Cervical Vertebral Trabecular Bone Mineral Density in Great Danes With and Without Osseous-Associated Cervical Spondylomyelopathy

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Background: Great Danes (GDs) with osseous-associated cervical spondylomyelopathy (CSM) have osteoarthritis (OA) of the cervical vertebrae. OA is often associated with increases in bone mineral density (BMD) in people and dogs.

Hypothesis/Objectives: To compare the trabecular BMD of the cervical vertebrae between clinically normal (control) GDs and GDs with osseous-associated CSM by using computed tomography (CT). We hypothesized that the vertebral trabecular BMD of CSM-affected GDs would be higher than that of control GDs.

Animals: Client-owned GDs: 12 controls, 10 CSM affected.

Methods: Prospective study. CT of the cervical vertebra column was obtained alongside a calibration phantom. By placing a circular region of interest at the articular process joints, vertebral body, pedicles, and within each rod of the calibration phantom, trabecular BMD was measured in Hounsfield units, which were converted to diphosphate equivalent densities. Trabecular BMD measurements were compared between CSM-affected and control dogs, and between males and females within the control group.

Results: Differences between CSM-affected and control dogs were not significant for the articular processes (mean = –39; P = .37; 95% CI: –102 to 24), vertebral bodies (mean = –62; P = .08; 95% CI: –129 to 6), or pedicles (mean = –36; P = .51; 95% CI: –105 to 33). Differences between female and male were not significant.

Conclusions and Clinical Importance: This study revealed no difference in BMD between control and CSM-affected GDs. Based on our findings no association was detected between cervical OA and BMD in GDs with CSM.

Key words: Cervical spine; Computed tomography; Dog; Osteoarthritis; Wobbler syndrome.

Osseous-associated cervical spondylomyelopathy (CSM) typically occurs in young adult giant breed dogs; with Great Danes (GDs) being most commonly affected.1–4 The prevalence of CSM in GDs presented to North American teaching hospitals is high at 4.2%, but the etiology remains unclear.a The main abnormalities present in osseous-associated CSM include bony malformations and osteoarthritic changes of the cervical vertebral articular process joints, pedicles, and dorsal lamina, resulting in vertebral canal stenosis and spinal cord compression.2–4 It is not known why affected dogs develop osteoarthritis (OA) of their cervical vertebrae. OA in people has a complex pathogenesis resulting from various factors including genetics, obesity, previous injury, abnormal biomechanics, and joint overload.5,6 In studies investigating bone mineral density (BMD) in people, vertebral articular process joint OA is associated with a higher BMD when compared to unaffected vertebral areas.7–16

Bone mineralization can be noninvasively measured, by using dual-energy x-ray absorptiometry, quantitative computed tomography (CT), and peripheral quantitative CT.8,9,11,17,18 CT utilizing calibration phantoms is considered the gold standard for measuring BMD in vivo.13,19,20 Its superior spatial resolution, allows for discrimination between trabecular and cortical bone, facilitating noninvasive BMD measurement.12,20,21 This is especially important in trabecular bone, where measurement changes are more sensitive than in cortical bone.12 Vertebral trabecular bone is nonhomogenous, and each subregion can yield different bone densities because the trabecular space is filled with a mixture of bone, red marrow and yellow fatty marrow.15 Fat in the marrow lowers the attenuation coefficient of the region of interest (ROI).22 In vivo imaging also poses challenges regarding the prevention of and compensation for motion, with image registration serving as a contributor to reproducibility.23 To detect small differences between and within subjects, it is essential that the same volume is analyzed for each ROI. A few studies have evaluated BMD in clinically normal dogs and cats, and dogs with OA of the appendicular skeleton.19,24–26 No data are available on the use of CT to examine BMD in dogs with osseous-associated CSM.

The goal of this study was to compare the trabecular BMD of the cervical vertebrae between clinically

Abbreviations:

BMD bone mineral density
CI confidence interval
CSM cervical spondylomyelopathy
CT computed tomography
GDs Great Danes
HUs Hounsfield units
OA osteoarthritis
ROI region of interest

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normal (control) GDs and GDs with osseous-associated CSM as determined using CT with a calibration phantom. As osseous-associated CSM is a disease characterized in part by OA of the cervical vertebral articular process joints, pedicles, and lamina, we hypothesized that the vertebral trabecular BMD of affected GDs would be higher than that of control GDs.

