

Canine Hip Dysplasia: A Natural Animal Model for Human Developmental Dysplasia of the Hip

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ABSTRACT: Developmental dysplasia of the hip (DDH) in humans is a common condition that is associated with hip pain, functional limitations, and secondary osteoarthritis (OA). Surgical treatment of DDH has improved in the last decade, allowing excellent outcomes at short- and mid-term follow-up. Still, the etiology, mechanobiology, and pathology underlying this disease are not well understood. A pre-clinical animal model of DDH could help advance the field with a deeper understanding of specific pathways that initiate hip joint degeneration secondary to abnormal biomechanics. An animal model would also facilitate different interventional treatments that could be tested in a rigorous and controlled environment. The dog model exhibits several important characteristics that make it valuable as a pre-clinical animal model for human DDH. Dogs are naturally prone to develop canine hip dysplasia (CHD), which is treated in a similar manner as in humans. Comparable to human DDH, CHD is considered a pre-OA disease; if left untreated it will progress to OA. However, progression to OA is significantly faster in dogs than humans, with progression to OA within 1–2 years of age, associated with their shorter life span compared to humans. Animal studies could potentially reveal the underlying biochemical pathway(s), which can inform refined treatment modalities and provide opportunities for new treatment and prevention targets. Herein, we review the similarities and differences between the two species and outline the argument supporting CHD as an appropriate pre-clinical model of human DDH. © 2017 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. *J Orthop Res*

Keywords: human hip dysplasia; canine hip dysplasia; pre-clinical animal model; osteoarthritis; mechanobiology

Developmental dysplasia of the hip (DDH) is a common condition that is associated with hip pain, functional limitations, and secondary osteoarthritis (OA). DDH and femoroacetabular impingement (FAI) are considered pre-osteoarthritic diseases. These two entities are the most common causes of secondary OA in the hip in young patients.¹ Cam-type FAI is characterized by excess bone formation at the anterolateral head–neck junction creating a nonspherical femoral head. The Cam deformity is forced into the acetabulum during flexion and internal rotation of the hip, leading to intra-articular damage such as acetabular labrum tears and cartilage delamination, which lead to hip OA.¹ On the other hand, DDH is associated with insufficient femoral head coverage and potentially, focal mechanical overload of the acetabular rim. Under these pathomechanical conditions, the acetabular rim complex undergoes a hip joint-specific degenerative OA cascade described as the “acetabular rim syndrome.”² DDH has been found in an estimated 20–40% of secondary OA cases and increases a patient’s risk for OA by 4.3-fold.^{1,3,4} Clinical and radiographic evaluations as well as surgical treatments for DDH

are well established. Current surgical treatments of DDH have improved in the last decade, allowing excellent outcomes at short- and mid-term follow-up.^{5,6} Still, both the mechanobiology and pathology underlying this disease are underinvestigated.^{7–9} In addition, there remains a proportion of patients that do not significantly improve clinically after a restorative surgical procedure, and patients who do not respond over short to mid-term and have a persistent risk for disease progression over long time periods.^{7,8,10} Improvement in understanding of the pathomechanics, pathophysiology, and predictors of treatment failure in DDH is essential to the development of future therapeutics to advance patient care.

Animal models have considerable importance for elucidating mechanisms underlying joint damage and as translational models for the development of new treatments. In addition, the responses to different surgical interventions and approaches can be rigorously tested in animals. Ideally, an animal model should be natural occurring and in a species where clinical and functional outcomes can be correlated with microscopic and histological changes.^{11,12} Several pre-clinical animal models of hip dysplasia have been proposed in various species such as chicken, mouse, rat, rabbit, and dog.^{13–16} Most of these models, however, do not transpire spontaneously and require an initiating intervention or surgery. In rats, for example, generation of a dysplastic hip has been achieved by immobilizing the hind limb in extension immediately after birth for a total of 10 days. Morphological changes can be observed

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as soon as 2 weeks with progressive joint degeneration around 4 weeks. Although this model has an economic advantage, there are several limitations in comparison to the human condition, including joint size, thinness of cartilage, and potential for improved intrinsic repair because of life-long open growth plate activity. In addition, the generation of dysplasia in these animals does not represent a natural process, thereby limiting translational potential. Rabbits have also been used for experimental induction of hip dysplasia. By maintaining the knee (stifle) in extension with a long leg cylinder cast, a large proportion of animals (~75%) developed morphological changes and progressive degeneration of the affected hip that mimic abnormalities generally seen in DDH. The rabbit model has also several potential limitations, and as with the rat model, the disease process is not spontaneous. Furthermore, the model also has a high morbidity and mortality of approximately 25%. Lastly, there are also numerous contraindications to using casts in rabbits, including skin injury, limb necrosis, and swelling, cast loosening, and chewing of the cast.¹⁴ Hip dysplasia with progression to OA has also been produced experimentally in dogs by eversion of the hip labrum in puppies. Four weeks following surgery, the acetabulum gradually becomes shallower and more vertically oriented, and the femoral head gradually subluxates but never dislocates. In addition, histological degeneration can be observed.¹⁷ However, this last model lacks some of the intrinsic characteristics normally observed in natural canine hip dysplasia (CHD) like concomitant joint laxity.¹⁸

