Identification of Areas of Epiphyseal Cartilage Necrosis at Predilection Sites of Juvenile Osteochondritis Dissecans in Pediatric Cadavers

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Background: The pathogenesis of human juvenile osteochondritis dissecans (JOCD) remains poorly understood, with multiple factors implicated, including ischemia, repetitive trauma, and genetic predisposition. Similarities in the predilection site and the diagnostic and clinical features of JOCD to the well-characterized veterinary counterpart, osteochondrosis dissecans, suggest that, similar to the animal disease, the pathogenesis JOCD may also be initiated in the first few years of life, when disruption of blood supply to the epiphyseal growth cartilage leads to failure of endochondral ossification. To gather data in support of the hypothesis that JOCD and osteochondrosis dissecans have a shared pathogenesis, biopsy specimens obtained from predilection sites of JOCD in juvenile human cadavers were histologically examined to determine whether they contained lesions similar to those found in animals diagnosed with subclinical osteochondrosis dissecans.

Methods: In this descriptive laboratory study, 59 biopsy specimens (6 mm in diameter) were harvested from the central aspect (i.e., the notch side) of the femoral condyles of 26 human cadavers (1 month to 11 years old). Specimens were histologically evaluated for the presence of areas of cartilage necrosis and the morphology of cartilage canal blood vessels.

Results: Locally extensive areas of necrotic epiphyseal cartilage were identified in 4 specimens obtained from 3 donors (ages 2 to 4 years). Areas of cartilage necrosis accompanied by focal failure of endochondral ossification or surrounded by subchondral bone were identified in biopsy specimens from 4 donors (ages 4 to 9 years).

Conclusions: The identification of epiphyseal cartilage necrosis identical to that described in animals with subclinical osteochondrosis, found in biopsy specimens obtained from femoral predilection sites of JOCD in pediatric cadavers, suggests a shared pathogenesis of JOCD in humans and osteochondrosis dissecans in animals.

Clinical Relevance: These findings imply that the pathogenesis of human JOCD likely starts 5 to 10 years prior to the development of clinical symptoms. Enhanced understanding of the temporal features of JOCD pathogenesis provides an opportunity for earlier diagnosis and treatment, likely resulting in improved outcomes for this condition in the future.

Juvenile osteochondritis dissecans (JOCD) is an orthopaedic developmental disease that affects children and adolescents and may result in secondary osteoarthritis¹. JOCD is characterized by the development of osteochondral lesions at joint-specific predilection sites, most often involving the medial femoral condyle of the femur². The pathogenesis of JOCD remains poorly understood, even 130 years after the disease was originally described³. Multiple factors, including ischemia, repetitive trauma, and genetic predisposition, have been implicated in

the etiology of the disease^{2,4,5}. Evaluation of patients with clinically apparent disease has led to the assumption by many that JOCD is an acquired lesion of the subchondral bone that is characterized by degrees of osseous resorption, collapse, and sequestrum formation^{2,6}.

Conversely, a nearly identical disease, osteochondrosis dissecans, has been documented in multiple animal species and is known to have origins in epiphyseal cartilage (i.e., immature joint cartilage located beneath the articular cartilage at the ends

Disclosure: The study received NIH grant funding (K01OD021293 and R01AR070020). The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (<http://links.lww.com/JBJS/E977>).

TABLE I Histological Findings*

Age Range	No. of Specimens	Normal Cartilage Canals†	Chondrifying Cartilage Canals†	Necrotic Cartilage Canals†	Chondro-Osseous Junction†	OCL†	OCM†
1-4 mo (n = 7)	21	21 (100%)	8 (38%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)
2-4 yr (n = 10)	19	14 (74%)	8 (42%)	8 (42%)	5 (26%)	4 (21%)	4 (21%)
5-7 yr (n = 3)	5	1 (20%)	1 (20%)	1 (20%)	3 (60%)	0 (0%)	0 (0%)
9-11 yr (n = 6)	14	0 (0%)	0 (0%)	1 (7%)	14 (100%)	0 (0%)	2 (14%)
Total	59	36 (61%)	17 (27%)	12 (20%)	22 (37%)	4 (7%)	6 (10%)

