

Spontaneous dog osteoarthritis — a One Medicine vision

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Abstract | Osteoarthritis (OA) is a global disease that, despite extensive research, has limited treatment options. Pet dogs share both an environment and lifestyle attributes with their owners, and a growing awareness is developing in the public and among researchers that One Medicine, the mutual co-study of animals and humans, could be beneficial for both humans and dogs. To that end, this Review highlights research opportunities afforded by studying dogs with spontaneous OA, with a view to sharing this active area of veterinary research with new audiences. Similarities and differences between dog and human OA are examined, and the proposition is made that suitably aligned studies of spontaneous OA in dogs and humans, in particular hip and knee OA, could highlight new avenues of discovery. Developing cross-species collaborations will provide a wealth of research material and knowledge that is relevant to human OA and that cannot currently be obtained from rodent models or experimentally induced dog models of OA. Ultimately, this Review aims to raise awareness of spontaneous dog OA and to stimulate discussion regarding its exploration under the One Medicine initiative to improve the health and well-being of both species.

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Osteoarthritis (OA) is the end point of synovial joint disease processes that interrupt the articular surface or cause instability and mechanical injury. In 2005, 26.9 million adults in the USA were estimated to have OA¹, and according to a 2016 white paper from the Osteoarthritis Research Society International (OARSI), globally, OA accounted for 2.4% of all years lived with disability². The importance of OA as a global disease and a modern major health challenge therefore necessitates new research strategies.

Experimentally induced models of OA are available in many large and small animal species³. Work in the 1970s and 1980s established the clinical, biochemical and histopathological changes that are induced by cruciate ligament transection in dog stifle joints (the Pond-Nuki model)^{4,5} or by medial meniscectomy in rabbits⁶. This work heralded the introduction of surgically induced OA models in small, genetically tractable species such as mice and rats. Because they are small, easy to house and relatively inexpensive, such rodent models have undeniably contributed to important advances in our understanding of basic disease mechanisms³. However, rodent models have proved to be poor predictors of the efficacy or toxicity of drugs in trials for human OA⁷. Rodent models of OA are usually either chemically induced or surgically induced; however, the veracity of the joint changes that occur following administration

of intra-articular papain or monosodium iodoacetate has been questioned, and many researchers have concluded that the use of chemically induced OA should be limited to studies of joint pain⁸. Hence, surgical joint destabilization is the most frequently employed model. Although the value of these rapidly changing rodent OA models should not be underestimated, naturally occurring disease in companion animals more closely reflects the complex genetic, physiological and environmental variations that occur in human OA^{9,10}.

Spontaneous, slow-progressing OA occurs in multiple strains of mice, as well as in guinea pigs, Syrian hamsters, non-human primates and dogs¹¹; the histopathology and pathogenesis of dog OA most closely resemble those of primary human OA. Similar to humans, OA is also a common disease in the dog, with a prevalence that varies from 2.5% overall in UK veterinary primary care practices¹² to over 20% in dogs over 1 year old in the USA¹³. The clinically affected dog shares complex naturally occurring traits and comorbidities, such as obesity, that occur in humans, and both humans and companion dogs live into old age, share environments and activities and often receive almost identical treatments, such as long-term administration of anti-inflammatory drugs or joint replacement surgery. Academic and private practice veterinary medicine can provide valuable biomedical research data, as referral centres are often equipped with

Key points

- Dogs have many analogous spontaneous diseases that result in end-stage osteoarthritis (OA).
- Inbreeding and the predisposition of certain dog breeds for OA enable easier identification of candidate genetic associations than in outbred humans.
- Dog OA subtypes offer a potential stratification rationale for aetiological differences and alignment to analogous human OA phenotypes.
- The relatively compressed time course of spontaneous dog OA offers longitudinal research opportunities.
- Collaboration with veterinary researchers can provide tissue samples from early-stage OA and opportunities to evaluate new therapeutics in a spontaneous disease model.
- Awareness of the limitations and benefits of using clinical veterinary patients in research is important.

MRI and CT scanners, arthroscopes and state-of-the-art pathology and molecular diagnostic capabilities. Academic veterinary centres also pilot advances in the use of anti-inflammatory and pain-modulating OA drug therapies^{10,14,15}. In this Review, we summarize research relating to common forms of spontaneous dog OA, focusing on the presentation and genetics of analogous diseases of the hip and knee, within a framework of human OA phenotypes. We also aim to encourage researchers to take on the principles of One Medicine (BOX 1) research to benefit both humans and dogs.

The dog as a model animal

The foreshortened lifespan of the dog, with its equivalent life stages to those in humans, holds potential for the longitudinal evaluation of disease and therapy in spontaneous OA (FIG. 1). Dog OA is generally considered to bear a close resemblance to human OA with regards to anatomic similarity, disease heterogeneity and progression¹⁶. For example, changes in articular cartilage proteoglycans that occur in slowly progressive spontaneous dog OA (regardless of the age of the dog) closely match changes that occur in human OA but differ from those seen in rapidly advancing experimental dog OA induced by cruciate ligament transection¹⁷. Although clear anatomical similarities exist, extrapolating data from the quadrupedal dog to bipedal humans requires some caution. Indeed, the dog has comparatively reduced total joint forces that are split 60:40 between the forelimbs and hindlimbs in addition to a 20-degree flexion of the femur during the stance phase of gait, which together could have an unknown effect on OA development¹⁸.

Intriguingly, distinct OA type-specific epidemiological patterns exist in dogs, notably between breeds, and OA is clearly influenced by body size, obesity, sex, neuter status and age¹². Obesity, for instance, is a known risk factor for human¹⁹ and dog OA²⁰, but evaluating its role as an independent risk factor in humans is difficult. However, work with inbred experimental dog colonies has revealed that dietary restriction reduces OA. Six week-old sex-matched and body weight-matched pairs of Labrador Retriever litter mates from closed colonies were either control fed (ad libitum) or diet restricted (75% of control fed); radiographic hip OA was found in 25% of control-fed dogs and only 4% of diet-restricted dogs by 2 years, which increased to 39% versus 13% by

5 years and 83% versus 50% at 15 years²¹. Interestingly, diet restriction also extended longevity, and weight correlated only moderately with disease severity²¹, suggesting that other factors related to increased food intake might affect OA²². In other studies, diet restriction also reduced the severity and prevalence of shoulder²³ and elbow OA²⁴. Although the aetiology of obesity-related OA remains unclear, biomechanical effects from the overloading of weight-bearing joints have been proposed as a mechanism despite the fact that the risk of hand OA is also increased in obese humans²⁵, which suggests a systemic role for obesity as a risk factor. An alternative mechanism in which adipose tissue promotes systemic low-grade inflammation via increased concentrations of adipokines has also been put forward²⁶, and dog adipocytes are known to express important adipokines, suggesting that metabolic factors associated with being overweight or obese exert an independent risk of developing OA²⁷.

Overall, although development of OA in dogs is likely to be more variable and protracted, and thus its study is likely to require larger numbers of animals to achieve an appropriately powered study design than rodent models, studies using these naturally occurring forms of dog OA could lead to an overall reduction in the number of animals used for experimental research and to a greater understanding of spontaneous OA. In the following sections, we outline some common forms of naturally occurring dog OA and review their suitability as models for analogous human disease (FIG. 2).

Analogous dog and human disease**Hip dysplasia**

Presentation. Hip dysplasia is a common risk factor for both human and dog OA^{28–31}. An estimated 20–40% of idiopathic human hip OA is caused by developmental dysplasia of the hip (DDH)³², with many patients requiring joint replacement later in life^{1,33,34}. Canine hip dysplasia (CHD) shares pathoanatomical, biochemical and clinical features with DDH and has been proposed as the best spontaneous large animal model for DDH^{17,35} (FIG. 3). Both DDH and CHD have delayed femoral capital ossification and an underpinning instability continuum (as detected by the Ortolani test), and severe forms are characterized by complete subluxation, focal cartilage overload and hip OA in untreated or undertreated children and dogs^{34,36–38} (FIG. 3b,c). DDH and CHD are morphologically similar; for example, collagenous fibrils in the articular cartilage of patients with DDH are sparse and disordered and closely resemble changes to the cartilage ultrastructure seen in CHD^{39,40}. Many older dogs that had no indication of joint laxity or osteoarthritic change at 2 years (early adulthood) develop OA as they age, which resembles human acetabular dysplasia and secondary OA^{41,42} (FIG. 3d,e).

