CHAPTER 89

Osteochondritis Dissecans

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INTRODUCTION: HISTORY AND TERMINOLOGY

The term "osteochondritis dissecans" (translation from the Latin term: "inflammation of bone and cartilage resulting in the formation of loose fragments") was first used by the German surgeon Franz König (1832–1910). In his paper on loose bodies in joints, he discussed three possible causes: (1) severe trauma that would lead to breaking off of fragments through direct mechanical impact; (2) lesser trauma causing necrosis of subchondral bone that would at a later stage result in separation of fragments; and (3) development of fragments formed without any substantial trauma, but as the result of some (unidentified) underlying lesion.[1] It was not until 50 years later that it became clear that the underlying lesions were because of disturbances of the process of endochondral ossification.[2] In the equine veterinary literature, the terms "osteochondritis dissecans" or "osteochondrosis" are almost exclusively used for König's third category (i.e., for fragmentation based on disturbances of endochondral ossification).

In 1986 the term "developmental orthopedic disease" (DOD) was coined during a symposium organized by the American Quarter Horse Association.[3] This term encompasses virtually all noninfectious orthopedic deranged developments of growing young horses, of which osteochondrosis is the most common, but includes also cervical vertebral stenotic myopathy (Wobbler disease), collapse of cuboidal bones, angular and flexural limb deformities, subchondral bone cysts, and physitis. During that same meeting the terms "osteochondrosis," "osteochondrosis dissecans," and "osteochondritis dissecans" were defined, which are often incorrectly used as synonyms. Osteochondrosis (OC) is the disorder itself, osteochondritis is the inflammatory response to it, and in osteochondritis dissecans (OCD), an area of cartilaginous or osteochondral separation is present.[4] More than 20 years later,

at a time when more was known about the pathogenesis of OC, the terms *OC latens*, *manifesta*, and *dissecans* were proposed, where *latens* is defined as a focal chondronecrosis of the resting zone of the growth cartilage with adjacent vascular necrosis; *manifesta* indicates a later stage that includes focally impaired endochondral ossification and cartilage retention; and *dissecans* is characterized by cleft formation through the necrotic cartilage.[5]

A new term, juvenile osteochondral conditions (JOCC), has been introduced in a consensus paper for those developmental orthopedic disorders that are related to the immature joint or growth plate.[6] The term includes OCD, cuboidal bone disease, and various other forms of failure of the immature skeleton, but not cervical vertebral stenotic myopathy, flexural limb deformities, or angular limb deformities. With the term DOD for the wide panel of orthopedic disorders related to disturbances in musculoskeletal development, JOCC for the subset of lesions representing the different types of epiphyseal/metaphyseal developmental disorders, and OC with the subdivision in *latens*, *manifesta*, and *dissecans* for the specific disturbance of endochondral ossification of the articular-epiphyseal complex, semantics now seem well covered with a maximum of clarity.

ENDOCHONDRAL OSSIFICATION

In all mammals, the primordial skeleton is laid down first as a cartilaginous structure that starts to transform into bone during the fetal stage, a process that continues until well after birth (Figure 89-1). Unlike mature articular cartilage, these fetal cartilaginous structures are well vascularized by vessels running through so-called cartilage canals. Ossification of the primary centers of ossification in the diaphyses of the long bones starts early in fetal life, and at the time of birth, all diaphyses are bony structures. However, many secondary centers of ossification located in the epiphyses of the long bones and in other sites such as apophyses and cuboidal bones, are still partly cartilaginous at the time of birth.

Longitudinal growth of long bones occurs at the growth plates or physes. In these structures, chondrocytes originating from a germinal layer of cells (resting cells) undergo mitosis, proliferate, and subsequently hypertrophy and undergo apoptosis. The chondrocytes are encased by a scaffold of extracellular matrix (see Chapter 75), which forms the basis for the apposition of primary bone by osteoblasts that originate from the metaphysis

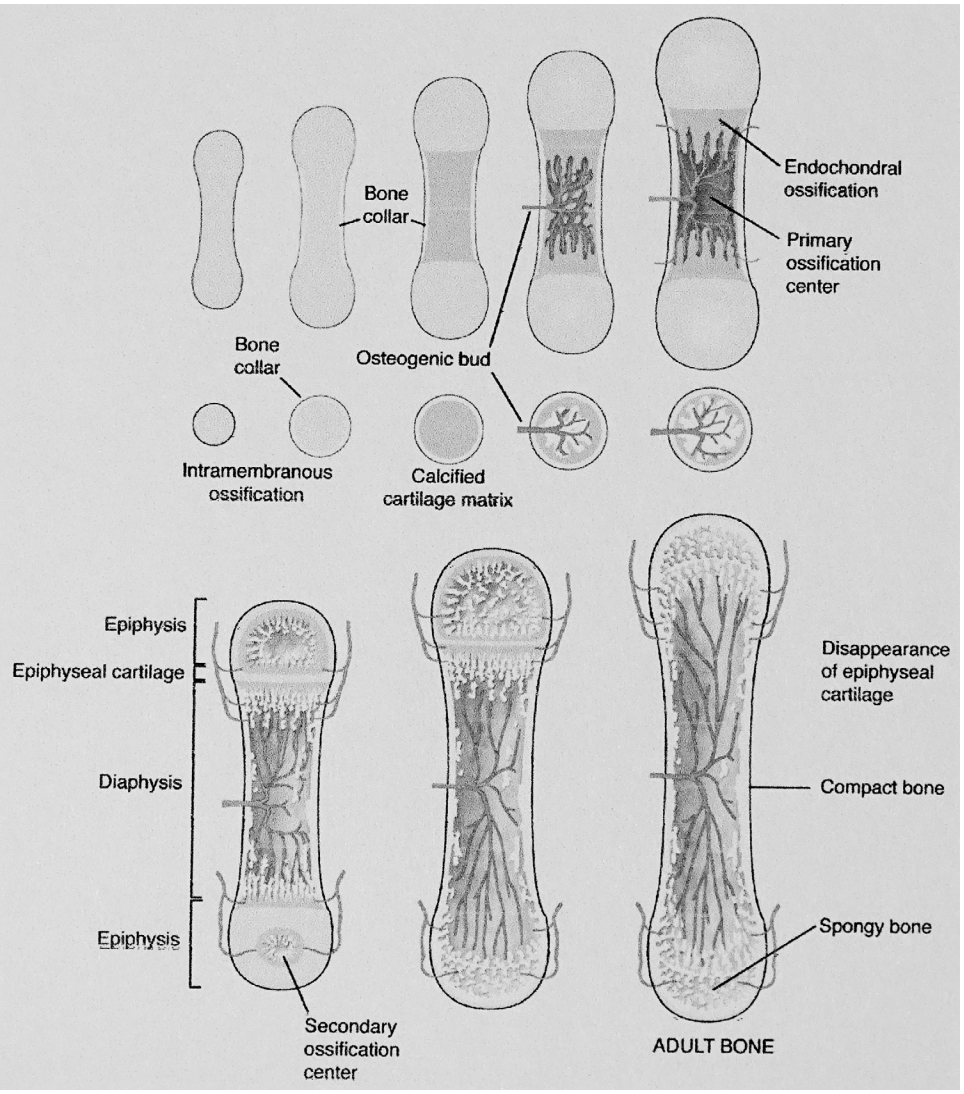

Figure 89-1. Semischematic drawing of the ossification process of the long bones in mammals. After closing of the growth plates, the only cartilage left is the articular cartilage. Note the rich vascularization of the cartilaginous precursor of the long bone and the absence of vascularization of mature articular cartilage. (Adapted from Van Weeren PR. Etiology, diagnosis and treatment of OC(D). *Clin Techn Equine Pract*. 2006;5:248–258.)

(Figure 89-2). The primary spongiosa that is formed will undergo continuous remodeling under the influence of biomechanical loading according to Wolff's law[7] during the entire growth period of the foal. It has been shown to be prepared for the direct postnatal loading in every precocial species such as the horse, possibly based on a genetic blueprint.[8] This entire process of cartilage remodeling, followed by calcification of cartilage, deposition of primary bone, and successive remodeling into bony trabeculae as occurs in the young, growing animal, is known as endochondral ossification.[9]

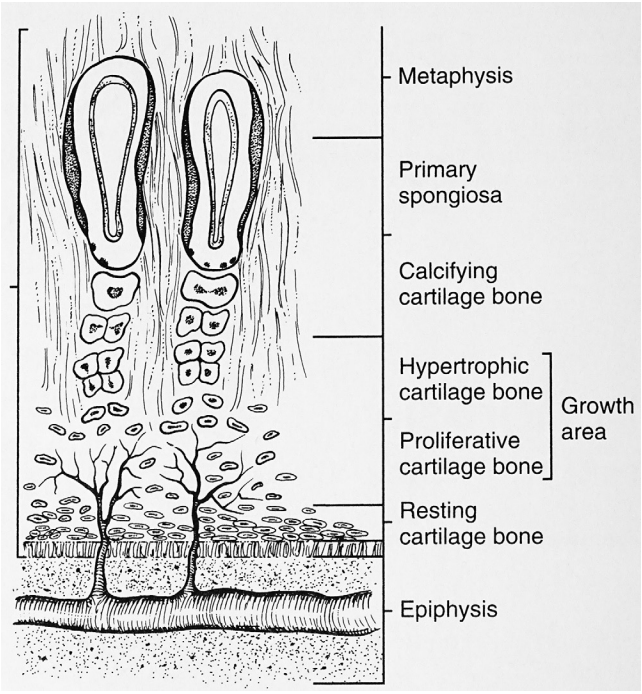

Figure 89-2. Schematic representation of the process of growth and ossification of long bones that takes place at the level of the physis. (From Van Weeren PR. Osteochondritis dissecans. In: McIlwraith CW, Frisbie DD, Kawcak CE, van Weeren PR, eds. *Joint Disease in the Horse.* 2nd ed. St. Louis: Elsevier; 2016:57–84.)