*No donors were between the ages of 4 months and 2 years or between 7 years and 9 years. OCM = osteochondrosis manifesta, and OCL = osteochondrosis latens. †Data are presented as the number of specimens with the finding, with the percentage of specimens in the age group in parentheses.

of growing long bones)⁷⁻⁹. Early (preclinical) lesions of osteochondrosis dissecans have been extensively characterized by histological examination of specimens harvested from predilection sites in young animals before the age at which clinically apparent disease develops⁹⁻¹². These sentinel studies have revealed that (1) failure of the cartilage canal vasculature that provides blood supply to the epiphyseal cartilage in growing animals leads to ischemic cartilage necrosis in discrete areas that are termed osteochondrosis latens; (2) as the ossification front advances, progression of the front may be delayed by osteochondrosis latens lesions, creating a radiographically apparent, irregular chondro-osseous junction that is termed osteochondrosis manifesta; and (3) these osteochondrosis manifesta lesions may either undergo healing by incorporation into the underlying subchondral bone or become separated from the parent bone to develop into clinically apparent osteochondrosis dissecans^{8,13}.

Because of the nearly identical clinical features, predilection sites, and morphology (i.e., gross appearance and imaging features) of JOCD in humans and osteochondrosis dissecans in

animals, these conditions have long been hypothesized to have a shared etiology and pathogenesis^{8,13-15}. This hypothesis has recently been strengthened by a study that employed magnetic resonance imaging (MRI) in children and adolescents with JOCD and described the existence of the early, cartilaginous form of JOCD, which is closely similar to osteochondrosis manifesta in animals¹⁴.

The purpose of the present study was to evaluate pediatric human femoral condylar specimens to determine if these tissues contained histological changes similar to those found in animals afflicted with subclinical osteochondrosis dissecans. Biopsies from the central aspect (i.e., notch side) of the femoral condyles were selected for evaluation because these sites are known to be the primary predilection sites of JOCD, with 61.7% of all JOCD involving the distal aspect of the femur¹⁶. Conversely, ankle, elbow, shoulder, and foot lesions only account for 25.4%, 12.0%, 0.6%, and 0.3% of all lesions, respectively. We hypothesized that histological evaluation of biopsy specimens obtained from predilection sites of

Fig. 1
Figs. 1-A, 1-B, and 1-C Histological photograph with hematoxylin and eosin staining showing cartilage canals (Link to [hematoxylin and eosin](#) whole slide image). **Fig. 1-A**. Normal cartilage canal containing an arteriole (arrow) and a venule lined with endothelial cells (arrowheads); adjacent chondrocytes are viable. **Fig. 1-B** Necrotic cartilage canal devoid of endothelial cell lining and surrounded by necrotic chondrocytes. **Fig. 1-C** Chondrifying cartilage canal characterized by partial filling of lumen with chondrocytes (arrowheads).

Fig. 2
Histological photograph with hematoxylin and eosin staining showing articular-epiphyseal cartilage complex from the central aspect (i.e., the notch side) of the medial femoral condyle from a 4-year-old female donor containing an osteochondrosis latens lesion. Left image: Well-demarcated area of cartilage necrosis (arrowheads) within epiphyseal cartilage, adjacent to a cartilage canal containing multiple degenerate vessels, none of which contains erythrocytes. The clefts in the superficial articular cartilage are artifactual. Upper inset (within rectangle, rotated 90° counterclockwise): High-magnification image of cartilage canal containing multiple degenerate vessels. Lower inset (within rectangle, rotated 90° counterclockwise): Dotted line indicates transition from viable (right of the dotted line) to necrotic (left of the dotted line) chondrocytes, some of which have expanded lacunae (arrows) and are surrounded by basophilic matrix.

JOCD—specifically, femoral condyles—in juvenile human cadavers would reveal lesions that are similar to those found in animals diagnosed with subclinical osteochondrosis dissecans. Until very recently, however, these histological studies could not be accomplished because of the lack of availability of human cadaveric joint specimens harvested from skeletally immature donors.