Although other forms of hip OA are potentially more common than CHD and DDH, these forms might not be analogous in dogs and humans. For example, femoroacetabular impingement (FAI), in which a thickened, aspherical femoral head–neck junction results in abutment against the acetabular labrum joint⁴³, is thought to be a common cause of hip pain in human hip OA. By contrast,

Stifle joints

An analogous term for the knee joints in quadrupedal animals.

Pond-Nuki model

An experimental model of knee instability-driven osteoarthritis in dogs involving surgical cranial cruciate ligament transection.

Ortolani test

Physical examination test performed in dogs and infants to assess for excessive laxity in the hip joint that allows dislocation.

Box 1 | One Health, One Medicine and veterinary medicine

The One Health concept, in which human health is recognized as being closely connected to animal health and the environment, dates back to Hippocrates and Aristotle. Claude Bourgelat, a founder of 18th century veterinary medicine, advocated this intimacy²²⁶, which was further emphasized by the 19th century physician Rudolf Virchow, who coined the term 'zoonosis' upon discovering that *Trichinella spiralis* from pigs causes human neurocysticercosis²²⁷. Despite historical recognition of the One Health concept, a culture of marked anthropocentricity emerged during the 1970s, shifting research emphasis towards induced, experimental animal models of disease.

One Health approaches regained momentum following outbreaks of the highly pathogenic H5N1 avian influenza in 1996 and of corona virus-associated severe acute respiratory syndrome (SARS) in 2003. Distinct from One Health, One Medicine is now emerging as a holistic paradigm wherein veterinary and human medical researchers and clinical practitioners collaborate to increase their understanding of shared diseases and to develop new therapies²²⁸. Companion animals are a large population, with ~70 million pet dogs living in the USA alone²²⁶. Dogs typically live into old age, come in a variety of shapes and sizes (from highly athletic to sedentary and overweight) and live in close proximity to humans. As dogs develop many age-related chronic diseases and comorbidities on a foreshortened timescale (breed-influenced life expectancy is ~8–12 years) that are analogous to those in humans, there is a growing view that developing our understanding and treatment of dog osteoarthritis (OA) could lead to breakthroughs in human OA¹⁵³.

the existence of FAI in the dog is uncertain, although whether FAI has simply not been looked for, or is not specifically recognized in the dog, is somewhat unclear.

Genetics. DDH occurs in between 1 and 20 live births per 1,000 worldwide⁴⁴, and predisposing factors include family history, being a first born, female sex and breech birth^{45,46}. Familial segregation studies^{47,48} suggest that DDH has a multifactorial genetic basis, but statistical support for this theory varies across populations and countries⁴⁹. For example, in a Chinese population, the recurrent risk of DDH in the siblings of affected individuals was approximately tenfold greater than in controls and had a heritability of ~85%⁴⁷. By contrast, the frequency of CHD varies between different dog breeds, reaching a peak of ~75% in Golden Retrievers and Rottweilers⁵⁰, and shows no sex predilection in most breeds; the exception is Polish Tatra Sheepdogs, in which the risk of CHD in females is greater than threefold the risk in males⁴¹. This intra-breed and inter-breed variation is proving valuable in identifying the genetic basis of CHD. CHD demographics most closely mirror DDH in late-onset acetabular dysplasia⁴¹. CHD heritability ranges from 20% to 60%⁵¹, and evidence from multipoint linkage studies and genome-wide association studies (GWAS)^{52–59} suggest that 5–10 quantitative trait nucleotides of modest effect control CHD⁶⁰.

Approximately 15 genes with known functions in embryonic patterning and extracellular matrix (ECM) structure and remodelling have been associated with DDH and hip OA, predominantly via screening for candidate genetic polymorphisms⁶¹. Many genetic associations lack replication, with the exception of *CX3CR1* (encoding the G protein-coupled receptor CX3-chemokine receptor 1 (CX3CR1); also known as fractalkine), which was first identified by linkage mapping and exome sequencing^{62,63}, with a single nucleotide polymorphism (SNP) being subsequently linked independently with DDH⁶⁴. *CX3CR1* is involved in

mesenchymal stem cell recruitment to the joint^{62,65}, and *Cx3cr1*-knockout mice develop acetabular dysplasia⁶⁶. The association between DDH and *GDF5* has also been replicated in a GWAS using data from the UK Biobank⁶⁷.

Whereas a genetic basis for DDH is likely, but not certain^{67,68}, it is undisputed in CHD⁶⁹. An intronic deletion in *FBN2* was associated with CHD in a linkage analysis of a direct hip laxity trait (the hip distraction index), and *FBN2* mRNA was upregulated in tissue samples from dysplastic dog hip joints⁷⁰. CHD-associated loci identified by a GWAS of Labrador Retrievers in the UK (>1,000 dogs) include those on canine chromosome 01 (CFA01) and CFA21 (REF.⁵⁵). Another GWAS that used several breeds of dog identified an SNP in *CTBP2* on CFA28 that was linked to CHD, specifically the Norberg angle⁵². This SNP and SNPs at two more loci near *TRIM2* and *DPP4* were subsequently associated with CHD in a post hoc analysis of the same data⁵³. However, similar to genetic studies of DDH, GWAS of CHD have also been difficult to replicate across different breeds and laboratories⁵⁵. Large-scale association studies indicate that the vast majority of significantly associated variants reside outside of protein-coding exons, which make up only 1.2% of the human genome⁷¹, a situation that is likely to be similar in the dog genome. Because not all structural variants, including deletions, duplications, inversions and translocations, in non-coding regions of the genome might be tagged by an SNP, genetic causes of complex trait variation will often be missed in GWAS. For example, in a study of 4,200 genotyped dogs, most variants were poorly tagged by markers in a high-density mapping array of >180,000 markers⁵²; other previous canine GWAS are also likely to have causal variant mutations. Whole genome sequencing and genotype imputation are probably needed to capture all causal mutations in canine GWAS.

Intriguingly, in a 2014 study, three human patients with sporadic DDH shared an identical frameshift mutation in *ZRANB1* (REF.⁶³), which is notable, as *ZRANB1* is in the same canine linkage disequilibrium interval as the *CTBP2* SNP on CFA28 (REF.⁵²). A locus on CFA37 in Bernese Mountain Dogs has also been associated with CHD and lies near *FNI*, which is associated with human DDH⁵⁹. These genetic similarities indicate that studying CHD in selected breeds of dog, such as Labrador Retrievers, Golden Retrievers or Rottweilers, could yield novel mechanistic insights into the aetiopathology of hip dysplasia in dogs and humans (FIG. 2). As strong evidence exists for similarities in the phenotype and progression of secondary OA in dysplastic hip joints in humans and dogs, parallel genomic, transcriptomic and methylomic biomarker analyses in both species are likely to be highly informative. Fresh samples can be retrieved readily from dogs undergoing joint salvage procedures, which could facilitate transcriptional screening to overcome the replication barrier, as genetic associations are likely to have been previously missed.

Using CHD as a means to understand DDH. Does CHD occur with sufficient predictability to provide a feasible model for DDH? CHD occurs with 75% prevalence in Golden Retrievers and Rottweilers⁵⁰. As in humans,

Norberg angle

An angle based upon a radiographic measure of a line that connects the centres of both femoral heads and the craniodorsal rim of the acetabulum on the same side; used as a surrogate measure of hip laxity and femoral head coverage by the acetabulum.