Materials and Methods

Animals

Twenty-two client-owned GDs were prospectively enrolled between April 2011 and October 2012. The first group was composed of 12 skeletally mature (>1 year of age) clinically normal GDs (control) based on a neurologic examination that did not reveal signs of neurologic disease and no history of neurologic disease. The second group included 10 GDs with clinical signs consistent with CSM and diagnostic confirmation on magnetic resonance imaging. The administration of medication(s) and duration of clinical signs at the time of study enrollment was recorded. All dogs were examined by 2 of the investigators (RCoC and PMV). The investigation was conducted in accordance with the guidelines and approval of The Ohio State University Clinical Research Advisory Committee and the Institutional Animal Care and Use Committee. Written owner consent was obtained before study enrollment.

CT Protocol and Trabecular BMD Evaluation

Noncontrast CT scans of the cervical vertebral column from C2–C3 to C7–T1 were carried out with dogs under sedation using an 8-slice fourth generation helical CT scanner. Each dog was sedated with hydromorphone (0.05–0.1 mg/kg IV) and dexmedetomidine (4–8 mcg/kg IV). Dogs were positioned in sternal recumbency with the head and neck in neutral position. Transverse images were acquired in axial mode with a slice thickness of 2.5 mm and slice alignment perpendicular to the vertebral canal, 120 kV, and automatic mA (min = 100 mA). A calibration phantom containing 5 rods of reference material (Fig 1), each with known water and diphosphate equivalent densities (Table 1) was also scanned alongside and positioned in the dorsal aspect of the cervical region of each dog. The density of the trabecular bone was measured in Hounsfield units (HUs) by a single investigator (JA), who was unaware of the clinical status of the dogs, by using ClearCanvas Workstation software. A circular ROI was placed at the level of the articular process joints, vertebral body, and pedicles at approximately the same position within and between CT scans (Fig 1). HUs were measured for ROIs placed within each rod of the calibration phantom. The ROI area was 1.65 ± 0.02 cm² (mean, SD). Using a previously developed and utilized software, HUs for each ROI placed in the articular processes, vertebral body, and pedicles were converted to diphosphate equivalent densities. Calibrations were completed on a slice-by-slice basis so that the attenuation of each voxel within a given ROI could be converted to a diphosphate equivalent density.

For each vertebra (C3–C7), 3 transverse slices from the CT scan were acquired for placement of ROIs at the desired locations. The most cranial, central, and most caudal slices for each vertebra were selected for analysis. HUs from ROIs placed at the articular process joints were obtained on cranial and caudal slices. Measurements from the vertebral bodies were obtained using all 3 slices (cranially, centrally, and caudally). Pedicle measurements were obtained on central slices. For all ROIs, HUs that exceeded the limits of the trabecular bone calibration phantom (>1,000 HUs) were excluded from analysis, as appropriate diphosphate equivalent densities could not be determined with the software used.

Statistical Analysis

All statistical analysis were selected and performed by a professional biostatistician using commercially available software. A random-effects linear regression model with observations nested within anatomic region, and further nested within dog, was used to analyze differences within neurologically normal GDs, and between the control and CSM-affected GDs at the articular processes, vertebral bodies, and pedicles. All P values were adjusted on individual region contrasts by using the Sidak method to conserve the overall type I error at 0.05 and determine 95% confidence intervals (CI). All results were adjusted for sex and age. For comparisons made between male and female dogs within the control population, results were adjusted for age and anatomic region.