CHD is a major problem in veterinary patients with a frequency up to 75% in mixed and pure breed dogs of approximately 70 millions dogs in American household.¹⁹ Dogs are exceptional models for DDH because they naturally develop hip dysplasia. Indeed, CHD has a natural progression that parallels humans, and dogs respond similarly to conventional therapies. In addition, dogs age 5–8 time faster than humans, which allows observation of the natural disease in a short time period. Previous reports have successfully probed that the dog is an excellent hip model to evaluate different orthopedic interventions for hip disease such as the total hip arthroplasty.²⁰ Finally, veterinarians have evolved their understanding, care, and treatment of CHD, which could eventually identify similar physiological mechanisms

that contribute to susceptibility to DDH and arthritis. The purpose of this review is to describe the similarities between both canine and human hip dysplasias and to summarize the potential for CHD as an alternative model for understanding the pathology of the cognate human disease. We particularly highlight anatomy, prevalence, molecular pathways, clinical presentation, and current treatments for both species in this review.

Anatomy

The canine hip joint exhibits remarkable structural similarity to that of human²¹ encompassing the ligamentum teres, a femoral head that articulates within the socket, labrum, the pulvinar, central acetabular fossa, a transverse acetabular ligament, and a capsule. (Figs. 1 and 2). Additionally, the vascularization of the femoral head depends, like that of the human, on the medial and lateral circumflex arteries, both of which branch from the profunda femoris artery.^{22,23}

Despite the anatomic similarity between species, the dog has the obvious drawback of being quadrupedal. Thus, it is unclear to what extent functional results from dogs can be translated to the upright bipedal human. Bipedal and quadrupedal locomotion involves very different patterns of muscle coordination.²⁴ Joint forces within the dog hip joint are significantly lower than those in humans, although the joint stresses (force divided by contact area) remain to be determined. It is, however, known that dogs bear relatively more load on the front legs (53–65% of body weight). In addition, reaction force of dog hip joint during gait is more posterior than in humans. This is consistent with the 20° angle of flexion in the dog femur during stance, another important difference between the dog and the human hip.²⁴ Despite these differences, the dog model has been used extensively for investigating orthopedic diseases.^{20,25,26}

Etiology and Prevalence of Hip Dysplasia in Both Species

The etiology of DDH is multifactorial, involving both genetic and environmental risk factors. Non-genetic risk factors include breech presentation, oligohydramnios, and primiparity. Embryologically, diarthrodial joints are differentiated as units in situ from a mass of skeletal mesenchyme. Development progresses normally in each joint if there is full congruity between articulating surfaces. If the fetus is positioned with the legs in

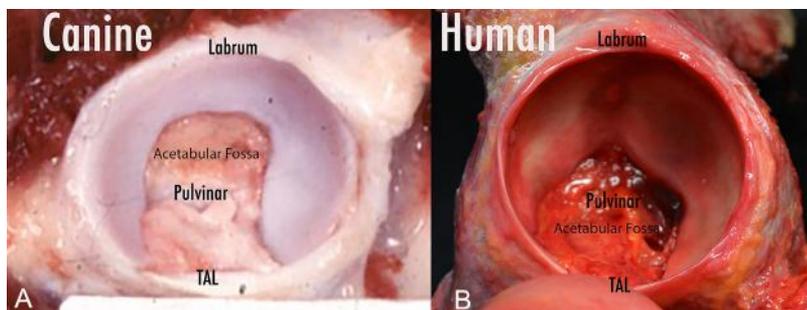


Figure 1. (A) Macroscopic dissection of a canine acetabulum. (B) Courtesy of Jorge Chahla. Macroscopic dissection of a human acetabulum. Both species have a labrum, horseshoe type acetabular cartilage surface, pulvinar, acetabular fossa, and a transverse acetabulum ligament (TAL).