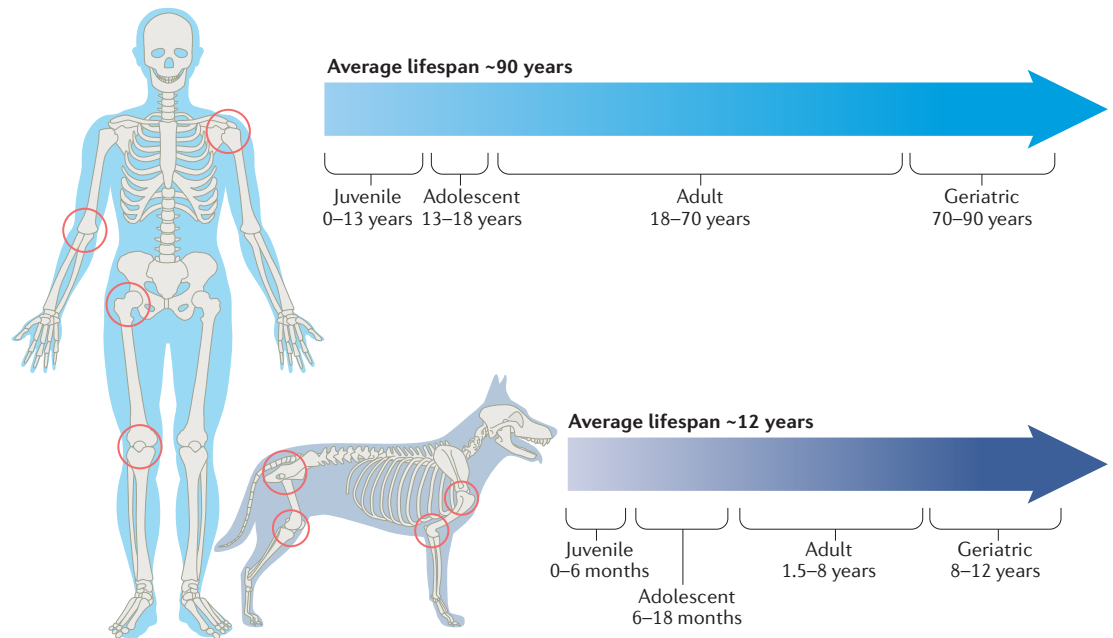


Fig. 1 | **Osteoarthritis in dogs and humans.** The most common locations for osteoarthritis in dogs include the knee, hip, shoulder and elbow, which are shown with their homologous equivalent in humans. The average lifespan of a large-breed dog is ~12 years, with a proportionately longer time spent in old age than in a typical human lifespan.

this high prevalence has heralded early-stage hip laxity screening in these breeds⁷² and health improvement programmes that include novel laxity measures (the PennHIP distraction view to calculate the distraction index), which enable the identification of dogs at the age of 4 months that are highly unlikely to develop OA by the age of 3 years⁷³. CHD resembles DDH clinically and pathologically but progresses over a compressed time frame, adding to its utility as a model. Many dog screening programmes and registries employ traditional hip extended pelvic radiography (FIG. 3a), and some have DNA banks (such as the Canine Health Foundation of the American Kennel Club), which presents an opportunity to identify genetic, epigenetic or environmental factors common to DDH and CDH. The phenotypic characteristics of these two diseases are similar enough to warrant simultaneous clinical and basic research to augment progress in treatment and prevention of dog and human hip OA secondary to dysplasia. Current treatment strategies for hip dysplasia in dogs and humans are highlighted in BOX 2. Researchers have also explored the role of fetal movement in the development of bone shape in patients with DDH using MRI⁷⁴. Although the cost of such MRI studies is currently prohibitive in dogs, the possibility of a One Medicine approach to advance research in this field by careful fetal tracking of the developmental emergence of joint incongruity in DDH and CDH is worth considering.

Knee cruciate ligament rupture

Presentation. Dog knees have human-like anatomy⁷⁵ including an anterior cruciate ligament (ACL) that is termed the cranial cruciate ligament (CCL) in dogs owing to their quadrupedal arrangement (FIG. 4). Experimentally, dogs have been used for several surgical

models of OA, including CCL transection⁴, partial transection⁷⁶, synovial debridement⁷⁶, transarticular impact⁷⁷, tibial osteotomy⁷⁸, meniscal sectioning¹¹ and articular cartilage scarification⁷⁹. In humans, ACL rupture can lead to OA⁸⁰, and the same is true in dogs⁸¹. Spontaneous CCL rupture (FIG. 4b,d,h) is common in dogs, and certain breeds such as West Highland White Terriers, Staffordshire Bull Terriers, Retrievers and Rottweilers are particularly predisposed^{82,83}. Analogous CCL transection is well documented to cause inflammation and reparative responses in the cartilage and synovium, yet ongoing instability prompts cartilage erosion and subchondral bone changes, thereby mirroring spontaneous knee OA⁸⁴. Spontaneous knee OA has a prevalence of ~20% in some breeds of dog⁸⁵, and ~50% of commonly affected breeds, such as Labrador Retrievers, develop contralateral knee CCL rupture within 1 year of diagnosis⁸⁶. Despite its ubiquity, the underlying cause of breed predilection remains elusive; biological and biomechanical explanations have been suggested, including the slope of the tibial plateau, intercondylar fossa impingement, underlying immune-mediated pathology, hormonal influences and genetics^{82,87}. Notably, the spontaneous rupture of a dog CCL often occurs during normal activities, such as walking or running. By contrast, human ACL rupture occurs most commonly during sporting activity⁸⁸. Although the underlying mechanisms of CCL pathology are undefined, predisposed dogs have thinner collagen fibrils in weaker CCLs that have increased expression of matrix metalloproteinase 2 than those of cruciate disease-resistant breeds such as Greyhounds⁸². Importantly, although ACL rupture in young humans is generally considered to be traumatic in cause, ~70% of macroscopically normal human ACLs also have histological evidence of pathology consistent with early degeneration⁸⁹.

Genetics. Non-contact rupture of a human ACL (such as occurs during pivoting and landing manoeuvres when playing sport), as distinct from a direct high energy impact to the knee, has a complex aetiology. As in the dog, variation in outcome is influenced by age, sex, genetics, obesity, muscle strength, activity and re-injury⁹⁰. Young female athletes have a threefold to sixfold higher risk of ACL injury than their male counterparts⁹¹. The risk of ACL injury is doubled in individuals with similarly affected relatives⁹² and is also raised in white individuals⁹³, suggesting the presence of sex-linked and genetically linked human determinants. Polymorphisms in *FBN2*, *VEGFA*, *KDR*, *COL1A1*, *DCN*, *ACN* (also known as *ACIN1*), *BGN*, *LUM* and *COL5A1* (many of which encode ECM proteins and growth factors) and interactions between *COL5A1* and *COL12A1* gene variants⁹⁴ are linked to human ACL rupture^{95–99}. Genetic associations with human ACL rupture found a *COL1A1* SNP that was replicated in several studies^{98,100–104}.

A systematic review¹⁰⁰ was followed by a GWAS that failed to reveal any ACL rupture-associated variants, highlighting the fact that replication and cross-species overlap will be mutually supportive in the investigation of complex traits.

Five-year-old dogs consistently have degenerative changes in their CCLs at both the macroscopic and microscopic levels (FIG. 4b). Susceptibility to CCL rupture is increased in Labrador Retrievers and Golden Retrievers, and the CCLs of these breeds have higher collagen turnover, less stiffness and less mature collagen crosslinks than the CCLs of Greyhounds, which are relatively rupture resistant⁸². The genetics of dog CCL rupture are complex; a 0.15–0.27 heritability exists in Newfoundlands, which have four putative quantitative trait loci (QTLs) by linkage analysis¹⁰⁵ and non-overlapping associations on CFA01, CFA03 and CFA33 by GWAS¹⁰⁶. A case–control comparison across four breeds revealed SNPs in genes involved in ligament