In the epiphyses of the long bones, a similar growth process takes place, but is less advanced than in the diaphyses at birth. Initially, there is a complete ring of cartilage around the ossification center that is located in the center of the epiphysis, connecting the cartilage at the articular side with the growth plate. Ossification of this cartilage ring takes place first at the border of the physis and at the perimeter of the epiphysis. The thick cartilage mass at the articular side of the epiphysis functions as a type of growth plate with simultaneously occurring processes of growth, remodeling, and ossification. It is at this level that the characteristic lesions of equine OC develop. After cessation of growth, a considerably thinner layer of articular cartilage remains in the mature animal. Although macroscopically very similar, this layer is right from the start distinct from the growth cartilage. In a benchmark study on the early development of articular cartilage in both fetuses (6–11 months' gestation length) and neonates (0–8 days) the future layer of articular cartilage could be well discerned from the epiphyseal growth cartilage that would become (subchondral) bone (Figure 89-3).[10] A later study showed the process of development of the future articular cartilage layer, starting at 4 months of gestation.[11]

CLINICAL PRESENTATION

The typical OC patient is a yearling that is presented with effusion of the tarsocrural or femoropatellar joint. The horse usually is not lame. Radiographic examination may present evidence of a fragment at the cranial end of the distal intermediate ridge of the tibia (Figure 89-4), or irregularities at the lateral trochlear ridge of the distal femur (Figure 89-5).

Not all cases are that typical, however, and many variations are possible. Age can vary from young foals to horses of over 10 years of age. In the latter category, lesions must have been present from foal age, as OC(D) is a disorder of endochondral ossification by definition and no new lesions can form after cessation of this process. OC often becomes manifest at the age the animals

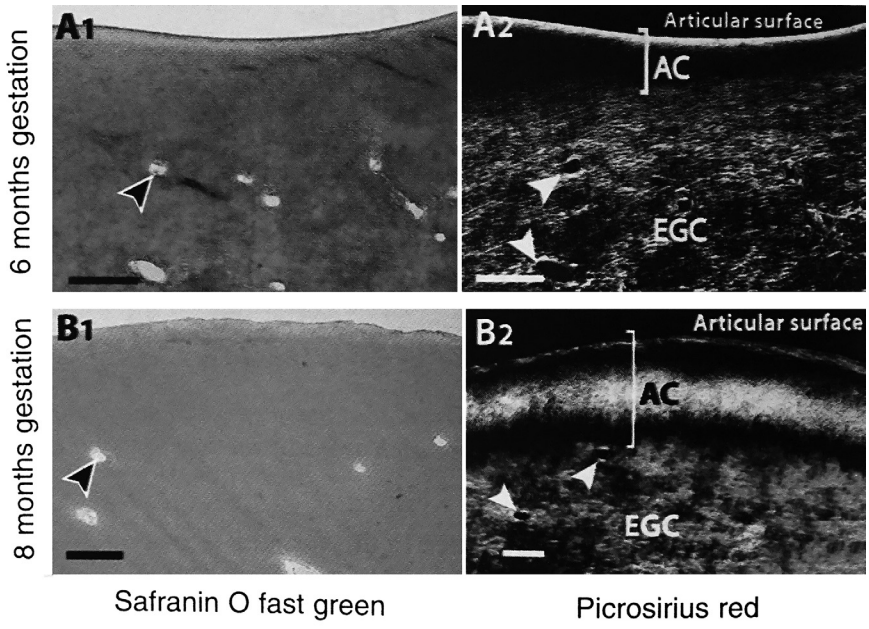

Figure 89-3. Equine fetal cartilage (*A*) 6-month-old fetus; (*B*) 8-month-old fetus stained with safranin O fast green and picrosirius red. In the picrosirius red–stained sections, viewed under polarized light microscopy, the future articular cartilage can be clearly distinguished; this is not possible in the safranin O fast green–stained sections. *AC,* Articular cartilage; *Arrowheads,* cartilage canals in the EGC, not present in the AC; *EGC,* epiphyseal growth cartilage. Scale bars = 500 µm. (From Lecocq M, Girard CA, Fogarty U, et al. Cartilage matrix changes in the developing epiphysis: early events on the pathway to equine osteochondrosis? *Equine Vet J.* 2008;40:442–454.)

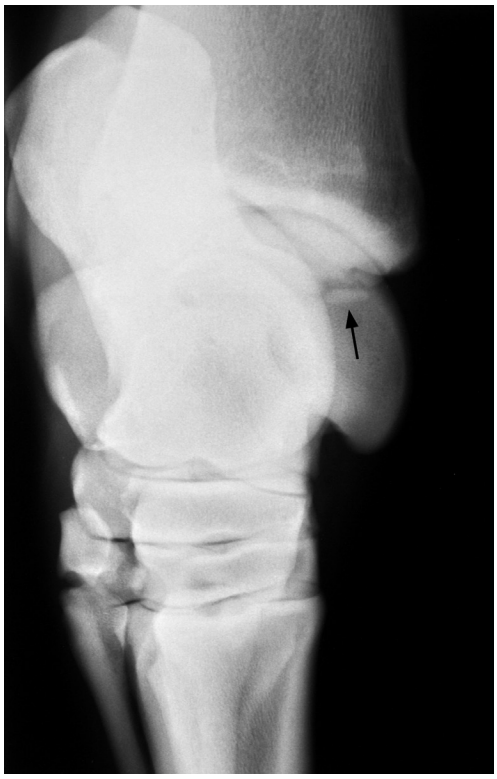

Figure 89-4. Radiograph showing a typical osteochondritic lesion of the dorsal aspect of the distal intermediate ridge of the tibia *(arrow)*. (Courtesy van den Belt AJM, Utrecht University. In: McIlwraith CW, Frisbie DD, Kawcak CE, van Weeren PR, eds. *Joint Disease in the Horse.* 2nd ed. St. Louis: Elsevier; 2016:57–84.)

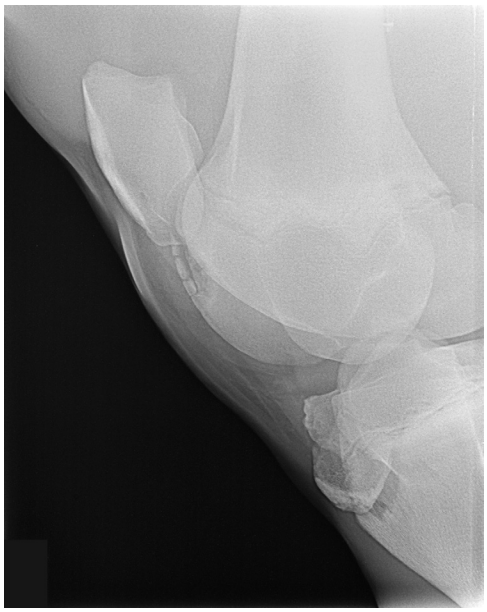

Figure 89-5. Oblique radiographic view showing osteochondrotic fragmentation at the lateral trochlear ridge of the distal femur. (In: McIlwraith CW, Frisbie DD, Kawcak CE, van Weeren PR, eds. *Joint Disease in the Horse.* 2nd ed. St. Louis: Elsevier; 2016:57–84.)

are put into training when the joints become more challenged by athletic activity. The joint effusion has been associated with histopathologic signs of synovial inflammation.[12] Although rare, lameness may be severe; especially in very young foals with large lesions in the femoropatellar joints. Radiographic signs may be less severe than the presence of fragments and may show as minor irregularities in the articular contour of the subchondral bone or as only a flattening of this contour. There has been much debate on whether subchondral bone cysts are manifestations of OC or not. The current view is that some of them may have the same vascular pathogenesis as the classic osteochondrotic lesions,[13] but they can have other origins as well. Subchondral bone cysts are presented in detail in Chapter 90.

Radiography still is the gold standard for diagnosing OC. The correlation between radiographic classification of OC of the distal intermediate ridge of the tibia and histology has proven to be as high as 0.87 ($p<0.001$).[14] However, this diagnostic modality has several drawbacks. Lesions limited to the cartilage layer are not detectable and also subtle bony lesions may be easily missed because of superimposition. In very young animals, the relative lack of mineralization of the subchondral bone may preclude diagnosis of all but the larger lesions. Cartilaginous changes may be more or less severe than suggested by the subchondral bone lesions visible on radiographs. Specificity of radiography for detection of OC lesions of the lateral femoral trochlear ridge has been reported to be excellent (89%–100%), but sensitivity was less (84%–88%),[15] and more advanced diagnostic modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) perform better but are not practical.[16] High-field MRI is a useful tool to image the layer of articular cartilage,[17] but this technique remains expensive and its availability is limited. Ultrasonography is a good alternative to radiography and outperforms it on those joint surfaces that can be imaged using this modality.[15,18] The technique has been validated histologically in an experimental *ex vivo* study.[19] Other approaches using a variety of biochemical and molecular markers and the use of infrared absorption spectral characterization of synovial fluid using Fourier-transform Infrared (FTIR) spectroscopy have been tried, but are not realistic for high-throughput screening.[20]

The Most Frequently Affected Joints and Predilection Sites

OC is most common in tarsocrural, femoropatellar, and metacarpo/metatarsophalangeal (MCP/MTP) joints, but has been described in most other diarthrodial joints as well (Figure 89-6). In a detailed study on the locations of lesions in 43 Warmblood foals that were genetically predetermined to develop OC,[21] lesions were most numerous in the tarsocrural joint (average of two lesions per animal), followed by the femoropatellar and the cervical intervertebral (facet) joints (one), the MTP joint (0.6), the MCP and carpal joints (0.4), the humeroradial joint (0.2), and the scapulohumeral joint (0.04).[14] The prevalence of OC in that study was artificially high and hence not representative for the overall population. However, the relative distribution was in agreement with clinical experience in the Warmblood. There are breed differences in prevalence of lesion locations. In Warmbloods and Standardbreds, tarsocrural OC is most frequent,[22–26] whereas in racing Thoroughbreds femoropatellar OC is predominant.[27]

Clinically, most lesions present unilaterally, but are often found to be bilateral in the tarsocrural and femoropatellar joints

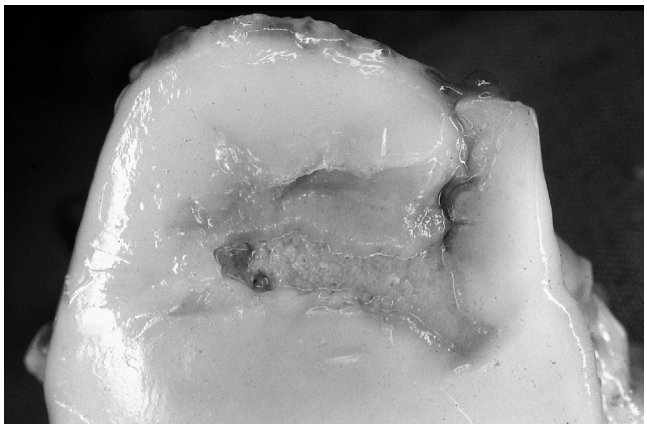

Figure 89-6. Osteochondrotic lesion on the articular surface of the caudal intervertebral process of the 6th cervical vertebra. (From Van Weeren PR, Barneveld A. The effect of exercise on the distribution and manifestation of osteochondrotic lesions in the Warmblood foal. *Equine Vet J*. 1999;31[suppl 31]:16–25.)