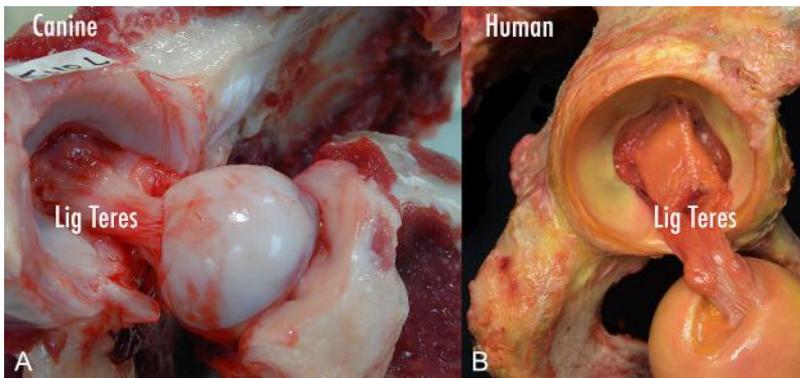


Figure 2. (A) Macroscopic dissection of canine femoral head, ligamentum teres, and acetabulum. (B) Courtesy of Jorge Chahla. Macroscopic dissection of human femoral head, ligamentum teres, and acetabulum.

adduction and extension (breech) the chances of hip dysplasia have been reported as high as 16%. In addition, the first born where the uterus has greater muscular tone, and there is less placental fluid, may be predisposed to hip joint incongruity. Other factors such as femoral anteversion and spastic shortening of the psoas muscle have been shown to favor femoral head dislocation when the leg is extended.²¹ Families with multiple members affected with DDH have been reported, indicating that the disease has a strong genetic component.^{27–29} Additional genetic studies involving linkage analysis, exome sequencing, and case-control association studies have identified several loci/gene variants associated with DDH.^{30,31} For example, Feldman et al.³² identified a variant in *CX3CR1* shared by all dysplastic affected members of four generations of a family. More recently, a mutation in the gene *UFSP2* was found to follow an autosomal dominant inheritance pattern with reduced penetrance (estimated at 80%) in a family from South Africa affected with “Beukes” hip dysplasia—a dysplasia variant in which pain develops in the hip joints in early childhood in the majority of affected persons and progresses to severe crippling joint disease by early adulthood.³³ Additionally, 15 genes have been associated with DDH. *CTBP2*, *DPP*, and *TRIM21* are candidate genes for CHD identified from genome wide association studies.^{34,35,36} These observations imply that both environmental and hereditary influences are important. Still, there is no full consensus on the heritability of DDH. Contrary to CHD, there is a lack of information on associations with muscle mass, rapid growth, and skeletal maturity with DDH.

The prevalence of CHD varies according to breed with heritability estimates for CHD ranging from 0.1 to 0.6.^{37,38} CHD is a polygenic trait, also influenced by environmental effects. Polygenic inheritance implies a large, but unknown number of alleles involved, scattered throughout the genome. Evidence for a major locus contributing to the dysplastic trait in dogs has been found in four independent studies based on variance estimates and Bayesian modeling.^{39–41} In addition, dogs have a unique feature, different from inbreeding rats, mice, or rabbits, which is the existence of ~300 dog breeds representing a huge range of

variation in numerous inherited traits such as height, weight, skeletal shape, and behavior. Online Mendelian Inheritance in Animals (OMIA)—a database of inherited disorders in farm and companion animals—currently lists 461 canine genetic traits (<http://www.angis.org.au/Databases/BIRX/omia>). An intronic deletion in *FBN2* has been associated with CHD but this finding, identified as a candidate gene following a linkage analysis of the distraction index, has not been replicated.⁴² Of significance to both the dog and to humans is the fact that many of these mapped traits provide insights into the genes and biochemical mechanisms of homologous human disease and provide models for interventions based on gene therapy. In addition, CHD is more frequent in large or giant breed dogs. Breeds with particularly high reported prevalence of dysplasia include the Bulldog (73.4%), Pug (69.7%), and St. Bernard (49.2%). However, these numbers do not indicate a true prevalence because breeders typically will not submit radiographs from dogs that are obviously dysplastic. There are also established correlations between body form, size, growth rate, quantity of subcutaneous fat, type of connective tissue, pelvic muscle mass, and the general body type within different breeds and predisposition to DDH.²¹ Phenotypes with high prevalence of CHD are large (head broad and oversized, feet oversized, and splayed), have excess body fat, slow, heavy footed gait, and rapid growth.²¹ It has been postulated that there is a disparity between primary muscle mass and disproportionately rapid skeletal growth. Specifically, the lag or failure of the muscle to develop and reach functional maturity at the same rate as the skeleton results in joint instability. There is evidence that bone changes of hip dysplasia occur, in part, due to lack of sufficient soft tissue strength to maintain congruity between joint articular surfaces.²¹ Coxofemoral joint laxity has been shown to demonstrate higher levels of heritability than bone joint changes. Laxity heritability estimates ranging from 0.46 in German shepherds and Labrador retrievers to 0.64 in golden retrievers, to 0.85 in Estrela mountain dogs. Breech presentation does occur in dogs, but it has never been related to CHD. (Table 1).

