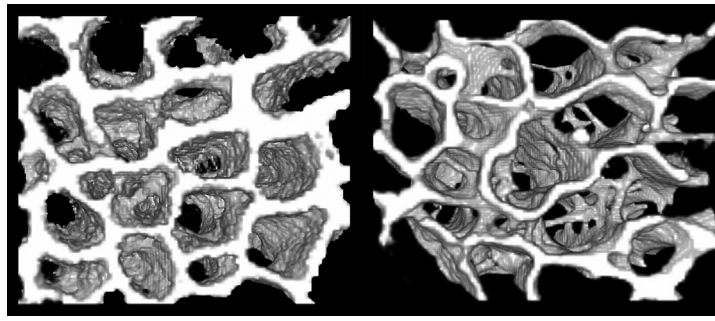

Fig. 4. Cancellous bone of a cat with chronic kidney disease (*right*) and a cat without chronic kidney disease (*left*). Note the overall reduction in bone mass in the affected cat and the lower trabecular thickness.

progresses over a shorter period of time. Therefore, in dogs, despite physiologic similarities in mineral metabolism, the effects on bone quality are less pronounced.

DOGS AND CATS AS A MODEL FOR RENAL OSTEODYSTROPHY IN HUMANS

Most studies use rodents to investigate the effects of renal SHPT on bone quality. The rat is one of the most commonly used animals in models for the human disease; however, there are marked differences between rat and human bone. Rodent bones are remarkably different from human bones in terms of type, architecture, structure, and biology, of which, most dramatically, rodent cortical bone does not remodel.[45] Moreover, findings in rats are not always consistent with regard to changes in BMD and mechanical properties,[46–48] which partly explains the shortcomings of this model. Dogs and cats can serve as an alternative and superior model for ROD in human patients. Both canine and feline adult skeletons show many structural similarities to the human bone. The cortex consists mostly of secondary osteons and remodels continuously as does the human bone.[46–49] Other advantages to study ROD in dogs and cats is that the disease occurs naturally (vs chemically, genetically, or surgically induced in laboratory animals), its prevalence is high in cats, and the disease has clinicopathologic similarities to human ROD. Canine and feline bones have technical advantages for study over rodent bones. Reliable measurement of material bone properties requires precise and accurate mechanical testing of carefully prepared geometric samples of cortical bone, such as beams or cubes. Such testing is difficult to achieve in rodents because of the small size of their bones; therefore rodent bones are often tested by three-point bending technique applied to whole bones, which is hampered by various technical limitations.[50,51] Canine and feline bones have much thicker cortices, which allow preparation of cortical bone beams for more accurate and reliable assessments using four-point bending testing.

SUMMARY

Secondary renal osteopathy exists in companion animals. Changes are more pronounced in cats compared with dogs, most likely caused by a longer disease course, but occur in both species. The documented changes further justify the need to control phosphorous concentration and to prevent SHPT in the management of CKD in dogs and cats. It is yet to be determined what is the clinical significance of these finding (if any) and whether interventions aimed to control this inevitable complication (eg, phosphorous control, administration of vitamin D derivatives) can negate, at least to some extent, the deterioration in bone quality of animals with CKD. Further studies assessing bone quality of dogs and cats with CKD are warranted because the aforementioned studies were based on a small number of animals with naturally occurring kidney disease. Variability of the severity and the chronicity of the disease existed among the animals, and therefore some of the statistical comparisons made were likely underpowered.

These studies provide evidence that dogs and cats with CKD have decreased bone quality. Until proven otherwise, the fracture risk of animals with CKD should be considered higher and fixation methods should take into account the lower bone quality of these patients.

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