Materials and Methods

Core biopsy specimens (6 mm in diameter and 10 to 20 mm deep) were collected by 1 of the authors (M.A.T.) from the central aspect of the medial and lateral femoral condyles of 26 pediatric cadavers (16 male, 10 female; AlloSource) with use of an osteoarticular transfer system to ensure repeatability across the specimens. The biopsies included the articular cartilage and the subjacent epiphyseal cartilage, with or without subchondral bone, depending on the age of the donor. At the time of death, the donors ranged in age from 1 month to 11 years (mean $\pm$ standard deviation [SD], 4.17 ± 3.67 years) (Table I). No donors were between the ages of 4 months and 2 years or between 7 years and 9 years. The most common cause of death among the donors was sudden, accidental death, and none were reported to have previously experienced symptoms of orthopaedic disease.

Specimens were collected bilaterally from both the lateral and medial condyles in 5 of 26 cadavers, from only the medial

femoral condyle either unilaterally (4 cadavers) or bilaterally (9 cadavers), unilaterally from both the lateral and medial condyles in 7 cadavers, and from 1 lateral and both medial condyles in 1 cadaver. This collection provided 59 core biopsy specimens for histological evaluation.

Immediately after harvest, the 59 core biopsy specimens were fixed in 10% neutral buffered formalin for 48 hours. The fixed specimens were decalcified in 10% EDTA (ethylenediaminetetraacetic acid) and split longitudinally, creating 2 half cylinders. Specimens were routinely processed and both halves of each sample were embedded in paraffin. Five- μ m-thick histological sections were cut from the surface of both halves, yielding 2 sections per specimen, and stained with hematoxylin and eosin. Serial sections from sites containing osteochondrosis latens or manifesta lesions were stained with toluidine blue and safranin O. Each section was examined by a board-certified veterinary pathologist, who was blinded to the clinical information for each specimen, with use of light microscopy to characterize the appearance of the following, if present: cartilage canals (Fig. 1 [Link to [hematoxylin and eosin](#) whole slide image]), chondro-osseous junction, and articular and epiphyseal chondrocytes and matrix (Table I). Cartilage canals that lacked distinct vascular spaces and that were filled with chondrocytes and cartilage matrix were considered to be chondrifying. Conversely, necrotic cartilage canals either lacked an endothelial lining or were lined with necrotic

Fig. 3
Histological photograph with toluidine blue staining showing articular-epiphyseal cartilage complex from the central aspect (i.e., the notch side) of the medial femoral condyle from a 2-year-old male donor containing an osteochondrosis latens lesion. Cartilage necrosis is characterized by the presence of vacuolated chondrocytes/empty lacunae accompanied by decreased staining of the extracellular matrix and is apparent in the left side of the image. In the right of the image, the presence of chondrocyte clones (white arrows), along with increased staining of the surrounding extracellular matrix, is consistent with an ongoing reparative process.

endothelial cells and had cystic interiors¹⁰. Failure of endochondral ossification was defined as a focal delay in the progression of the ossification front at the chondro-osseous junction. Cartilage necrosis was defined as the combined presence of shrunken, necrotic chondrocytes (characterized by pyknotic nuclei and cystic expansion of chondrocyte lacunae) and altered staining of the surrounding extracellular matrix (loss of staining in safranin O and toluidine blue-stained sections).

Results

Articular and epiphyseal cartilage was present in all sections. The percentage of sections that included the chondro-osseous junction increased with age, from 0% in the 1 to 4-month range to 100% in the 9 to 11-year range, reflecting the reduction in thickness of epiphyseal cartilage with age (Table I). Normal cartilage canals containing multiple vessels lined by endothelium were present in the epiphyseal cartilage in specimens obtained from all sections from donors ≤ 4 months old, but were only present in 74% of sections from donors between 2 and 4 years old and were not present in any sections from donors > 5 years old. Chondrifying cartilage canals, which represent physiological regression of cartilage canals, were identified in sections from donors as young as 1 month old and were present in 40% of the specimens from donors between 1 month

and 4 years old. Chondrifying cartilage canals were absent in children > 5 years old. Necrotic cartilage canals were observed in sections from donors as young as 4 months old and were present in 42% of sections from donors between 2 and 4 years old, after which age this percentage diminished.