Table 1. Comparison of Demographics, Etiology, and Pathology Between Both Species

Parameter	Canine Hip Dysplasia	Human Hip Dysplasia
Heritability	0.1–0.6	Unknown ³¹
Incidence	Varies with breed (20% labrador-50% St Bernards)	1/1,000 newborns
Hip anatomy	Ball-socket	Ball-socket
Gender	No sex predilection	80% females
Ambulation	Quadrupedal	Bipedal
Prevalence	Up to 75% depending on breed	20%
Physiopathology	Rim disease (overload)	Rim disease (overload)
Hip joint laxity	Yes	Yes
Progression of disease to advanced OA	1 year	30 years
Risk factors	Specific Phenotypes = large body types, rapid growth, obese	First born/breech/oligohydramnios
Intraarticular diseases	Cartilage-labrum-lig teres-capsule	Cartilage labrum-lig teres-capsule
Molecular pathway	ECM lost and inflammation	ECM lost and inflammation

OA, osteoarthritis; ECM, extracellular matrix.

Potential Molecular Pathways of Joint Degeneration in Hip Dysplasia

To date, literature on the molecular pathways that lead to joint degeneration in patients with DDH is limited. It is, however, increasingly evident that inflammatory mechanisms play a central role in mediating the effects of altered joint biomechanics that leads to the development of OA.⁴³ For example, cartilage contact pressure in patients with DDH is elevated,⁴⁴ and several studies have shown that chronic overload to the cartilage downregulates extracellular matrix production.⁴⁵ Cartilage samples from DDH patients had reduced collagen type II and aggrecan expression but increased MMP-13 expression compared to both healthy individuals and patients with advanced OA. This suggests that there is an active catabolic activity in articular cartilage of patients with DDH with loss of extracellular matrix synthesis.⁴⁶ In addition, Hashimoto et al.,⁴⁷ investigated the metabolic activity in cartilage from patients undergoing surgical treatment for FAI along with patients with advanced OA, and DDH. Interestingly, cartilage from patients with DDH had significantly lower concentrations of aggrecan compared to OA and patients with FAI.

In CHD, some biomarkers of cartilage matrix turnover have been found to be elevated suggesting a progressive loss in extracellular matrix synthesis and a high metabolic activity in articular cartilage. Among these, cartilage oligomeric matrix protein (COMP) and fibronectin have been studied extensively. COMP is a matrix protein, that is significantly elevated in synovial fluid from both dogs and humans with pre-OA and OA.^{48,49} Although not specific to CHD, COMP levels are elevated in this population and predictive of canine OA severity.^{49,50} Fibronectins are important extracellular molecules through which cells interact with their surrounding matrix. Preliminary studies indicate that some fibronectin isoforms increase up to 10-fold in OA cartilage while loss of fibronectin isoforms peculiar to articular cartilage appears to be a very early and sensitive marker of chondrocyte dedifferentiation.⁴⁹ In this regard, identification of biomarkers that reflect

the severity of pathology or predict the outcome of joint disease would have great value in the development of new therapies for DDH patients. Progress in this area is impeded by a lack of knowledge about the critical biologic events that are fundamental mediators of DDH and associated OA.

Clinical Presentation

In humans, patients with severe DDH concomitant with a subluxated or dislocated joint will present symptoms as early as they start ambulating. However, the focus in this review, with respect to identifying an appropriate animal model is on patients with mild to moderate dysplasia. These patients commonly present in adolescence or young adulthood with pre-arthritis disease. In this population, the presenting symptoms can be variable and radiographic analysis can be challenging, especially in individuals with mild acetabular deformities. Most patients with DDH present with an insidious onset of activity-related pain localized to the groin and/or the lateral aspect of the hip. Physical examination findings often reveal a limp with a positive Trendelenburg sign and a positive impingement test. However, clinical examination is not enough to make the diagnosis and acetabular pathomorphology is best confirmed using anteroposterior and lateral pelvic radiographs.⁵¹

The clinical presentation of dogs with CHD is variable and does not correlate with the radiographic changes in joint morphology.⁵² In general, there are two ages at which animals present with clinical signs of CHD: (i) dogs younger than 1 year of age with hip instability and overloading of articular areas, which causes painful tearing or stretching of the round ligament, synovitis, and cartilage damage^{21,53}; and (ii) adult dogs (older than 12 months old) with chronic pain from advanced OA.⁵² Gait abnormalities, such as stiffness, reduced height of step, shortened stride length, bunny hopping, difficulty in rising, climbing stairs, or in jumping over obstacles are typical clinical signs of impaired function related to CHD.²¹ Similar to humans, radiographs are used to confirm clinical presentation.