Results

Clinical Data

Of the 12 control GDs, 5 were castrated males, 1 was an intact male, 5 were spayed females, and 1 was an intact female. Control GDs had an overall median age of 2.3 years (range, 1.2–6.3 years). The median age for females in the control group was 2.3 years and for males was 1.9 years. Among the 10 affected dogs, 8 were castrated males, 1 was an intact male, and 1 was a spayed female. The overall median age of affected GDs was 3.9 years (range, 1–7.25 years). The median age for males in the affected group was 4.8 years and

Table 1. Reference rod calibrations (mean, SD).d

| Rod | Water Equivalent Density (mg/cm³) | Diphosphate Equivalent Density (mg/cm³) |
|-----|----------------------------------|----------------------------------------|
| 1   | 1,012.25 ± 2.27                  | −51.83 ± 0.12                          |
| 2   | 1,056.95 ± 1.94                  | −53.40 ± 0.10                          |
| 3   | 1,103.57 ± 1.69                  | 58.88 ± 0.09                           |
| 4   | 1,119.52 ± 1.82                  | 157.05 ± 0.26                          |
| 5   | 923.20 ± 2.12                    | 375.83 ± 0.86                          |

Fig 1. Cranial, central, and caudal computed tomography slices from C5 and the calibrating phantom demonstrating the location of the selected regions of interest (circles) that were used to calculate diphosphate equivalent densities. Filtered for bone, 120 kV and automatic mA (min = 100 mA).
the only female was 3 years old. The median duration of clinical signs compatible with CSM before enrollment was 25.2 months (range, 0–53 months). At the time of study enrollment, 6 of the 10 CSM-affected GDs enrolled were receiving corticosteroids, 2 of the affected GDs were receiving nonsteroidal anti-inflammatory drugs, and 2 affected dogs were not receiving any medication. Of the 6 GDs receiving corticosteroids, 5 were receiving prednisone, ranging from 0.34 mg/kg every third day to 0.3 mg/kg every 12 hours, and 1 was receiving dexamethasone at a dose of 0.06 mg/kg every 24 hours. None of the 12 control GDs were receiving medication at the time of study enrollment. Magnetic resonance imaging confirmed the presence of osseous-associated CSM in all affected dogs, with lateral and dorsolateral spinal cord compression secondary to OA involving the articular process joints and pedicles present in all dogs. Eight of the 10 CSM-affected GDs had multiple sites of spinal cord compression (ranging from 2 to 4 compressive sites). All of the most severe compressive lesions were located in the caudal cervical region (C4–5, C5–6, and C6–7).

**Trabecular BMD Results**

Across the 22 CT scans, the ROI size for the articular process joints was 0.05 ± 0.022 cm² (mean, SD), for the vertebral bodies 0.05 ± 0.002 cm², and for the pedicles 0.044 ± 0.011 cm². The most cranial, central, and most caudal slices for each vertebra on the transverse plane images were analyzed for all dogs. In 1 affected dog, approximately one third of slices had to be excluded because of artifacts. All other data for this dog were retained and statistical analysis was adjusted accordingly.

The diphosphate equivalent density for the articular process joints for the 12 control GDs was 359 ± 121 (mean, SD), for the vertebral bodies 345 ± 133, and for the pedicles 260 ± 89. Within the control GDs,
Diphosphate equivalent densities were 342 ± 121 for males, and 335 ± 127 for females, but this comparison revealed no statistically significant differences once adjusted for age and region using a random-effects linear regression model (mean = −16.4; P = .55; 95% CI: −70 to 7.3).

Diphosphate equivalent densities for CSM-affected GDs measured 323 ± 114 for the articular process joints, 285 ± 122 for the vertebral body, and 227 ± 82 for the pedicles. Overall, diphosphate equivalent densities, at the 3 locations studied, yielded no statistically significant differences between normal and diseased groups at any of the locations (Figs 2, 3): articular process joints, 285 times 10^6; vertebral bodies (mean = −62; P = .08; 95% CI: −129 to 6), and pedicles (mean = −36; P = .51; 95% CI: −105 to 33).

Discussion

In this study, we used for the first time CT to measure the trabecular BMD of the cervical vertebral articular process joints, vertebral bodies, and pedicles in clinically normal GDs and GDs with osseous-associated CSM. We did not detect statistically significant differences in trabecular BMD between clinically normal and CSM-affected GDs at any of the 3 locations investigated (articular process joints, vertebral bodies, and pedicles). In addition, BMD in male and female control dogs was not statistically significant.