An area of epiphyseal cartilage necrosis (Figs. 2 and 3), having features identical to those of osteochondrosis latens in animals, was identified in a medial femoral condyle sample from a 2-year-old male donor (the only site available for study from this individual) and in a lateral femoral condyle sample from a 4-year-old female donor (contralateral limb was unavailable for examination), as well as bilaterally in the medial femoral condyles of another 4-year-old female donor. One of the medial femoral condyles of the latter 4-year-old female donor contained 2 distinct osteochondrosis latens lesions. In 3 of the 4 sites, osteochondrosis latens lesions were located immediately adjacent to a degenerating cartilage canal vessel.

Lesions of cartilage necrosis accompanied by focal failure of endochondral ossification (Fig. 4 [Link to [hematoxylin and eosin](#) whole slide image]), termed osteochondrosis manifesta in animals, were identified in specimens from a 4-year-old male donor, a 9-year-old male donor, and in the same specimens that were obtained from the two 4-year-old female donors that also included the osteochondrosis latens lesions described above (i.e., osteochondrosis latens and manifesta lesions were concurrently present in 1 of the femoral condyles of both of these 4-year-old female subjects). Specifically, 1 of the 4-year-old female donors had 3 separate osteochondrosis manifesta lesions: 1 in the medial femoral condyle and 2 in the lateral femoral condyle; the contralateral femur was not examined. Two of these lesions were incorporated into the subchondral bone, consistent with healing (Fig. 5 [Link to [hematoxylin and eosin](#) whole slide image]). The other 4-year-old female donor and the 4-year-old male donor both had a single, unilateral osteochondrosis manifesta lesion involving 1 medial femoral condyle. Finally, 4 osteochondrosis manifesta lesions were observed in a 9-year-old male donor, 2 in each condyle; the contralateral femur was not examined. One of these 4 lesions was incorporated into the subchondral bone, consistent with healing.

Discussion

Well-demarcated areas of necrotic epiphyseal cartilage were identified in distal femoral specimens from skeletally immature human cadavers and were closely similar in appearance and location to osteochondrosis latens and manifesta lesions seen in pigs and horses^{11,12,17,18}. To our knowledge, the existence of these areas of epiphyseal cartilage necrosis, often characterized in the present study by cystic expansion of chondrocyte lacunae and pallor of surrounding extracellular matrix in sections stained with safranin O and toluidine blue, has not been previously reported in humans. These findings suggest that the etiology of JOCD in humans and osteochondrosis dissecans in pigs and horses may be similar and that precursor lesions to JOCD may be present 5 to 10 years before the onset of symptomatic disease in human subjects.

Fig. 4

Histological photograph with hematoxylin and eosin staining showing articular-epiphyseal cartilage complex and subjacent bone from the central aspect (i.e., the notch side) of the medial femoral condyle from a 9-year-old male donor containing an osteochondrosis manifesta lesion (Link to [hematoxylin and eosin](#) whole slide image). Left image: A well-demarcated area of necrotic epiphyseal cartilage (within rectangle) has resulted in a focal failure of endochondral ossification. Right image: High-magnification image of necrotic epiphyseal cartilage, partially surrounded by bone. The small cleft is artifactual.