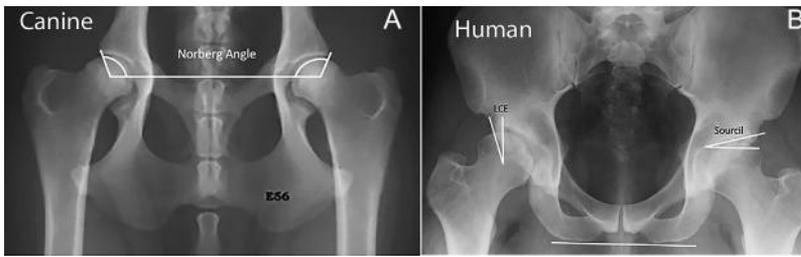


Figure 3. The standard ventrodorsal hip extended view (SVDV) pelvis in canine. (A) The Norberg angle is measured by drawing a line between the center points on each of the two of the femoral heads and the cranio-lateral aspect of the acetabular rims. A Norberg angle $<105^\circ$ indicates CHD. (B) AP pelvis view of human pelvis. LCE angle: Formed by a vertical line and a line connecting the femoral head center with the lateral edge of the acetabulum. Normal angle is considered between 25° and 39° DDH is indicated in patients with a LCE <20 . The Norberg angle mimics this method but adds another 90° . Sourcil or acetabular roof angle of Tönnis: The angle between a line intersecting the inferior part of the medial sourcil parallel to the inter-teardrop-line and a line running from the inferior part of the medial sourcil to the lateral acetabular rim. A sourcil angle $>10^\circ$ indicates DDH.

Screening Tests in Infants and Puppies

Both species are assessed for hip dysplasia using similar clinical maneuvers. Ortolani and Barlow tests are normally performed in both species. These two clinical tests are performed together since one (Barlow) dislocates the joint and the other (Ortolani) reduces it.^{54,55} These maneuvers were initially described to detect DDH in new born babies and were then adapted by veterinarians to do similar screening tests in puppies. The Barlow maneuver is a provocative test with flexion, adduction, and posterior pressure through the infant's hip. A palpable *clunk* during the Barlow maneuver indicates positive instability with posterior displacement. The Ortolani test is a reductive maneuver requiring abduction with posterior pressure to lift the greater trochanter. A clunk sensation with this test is positive for reduction of the hip. Similarly, the puppy is placed in lateral recumbency while the examiner stands behind the animal and grasps the upper stifle and firmly adducts the femur parallel to the surface of the examination table. A proximally directed force is applied to the shaft of the femur to elicit hip subluxation, while the pelvis is supported with the other hand. Then the stifle is slowly abducted to reduce the hip joint. The Ortolani test has been used by the veterinarians for treatment decision; dogs with a positive maneuver are good candidate for preservation surgery.

Radiographic Measurements

Radiographic evaluation plays a critical role in the diagnosis of DDH in the adult human. Patients are

normally evaluated with an anteroposterior pelvic radiograph and the false profile view. Specifically, patients with a lateral center-edge (LCE) angle $<20^\circ$, anterior center-edge angle $<18^\circ$, and sourcil or Tönnis angle $>10^\circ$ are classified as dysplastic.⁵⁶ The false-profile view allows further examination of anterior coverage of the femur, confirming DDH in those patients with an anterior center-edge angle $<18^\circ$. In dogs, radiographic studies can be separated into two main groups: (i) to evaluate joint congruence using the standard ventrodorsal hip extended view (SVDV) and (ii) to provide information on hip joint laxity demonstrated by stress radiography such as the Pennsylvania Hip Improvement Program (PennHIP) and the dorsolateral subluxation [DLS] score. The Norberg angle has been used to diagnose CHD, in the SVDV, an angle $\leq 105^\circ$ is indicative of the presence of hip dysplasia.⁵⁷ This angle measures femoral head coverage, similar to the LCE angle used in humans. In addition, The Orthopedic Foundation for Animal Hip Scoring (OFA) is based on the percent of the femoral head normally covered by the entire acetabular rim. OFA assess multiple anatomic landmarks to assess the presence of CHD including: Lateral rim, cranial rim, fovea capitus, and acetabular notch among others. The hip is then graded as excellent, good, fair, borderline, mild, moderate, or severe CHD.⁵⁸ In the human hip, a similar measurement known as the femoral head extrusion index is normally use to quantify how much of the femoral head is covered by the acetabulum.⁵⁹ (Figs. 3 and 4).