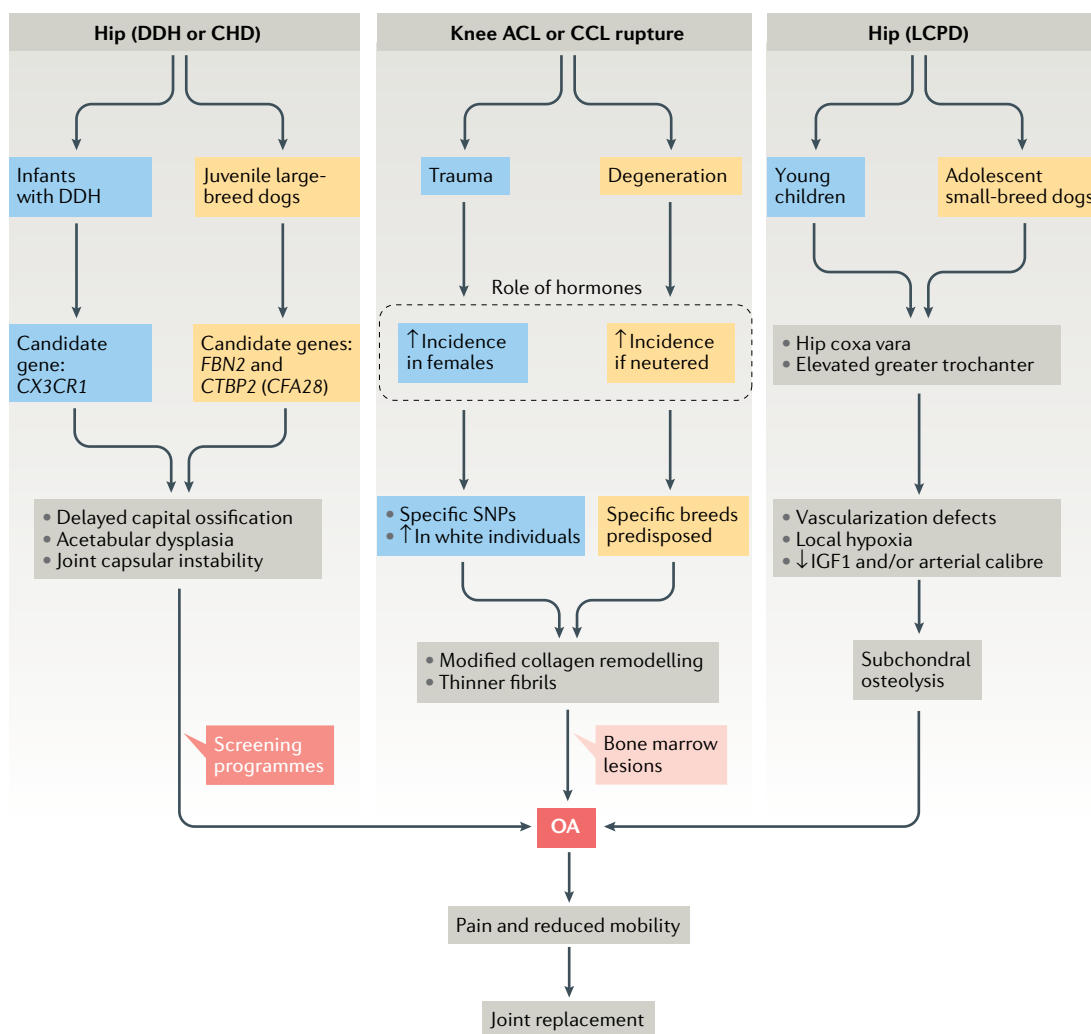


Fig. 2 | **Analogous disease in dogs and humans.** Similarities in the aetiopathology of dog (yellow) and human (blue) forms of osteoarthritis (OA) are shown for developmental vascular OA of the hip (Legg-Calvé-Perthes disease (LCPD) in dogs and LCPD and avascular necrosis of the femoral head in humans), developmental joint instability OA (canine hip dysplasia (CHD) in dogs and developmental dysplasia of the hip (DDH) in humans) and acquired adult joint instability OA (knee anterior cruciate ligament (ACL) rupture in humans and cranial cruciate ligament (CCL) rupture in dogs). IGF1, insulin-like growth factor 1; SNP, single nucleotide polymorphism.

ECM composition and strength that were associated with susceptibility to CCL rupture¹⁰⁷. Subsequent studies reported significant associations on CFA7-9 in several dog breeds³³ and genome-wide significance for CFA24 in ACL ruptures in Labrador Retrievers¹⁰⁸. This lack of replication is probably caused by limitations similar to those for CHD. Functional studies that utilize relevant temporal tissue samples from dog OA at various stages to identify expression QTLs that overlap with genomic QTLs will be necessary to establish causation (FIG. 2).

Using CCL rupture as a means to understand ACL rupture. Spontaneous CCL rupture might be analogous to experimental transection in dogs, as osteophytes and sclerosis develop at an early stage⁸¹ and end-stage OA develops over several years^{109,110} (FIG. 4d). However, the aetiology is likely to differ, as the CCL ruptures at its mid-substance during normal activity, which is often linked with prior degeneration and moderate to severe OA^{82,87}. Although CCL transection induces synovitis, lymphocytic–plasmacytic synovitis also occurs in spontaneous CCL rupture^{111,112}. The propensity for bilateral

disease to develop following CCL rupture has enabled investigation into early-stage and incipient disease, which has intriguingly revealed increased numbers of CD4⁺, CD8⁺ and CD3⁺CD4⁻CD8⁻ T cells in dogs with CCL ruptures compared with healthy controls, with the number of CD3⁺CD4⁻CD8⁻ T cells correlating inversely with radiographic severity¹¹³. Similar to the M1-like macrophage polarization that occurs in human knee OA¹¹⁴, preliminary data suggest that dog joints with CCL rupture also exhibit an M1-like macrophage polarization, whereas M2-like macrophages predominate in healthy joints¹¹⁵. The predictability of contralateral disease development in dogs with ruptured CCLs has also offered unique opportunities for biomarker studies, which have revealed an increase in IL-8 concentrations in synovial fluid before CCL failure¹¹⁶. Changes identifiable on MRIs of partially ruptured dog CCLs might also improve our understanding of OA progression¹¹⁷. However, owing to the differing pathogenesis of rupture, it remains to be seen whether changes predicted by incipient contralateral disease in dogs are recapitulated in human OA.

Comparisons between OA associated with dog CCL rupture and OA associated with human ACL rupture might also help to explain the relationships that exist between hormonal status and OA. Oestrogen reduces collagen synthesis in fibroblasts from human ACLs in vitro^{118,119}, and the risk of ACL rupture in female human athletes is increased on the first days of the menstrual cycle¹²⁰. Likewise, the commonplace neutering of dogs increases CCL rupture risk, as does being female and being overweight^{83,121}. Hence, examination of the at-risk female dog might offer insight into the function of hormones or post-neutering weight gain¹²². A more complete understanding of the similarities and differences between OA related to dog CCL rupture and OA related to human ACL rupture might reveal the hormonal influences that underpin the markedly higher primary human knee OA incidence in postmenopausal females than in age-matched men¹²³.

We are not arguing that human and dog cruciate ligament ruptures have identical causes nor identical management strategies (BOX 3) but instead aim to highlight that both involve mechanical instability and intractable progression to knee OA, thereby making simultaneous research in both species potentially beneficial.

Other conditions of interest

Osteochondritis dissecans. Dog shoulders develop both age-related primary OA²³ and osteochondrosis, which presents as osteochondritis dissecans lesions¹²⁴ (FIG. 5) that are characterized by disordered endochondral ossification superimposed upon previously normal growth^{125–127}. Osteochondrosis predominates in medium and large breeds of dog, affects males more frequently than females and is often bilateral and site-specific¹²⁸. Intriguingly, male humans are also more frequently affected with osteochondrosis, and bilateral disease is also common^{129,130}. Unilateral osteochondrosis in young dogs enables tissue samples of early contralateral lesions to be collected and arthroscopic autologous or biomaterial articular resurfacing to be carried out^{131,132}.

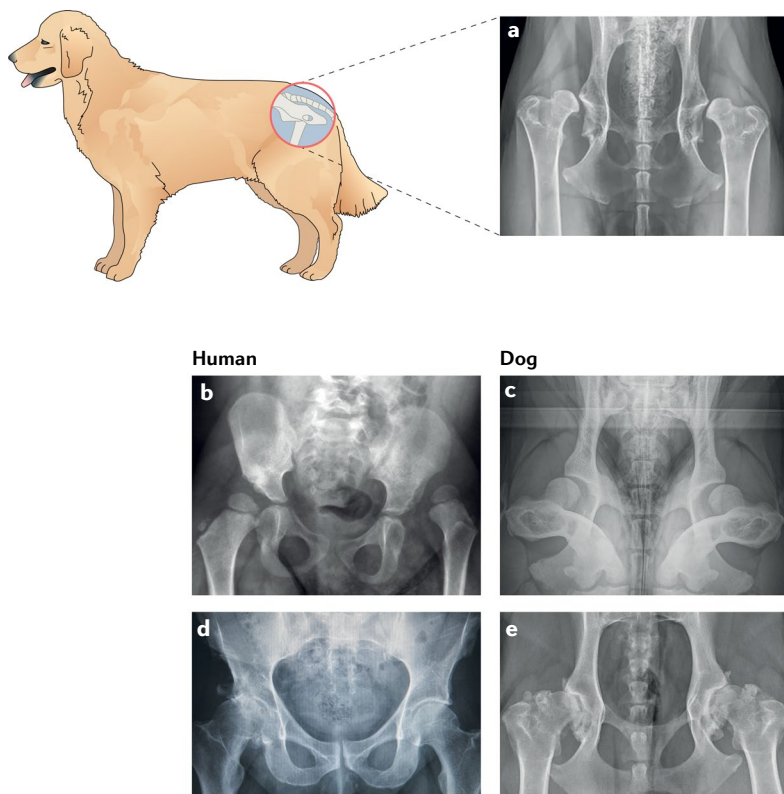
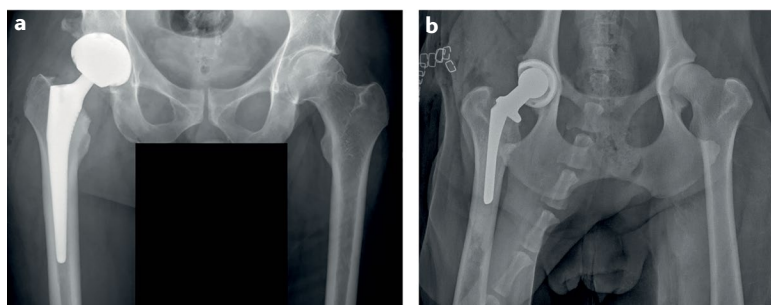