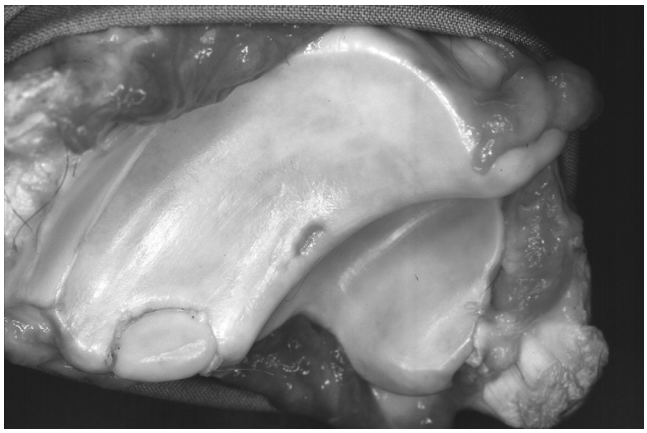

Figure 89-7. Typical osteochondrotic lesion of the distal intermediate ridge of the tibia at necropsy. The thin cartilage area in the center of the intermediate ridge is a synovial groove, which is a physiological phenomenon in non–weight bearing areas common to many diarthrodial joints.

and bilateral or even quadrilateral in the MCP/MTP joints upon further examination.[28,29] Concomitant occurrence in other joints or joint pairs is much less common, possibly because of the differences in time windows during which OC lesions develop in different joints (see later). In a study of 225 horses with tarsocrural OC, lesions in other joints were seen in only eight cases.[29] It is therefore advisable in clinical cases to check contralateral joints routinely, but not other joints, unless clinical signs exist.

Lesions of OC almost always occur at certain predilection sites. In the tarsocrural joint, the cranial end of the distal intermediate ridge of the tibia (see Figure 89-4 and Figure 89-7) is most frequent, followed by the distal end of the lateral trochlea of the talus and the medial malleolus of the distal tibia.[30] In the femoropatellar joint, the lateral trochlear ridge of the femur is most commonly affected.[28] In the shoulder joint, OC is commonly located on the glenoid and the humeral head.[31] The predilection site in the MCP/MTP joints is the dorsal aspect of the sagittal ridge of the metacarpus (MCIII) and metatarsus (MTIII). The interpretation of radiographs of the MCP/MTP joints is complex, because other fragments may be found that are not osteochondrotic in origin. Palmar or plantar osteochondral fragments (POFs) were originally reported to be part of the OC complex,[32] but later confirmed to be traumatic in origin[33,34] and to be related with traumatic overload arthrosis.[35] Histologically, POFs show more indications of osteoarthritis than of OC[36] and the synovial fluid shows a different biomarker profile. OC joint fluid has an increase of the collagen degradation marker C2C, while traumatic joint injury fluid has an increase in the collagen synthesis marker CPII.[37] Genetically, there is no correlation between POFs and OC in a given joint.[38]

NATURAL HISTORY OF OC AND PREVALENCE

Natural History

Development of OC is by definition restricted to the period in life when there is active endochondral ossification. Studies that monitored lesion development radiographically in cohorts of growing foals confirmed this,[39] but interestingly also brought to light that during the early juvenile phase, lesions that had formed could also regress.[25] This dynamic character of OC was definitively established in a large experimental study focusing on the influence of exercise at early age on the development of OC, the so-called EXOC-study (for exercise and osteochondrosis).[21] In that study the tarsocrural and femoropatellar joints of 43 foals were radiographed on a monthly basis from the age of 1 month until age 5 months, and 19 of these foals were followed until 11 months of age. The study showed that not only minor lesions but also radiographically visible larger fragments could repair spontaneously.[40] The predominant ages at which lesions originated and at which most of them had spontaneously healed varied for each joint (Figure 89-8). In the tarsocrural joint, lesions originating during the first few months of life had mostly resolved at 5 months of age. The remaining lesions did not resolve. In the femoropatellar joint, where the epiphyseal maturation is known to be late compared to other joints,[10,41] lesions originated from approximately 3 months onward, peaked at 6 months and reached a stable condition around 8 months of age with most lesions healed. This pattern was later confirmed in other longitudinal studies.[42–44] The general pattern seems to hold for most breeds, with some variations and differences in timing between breeds. In a study in Lusitano foals,[45] the researchers found more lesions in the femoropatellar joint at the early age of 1 month than in the original study.[40] Also, they established the "age of no return" at 12 months, rather than at the originally proposed 5 months for the tarsocrural joint and 8 months for the femoropatellar joint. It seems most prudent to stick to 12 months for all joints after which no major OC lesions should be formed, nor will existing large lesions be expected to resolve. However, resolution of minor lesions has been reported up to 24 months of age.[46]

The dynamic character of OC can be explained by the interaction of several etiologic factors and the specific characteristics of articular cartilage metabolism in young, growing individuals. Collagen turnover in mature cartilage is known to be virtually nil,[47] but the situation is essentially different in the young, growing individual where continuous remodeling and formation of cartilage takes place. This huge difference in metabolism is reflected by the presence of synovial fluid levels of certain proteinases. Matrix metalloproteinase-3 (MMP-3, stromelysin) levels are increased 80-fold in fetal joints compared to joints from mature individuals. At 5 to 11 months of age, MMP-3 levels

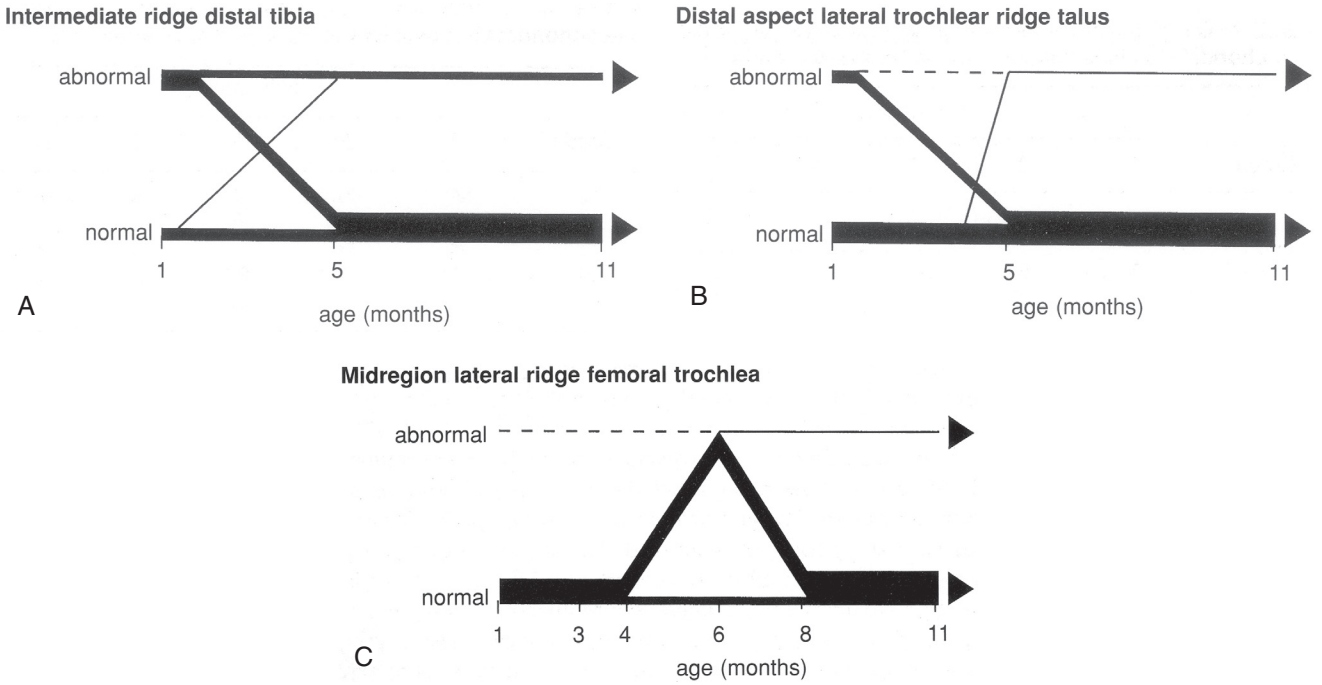

Figure 89-8. (A) Schematic diagram of the early development of osteochondral lesions at the distal intermediate ridge of the tibia. Already at age 1 month there are several lesions detectable. Most of these will heal *(thick black arrow, pointing downwards)*. Only a few lesions originate after the age of 1 month *(thin black arrow pointing upwards)* and from the age of 5 months, the situation remains stable. (B) Comparable diagram of the early development of osteochondral lesions at the distal aspect of the lateral trochlear ridge of the talus. The same general pattern exists as in (A), but the healing potential is better. (C) Diagram of the early development of osteochondral lesions of the lateral ridge of the femoral trochlea. The pattern is clearly distinct here, probably because the development of the femoropatellar joint lags behind in comparison to most other joints of the limbs. Lesions develop only after the age of 3 months, peak at about 6 months, and for the major part have resolved at the age of 8 months, but some may remain. (From Dik KJ, Enzerink EE, van Weeren PR. Radiographic development of osteochondral abnormalities, in the hock and stifle of Dutch Warmblood foals, from age 1 to 11 months. *Equine Vet J*. 1999;31(31): S9–15.)