Joint laxity has been proposed as a critical factor for hip dysplasia in both species. Although dogs with hip laxity do not always have CHD, all dogs with CHD have



Figure 4. (A) The standard ventrodorsal hip extended view (SVDV) in the canine. The OFA score is based on the percent of the femoral head that is covered by the acetabular rim. Normally, at least 50% of the femoral head has to be covered by the dorsal acetabular rim in the SVDV projection. (B) AP pelvis: In the human, the femoral head extrusion index (FHEI) quantifies how much of the femoral head is covered by the acetabulum, that is, lies medial to the lateral edge of the acetabulum ($A/B \times 100$).

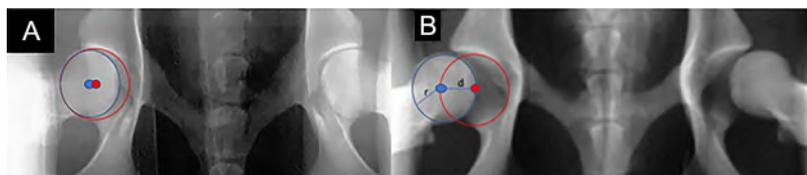


Figure 5. Radiographs showing measurement of the canine DI (distraction index), which is evaluated considering d/r . d : Distance between center of the femoral head and center of acetabulum. r : Radius of the femoral head. (A) represents a tight hip or normal hip, and (B) loose hip with hip dysplasia and a value closer to 1.^{54,82}

hip laxity. Therefore, it can be argued that hip laxity can be considered an intermediate phenotype for CHD. Joint laxity can be diagnosed in dogs using the PennHIP method and the dorsolateral subluxation test (DLS). The PennHIP method is measured in addition to radiographic confirmation as a dynamic study. It consists in measuring the maximum amount of lateral passive hip laxity through the distraction index. It involves measuring the maximum distance between the centers of the femoral head and acetabulum and the radius of the femoral head (Fig. 5). The closer the score is to 0, the better the fit, while a score of 1 indicates severe laxity and associated femoral distraction.⁶⁰ (Fig. 6). The PennHIP distraction index (DI) and the DLS score were found to have strongly correlate with gross structural changes in the articular cartilage, potentially indicating a relationship between joint laxity measured by this technique and articular surface degeneration.⁶¹ However, the DI is considered an unnatural phenomenon since the dogs are laying on their backs with their femoral heads maximally laterally distracted. In contrast, the DLS is obtained by positioning the dogs in a weight bearing position (Fig. 6) allowing a true dynamic evaluation of hip joint laxity. A DLS score of 50% marks the transition from a positive Ortolani test (lower score) to a negative one (higher score).⁶¹

In humans, evaluation of laxity is part of the clinical assessment of the dysplastic hip. The assessment of the Beighton's criteria allows for some estimation of the degree of underlying soft tissue laxity, yet there is no hip joint specific laxity measure that is widely accepted.⁶² The Beighton score consists of evaluating the capacity of doing specific maneuvers including: Bending the thumb back on to the front of the forearm, bending forward, and putting hands on the floor, bending elbow backwards, bending knee backwards, and extending the little finger more than 90°. A high Beighton score is considered a risk factor for joint laxity. Table 2

compares clinical, radiographic, and surgical treatments for both species.

Computed tomography (CT) is routinely used for the diagnosis and assessment of DDH.^{63,64} Three-dimensional CT models of the hip joint are becoming a contemporary tool in the assessment of DDH.⁶⁵ Recent evidence supports the advantages of CT over standard radiography to assess early joint conformational changes characteristic of DDH and CHD.⁶³ Specific angles measured in the CT has proven to correlate with cartilage damage in the dog.⁶⁶ CT measurements in dogs correlate strongly with the DLS score.⁶⁷

Macroscopic Intra-articular Findings

Multiple intra-articular lesions are commonly observed in CHD. These lesions are evident as early as 4 weeks after birth and continue to progress within the first 6 months. The first pathological finding related to CHD is the presence of an edematous ligamentum teres with associated tears. Capillary hemorrhage can also be observed. It is thought that the teres ligament is largely responsible for holding the femoral head in place for the first month. These abnormalities may be related to the length of the ligamentum teres. During the first 2 weeks, the teres ligament is so short that that the femoral head attachment fractures at the fovea when luxation of the femoral head is forced in dysplastic hips. Within time the ligamentum teres is lengthened. By 12 weeks, affected dogs exhibited changes in both the synovium and the articular cartilage.⁶⁸ Lesions include synovial inflammation, articular cartilage damage, osteophytes, hypertrophic labrum, and lesions of the ligamentum teres. The most pathognomonic lesions are normally observed surrounding the femoral insertion of the ligamentum teres (perifoveal area) with reported cartilage lesions grade 2–4 in 80% of arthroscopied joints.⁶⁹ Less frequently, cartilage lesions are observed in the cranial portion of the acetabulum.⁶⁹ (Fig. 7).