Fig. 3 | Hip dysplasia and hip osteoarthritis in dogs and humans. Hip dysplasia commonly occurs in juvenile large-breed dogs, such as Golden Retrievers, and can result in osteoarthritis (OA) in later years. **a** | Radiograph of an adult dog with severe hip dysplasia and luxated hips. The image was acquired as a ventrodorsal extended limb radiograph. **b** | Radiograph of a human infant with a dysplastic luxated left hip. **c** | Radiograph of a 3-month-old dog with bilateral dysplastic and subluxated hips. The image was acquired in a dorsolateral subluxation screening position. **d,e** | Radiographs of the hip joints from a middle-aged male human with primary OA (part **d**) and a middle-aged female large-breed dog with secondary OA subsequent to hip dysplasia (part **e**). Both human and dog osteoarthritic hips show evidence of advanced new bone formation and sclerosis of the acetabulae and the femoral head and neck region. Part **b** courtesy of R. T. Loder, Riley Children’s Hospital, USA.

Box 2 | Clinical treatment of dysplastic hips

Treatment options for canine hip dysplasia (CHD) and developmental dysplasia of the hip (DDH) consist of similar symptom management, hip reconstructions and replacement methods. Radiographic images show a human total hip replacement using an uncemented stem and cup (see the figure, part a) and a dog total hip replacement using a cemented stem and uncemented cup (see the figure, part b). Trait similarities and a relatively truncated dog lifespan will probably make the discovery of common early features of hip osteoarthritis (OA) more rapid in dogs with CHD than in humans with DDH. The dog is also an excellent model for human total hip replacement^{202,229}. Both dogs and humans have similar bone remodelling characteristics and respond well to hip replacement for non-responsive and debilitating end-stage OA^{201,224,230}. The treatments for CHD and DDH use similar clinical and functional measures, including gait analysis and accelerometer measurements, validated clinical questionnaires and imaging techniques^{168,229,231,232}.



Aberrant re-induction of endochondral ossification processes has been described in articular cartilage in several forms of human and mouse OA^{133,134}, and it is therefore intriguing that the dog shoulder is targeted in this particular way, much more so than in the human.

Control of endochondral ossification differs markedly in different breeds of dog, which can have an astounding several-fold size variation and differ in growth rate and/or physeal closure at puberty. Earlier physeal closure in small breeds is consistent with more rapid growth and potential predisposition to osteochondritis dissecans. Growth plates in large breeds, such as Great Danes, have an expanded hypertrophic region and more active bone morphogenetic protein 2 (BMP2)–BMP6 signalling than miniature breeds¹³⁵, suggesting that studies of osteochondritis dissecans could provide unique insights into the function of longitudinal bone growth in these disease processes. Another possible connection has emerged from studies that established direct links between genetic selection for high growth rates, failure of mechano-adaptive bone changes and predisposition to skeletal diseases in birds^{136,137}. Whether similar relationships persist in dogs and humans has yet to be explored.

Legg-Calvé-Perthes disease. Legg-Calvé-Perthes disease (LCPD), a form of avascular necrosis of the femoral head, involves slow femoral head destruction in children. LCPD has a direct analogue in small-breed dogs (FIG. 6), such as Yorkshire Terriers, Maltese, Miniature Poodles and Chihuahuas, during early life that peaks at skeletal maturity (6–7 months)¹²⁴. Bilateral hip OA is common in human LCPD, peaking at 4–8 years of age, and occurs approximately four times more frequently in boys than in girls¹³⁸. By contrast, no sex bias for LCPD exists in dogs, and the trait is often unilateral¹²⁴. Familial

and isolated human LCPD occurs with an estimated ~0.84 heritability in relatives of probands (first affected family member)^{139–141} and has links to environmental and demographic factors¹⁴². A similarly high degree of heritability was found in an experimental pedigree of Manchester Terriers¹⁴³. Further genetic studies have been described in both dogs and humans, with intriguing differences and similarities^{144–148}, discussion of which is beyond the scope of this Review.

A One Medicine approach

The idea that OA is not one disease but a syndrome encompassing heterogeneous, stratified groups of patients with characteristic aetiologies has been gaining acceptance. This shift in thinking has led to an increased appreciation that the development of new targeted therapeutic approaches might be accelerated by patient stratification on the basis of phenotype (or endotype), which might also improve alignment with preclinical animal models. An initial attempt at disease stratification of patients with knee OA proposed five OA phenotypes, which are defined by the severity of joint involvement, muscle strength, obesity and depression¹⁴⁹. A subsequent systematic review¹⁵⁰ identified six phenotypic groups: those with central chronic pain sensitization; inflammation; systemic metabolic changes; bone and/or cartilage remodelling; mechanical overload with varus deformity and compartment diseases; and minimally symptomatic OA. OARSI suggests five clinically distinct phenotypes that are based on presentation with pain sensitization, psychological distress, radiographic severity, BMI, muscle strength, inflammation and comorbidities¹⁵¹. Another systematic review of knee OA identified obesity and other metabolic abnormalities, sex, cartilage damage patterns and inflammation as variables upon which distinct structural OA phenotypes could be delineated¹⁵². We conjecture that the common dog OA types we have highlighted herein provide models for ready alignment with human OA on the basis of anatomy, aetiology and pathophysiology (TABLE 1) and propose a system for their use with a view to analogous human OA.

Advantages

Is there any prospect that the study of spontaneous dog OA might accelerate new developments in human OA? Currently, cancer research is the field that has most readily adopted and successfully applied a One Medicine approach. Cancers account for >25% of dog mortalities¹⁵³ and, like OA, the multifactorial and complex aetiology of cancer reduces the predictive value of rodent models. The [Canine Comparative Oncology Genomics Consortium](#) initiated an extensive, naturally occurring canine cancer tissue bio-repository. Partnerships between veterinary and human oncologists and biologists subsequently generated a Comparative Oncology Trials Consortium¹⁰, which rapidly discovered new facets of carcinogenesis^{154,155} that could be translated into human trials¹⁵⁶. From the diseases highlighted in this Review, we outline five clear opportunities provided by adopting a similar One Medicine approach in OA research.