decrease dramatically, but are still two- to threefold higher than in mature joints.[48] The process of endochondral ossification takes place in this period of turbulent remodeling, which permits quick and almost immediate repair of lesions once they have formed. The sharp decrease in metabolic activity after birth, with the concomitant reduction of repair capacity, makes cartilage lesion healing more difficult with increasing age. This gradual closing of the window of repair that is not a synchronous event in all joints, explains the differences in the evolution of lesions in different joints (see Figure 89-8). Lesions that remain after the window for repair has closed in a certain joint may become clinically manifest then or when the joint is challenged by increased loading (for example when training starts). Figure 89-9 presents a flow chart for the assumed sequence of events in OC based on this concept. Clinical OC can be considered as the final outcome of at least two complex, but probably unrelated, processes: The initiation of lesions by specific etiologic factors, and the ensuing repair process, making OC a very complex disorder.[49]

Prevalence of OC

Given the dynamic character of OC, statistics on its prevalence should be considered with utmost caution. It follows from the above discussion that any survey performed at ages younger than approximately 12 months cannot be considered to be representative of a stable condition. However, the common age for screening by studbooks (3 or 4 years) is far from ideal either, as any form of preselection by breeders (which is common) will affect the statistics. These effects may be dramatic. In a study on 811 non-preselected Dutch Warmblood yearlings, a staggering 67.5% prevalence of OC was reported, when combining results from tarsocrural, femoropatellar, MCP, and MTP joints.[50] At the age of 3 years, the mean prevalence for this breed is approximately 30%. A similarly high prevalence for tarsocrural and MCP/MTP OC (61.7%) was found in a population of South German Coldbloods that contained many young animals.[51] All surveys conducted at the conventional ages of 3 or 4 years can be said to yield severe *underestimations* of the real prevalence of OC and even surveys in populations that have not been preselected will not identify animals that have had (radiographically detectable) OC lesions in one or more joints at foal age and that have resolved spontaneously. This has had a great impact on genetic studies and may be one of the reasons why genetic research into OC (see later) has yielded relatively little conclusive data thus far. A last important point related to epidemiological OC data is that OC has been described in almost every diarthrodial joint, but screenings are normally restricted to a few joints only. These factors and the differences

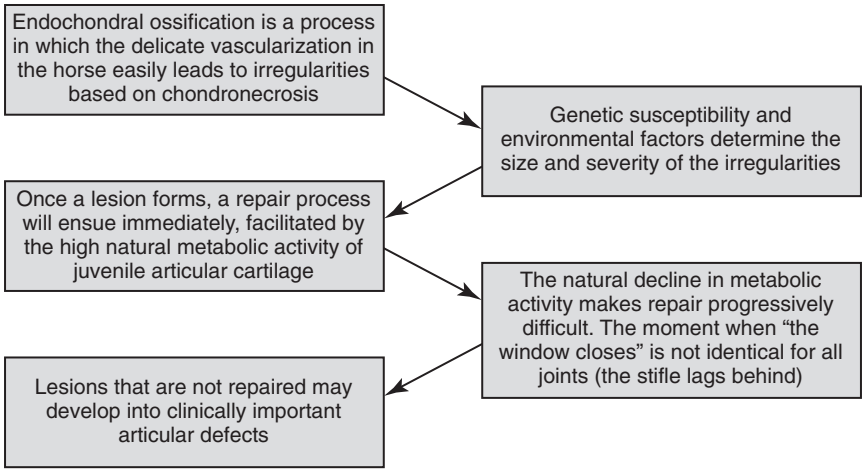

Figure 89-9. Flow chart of events over time in osteochondrosis, emphasizing the dynamic character of the disorder in which many of the lesions that originate will repair, depending on the age of the animal.

in experimental design between many surveys make comparisons between these studies into a very hazardous undertaking and may to a large extent explain the wide range in statistics that have been reported.

Even though inherently unreliable and severely underestimated, the published statistics on the prevalence of OC are still impressive and give indications of the important breed differences. In Standardbreds, a prevalence of 10.5% was reported in the tarsal joints in Sweden,[26] which is comparable to the 12% found by other authors[23] and not too far from the more recent work in Norway,[52] where a prevalence of tarsocrural OC/OCD of 19.3% was reported. Conversely, a much higher prevalence of 35% was reported in a Canadian population of Standardbreds in the femoropatellar and MCP/MTP joints combined.[53]

A recent study of 1962 Thoroughbred yearlings showed an overall prevalence of OC of 23%, with lesions identified in 10% of stifles, 6% of tarsi, and 8% of MCP/MTP joints.[54] That study was based on clinical records. Most studies in this breed are based on repository radiographs used at yearling sales, which in general show lower figures as a result of preselection. A study in the United States found a prevalence of OC in the sagittal ridge of the MCP joints, tarsocrural joints, and femoropatellar joints of 60.8%, 12.2%, and 6.2% respectively[55]; whereas a study in South Africa reported 15.7%, 4.4%, and 0.4% in these same locations.[56]

In the Warmblood, figures vary as well. In the Dutch Warmblood, a 25% incidence in the tarsocrural joint and 15% in the femoropatellar joint were reported.[40] Later work in a non-preselected population of the same breed from a single breeder comprising views of the distal and proximal interphalangeal, MCP and MTP, tarsocrural and femoropatellar joints, found an overall prevalence of not less than 44.3%.[57] A large-scale field study in Germany focusing on several Warmblood breeds came up with figures of 19.5% for the MCP/MTP joints, 11.1% for the tarsocrural joint, and 7.2% for the femoropatellar joint.[58] In general, Warmbloods are at higher risk to develop OC than Thoroughbreds.[59] In Spanish horses, a recent study reported 1.3% for the femoropatellar joint, 33.3% for the tarsocrural, and 25% for the dorsal MCP/MTP region.[60]

It is interesting to note that osteochondrotic lesions are only rarely encountered in ponies,[61] which has tentatively been linked to a different blood supply of the growth cartilage compared to horses.[62] Further, in feral horses the disease is seen, but the prevalence is very low. In a survey of 80 feral horses, 2.5% of tarsocrural joints were affected and not a single femoropatellar joint.[63] Because OC is a disease that has been described only relatively recently and of which the incidence has soared since the 1970s, these observations strongly implicate breeding policies and possibly management aspects as key factors in this disease.

PATHOGENESIS OF OSTEOCHONDROSIS

The etiopathogenesis of OC has been a heavily debated issue since the first descriptions of the disorder. Recognition of the fact that both genetics and many environmental factors seemed to influence the manifestation of the disease, the presence of clear predilection sites, and the different clinical presentations of OC has led to a multitude of hypotheses regarding the pathogenesis of OC. There is now compelling evidence that damage to vessels in cartilage canals is a crucial element of early pathogenesis of lesions. However, there are other elements as well that play a role in the etiopathogenesis of the disease, which are as yet less clear. Studies have focused on cellular alterations and changes in gene expression patterns of the chondrocytes, changes in the components of the extracellular matrix, aberrations in the regulation of the process of endochondral ossification, the possible implication of subchondral bone, and changes in the vascularization of the growth cartilage. A problem with many of the clinical studies is that samples were often taken from chronic lesions that had undergone extensive secondary remodeling, which had long effaced any possible traces of primary events.[64] Therefore it is impossible to determine whether abnormalities are a primary or a secondary response, because the reactive repair process is known to start immediately after initial lesion formation. The definitive evidence for a vascular pathway as a primary event came from experimental studies.

Vascular Events in Early OC: The Early Pathogenetic Mechanism

The thick layer of epiphyseal cartilage of the growing joint that is destined to change into bone via the process of endochondral

ossification is nourished by vessels running through so-called cartilage canals. With ongoing ossification, these canals are obliterated in a process called *chondrification*, the timing of which is joint-dependent. Patent cartilage canals are not seen in the proximal phalanx after 3 weeks of age, whereas they are still present at 4.5 months in the femoral condyle (but disappear by 7 months of age). The timing of canal abolishment in distal tibias was in between.[65]

The initial studies on the vascularization of juvenile cartilage and its disturbances were conducted in the pig. It was shown in this species that areas of chondronecrosis related to obliterated cartilage canals could be found, which were much larger in commercial pig breeds than in pigs from wild hog ancestry.[66] In an experimental study in which only specific cartilage canals were artificially interrupted, OC-like lesions could be produced.[5] This suggested that the early pathogenetic mechanism of OC was the formation of chondronecrotic areas, caused by damage to cartilage canals, especially to the anastomosing branches that run through the ossification front from the bone marrow.[67] These initial chondronecrotic areas were clinically silent, not visible macroscopically or with help of standard imaging methods and were called *OC latens*. Depending on environmental factors and the efficacy of the repair processes, these lesions would resolve, or become clinically apparent, in which case they are designated as *OC manifesta*.[68] Apart from the histological evidence, there is also indirect genetic support for this involvement of vascular disturbances in the pathogenesis of OC. In a genome-wide association study in pigs, a single nucleotide polymorphism (SNP) in the gene encoding T-box transcription factor 5 (TBX5) (a transcription factor interacting with two genes involved in vascularization) was significantly associated with OC lesion scores.[69]

In the horse, a cross-sectional study in random source foals (ranging from 191 days gestation to 153 days of age) showed that *OC latens* lesions similar to those in pigs were present in the distal tibia of 9 of 100 animals (Figure 89-10).[70] A follow-up experimental study on the development of the vascularization of the tarsus of seven very young foals (0–7 days) showed how the advancing ossification front induces a change in the arterial supply of the cartilage canals. Initially supplied by arteries from perichondral origin, the advancing ossification front engulfs the midportion of the vessels in the canal, necessitating a shift towards subchondral, rather than perichondral arterial sources. This shift suggests that crossing the ossification front leaves the vessels more vulnerable to mechanical influences (Figure 89-11). In support of this suggestion, all 12 lesions found in the seven foals were located where vessels crossed the ossification front.[71] In a study on the distal femur, comparable changes in vascularization were found, but the regression of blood vessels was much less extensive at this early age than in the tarsus and no lesions could be found.[72] This coincides with the later peak of osteochondrotic lesion development in this joint.[40] In a later study, vascular lesions related to vascular damage in the distal femur were found in 7 of 30 examined foals aged from 31 to 336 days (mean 148 days).[73] In the MCP/MTP joint a similar pattern of changes in vascularization was observed; in this case one *OC latens* lesion was found.[74] A very interesting observation made by micro-computed tomography of the early lesions was that the secondary repair process follows almost immediately after the formation of the lesion (Figure 89-12).[75]

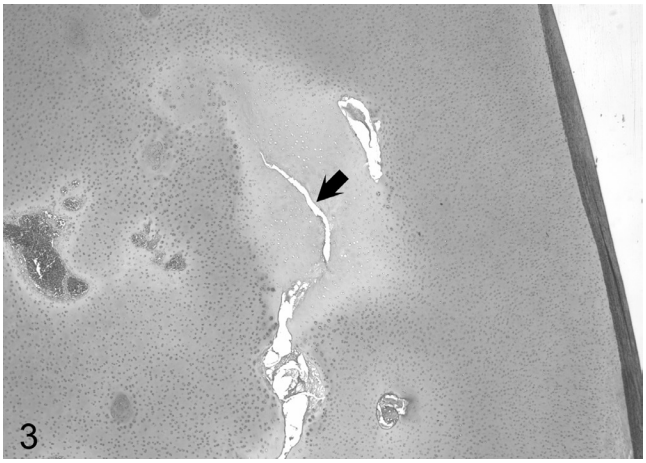

Figure 89-10. Microphotograph of a femur of a 114-day-old foal. The *arrow* indicates a necrotic cartilage vessel, surrounded by an area of necrotic matrix. (From Olstad K, Ytrehus B, Ekman S, Carlson CS, Dolvik NI. Early lesions of articular osteochondrosis in the distal femur of foals. *Vet Pathol*. 2011;48:1165–1175.)