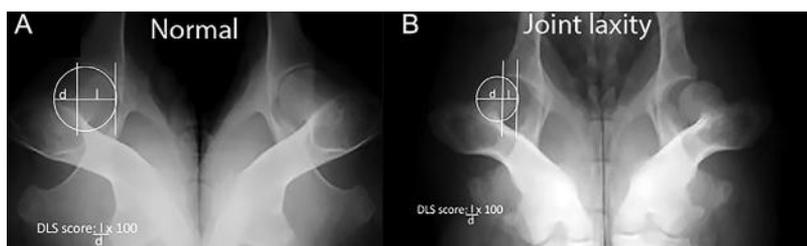


Figure 6. Radiographs showing canine DLS (dorsolateral score). (A) Note a normal hip with >55%, unlikely will develop OA. (B) DLS in a dog with joint laxity. Score <45% very likely will develop OA.

Table 2. Comparison of Clinical, Radiographic, and Treatment Parameters Between Dog and Human Hip Dysplasias

	Canine Hip Dysplasia	Human Hip Dysplasia
Parameter		
Diagnosis	Clinical and radiographic	Clinical and radiographic
Symptoms	Early (<1 year old) vs. Late onset	12–30 years old
Screening test	Barlow–Ortolani	Barlow–Ortolani
Radiographic		
Lateral coverage	Yes = Norberg angle	Yes = LCE angle
Acetabular inclination	Dorsal acetabular rim ⁶⁷	Tonnis angle or acetabular inclination
Extrusion of the femoral head	Percent of femoral head coverage	Femoral head extrusion index
Stress radiographs	Yes = PennHip/DLS score (determines subluxation of the joint)	No
Surgical treatments	Triple pelvic osteotomy-hip arthroscopy	PAO-hip arthroscopy

LCE: lateral center to edge, PAO, periacetabular osteotomy.

A detailed timeline of intraarticular disease is not fully understood for DDH. Most of the intraarticular findings identified in this population has been described during hip arthroscopy, at which time the average age of patients is 30 years old.^{6,70–74} Lesions are similar to those observed in dogs including torn labrum, synovial inflammation, cartilage lesions on the acetabular rim and femoral head, and ligamentum teres tears⁷¹ (Figs. 8 and 9). The locations of cartilage lesions differ between dogs and humans, with high prevalence of rim cartilage lesions in the human and femoral head cartilage lesions in the canine.

Microscopic Intraarticular Findings

Histopathological changes described in both species are largely related to degenerative changes secondary to OA.⁷⁵ Cartilage lesions include: Collagen fraying, loss of proteoglycans, and chondrocyte clustering. Typically these lesions are located in the acetabular rim and in the femoral head.⁷⁵ Associated chronic synovitis including lymphoid infiltration (lymphocytic plasmatic synovitis) and neovascularization is normally seen.

In humans, intraarticular DDH histopathological changes have not been well described. There is a paucity of information about histopathological changes, critical signaling pathways, and other mechanical cues that mediate the formation joint degeneration in the dysplastic hip. To date, the mechanobiological mediators of DDH and associated OA are poorly understood. The fundamental biologic mediators of this disease need still to be investigated.

Treatments

A variety of hip preservation procedures have been developed and proposed for the treatment of symptomatic DDH.^{76–80} In 1988, Ganz et al.⁷⁷ introduced the Bernese Periacetabular Osteotomy (PAO) for acetabular reorientation for the treatment of DDH. Contemporary refinements of this technique include concomitant hip arthroscopy to address intra-articular disease and femoral head–neck osteochondroplasty to avoid secondary FAI.⁶⁵ Outcomes of this procedure have been continually improving, with current survival rates of 85% at 10 years.⁷ Similarly, the TPO (triple pelvic osteotomy) has been used in adolescent canines to

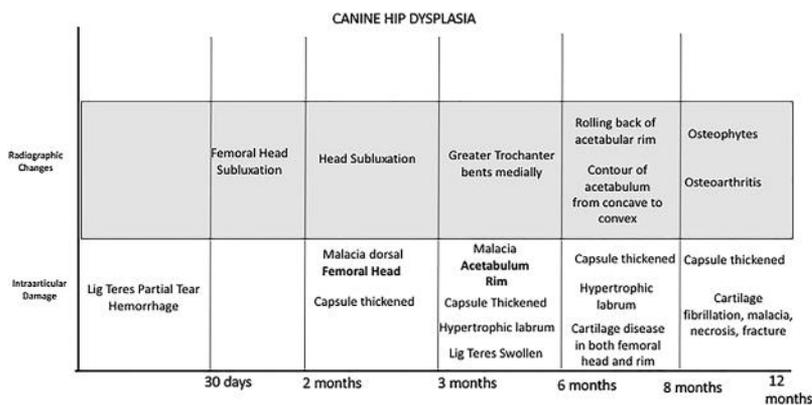


Figure 7. Timeline representing the intraarticular and radiographic changes observed in dogs with canine hip dysplasia. Most of the changes are observed during first year of life.