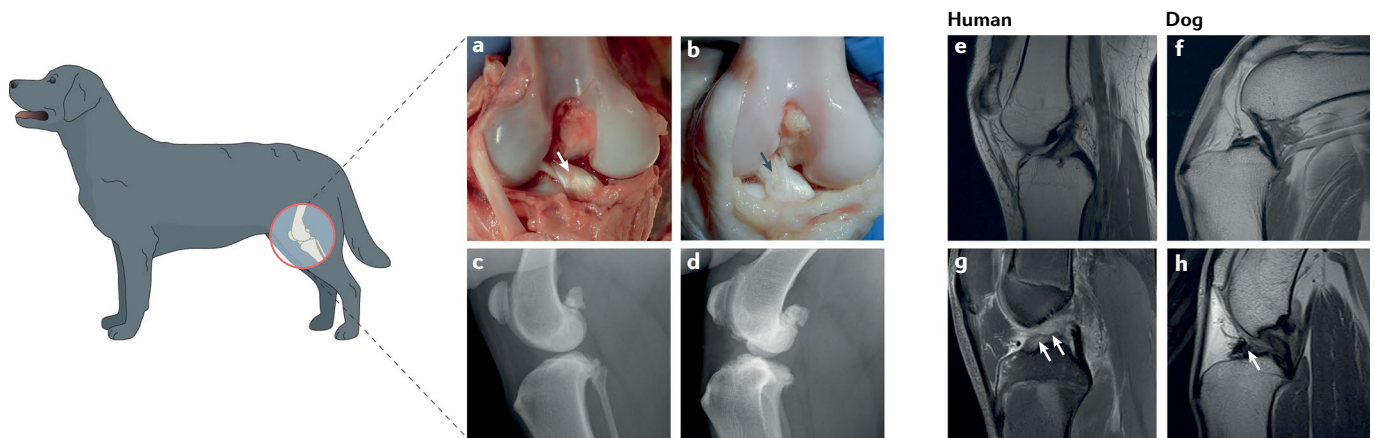


Fig. 4 | Cruciate ligament rupture and knee osteoarthritis in dogs and humans. Cranial cruciate ligament (CCL; analogous to the human anterior cruciate ligament (ACL)) rupture occurs in most breeds of dog but is particularly common in young large-breed dogs, such as Labrador Retrievers, and older small-breed dogs. **a** | Post-mortem dog knee with a healthy CCL (arrow). **b** | Post-mortem dog knee with a spontaneously degenerated, partially ruptured CCL (arrow shows degeneration of the craniomedial (anteromedial) band). **c** | Mediolateral radiograph of a healthy dog knee that shows no signs of effusion, sclerosis, soft tissue thickening or osteophytosis. **d** | Mediolateral radiograph of a dog knee with a ruptured CCL and osteoarthritic changes. Radiographic joint effusion and new bone formation associated with the distal pole of the patella, the tibial plateau, trochlear ridges and the insertion of the CCL are evident. **e** | Proton density turbo spin echo sequence sagittal MRI of a healthy human knee. **f** | T1-weighted sagittal MRI of a healthy dog knee showing the CCL in part and the caudal cruciate ligament in full. **g** | MRI of an adolescent human knee with a ruptured ACL (arrows indicate the space without an intact ligament). **h** | MRI of a dog stifle joint with a ruptured CCL (arrow indicates space without a CCL). Part **e** courtesy of K. Chappell, Imperial College London, UK.

A source of tissue for research. From the examples provided in the proposed OA sub-categorization (TABLE 1), researchers could identify a clinical dog syndrome and then perform studies to verify the validity of the alignment we propose. For example, such an approach could involve an exploration of whether two distinct subgroups of patients with symptomatic knee OA exist in dogs on the basis of inflammatory gene expression profiles in peripheral blood leukocytes¹⁵⁷ or whether dogs have alternative metabolic or cell senescent mechanistic OA phenotypes¹⁵². In addition, clinical samples such as fragments of osteochondritis dissecans lesions, resected ruptured CCL remnants, excised damaged menisci, or plasma, urine or synovial fluid samples could be retrieved for biomarker assessment as part of the clinical disease management of a dog. Dogs with unilateral CCL disease often have premonitory radiographic and clinical signs of synovial effusion, and partial CCL tears are often associated with painful lameness in affected dogs, even when instability is minimal. Measuring soluble biomarkers in biological fluids might therefore facilitate early diagnosis or evaluation of interventions¹⁵⁸. Similarly, resected osteoarthritic femoral heads and synovium from hip replacement procedures could be used to facilitate a greater understanding of OA mechanisms and could perhaps be used to improve diagnostic and prognostic criteria.

The correlation of arthroscopic, surgical and advanced imaging data with stage-specific changes in tissue samples taken from dogs with specific OA phenotypes would also be possible, for example, correlating analyses of synovial fluid and serum samples with clinical joint scores in dogs with CCL rupture. Similar correlations have previously been performed in experimental models of OA

but could also be evaluated in spontaneous dog OA with appropriate staging and radiographic scoring^{111,159–162}. Dog joints enable longitudinal study using modern imaging techniques (such as CT, MRI and arthroscopy), serial force plate analysis and tissue sampling and have the potential to reveal additional insights into OA at early and late stages compared with mouse models of OA, in which such evaluations are not technically feasible. Indeed, tissue sampling could be included as part of a clinical trial as soon as clinical, radiographic, CT or MRI evidence of abnormal joint architecture is identified. Gaining usable samples of sufficient quantity is a practical possibility when working with dogs with spontaneous OA through schemes such as the [Cornell Veterinary Biobank](#) or the [Vetmeduni Vienna VetBiobank](#).

A means to identify the genetic basis of analogous disease. The study of purebred dogs lends itself to the genetic analysis of complex diseases such as hip dysplasia, osteochondritis dissecans and LCPD. Residual blood collected for routine haematology or biochemistry tests in the clinic could be used for many purposes, including as a source of DNA for genetic research; removed tissues could also be utilized for such studies. Making use of the broad linkage disequilibrium introduced by selective breeding in breeds with a high predilection for a disease compared with breeds with a low predilection for a disease will help to identify common candidate disease-associated genes in these polygenic conditions.

A source of clinically applicable functional outcome measures. One clear difference between dogs and humans is the ability to self-report pain. As subjective pain measures can be readily quantified in humans,

Force plate analysis

Instruments that measure ground reaction forces as they are walked over by a human or an animal; used to provide parameters of gait and limb function.

Telemetric accelerometry

A device that measures and records proper acceleration; used to determine activity and gait parameters.

Quantitative Sensory Testing

A non-invasive test of nerve function and/or pain that uses temperature or skin vibration.

Peak vertical force

A biomechanics term that identifies a component of locomotor ground reaction force.

'Three Rs' agenda

An initiative to improve the use of or reduce the numbers of animals used in scientific research through three key initiatives — replacement, reduction and refinement.

objective data have been used sparingly¹⁶³. Instead, clinical metrology instruments and a patient-centred approach to outcome assessment have become mainstays in the assessment of human OA. A patient-centred approach has also been incorporated into veterinary assessments; clinical metrology instruments and validated outcome questionnaires are used to capture pain-related behaviour over long periods of time in home environments¹⁶⁴, and pet owners can provide proxy assessments, just as parents or caregivers would for young children or adults with dementia^{165,166}. Although objective assessment methods are less readily available than proxy reporting, these instruments have been validated, they are inexpensive and are straightforward to use, the data they produce are easy to analyse, and they do not have the relevancy issues associated with proxy reporting. Instruments such as the Canine Brief Pain Inventory^{167,168}, which is analogous to the human Brief Pain Inventory, have the potential to expand the ability to gain outcome assessment data from veterinary clinical trials. Such inventories (including the Liverpool OA in Dogs index¹⁶⁹) have to be valid, reliable and responsive to clinical change; measure what they seek to measure; be validated against a gold standard, such as force plate analysis; and demonstrate reliability to generate the same outcome whenever an individual with unchanged disease is re-assessed^{167,169}. The power of such inventories has been verified for outcomes such as disturbed sleep in dogs with OA¹⁷⁰.

The size of a dog compared with rodents enables different types of functional outcome assessments to be used, many of which are clinically applicable to humans. Although many veterinary researchers use visual lameness and clinical pain assessments (which report only single outcome measures), force plate analysis and radiography are also used¹⁷¹, which has led to objective force plate outcome measurement becoming a common gold

standard for functional assessment in dogs. Kinematic evaluation, as well as the more commonly used kinetic gait analyses using force plates and pressure mats, provides objective snapshots of impairment^{172,173}, and the size and amenable nature of dogs make them suitable for such assessments^{173,174}. Additionally, the introduction of miniaturized data recording technology has made telemetric accelerometry and activity monitoring practical in the clinical setting¹⁷⁵. These objective assessments are less expensive and less complicated to use than force plates and offer easy longitudinal assessment for OA interventions and disease progression^{174–177}. Many other tests could be useful in OA monitoring, including thermal imaging and mechanical nociceptive threshold testing^{178,179}. Functional activity monitoring, force plate analysis and advanced MRI are performed on dogs in a manner that mirrors their use in human patients, and brain imaging in conscious pet dogs is also reliable and practical and could potentially be used for comparative neuroscience studies^{180,181}.

Quantitative sensory testing (QST), a method of quantifying pain, has been used to demonstrate central sensitization in human OA^{182,183}, experimental dog OA¹⁸⁴ and spontaneous dog OA¹⁸⁵. QST has also been used to demonstrate the efficacy of dog total hip replacements for reversing hyperalgesia¹⁸⁶, as occurs in humans¹⁸⁷. Dogs with spontaneous hip OA could therefore be good candidates for testing anti-hyperalgesia therapies while simultaneously experiencing the potential benefits. Overall, compelling evidence exists that veterinary randomized controlled trials (V-RCTs) in companion dogs with OA and chronic pain might reliably predict treatment efficacy in humans^{168,177,188}. Parallel drug intervention studies are thus appropriate to accelerate therapeutic trials in dogs of drugs designed to treat pain in humans and might improve access to pain treatment not currently licensed in dogs, which could improve their welfare.