The final evidence for the role of vascular disturbances in the pathogenetic mechanism of OC in the horse was provided by an experimental study in which at the age of 13 to 15 days, two vessels supplying the epiphyseal growth cartilage of the lateral trochlear ridge of the femur were transected in 10 pony foals. The transection of blood vessels running in epiphyseal cartilage canals resulted in ischemic chondronecrosis that was associated with a focal delay in endochondral ossification (OC) in foals examined 21 days or more after transection. In one foal a pathological cartilage fracture (OCD) was observed 42 days after transection.[76]

The vascular pathogenetic mechanism of OC can explain a number of commonly observed features of the disease, such as the joint-specific windows in time (related to joint-specific patterns in the progress of the ossification front and subsequent vascular rearrangements), and the frequent bilateral occurrence. However, the complex vascular rearrangements during the process of endochondral ossification are common to all individuals and not specific for those developing osteochondrotic lesions and offer no explanation for the individual susceptibility for OC. It has been suggested that bacterial infections at early age may produce direct damage to the vascular structures,[13] of which a large proportion has been shown to be surrounded by an acellular wall consisting of collagen type I, permitting bacterial binding.[77] However, a variety of more indirectly acting molecular mechanisms related to dysfunction of chondrocytes, extracellular matrix components, and signaling pathways have been suggested to play a role as well.

Molecular Events in OC: The Possible Underlying Pathways

Many studies have focused on changes in the events at the cellular and molecular level in OC-affected tissue compared with normal tissue. However, as pointed out earlier, it is often impossible in observational studies to determine what the primary OC lesion is and what is secondary, because the onset of repair is almost immediate after formation of a lesion and juvenile cartilage has still considerable regenerative capacity. Osteochondrotic fragments could not be discerned from surgically created osteochondrotic fragments, however, the OC tissue bed stained positive for

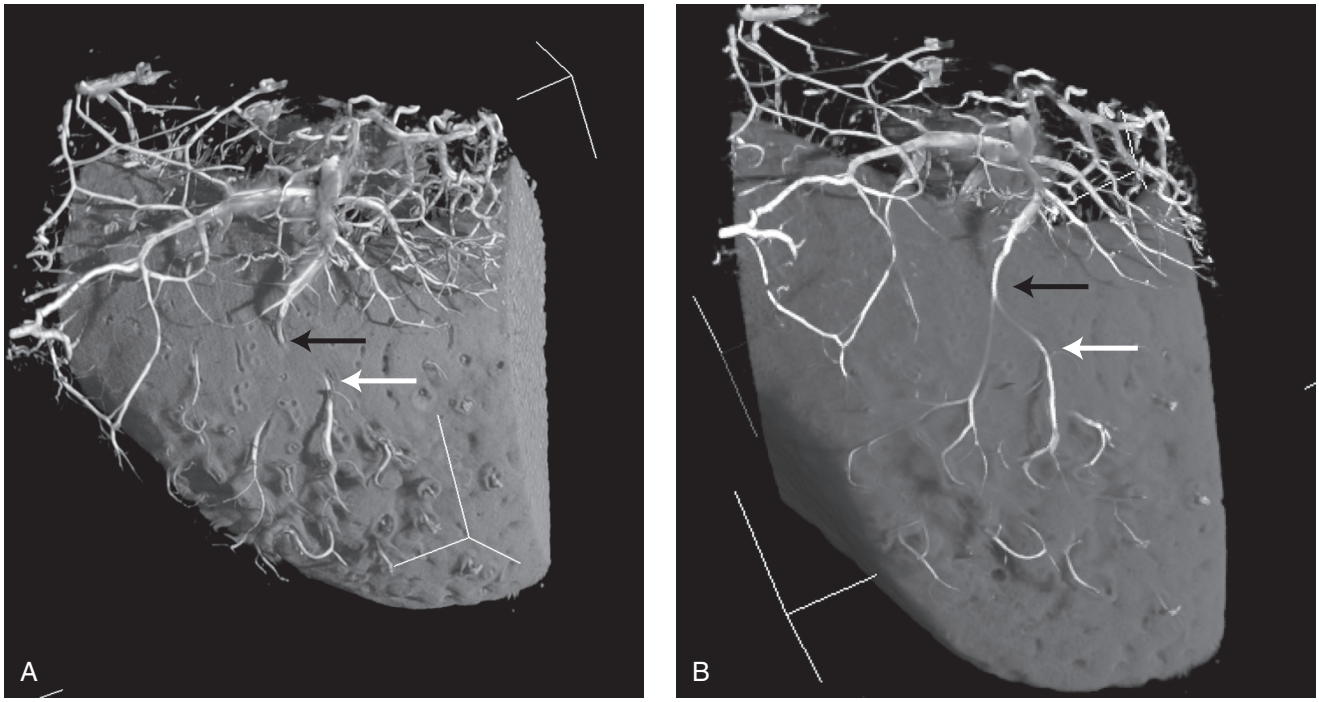

Figure 89-11. Images of three-dimensional volume rendered models of micro-computed tomography scans of a tissue block (measuring approximately 2 cm in all directions) from the cranial part of the distal intermediate ridge of the tibia of a 3-week-old foal. The block contained a permanent barium angiogram, and only the grayscale segments representing barium and bone are shown. (A) A vessel originating from the perichondrial plexus on the cranial aspect of the distal tibia courses into the subchondral bone towards the cranial apex of the distal intermediate ridge *(black arrow)*. Distal and caudal to this, towards the distal articular surface of the intermediate ridge, vessels emerge into the growth cartilage directly from subchondral bone *(white arrow)*. (B) The greyscale segment for bone has been rendered less opaque/more translucent than in (A), illustrating how the midsection of cartilage canal vessels is incorporated into the advancing ossification front during growth. This traversing of junctions between tissues of different qualities such as bone and cartilage, is believed to render vessels particularly vulnerable to failure. (Images courtesy Dr. K. Olstad, Norwegian School of Veterinary Science.)

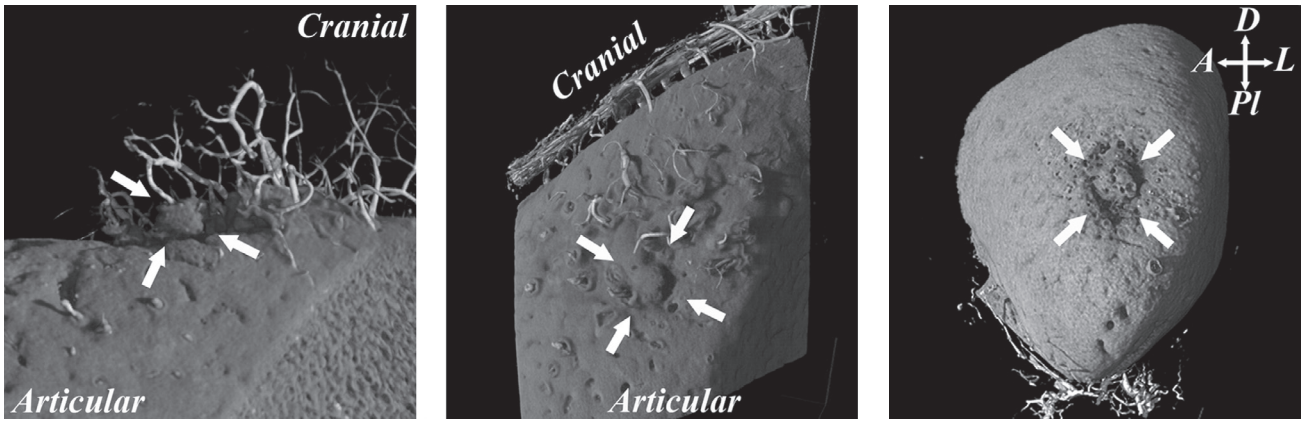

Figure 89-12. Lesions of osteochondrosis associated with ongoing ossification. The figure shows images of three-dimensional volume rendered models of blocks containing permanent barium angiograms; only the grayscale segment representing bone and barium is shown. (A) A 2-week-old foal, distal intermediate ridge of tibia, oblique distal view: A perfused vessel descended on the cranial aspect of the process to terminate within the growth cartilage immediately superficial to a triangular indented defect in the subchondral bone plate. The vessel terminus was surrounded by a spherical bone opacity *(arrows)*. This appearance was compatible with a separate center of ossification, seen as an early manifestation of the repair process. (B) A 3-week-old foal, intermediate coronoid process, distal view: There was a circular indented defect in the subchondral bone plate *(arrows)*. The defect was partially filled by a hemispherical bone opacity. In cross-section, endochondral ossification appeared to be progressing within the hemisphere. (C) A 7-week-old foal, lateral trochlear ridge, distal view. There was a circular indented defect in the subchondral bone plate *(arrows)* that was partially filled by a hemispherical bone opacity, representing the repair process. *A,* Axial; *D,* dorsal; *L,* lateral; *Pl,* plantar. (Images courtesy Dr. K. Olstad, Norwegian School of Veterinary Science.)

chondroitin sulfate and collagen type II, and the fracture bed did not.[41] It is additionally clear that the molecular background of OC is extremely complex and that an approach using system biology will probably be the only way to fully understand the entire chain of events that occurs in the disorder. A comprehensive approach using both proteomics and metabolomics showed involvement of proteins related to cell cycle, energy production, cell signaling and adhesion, as well as chondrocyte maturation, extracellular matrix, and mineral metabolism,[78] the latter processes signifying a role for the subchondral bone as well.[79]

The Role of the Chondrocyte in OC

Failure to undergo hypertrophy has been suggested as a main cause for OC or "dyschondroplasia."[80,81] However, a study in which OC was induced in 3 to 6 months old foals by a high-energy diet showed normal expression of hypertrophy-related genes, making this hypothesis unlikely.[82]

Chondrocytes harvested from early osteochondrotic lesions have a higher metabolic rate, but cannot be further stimulated to a higher level than chondrocytes from normal cartilage. In fact, when harvested from longer-existing lesions, their metabolic rate is lower than in normal cells and stimulation is not possible.[83] This phenomenon, which is almost certainly secondary, may indicate a reactive upscaling of metabolic activity in response to lesion formation, which, when repair is unsuccessful, may develop into exhaustion and loss of vitality of the chondrocytes.