In 6 of the 59 biopsy specimens, 1 or more areas of necrotic cartilage were present, either incorporated into the subchondral bone or associated with focal failure of endochondral ossification, which is known in animals as osteochondrosis manifesta. Identical osteochondrosis manifesta lesions in animals are considered to be virtually pathognomonic of preclinical osteochondrosis dissecans. We believe that the observation of these areas of focal failure of endochondral ossification seen in the human cadaveric specimens supports the hypothesis that early changes involving the epiphyseal growth cartilage during the pathogenesis of JOCD eventually lead to a disturbance in endochondral ossification. Indeed, alterations to endochondral ossification have been reported in skeletally immature human subjects undergoing

MRI for JOCD^{19,22} and were considered either JOCD or “ossification variants.” Ossification variants were described as lacking bone edema, being restricted to the posterior aspect of the femoral condyle, being free of an intercondylar extension, and being present in sites in which >30% of the epiphyseal growth cartilage remained¹⁹. Regrettably, in these studies, it was not determined whether alterations to endochondral ossification were associated with epiphyseal cartilage necrosis because this would have required obtaining osteochondral specimens for histological evaluation from children with asymptomatic joints. With the recent development of MRI techniques that are capable of *in vivo* imaging of the cartilage canal vasculature^{23,24} and identifying areas of necrotic epiphyseal cartilage^{25,26}, this question can be addressed noninvasively.

Fig. 5
Histological photograph, hematoxylin and eosin staining showing articular-epiphyseal cartilage complex and subadjacent bone from the central aspect (i.e., the notch side) of the lateral femoral condyle of a 4-year-old female donor containing a healing osteochondrosis manifesta lesion (Link to [hematoxylin and eosin](#) whole slide image). Left image: Area of necrotic cartilage surrounded by epiphyseal bone (within rectangle). A degenerate cartilage canal is present within the epiphyseal cartilage (arrow). Right image: High-magnification image of necrotic cartilage surrounded by bone.

Several histological studies have evaluated osteocartilaginous specimens harvested from patients during the surgical repair of clinically apparent JOCD^{6,27-30}. Evaluation of cylindrical osteochondral plugs harvested from these patients in some cases has led to the conclusion that the initial lesion during the pathogenesis of (J)OCD involves the subchondral bone^{6,27}. In other studies, however, Barrie reported that >50% of the loose bodies removed from patients were purely cartilaginous and were composed of hypertrophied cartilage^{29,31}. The histological appearance of these lesions led Barrie to suggest that cartilage hypertrophy was secondary to retardation of the ossification front and that these finding antedated the separation of the loose body^{29,32}. In fact, cartilage hypertrophy is commonly seen in association with osteochondrosis dissecans in animals and occurs as a reaction of adjacent viable cartilage to the area of necrosis¹³. These early findings are corroborated by recent works that describe purely cartilaginous JOCD lesions as having no²⁸ or infrequent³⁰ bone necrosis. These latter histological studies and recent MRI findings^{14,22}, along with the results of the present study, provide ample support for the theory that the patho-

genesis of JOCD primarily involves the epiphyseal growth cartilage and not the subchondral bone.

The relatively high prevalence of epiphyseal cartilage necrosis in the specimens included in this study compared with the low rate of knee JOCD that has previously been reported (9.5 out of 100,000) can be explained by the high propensity for subclinical osteochondrosis latens and osteochondrosis manifesta lesions to heal as demonstrated in animals³³. Subclinical osteochondrosis latens lesions are known to be present in nearly 100% of young piglets, but only a small fraction of these lesions develop into clinically apparent disease¹². The presence of areas of necrotic cartilage surrounded by bone in 3 of the biopsy specimens in the present study indicates that a similar healing process also occurs in humans. This capacity for subclinical osteochondrosis lesions to heal, however, should not result in the dismissal of their role in the pathogenesis of JOCD, as the progression of individual osteochondrosis manifesta lesions to clinically apparent osteochondrosis dissecans has been conclusively demonstrated with use of sequential computed tomography imaging in pigs³⁴. The role of various factors predisposing to development of clinically apparent disease,

including the size and location of the subclinical lesion and the exposure it has to (repetitive) biomechanical trauma, should be investigated.