Bony malformations and osteoarthritic changes of the articular process joints, pedicles, and dorsal lamina are common in dogs with osseous-associated CSM.1–3,27,28 In our study, magnetic resonance imaging confirmed the presence of osseous-associated CSM in all affected dogs, with lateral and dorsolateral spinal cord compression secondary to OA involving the articular process joints, pedicles, or both, present in all dogs. In general, the presence of joint OA has been associated with an increased BMD in both human and veterinary studies.9,11,25,29 Bone mineral densities in dogs with femoral head OA were 6–8% higher in subchondral bone and 10% higher in non-subchondral bone when compared to BMD of unaffected dogs.25 On the contrary, the results of our study showed lower BMD values in CSM-affected GDs with osteoarthritic changes of the cervical vertebrae when compared to control GDs. The use of oral corticosteroids as part of the medical management for 6/10 of the CSM-affected GDs could have had an effect on the BMD results obtained from this group of dogs. In people, the use of oral corticosteroids can cause bone mass and BMD loss, especially of trabecular bone, and can induce osteoporosis.30–32 A dose of 5 mg/day and long-term (at least 3 months) use of corticosteroids appear to increase the risk of corticosteroid-induced osteoporosis in people.30 Similarly, trabecular BMD in the vertebral body of the second lumbar vertebra in clinically normal dogs administered 30 days of prednisone at a dose of 2 mg/kg every 24 hours is reduced.26 Six of 10 CSM-affected GDs enrolled in this study were receiving corticosteroids at the time of enrollment. The doses of prednisone used in the CSM-affected GDs in this study were lower than 2 mg/kg in all cases, but they had been administered for over 3 months in most of the dogs. Therefore, it is possible that the medical therapies received by the dogs enrolled in this study might have influenced the findings for measured BMD. It is not uncommon for dogs with presumptive CSM to be administered corticosteroids before they are referred to a specialty practice. Six of 10 CSM-affected GDs enrolled in this study had been administered corticosteroid treatment before referral to our practice. While the authors acknowledge this fact as a limitation of the study, this also reflects common practice, and it is an inherent problem of studies based on referral populations.

The relatively small sample size is another limitation of this study that might have caused a type II error. This is reflected by the large confidence intervals about the mean differences.

In the human cervical vertebral column, the average BMD varies significantly by level such that C3 and C6 BMD is significantly less than C4 and C5, and C7 BMD is significantly less than all other levels.33 Pedicles have been described as having significantly higher BMD than all other anatomic locations investigated and it has also been described that cervical vertebral body BMD is highest at C5 and decreases in the direction of C3 and C7.13,33 In people, anatomic differences in BMD can be explained by the fact that individual vertebrae are subjected to different in vivo loads; such that in areas where loading is highest, bone density would also be highest in accordance with Wolff’s Law.33 Anatomic variations in trabecular BMD values have also been described in the thoracolumbar spine of normal cats.19 In human studies, part of this variation has been attributed to the shape and overall volume of bone sampled, such that BMD measures within hypertrophied or abnormally shaped bone may result in the final measurement of a lower BMD.35

With regard to changes in BMD as a function of sex, no significant differences were identified in the control group, noting the low statistical power of that aspect of our study. This was not evaluated in the CSM-affected GDs because only 1 of the 10 affected GDs was a female dog.

No significant differences in diphosphate equivalent densities and BMD were detected between CSM-affected and control GDs at the articular processes (mean = −39; P = .37; 95% CI: −102 to 24), vertebral bodies (mean = −62; P = .08; 95% CI: −129 to 6), and pedicles (mean = −36; P = .51; 95% CI: −105 to 33). The use of corticosteroids in the affected dogs before referral may have interfered with our results. Our study reports the use of CT to measure BMD in dogs with osseous-associated CSM. Further studies of the cervical vertebral column BMD using other methods such as dual-energy X-ray absorptiometry, and evaluating the presence of potential mediators of OA would be warranted to further elucidate the pathogenesis of osseous-associated CSM.

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Footnotes

a Veterinary Medical Database survey – 2010 – http://www.vmdb.org/vmdb.html
b GE Lightspeed Ultra 8-slice; GE Healthcare, Waukesha, WI
c Dexdomitor; Pfizer Animal Health, New York, NY
d Model 3 CT; Mindways Software, San Francisco, CA
e ClearCanvas Inc, Toronto, ON
f Stata, version 12.1; Stata Corporation, College Station, TX

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Conflict of Interest Declaration: The authors disclose no conflict of interest.

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