Box 3 | Clinical treatment of knee cruciate ligament rupture

Surgical repair for cranial cruciate ligament (CCL) rupture was initially based on a modification of the Hey-Groves human repair process. A strip of autograft lateral fascia was tunneled within the joint to mimic the defective CCL (the so-called Paatsama procedure) and was advocated for use in dogs in the 1950s²³³. Such intra-capsular repairs or extra-capsular prosthetic ligament placement techniques and their modifications over the years improved outcomes over non-surgical management and remained in use for the next three decades²³³. A shift in approach was proposed in 1993 by Slocum and Devine-Slocum, in which the angle of the tibial plateau would be changed by proximal osteotomy to reduce the anterior vector force that was causing subluxation²³⁴. This technique remains a preferred approach and contrasts markedly with the current management of human anterior cruciate ligament (ACL) rupture, for which grafting reconstruction techniques still dominate²³⁵. This divergence in surgical approaches might be a result of the smaller size of canine joints, the suitability of autografts, suboptimal materials or, perhaps, surgical expertise. However, fundamental biomechanical disparities between dog CCLs and human ACLs might also be important. Dogs have a more sloped tibial plateau⁸² and flexed standing angle than humans, which creates greater continuous biomechanical cruciate ligament strain than the upright bipedal human stance with its flatter tibial plateau. The synovitis associated with dog CCL degeneration could potentially also affect graft survival. Irrespective of the route by which a cruciate ligament is ruptured, the resultant mechanical instability and trauma in both dogs and humans promote the progression of osteoarthritis (OA) and any linked meniscal pathology⁹⁰. Importantly, no current treatment prevents or reduces the development of OA for either species^{90,110}.

An intermediary between preclinical studies and clinical trials. Dog OA is ideally suited for V-RCTs because of the rigour of the functional outcome measures used. A study in which peak vertical force (PVF) and accelerometer data were compared to continuously track activity at home in dogs with spontaneous CCL disease showed excellent between-session reliability that aligned well with locomotor activity¹⁸⁹. These results indicate that PVF and accelerometry are robust, reliable and reproducible non-invasive tools for monitoring and assessing the effectiveness of new therapies in spontaneous knee OA¹⁸⁹. V-RCTs are free from the ethical objections associated with the use of experimental dog models, are aligned with the 'Three Rs' agenda¹⁹⁰, are less expensive than using experimental dog models and increase the possibility of biological tissue sampling without using additional dogs. The approach of considering a V-RCT as an alternative intermediary when developing new therapies is highlighted by the similar clinical benefits that have been achieved when novel treatments are trialled in dogs and humans, suggesting that good clinical responses in dogs with OA undergoing treatment might also be seen in humans. Examples include treatment

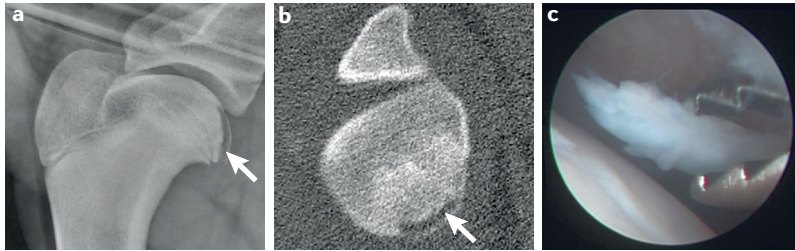
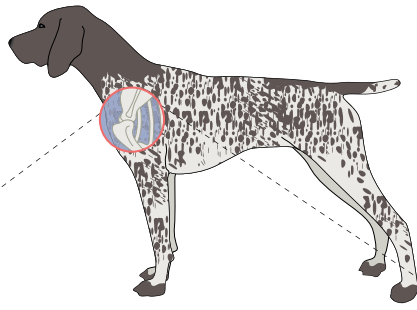


Fig. 5 | Shoulder osteochondritis dissecans in dogs. Shoulder osteochondritis dissecans lesions predominantly occur in adolescent large-breed dogs. **a,b** | Lateral radiograph (part **a**) showing a classical mineralized flap over the caudal region of the humeral head, which can also be seen in a transverse CT (part **b**) of the same shoulder with associated subchondral sclerosis (arrows mark the lesion). **c** | Osteochondritis dissecans flap being removed arthroscopically.

with anti-nerve growth factor antibodies in dogs¹⁷⁷ and humans¹⁹¹ and the use of novel anti-inflammatory agents, such as resiniferatoxin and the combination of licoferone and doxycycline, which were similarly effective in dogs with spontaneous OA^{192–194} and in patients with OA in phase III trials^{195,196}. Intra-articular hyaluronan injection in humans with OA¹⁹⁷ and in dogs with CHD¹⁹⁸ also showed comparable short-term symptomatic benefit without structure-modifying efficacy.

One example of how dog OA studies have proved useful in a One Medicine approach is in trials of stem cell therapy, which have advanced more rapidly in dogs than in humans. Allogeneic adipose tissue-derived mesenchymal stem cells harvested from visceral adipose surgical waste from ovariectomy procedures have been combined with hyaluronan and injected intra-articularly into osteoarthritic dog elbow joints, leading to reduced

lameness and the regeneration of hyaline-type cartilage¹⁹⁹. In another study, the measurement of PVF and vertical impulse using force plates showed transitory improvement in severe hip OA after intra-articular administration of adipose tissue-derived mesenchymal stem cells²⁰⁰.

The ability to pilot new technologies or therapies. The use of dogs with spontaneous OA for therapeutic intervention studies has several benefits, including the use of human-scale implants and instruments for procedures such as arthroscopic treatment. For example, total hip replacements have been in veterinary clinical usage since the 1970s²⁰¹. Outcomes for this intervention are good, with <20% complication rates for cementless hip replacements after 4 years²⁰². The development of similar implants for humans, including resurfacing hip replacements²⁰³, porous implants²⁰⁴ and hydroxyapatite-coated prostheses²⁰⁵, relied heavily on experimental testing in dogs, and current veterinary modular hip replacements include both cemented and uncemented osseointegrative replacements. In addition, similar complications are seen in dogs and humans, such as aseptic loosening, bone remodelling and implant infection.

The relatively short lifespan of a dog (~8–12 years) also enables end-of-life retrieval studies. Post-mortem retrieval of implant material from veterinary patients is relatively inexpensive and straightforward and could provide additional insights into common surgical complications. Such samples have been used to examine the mechanical, histomorphologic and radiographic features of aseptic loosening, which is a particular concern for total hip replacements in humans under the age of 50 (REF.²⁰⁶). The results of one such study suggested that failure was initiated by poly(methyl methacrylate) de-bonding from the metal implant²⁰⁶. Improved implant designs, if appropriately and ethically managed, could therefore be piloted in V-RCTs in dogs, as they offer a comparatively short time frame for implant retrieval compared with a human clinical trial.

Remaining challenges

Accurately quantifying pain in animals. Pain is a cardinal symptom of OA, and symptomatic management of pain using a limited repertoire of drugs, including analgesics and anti-inflammatory agents, is central in both veterinary²⁰⁷ and human clinical practice²⁰⁸. FDA guidelines for drugs, devices and biological treatments for OA are available, but preclinical research advances are not yet being translated into effective new drugs in clinical practice, leading to questions regarding the predictive utility of current animal models of OA^{7,209–211}.

Similarities in neurophysiology across mammals strongly suggest that the type of pain experienced by humans and animals is analogous²¹⁰. However, pain experiences in OA are complicated and involve peripheral nociceptive sensitization, structural changes to joint innervation, central nervous system sensitization, neuropathic changes and a host of mediators, as well as simple nociceptive input from damaged joint tissues²¹². Pain severity correlates poorly with radiographic structural changes in humans²¹³ and dogs²¹⁴ with OA.

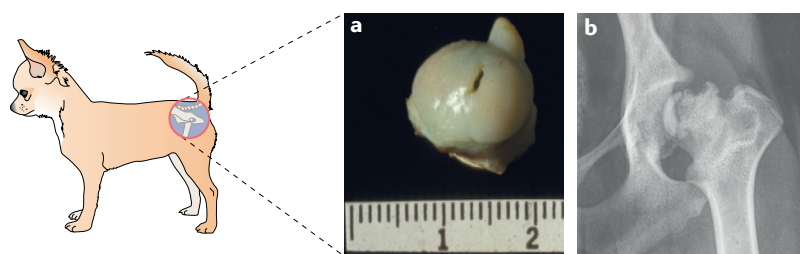


Fig. 6 | Avascular necrosis of the femoral head (Legg-Calvé-Perthes disease) in dogs. Legg-Calvé-Perthes disease (LCPD) occurs predominantly in the hip joints of small-breed dogs. **a** | Excised femoral head with an abnormal articular surface morphology and a central dark line indicating an articular surface defect. **b** | Ventrodorsal radiograph of a dog hip joint showing typical LCPD focal lucencies and new bone formation, as seen in advanced lesions.