Another factor that makes associating epiphyseal cartilage necrosis with JOCD difficult is the presence of epiphyseal cartilage necrosis in human specimens obtained from subjects as young as 2 years old, whereas the majority of patients with clinically apparent JOCD are between 12 and 19 years of age³³. Identification of these presumed precursor lesions of JOCD in the predilection sites of the femoral condyles at a very young age, however, can be explained by the early regression of vascular supply to the epiphyseal cartilage in this site. This regression of vascular supply has been documented by studies utilizing MRI in cadaveric pediatric human knee specimens and has also been well documented in growing pigs^{9,24}. Indeed, a large number of subclinical lesions were observed in 12-week-old pigs¹², an age that is not dissimilar developmentally to a 2-year-old child, considering the much faster maturation of pigs compared with humans.

The weaknesses of our study include the relatively low number of specimens, the uneven age distribution, and the comparatively small size (6 mm in diameter) of the specimens available for histological evaluation. Unfortunately, access to any human pediatric tissues, including joints, is exceptionally rare. We attempted to address the inability to evaluate the entire distal femoral epiphysis by harvesting biopsy specimens from known predilection sites of JOCD. The small size of the biopsy specimens also interfered with our ability to accurately measure the size of the lesions, because lesions often extended an unknown distance beyond the margins of the biopsy specimens. Regardless, we believe that the size of the majority of lesions were rather small, likely <5 mm in diameter.

Although our study conclusively proves that islands of necrotic epiphyseal cartilage are occasionally present at the central aspect (i.e., the notch side) of the distal femoral condyles harvested from pediatric cadavers, it is not possible to determine whether or not healing, as opposed to progression to JOCD, would have occurred in these cases. Ongoing, longitudinal studies that utilize novel MRI sequences capable of identifying islands of ischemic cartilage necrosis in vivo, and that are able to monitor the progress of these lesions toward either healing or JOCD, will provide conclusive proof whether these islands of necrotic cartilage are truly precursors to JOCD in humans. If future studies are successful in the ways described above, it would be logical to use the terms osteochondrosis latens and osteochondrosis manifesta when referring to pre-clinical/occult lesions of JOCD of the knee. Extending the findings of the present study to other known predilection sites of JOCD, such as the medial and lateral talar ridges or the

capitellum of the humerus, will require histological evaluation of cadaveric specimens obtained from these regions.

In summary, areas of epiphyseal cartilage necrosis with or without failure of endochondral ossification were present in multiple biopsy specimens obtained from the femoral predilection sites of JOCD in pediatric human cadavers. These changes are histologically identical to subclinical osteochondrosis latens and osteochondrosis manifesta lesions that are described in animals, which are known to be precursors of osteochondrosis dissecans. Awareness of the existence of these purported precursor lesions of JOCD in human subjects, 5 to 10 years prior to the onset of clinical symptoms, will provide an opportunity to develop novel diagnostic and treatment methods that will impact the clinical management of this condition in humans. ■

Note: The human cadavers were donated by AlloSource; the authors thank Lisa Houck, Todd Huft, Peter Stevens, and Tom Cycota for their help acquiring these cadavers. The authors thank the families, who have made the gift of cadavers to allow the completion of this research. The authors also thank Lindsey Harper, Paula Overn, and William Fedje-Johnston for their help with specimen processing.

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References

- Adachi N, Deie M, Nakamae A, Okuhara A, Kamei G, Ochi M. Functional and radiographic outcomes of unstable juvenile osteochondritis dissecans of the knee treated with lesion fixation using bioabsorbable pins. *J Pediatr Orthop*. 2015 Jan;35(1):82-8.
- Edmonds EW, Polousky J. A review of knowledge in osteochondritis dissecans: 123 years of minimal evolution from König to the ROCK study group. *Clin Orthop Relat Res*. 2013 Apr;471(4):1118-26.
- König F. [On loose bodies in the joint]. *Dtsch Z Chir*. 1887;27:90-109. German.
- Cahill BR. Osteochondritis dissecans of the knee: treatment of juvenile and adult forms. *J Am Acad Orthop Surg*. 1995 Jul;3(4):237-47.
- Crawford DC, Safran MR. Osteochondritis dissecans of the knee. *J Am Acad Orthop Surg*. 2006 Feb;14(2):90-100.