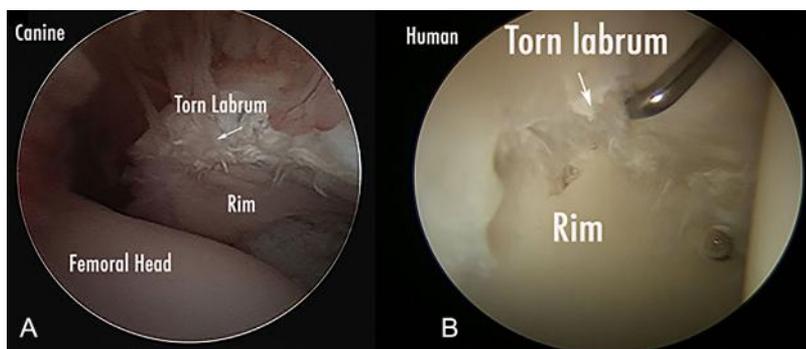


Figure 8. (A) Arthroscopic view of a torn labrum in a dog with CHD. Courtesy acknowledgement of K. Schulz. (B) Similar, hip arthroscopy in a patient with DDH confirming the presence of a torn labrum.

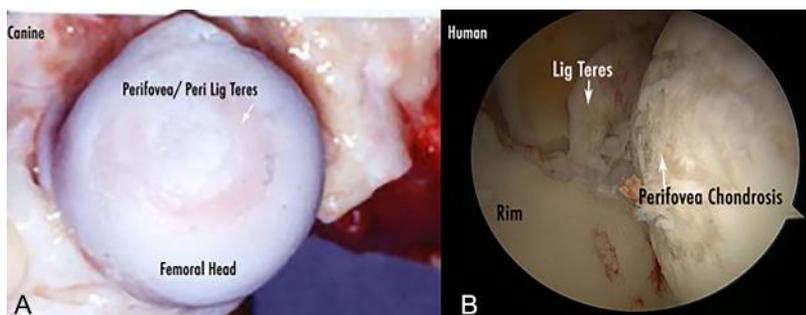


Figure 9. (A) Macroscopic view of a dog's femoral head showing the typical per fovea lesions normally seen in CHD. (B) Similarly, perifoveal lesion with severe chondrosis in a patient with DDH.

treat CHD. Similar to the PAO, TPO is used to provide a stable joint by covering the femoral head and increasing the contact surface between the femur and acetabulum.⁸¹ In addition, hip arthroscopy can be used in the canine to treat intraarticular pathology. Clinical results of the TPO in the canine has been more controversial than PAO in humans, with some authors suggesting that progression to OA may continue regardless of TPO intervention. Unpredictable results with this procedure in dogs has been attributed to late diagnosis of the disease. In addition, animals cannot be kept non weight-bearing after surgery.⁸¹

Despite the many similarities, it is important to note that the canine model may have some limitations, including potential ethical concerns; the strong bond between dogs, and humans and their popular status as companion animals; high expenses in procuring and caring for the animals; and the need for highly specialized facilities. Nonetheless, using the canine model as a pre-clinical animal model of DDH, in parallel to the human, to investigate the biological aspect of the condition, response to interventional treatments, and optimum time to intervene in a controlled environment may help advance the field and lead to refinement of current treatments, and open new targets and methods for treatment and prevention of both the human and canine condition in the true spirit of One Medicine. Identification of specific molecular pathways that initiate joint degeneration in both species may open a broad spectrum for a potential future application of diagnostic tools and interventional disease modifying OA drugs

(DMOAD) for the treatment of pre-OA and OA secondary to hip dysplasia.

CONCLUSIONS

Dogs and humans have comparable anatomy, morphology, intraarticular disease, diagnostic modalities, and treatment interventions. The natural history of hip dysplasia in both species is similar and progresses to end stage OA. Yet, progression to OA in the dog is significantly faster which allows observation of the natural history of this disease in a short time period. In addition, the timeline of intraarticular degeneration has been described in detail in the dog. This known natural detail provides an excellent starting point to determine the success of treatment interventions and elucidate mechanisms underlying joint damage for the development of new treatments. Taken together, CHD provides a spontaneous and natural model of DDH.

AUTHORS' CONTRIBUTIONS

CPG contributed in Idea-design, drafting, writing, and images. FG, MFR, MDH, and KAP contributed in drafting and editing. MJL, RJT, and JCC contributed in drafting-editing and images. All authors were actively involved during the process of the manuscript development. They all read and approved the final version for submission. Supported in part by NIH grant AG15768.

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