Vertical impulse

An index of limb function generated from force plate analysis and derived from the vertical vector force applied and the duration that it is imparted for.

The development of new therapies for pain in OA will therefore require effective models that recapitulate the joint changes that occur in OA, as well as the clinical symptoms.

Levels of pain in OA are affected by synovitis, osteochondral pathology and sensitization, which are not accounted for by structural radiographic changes^{212,215}. Good models of OA therefore need to reflect the longitudinal natural history of human OA phenotypes^{216,217}. This premise is perhaps most elegantly demonstrated in studies of spontaneous dog OA in which advanced non-invasive imaging has revealed evidence of disease progression similar to some human OA phenotypes^{216,217}. Indeed, powerful, reliable and validated semi-quantitative MRI approaches have already been used in multicentre clinical trials in patients with OA^{218,219}. The presence, number and size of bone marrow lesions (identified by characteristic MRI signal intensity changes) have been linked to the severity of pain in patients with OA²²⁰. Natural animal models for bone marrow lesions are clearly required, and indeed,

bone marrow lesion-like structures with focal articular cartilage changes have been linked with disability in the dog CCL transection model of OA and in dogs with spontaneous CCL-rupture-induced OA^{221,222}. In the search for models of human pain, researchers also need to carefully consider the evolutionary role of pain responses. As prey, rodents are thought to show less overt signs of pain than predators such as humans and dogs. As signs of pain are common end points for measuring pain, fellow predator species are likely to more accurately represent human pain physiology than rodents. Considering the important veterinary clinical desire to understand and manage pain in dogs with OA, potential exists for beneficial sharing of ideas between clinical researchers and veterinary researchers.

Reliability of veterinary data. V-RCTs clearly differ from experimental animal research; they require ethical review and incentivization, and longitudinal follow-up can be problematic. Ideally, data retrieval methods need

Table 1 | Proposed stratification of dog osteoarthritis and alignment with human disease

OA subtype	Disease in dogs	Epidemiology in dogs	Analogous disease in humans	Epidemiology in humans
Acquired juvenile instability	CHD	<ul style="list-style-type: none"> Occurs in dogs from large and/or giant breeds (prevalent in Golden Retrievers, Labrador Retrievers, Rottweilers and German Shepherds; extremely rare in Greyhounds and Borzois) that are 3–12 months old^a Progression to OA in 1 year 	DDH	<ul style="list-style-type: none"> Occurs in infants Prevalent in females Progression to OA in 30 years
Acquired adult instability	CCL rupture and meniscal injuries	<ul style="list-style-type: none"> Occurs in young adult dogs from medium or large breeds (Rottweilers, Golden Retrievers, Labrador Retrievers and Staffordshire Bull Terriers) that are commonly >2 years old or in dogs from small breeds (Yorkshire Terriers and West Highland White Terriers) that are >6 years old ~50% of dogs develop contralateral disease within 2 years <50% of dogs have meniscal (mostly medial) pathology Increased risk in neutered females 	ACL rupture and meniscal injuries	<ul style="list-style-type: none"> Occurs in active adults, commonly during sporting activities Influenced by the menstrual cycle
Developmental vascular	LCPD	<ul style="list-style-type: none"> Occurs in dogs from small breeds (toy dogs and Terriers) that are 4–11 months old and has no sex predilection Autosomal recessive trait in Miniature Poodles and West Highland White Terriers 	<ul style="list-style-type: none"> LCPD Adolescent ANFH 	<ul style="list-style-type: none"> LCPD occurs in children between 4 and 8 years old and is more prevalent in boys than girls Adolescent ANFH occurs in adolescents near skeletal maturity and is associated with low circulating concentrations of IGF1 and poor caliber arteries
Developmental endochondral	Osteochondritis dissecans of the shoulder or knee	<ul style="list-style-type: none"> Occurs in dogs from large or giant breeds (Great Danes, Labrador Retrievers and Border Collies) that are 5–18 months old More prevalent in males and often bilateral 	Osteochondritis dissecans	<ul style="list-style-type: none"> Occurs in children, adolescents and young adults Family history More prevalent in males and often bilateral
Environmental: obesity-related	OA of the elbow, hip or shoulder	Can occur in any breed, often between 4 and 8 years of age	OA of the knee and small joints of the hands	Occurs in middle-aged and older adults; multiple joints are often affected
Environmental: trauma-related	OA of the hip, elbow, hock (ankle), carpus or digits	Occurs in racing Greyhounds that are 4–8 years old as digital OA and carpal sprains that lead to OA	Physical occupation-associated OA	Occurs in athletic individuals, often in middle age

ACL, anterior cruciate ligament; ANFH, avascular necrosis of the femoral head; CCL, cranial cruciate ligament; CHD, canine hip dysplasia; DDH, developmental dysplasia of the hip; IGF1, insulin-like growth factor 1; LCPD, Legg-Calvé-Perthes disease; OA, osteoarthritis. ^aThe potential exists to classify an adult form of CHD (with acetabular dysplasia) in which late-onset hip OA occurs in aged dogs that are otherwise normal upon screening at 2 years of age.

to be non-invasive, non-harming and in line with clinical management, such as walking upon a pressure walkway or owner-assessed metrics. Non-invasive imaging, such as MRI, CT and arthroscopic imaging, can be highly informative, but its use is often limited by cost and the need to show a clinical indication. Excellent V-RCTs are possible but require careful planning²²³.

A further issue is the throughput of veterinary studies; a disease might be common, but unlike many human health-care providers such as the National Health Service (NHS) in the UK, the veterinary profession has historically been composed of many independent veterinarians, each of whom see a relatively small number of animals with a particular condition. However, the growth of multi-practice corporate ownership might promote uniformity in veterinary clinical approaches and increase the number of animals available for a study. Initiatives such as the UK National Veterinary Canine Hip Replacement Registry²²⁴ and the Comparative Oncology Trials Consortium¹⁰ are also seeking to improve the acquisition of animals with particular diseases, and more standardized clinical outcome assessments are slowly being adopted across veterinary groups²²⁵. As with human trials, loss to follow-up and mid-trial exclusions also make obtaining suitable numbers of patients for analysis challenging. The lack of any centralized funding is also an issue, and veterinary medical care is essentially privately funded, which complicates the development of new therapies or research avenues. Research is currently further hampered by the fact that funding bodies often want results in a 1–2-year time frame, which is not feasible for OA outcome assessment.

Moreover, scepticism seems to exist concerning the variability in noisy veterinary clinical data, compared with data from animal models that have controllable genetic backgrounds but poorly defined disease processes. Such attitudes ignore the fact that veterinary clinical studies conveniently mirror the noise encountered in human trials. Even when conducted well, it can

be difficult to acquire good quality veterinary research published in high impact journals (perhaps partly owing to lack of aspiration from the authors), which can slow the dissemination of research; the inclusion of veterinarians on scientific review boards could be advantageous to alter this trend. Despite these issues, a great deal of potential and opportunity exist to develop veterinary research that could be highly informative and could offer different advantages to animal model research and human clinical trials.

Conclusions

In this Review, we have sought to highlight the potential benefits for dog and human health that could follow the adoption of One Medicine approaches to basic and clinical research and practice for OA. Human and dog OA are heterogeneous and spontaneous, and we have emphasized some analogous forms of OA in which the dog is potentially the best model for the human counterpart and have also highlighted some homologies that underpin OA disease mechanisms, similar comorbidities and known distinctions. Much can be gained from studying a large animal with spontaneous OA, and understanding the reasons behind any differences will be just as informative as understanding the similarities.

We have consequently also sought to increase awareness of V-RCTs (a database is currently being developed by the American Veterinary Medical Association), national repositories of dog OA tissue samples, national retrieval banks for implants and V-RCT guidelines (including standardized outcome assessments to enable their amalgamation into an OA One Medicine paradigm). These resources have barely been exploited, and their integration into research using a One Medicine approach could generate breakthroughs in OA treatment in dogs and humans and in understanding how genetics, epigenetics, biomechanics and lifestyle affect OA aetiology and pathogenesis.

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Author contributions

R.L.M. researched data for the article. R.L.M., R.J.T. and A.A.P. contributed substantially to discussions of content. All authors wrote the article and reviewed or edited the manuscript before submission.

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