Matrix Components

Many studies have focused either on the molecular composition of either the protein, the expression level, or on proteinases and growth factors known to influence matrix composition and metabolism. Other studies have indirectly, in the quest for biomarkers, investigated possible predictive changes in products or regulatory molecules of matrix metabolism. These studies suffer from the methodological issue mentioned above and may in fact reflect the increased metabolism related to the repair response. However, they have provided insight into the molecular changes that are involved in OC.

Distribution of collagen VI was different in OC lesions compared to normal tissue.[84] Further, differences in posttranslational modifications of collagen type II have been demonstrated in samples from early lesions.[85] There was strong TGF-ß mRNA expression in chondrocyte clusters immediately surrounding an OC lesion.[86] In a study on expression patterns and chondrogenic potential of osteochondrotic cartilage, OC cartilage showed increased expression of collagen types I, II, III, and X, and of MMP-13, ADAMTS-4, and TIMP-1, and decreased expression of TIMP-2, and TIMP-3.[87] However, expression of MMP-16 or membrane-type matrix metalloproteinase-3 (MT3-MMP) is not significantly altered in osteochondrotic cartilage.[88] A strong increase in cathepsin B activity in chondrocyte clonal clusters in OC has been demonstrated,[89] which was later confirmed in a study on the effect of copper supplementation.[90] Also the proteoglycan component of the ECM is involved, as pellet cultures produced from OC tissues contained significantly less GAGs[87] and there was an increase in activity of gelatinases (MMP-2 and MMP-9) in osteochondrotic cartilage.[91] Insulin-like Growth Factor 1 (IGF-1) was found to be upregulated in osteochondrotic tissue, but was judged to be most likely related to the repair response rather than being primary.[92]

In biomarker research, there was a strong correlation between serum osteocalcin levels in synovial fluid as early as 2 weeks of age and radiographically scored OC of foals at 5.5 and 11 months of age as well as postmortem scores at 11 months,[93] suggesting the association of bone in the early events in OC. However, this observation was not confirmed in another study.[94] Biomarkers of collagen degradation and osteocalcin were positive indicators of OC severity at 5 months of age, but in foals with lesions at 11 months of age, OC severity correlated negatively with osteocalcin and the collagen degradation marker and positively with the anabolic marker.[95]

Signaling Pathways

The Wingless-related integration site (Wnt)/β-catenin, Indian Hedgehog (Ihh)/parathyroid hormone related protein (PTHrP), and retinoid signaling pathways are known to regulate cartilage differentiation, growth and function during development, and to play a key role in endochondral ossification. After earlier evidence for implication of the Ihh/PTHrP feedback loop in the role of OC,[81,96] there is recent evidence for a major role of the Wnt/β-catenin signaling pathway.[97] There is differential expression of canonical and noncanonical Wnt signaling and their inhibitors surrounding the cartilage canals and osteochondral junction in normal cartilage during the process of endochondral ossification.[98] However significantly decreased Wnt-11 and increased β-catenin, Wnt-5b, Dkk-1, Lrp6, Wif-1, Axin1, and SC-PEP gene expression could be shown in early OC cartilage canal chondrocytes and also significantly increased β-catenin gene expression in early OC osteochondral junction chondrocytes compared to controls.[99] Further, a Wnt signaling inhibitor, sclerostin, was strongly upregulated in OC lesions.[100] There is an interesting potential link with one of the environmental factors known to have a great influence of OC: high-energy diets characterized by easily digestible carbohydrate overload and their hormonal influences (see later). Wnt signaling is known to regulate mitochondrial physiology and insulin sensitivity[101] and abnormal mitochondria have been observed in the deep zone of OC cartilage.[102]

GENETICS

The osteochondrotic phenotype is determined by a genetic component and environmental factors. Genetics of OC have classically been researched by population genetics, focusing on determining the heritability. In more recent years, the rapidly developing molecular genetic techniques have enabled an intensive quest for genes that could be associated with OC and related genetic markers.

Heritability

Heritability (h^2) is a statistic that estimates how much variation in a phenotypic trait in a population is a result of genetic variation. The value can vary between 0 and 1.0; the higher this value, the bigger the influence of selective breeding on that trait. Determining h^2 estimates for OC is far from straightforward. Any genetic study is dependent on the definition of the phenotype, which is variable in OC for many reasons. In all heritability studies on OC, the phenotype is determined radiographically. Therefore

outcome is dependent on the radiographic protocol. Less extensive protocols with limited numbers of views, such as those used in large-scale field studies[103] are more likely to miss lesions than the more extensive protocols used for repository films at sales. For the latter, bias by preselection becomes a problem. Another confounding factor is that in some studies all loose fragments, including for instance POFs, are (incorrectly) counted as OC lesions. The outcome of genetic studies will also depend on whether OC is defined at the animal level or at the joint level, and given the highly dynamic character of the disorder, the age at which phenotypic measurements are performed is of great importance. Further, not all studies use the same methodology. Sire models account only for paternal half-sibling relationships. Animal models use information on all relatives of an animal without reduction to specific structures of relatives. OC is virtually always a categorical variable and in those cases a threshold model or a transformation to the underlying distribution has to be applied to avoid underestimation of the heritability.[104] All these factors together make genetic studies on OC into somewhat hazardous undertakings and may explain the widely varying outcome.

There are distinct differences in heritability of OC per joint. In most breeds, heritability is highest for the tarsocrural joint with an average value of around 0.30,[105,106] but covering a range from 0.04 (in Coldbloods[107]) to 0.52 (in Standardbred Trotters[108]). For the MCP/MTP joints this value is approximately 0.15.[106,107,109] Reported h^2 values in the stifles are mostly lower, not rising over 0.10[54,109,110] with values as low as 0.05 for OC and 0.02 for OCD in the Dutch Warmblood.[106] A detailed overview on this subject was recently published.[104]

Heritability measures the proportion of the phenotypic variance that is the result of genetic factors. In theory, the higher the heritability, the quicker progress to eliminate a defect can be made by selection. In practice, selection against OC has proven extremely difficult and progress, if any, has been slow. There are various explanations for this that relate to the confounding factors for heritability studies mentioned earlier. First, it has become clear that OC is heavily polygenic with different genes involved in different joints resulting in a different h^2 per joint. There are even indications that different manifestations of OC (fragmentation versus flattening) may represent different traits.[106] A second complicating factor is the dynamic nature of OC. Animals radiographically free of lesions at age 3 or 4 when they enter the stallion selection procedures may well have had the disease at foal age. These foals may be genetically predisposed to OC and pass the condition on. A third and not unimportant factor is that some traits that are known to be implicated in OC (such as a high growth rate) are seen as desirable and actively selected for or that certain conformational traits are both related with good athletic performance and increased risk for OC.[111]

Molecular Genetics

The genome of the horse was published in 2009[112] and in 2008 the first equine microarray containing more than 54,000 SNPs came on the market, allowing genome-wide association studies,[104] many of which have focused on OC. A comprehensive review of these studies is outside the scope of this chapter, but the studies provide further evidence for the complexity of OC and the intricate relationship with other factors and processes.

Linkage and association analyses and genome-wide association studies have identified regions of the genome associated with some phenotypic manifestation of OC on about two thirds of the 33 chromosomes of the horse.[104] In a study on risk loci for tarsal OC in two different populations of trotters, a region on chromosome 14 was most important and most consistently involved, but a total of 240 putative risk regions were found on 10 chromosomes.[113] The location of OC may make a difference. There is little overlap between MCP/MTP OC and tarsal OC, suggesting a different genetic background.[104,106] Also, many of the identified quantitative trait loci (QTL) are breed specific. Of 24 QTLs found to be associated with OC in Hanoverian Warmbloods, only two could be confirmed in Thoroughbreds.[114] Additionally, many loci positively associated with desired traits in breeding have a relation with OC too. Of 10 loci associated with conformational and locomotion-associated traits, nine were also associated with OC.[115]

A different approach using leucocytes as cell source for DNA instead of articular tissues, identified dysregulation of a number of pathways, among others Wnt, Ihh, and TGF-β signaling, in OC-affected animals.[116] The material in the original study came from mature animals, precluding discrimination between primary and secondary processes, but the findings were later confirmed in studies in different age groups, including foals.[117] An interesting gene emanating from those studies is the mannosyl glycoprotein acetylglucosaminyltransferase (MGAT4A) gene, which was the only gene to be strongly upregulated in all age groups. This gene is implicated in the intracellular transport of glucose and it can be conjectured that expression of this gene may be triggered by high levels of glucose and triglycerides, as resulting from the intake of high-energy diets, which is one of the most important environmental risk factors for OC (see later). Transient hyperglycemia peaks may lead to long-lasting changes through epigenetic changes,[118] including superoxide anion-mediated mitochondrial damage. Abnormal mitochondria and endoplasmic reticulum have been observed in the deep zone of OC cartilage.[102] Though still alleged, this may be a mechanistic link between environmental factors and OC.[117]

Current knowledge shows that OC can never be selected against using a simple genetic test that detects one or two culprit genes. This does not mean that there may not be a place for genomic selection, which has the big advantage of reducing the generation interval, especially in the horse.[119] However, the relative contribution of genetics to the total variance in the population is variable given the large breed and joint-related differences, and it remains clear that environmental factors contribute relatively more to the manifestation of OC than genetics.