6. Uozumi H, Sugita T, Aizawa T, Takahashi A, Ohnuma M, Itoi E. Histologic findings and possible causes of osteochondritis dissecans of the knee. *Am J Sports Med.* 2009 Oct;37(10):2003-8. Epub 2009 Sep 8.
7. Carlson CS, Hilley HD, Meuten DJ. Degeneration of cartilage canal vessels associated with lesions of osteochondrosis in swine. *Vet Pathol.* 1989 Jan;26(1):47-54.
8. McCoy AM, Toth F, Dolvik NI, Ekman S, Ellermann J, Olstad K, Ytrehus B, Carlson CS. Articular osteochondrosis: a comparison of naturally-occurring human and animal disease. *Osteoarthritis Cartilage.* 2013 Nov;21(11):1638-47. Epub 2013 Aug 15.
9. Ytrehus B, Ekman S, Carlson CS, Teige J, Reinholt FP. Focal changes in blood supply during normal epiphyseal growth are central in the pathogenesis of osteochondrosis in pigs. *Bone.* 2004 Dec;35(6):1294-306.
10. Carlson CS, Meuten DJ, Richardson DC. Ischemic necrosis of cartilage in spontaneous and experimental lesions of osteochondrosis. *J Orthop Res.* 1991 May;9(3):317-29.
11. Olstad K, Ytrehus B, Ekman S, Carlson CS, Dolvik NI. Early lesions of articular osteochondrosis in the distal femur of foals. *Vet Pathol.* 2011 Nov;48(6):1165-75. Epub 2011 Feb 14.
12. Tóth F, Torrisson JL, Harper L, Bussières D, Wilson ME, Crenshaw TD, Carlson CS. Osteochondrosis prevalence and severity at 12 and 24 weeks of age in commercial pigs with and without organic-complexed trace mineral supplementation. *J Anim Sci.* 2016 Sep;94(9):3817-25.
13. Olstad K, Ekman S, Carlson CS. An update on the pathogenesis of osteochondrosis. *Vet Pathol.* 2015 Sep;52(5):785-802. Epub 2015 Jun 16.
14. Ellermann J, Johnson CP, Wang L, Macalena JA, Nelson BJ, LaPrade RF. Insights into the epiphyseal cartilage origin and subsequent osseous manifestation of juvenile osteochondritis dissecans with a modified clinical MR imaging protocol: a pilot study. *Radiology.* 2017 Mar;282(3):798-806. Epub 2016 Sep 15.
15. Olsson SE, Reiland S. The nature of osteochondrosis in animals. Summary and conclusions with comparative aspects on osteochondritis dissecans in man. *Acta Radiol Suppl.* 1978;358:299-306.
16. Weiss JM, Nikizad H, Shea KG, Gyurdzhyan S, Jacobs JC, Cannamela PC, Kessler JI. The incidence of surgery in osteochondritis dissecans in children and adolescents. *Orthop J Sports Med.* 2016 Mar 16;4(3):2325967116635515.
17. Ytrehus B, Carlson CS, Lundeheim N, Mathisen L, Reinholt FP, Teige J, Ekman S. Vascularisation and osteochondrosis of the epiphyseal growth cartilage of the distal femur in pigs—development with age, growth rate, weight and joint shape. *Bone.* 2004 Mar;34(3):454-65.
18. Ytrehus B, Grindflek E, Teige J, Stubbsøen E, Grøndalen T, Carlson CS, Ekman S. The effect of parentage on the prevalence, severity and location of lesions of osteochondrosis in swine. *J Vet Med A Physiol Pathol Clin Med.* 2004 May;51(4):188-95.
19. Jans L, Jaremko J, Ditchfield M, De Coninck T, Huysse W, Moon A, Verstraete K. Ossification variants of the femoral condyles are not associated with osteochondritis dissecans. *Eur J Radiol.* 2012 Nov;81(11):3384-9. Epub 2012 Jan 31.
20. Jans LB, Jaremko JL, Ditchfield M, Huysse WC, Verstraete KL. MRI differentiates femoral condylar ossification evolution from osteochondritis dissecans. A new sign. *Eur Radiol.* 2011 Jun;21(6):1170-9. Epub 2011 Jan 26.
21. Jans LB, Jaremko JL, Ditchfield M, Verstraete KL. Evolution of femoral condylar ossification at MR imaging: frequency and patient age distribution. *Radiology.* 2011 Mar;258(3):880-8. Epub 2010 Dec 21.
22. Laor T, Zbojniewicz AM, Eismann EA, Wall EJ. Juvenile osteochondritis dissecans: is it a growth disturbance of the secondary physis of the epiphysis? *AJR Am J Roentgenol.* 2012 Nov;199(5):1121-8.
23. Nissi MJ, Tóth F, Zhang J, Schmitter S, Benson M, Carlson CS, Ellermann JM. Susceptibility weighted imaging of cartilage canals in porcine epiphyseal growth cartilage ex vivo and in vivo. *Magn Reson Med.* 2014 Jun;71(6):2197-205. Epub 2013 Jul 15.
24. Tóth F, Nissi MJ, Ellermann JM, Wang L, Shea KG, Polousky J, Carlson CS. Novel application of magnetic resonance imaging demonstrates characteristic differences in vasculature at predilection sites of osteochondritis dissecans. *Am J Sports Med.* 2015 Oct;43(10):2522-7. Epub 2015 Aug 18.
25. Tóth F, Nissi MJ, Wang L, Ellermann JM, Carlson CS. Surgical induction, histological evaluation, and MRI identification of cartilage necrosis in the distal femur in goats to model early lesions of osteochondrosis. *Osteoarthritis Cartilage.* 2015 Feb;23(2):300-7. Epub 2014 Nov 15.
26. Wang L, Nissi MJ, Tóth F, Shaver J, Johnson CP, Zhang J, Garwood M, Carlson CS, Ellermann JM. Multiparametric MRI of epiphyseal cartilage necrosis (osteochondrosis) with histological validation in a goat model. *PLoS One.* 2015 Oct 16;10(10):e0140400.
27. Koch S, Kampen WU, Laprell H. Cartilage and bone morphology in osteochondritis dissecans. *Knee Surg Sports Traumatol Arthrosc.* 1997;5(1):42-5.
28. Yonetani Y, Nakamura N, Natsuume T, Shiozaki Y, Tanaka Y, Horibe S. Histological evaluation of juvenile osteochondritis dissecans of the knee: a case series. *Knee Surg Sports Traumatol Arthrosc.* 2010 Jun;18(6):723-30. Epub 2009 Sep 4.
29. Barrie HJ. Hypertrophy and laminar calcification of cartilage in loose bodies as probable evidence of an ossification abnormality. *J Pathol.* 1980 Oct;132(2):161-8.
30. Zbojniewicz AM, Stringer KF, Laor T, Wall EJ. Juvenile osteochondritis dissecans: correlation between histopathology and MRI. *AJR Am J Roentgenol.* 2015 Jul;205(1):W114-23.
31. Barrie HJ. Intra-articular loose bodies regarded as organ cultures in vivo. *J Pathol.* 1978 Jul;125(3):163-9.
32. Barrie HJ. Osteochondritis dissecans 1887-1987. A centennial look at König's memorable phrase. *J Bone Joint Surg Br.* 1987 Nov;69(5):693-5.
33. Kessler JI, Nikizad H, Shea KG, Jacobs JC Jr, Bebchuk JD, Weiss JM. The demographics and epidemiology of osteochondritis dissecans of the knee in children and adolescents. *Am J Sports Med.* 2014 Feb;42(2):320-6. Epub 2013 Nov 22.
34. Olstad K, Kongsro J, Grindflek E, Dolvik NI. Ossification defects detected in CT scans represent early osteochondrosis in the distal femur of piglets. *J Orthop Res.* 2014 Aug;32(8):1014-23. Epub 2014 Apr 17.