ENVIRONMENTAL FACTORS

There are two major environmental influences playing a role in equine OC: loading and nutritional factors. Biomechanical loading is mainly determined by the exercise regimen, but roughness of the terrain and conformation also may be contributing factors. Nutrition can affect growth rate (which is also partially genetically determined), but may also influence hormonal balances, especially with respect to glucose metabolism, or can affect the mineral and trace element status of animals.

Loading

Joint loading generated by physical exercise has a crucial role in the early juvenile period in the conditioning of the entire musculoskeletal system. It has significance for injury resistance

but may make foals prone to develop chronic degenerative joint disorders later in life.[120–122] It is during this early juvenile period of rapid growth and development that JOCC, of which OC is one, develop, and loading is thought to play a prominent role.[6] Also, the consistent predilection sites of OC within joints can hardly be explained by other than mechanical influences. It is probable that the dramatic changes in loading that take place after birth are an important trigger factor. The youngest animal in which an OC lesion (*OC manifesta*) has been diagnosed was 3 days old[123] and repeated attempts to find this type of lesion in premature or stillborn animals have failed. In a study in fetuses, tiny areas of chondronecrosis were found in all 21 animals studied.[10] It might be argued that these were *OC latens* lesions, but the researchers classified them as a feature of normal development because no specific changes in the collagen matrix compatible with early OC were encountered in any of them.

A triggering role for biomechanical forces fits very well with the early pathogenesis of vessels in cartilage canals passing through a time window of enhanced vulnerability.[13,67,124] Whether or not a lesion will develop will be determined by the character of the biomechanical insult (magnitude, direction of force, repetition) and the degree to which the resistance of the vessel is impaired. The latter factor may be influenced by genetics, but also by hormonal imbalances or inflammation, influencing matrix composition and signaling pathways.

Biomechanical (over)loading of joints may be caused by a variety of factors. In the pig, rough transport has been shown to be an important causative factor of OC.[125] In the horse, the joints are principally challenged by the exercise regimen the animals experience. In a large field study conducted in France, it was shown that there were associations of both prevalence and the severity of OC lesions with irregular access to pasture, as well as with keeping animals in very large plots.[59,126] "Mixed housing" (stabling overnight and pasture access during the daytime, as opposed to the same environment day and night) and rough and slippery grazing grounds were risk factors as well.[127] Another study on the relationship between breeding management and OC confirmed these findings by showing that foals housed exclusively at pasture until one year of age were significantly less affected by OC than foals exclusively housed in boxes, or alternatively, in box and at pasture.[128]

It can be concluded that loading is considered a necessary additive factor rather than a sole cause of OC. A basic level of exercise is needed for the proper development of the musculoskeletal system in general and articular cartilage in particular. This exercise regimen should be characterized by regularity and devoid of high peak loading.

Nutrition

Nutritional factors have been extensively studied as possible causes for OC, especially in two distinct areas: excesses in energy intake and imbalances in mineral and trace element supply.

Energy Intake

Research into high energy intake was prompted by the observation in many species that OC seemed to be a disorder of large-framed, rapidly growing individuals or breeds.[129,130] Later work showed that this relationship was not that straightforward. Growth rate is indeed associated with OC, but this is irrespective of whether the high growth rate is caused by high nutritional levels or linked to genetic factors.[42] Moreover, it is not so much overall growth rate but growth at defined age intervals that become significant. In the large Normandy field study alluded to earlier, a poor osteoarticular status (including disorders other than OC alone) was associated with overall increase in height from 0 to 6 months and height at the withers and girth perimeter at 30 days of age.[126] The lack of a direct relationship between OC and absolute body weight, but a clear relationship between the occurrence of lesions with growth rate *in a specific time window* may be clarified by the known "windows in time" when certain joints are more susceptible to develop lesions.

A high growth rate based on nutritional level is almost invariably linked to excessive intake of carbohydrates, often in an easily digestible form, such as concentrates. This nutrition leads to a strong postprandial hyperinsulinemia.[131] This hormonal response varies between horses and may explain some of the (genetically determined) variation in OC susceptibility. In support of this, horses with OC have been shown to have higher postprandial glucose and insulin responses to feeding high-grain ratios than did unaffected horses.[132]

Insulin and its derivatives IGF-I and IGF-II have a direct effect on the process of endochondral ossification, acting as mitogens for chondrocytes and stimulating chondrocyte survival or suppressing apoptosis.[133] OC-affected foals have a significantly lower IGF-I activity than OC-negative foals.[134] Insulin also stimulates a rapid removal of the thyroid hormones T3 and T4 from the circulation.[135] T3 and T4 are involved in the final stages of chondrocyte differentiation and in the invasion of growth cartilage by blood vessels prior to its conversion to bone.[80] It is interesting to note that the effect of carbohydrates on thyroid hormone levels can be demonstrated in weanlings, but not in yearlings.[131] In current management practice, many horses are fed excessively and have low activity levels. As in humans, these conditions may lead to obesity and insulin resistance. The latter condition has been related to many pathological conditions, including laminitis and OC,[136,137] likely through the mechanisms explained above.

Experimentally, it has been possible to induce cartilaginous lesions by feeding high levels of digestible energy.[138,139] In field studies, unambiguous effects of nutrition have been more difficult to demonstrate because roughage intake cannot be controlled.[126] However in a field study in Kentucky, there was a clear influence of the season on the development of OC in foals. Early foals had a significantly higher incidence of OC in the tarsocrural joints, but late foals had a higher incidence in the femoropatellar joints. This effect could be explained by the different *windows of vulnerability* of these joints, which appeared to coincide with the spring and autumn peaks in the high-energy value of Kentucky blue grass.[140] There was no effect of feeding level of foals in a study in 223 foals in Belgium. However, the feeding practice of the mare had an influence because mares not fed concentrates during pregnancy were less likely to produce an offspring with OC than mares that did receive concentrates.[128] In an experimental study, only a trend in the same direction was seen.[141] In a follow up, foals fed with concentrates had a higher probability to develop OCD lesions, while foals not receiving concentrates had a higher probability of healing existing OCD lesions.[142]

It is clear that nutrition-related hormonal imbalances play a role in the development of equine OC, probably by increasing vulnerability for early vascular damage. However, it is highly unlikely that it is the sole etiological factor, as OC lesions can

also be found in horses eating normal diets without any abnormalities in their insulin metabolism. Further, many lesions provoked by the administration of high-carbohydrate diets were similar, but not identical to clinical OC lesions. Lastly, many experimentally induced lesions were seen in the growth plate,[143] where clinical OC is rarely, if ever, seen in horses.

Imbalances of Minerals and Trace Elements

Imbalances in trace elements, in particular copper and its antagonists zinc and cadmium, have been implicated in the development of OC, based on a report on the relationship between low copper levels in serum, and horses with the disorder.[144] The mechanism was thought to act via lysyl oxidase, a copper-dependent enzyme that is essential for the formation of collagen cross-links. Epidemiological studies on stud farms in Kentucky and Ohio demonstrated a low copper level in the feed and a possible relationship with the incidence of DOD in general (not only OC).[145] These studies questioned the rather low official recommendation for copper at that time (10 ppm),[146] which was based on very poor scientific evidence, and suggested an important role for copper in OC. However, following experimental work showed that only excessively higher or lower levels of these trace elements fed in experimental diets could provoke OC lesions, which were dissimilar to the naturally occurring ones. Therefore copper is no longer incriminated as being the main culprit for the development of OC.[147] Moreover, field studies in New Zealand, a country with a low incidence of OC and where many horses are kept year round on grass only, showed that the low natural copper level of 4.3 to 8.6 ppm in the local grass was sufficient for a healthy development of bone and cartilage.[148] Conversely, Cu supplementation of pregnant mares or newborn foals may still have clinical benefit. Mare milk contains hardly any copper and foals are born with a large stock of copper in the liver that declines gradually to normal levels when they eat enough grass to ensure sufficient daily intake.[149] In Thoroughbreds, mean liver copper concentrations have been reported to decline from 374 mg/kg DM at birth to 21 mg/kg DM at 160 days.[150] Liver copper concentration in newborn foals can be influenced by prenatal supplementation of mares during late pregnancy or of newborn foals[151,152] and has been shown to be positively related to the resolution of osteochondrotic lesions.[153]

The calcium / phosphorus ratio is important for bone metabolism and (severe) aberrations will cause various bone disorders. High calcium levels were shown to have no influence on the incidence of OC in foals, but high levels (four times the Nutritional Research Council [NRC] recommendation) of phosphorus resulted in significantly more lesions.[154] The mechanism of action was suggested to be the induction of secondary hyperparathyroidism, which would lead to increased osteoporosis and subsequent weakening of the subchondral bone. The study is interesting because foals were evaluated in the period from 2.5 to 6.5 months of age, an age in which the dynamic process of OC is very active and animals are very susceptible to the disorder.

TREATMENT

The need and reasons for treatment of OC vary according to the severity of the symptoms. The presence of lameness makes intervention necessary to obtain functional recovery, but many animals are asymptomatic and are treated only for esthetic or, in the majority of cases, economic reasons. Horses with (radiographically) visible signs of OC sell with more difficulty and at substantially lower prices than "clean" animals. Potential effect on long-term performance may be another reason, but this effect is generally minor (see later). Treatment options include conservative and surgical management. The latter is the option of choice in the vast majority of cases.

Conservative Treatment

Nonsurgical treatment consists principally of rest and controlled exercise. Systemic NSAIDs and intraarticular medication (corticosteroids and disease-modifying osteoarthritic drugs such as hyaluronan, chondroitin sulfate, or pentosan sulfate) may be administered, but are not seen as of great value,[155] and may even be associated with risks. There are anecdotal reports of horses treated with intraarticular corticosteroids to reduce effusion before going to sales that developed acute lameness because of acute detachment of cartilage.[156]

Theoretically, nonsurgical management can only be successful in either very young animals, in which there is still good capacity for regeneration, or in very mild cases. Stifle lesions change over the longest period of time[40] and several animals in three crops of Thoroughbred foals that were longitudinally followed without intervention showed improvement and repair of a variety of stifle lesions.[27] Healing with conservative treatment is deemed likely when lesions are less than 2 cm long and less than 5 mm deep without radiographic fragmentation.[156] Also when flattening without fragmentation (type IOC) occurs in the sagittal ridge of the MCIII or MTIII initial conservative treatment is advised.[156] While conservative treatment of OC in the scapulohumeral joint was earlier seen as having a very poor prognosis,[157] recent data suggests that it may be a worthwhile option in mild cases where the glenoid cavity is involved.[156] With regard to tarsocrural OC, some authors advise surgical intervention in all horses with clinical signs and destined for an athletic career,[156] but a favorable outcome with nonsurgical treatment of tarsocrural OC has been described in a group of Standardbreds. Of these, half were treated nonsurgically and half surgically. However, results were biased as the more severe cases tended to be treated surgically.[158]

Surgical Treatment

Surgical management by arthroscopy is the treatment of choice in most cases.[156] Standard approaches and some variations thereof have been described for every relevant joint.[159] The approach is relatively straightforward for the majority of joints (tarsocrural, femoropatellar, MCP/MTP joints), but is much more difficult in the scapulohumeral joint.[31]

After extensive inspection and careful probing of the cartilage to detect loose flaps or hidden cysts, loose fragments and/or loose cartilage flaps are removed and the remaining surrounding tissue débrided (Figure 89-13). In young animals, the subchondral bone should not be débrided too aggressively, as it is often still relatively soft.[156]

A number of reparative approaches to OCD have been described. Large flaps of partially detached cartilage have been reattached to their osseous bed by the use of resorbable polydioxanone pins.[160] Long-term follow-up in 26 horses with reattached flaps showed a 95% success rate in those horses (N=20) for which performance data were available.[161] Recently, regenerative medicine techniques have been used to try to heal osteochondrotic

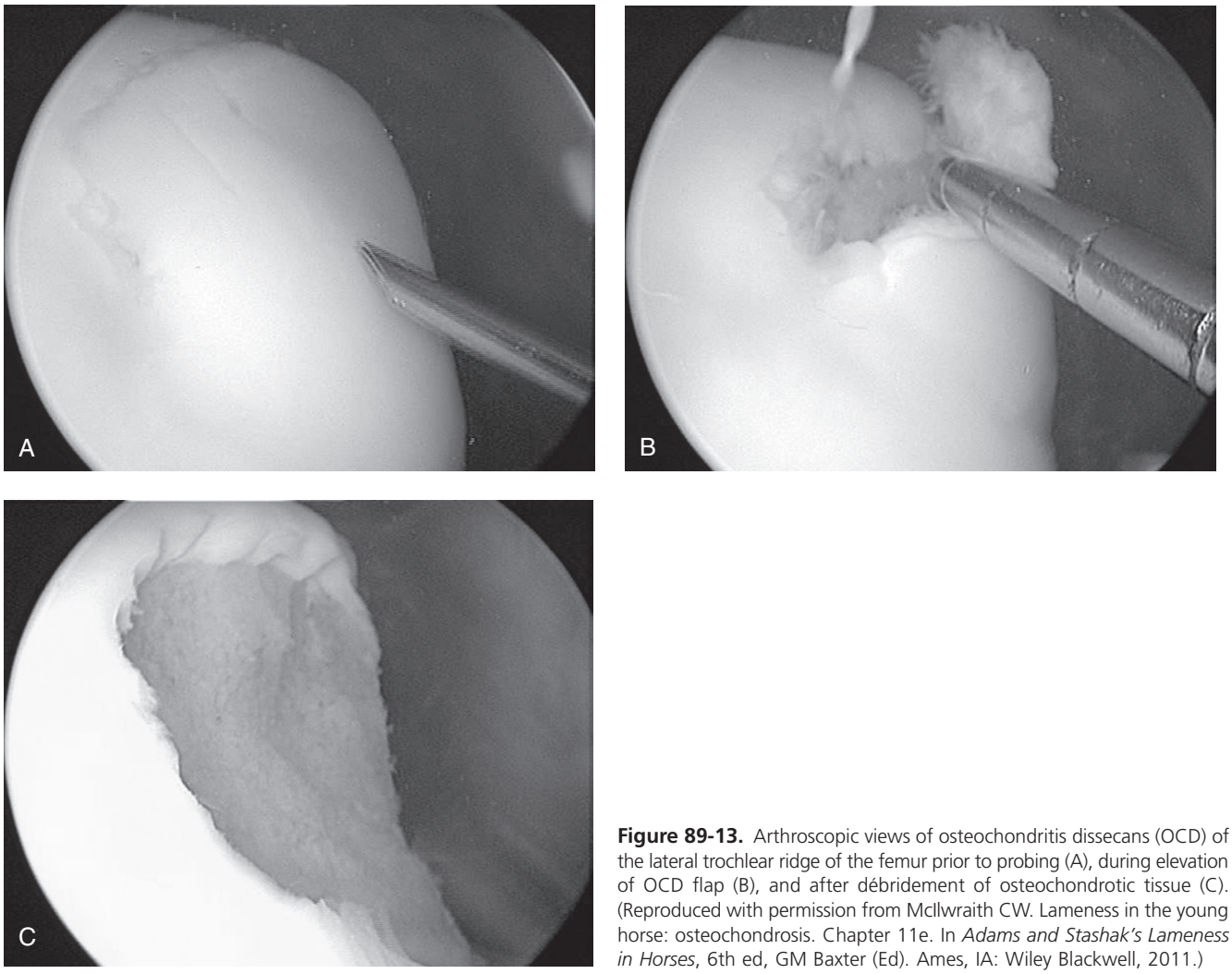

Figure 89-13. Arthroscopic views of osteochondritis dissecans (OCD) of the lateral trochlear ridge of the femur prior to probing (A), during elevation of OCD flap (B), and after débridement of osteochondrotic tissue (C). (Reproduced with permission from McIlwraith CW. Lameness in the young horse: osteochondrosis. Chapter 11e. In *Adams and Stashak's Lameness in Horses*, 6th ed, GM Baxter (Ed). Ames, IA: Wiley Blackwell, 2011.)

defects. A sponge impregnated with platelet-rich plasma, bone morphogenetic protein-2, mesenchymal stem cells, and gelatin β-tricalcium phosphate was applied to the medial malleolus of the talus in a Thoroughbred filly after taking out the fragment and débriding the defect. At 16 weeks after surgery the animal was performing well clinically and there was good repair as judged from imaging and arthroscopic inspection. A biopsy at that moment showed, however, the formation of fibrocartilage, not of hyaline cartilage.[162] In another case, a multilayered osteochondral scaffold was used to treat a severe osteochondrotic lesion of the lateral femoral trochlear ridge in a 15-month-old filly. At follow-up at 22 months, the filly was performing well and the radiographic contour of the bone had become much more regular, although a slight flattening remained. At arthroscopy, the bone was covered with a cartilaginous layer, but no biopsy was taken and the nature of this layer remained elusive.[163]

PROGNOSIS

The prognosis after surgical intervention varies between joints and depends on the amount and extent of the lesion and on the definition of "favorable outcome." In the racing breeds, this is mostly defined as horses that can compete at their maximal athletic capacity. The presence of some effusion is of less importance. In many show horses, biomechanical challenges are less, but cosmetic appearance assumes more importance. In horses meant for sale, the goals are often to make them look "clean" on the radiographs, and have no effusion of the joints. In general, prognosis for a return to athletic activity is fair to good for the majority of joints involved.

For the femoropatellar joint, a 64% success rate was reported in a mixed population of racehorses and nonracehorses.[164] Horses with smaller lesions (Grade I, <2 cm in length) were more successful than horses with larger lesions (Grade II, 2–4 cm and Grade III, >4 cm). A similar figure of 65% complete functional recovery was found in a more recent study in which the depth of the lesion was significantly associated with short-term complications (effusion and lameness), but not with the long-term outcome. Involvement of structures other than the lateral trochlear ridge (patella, medial trochlear ridge) was associated with a worse prognosis.[165] In another study, 19 of 25 arthroscopically treated horses (76%) were able to perform as intended.[166] A recent study in a group of 278 Standardbred trotters and pacers showed that, when undergoing early removal of tarsal OC lesions, affected horses can be expected to perform equivalently to their unaffected counterparts.[167]

In a large survey of 183 horses operated for tarsocrural OC, success rates were 73% and 83% in racehorses and nonracehorses, respectively. Synovial effusion resolved in 89% of racehorses and 74% of nonracehorses.[30] Score reductions for lameness and reaction to the flexion test of 80% to 90% and resolution of joint effusion in around 50% of cases of tarsocrural OC have been reported in a mixed population of Standardbreds and Warmblood horses.[168]

In the MCP and MTP joints, a discrimination is made between lesions type I (flattening only), type II (flattening with fragmentation), and type III (flattening with or without fragmentation at the lesion site and a loose body present) of the sagittal ridge of MCIII/MTIII. The advice is to treat type I conservatively, but the other two surgically shortly after diagnosing them, as treatment at a later stage is associated with the development of osteoarthritis.[156] A 90% return to athletic activity has been reported if the lesion is located in the more proximal part of the sagittal ridge, but an unspecified lower rate for lesions in weight-bearing areas.[169]

Shoulder OC has the least favorable prognosis. One study reports a favorable outcome of only 15% in racehorses (but better in nonracehorses) suffering from shoulder OC, which was similar after surgical or conservative treatment,[170] but other reports mention successful outcome in approximately 50% of cases.[156]

IMPACT OF OC

Effects on Performance

In few cases, OC may result in very severe lesions that cannot be treated (Figure 89-14). Additionally, severe sequelae to OC have been described, such as development of cervical vertebral stenotic myelopathy as a consequence of OC of the cervical facet joints,[171] but in the majority of cases, clinical signs are minimal and gait alterations minimal.[172]

The effects of OC on performance have been most heavily studied in the racing breeds. For tarsocrural OC in Standardbreds, the general trend is that fewer and smaller lesions may delay the start of the racing career, but will have very little, if any, effect on performance.[158,173,174] Even a positive association between presence of tarsocrural OC and performance has been described.[111] However, severe or multiple abnormalities significantly compromise a potential future racing career.[175]

Racing performance in Thoroughbreds treated for OC in the femoropatellar joint was not different from that in unaffected siblings, but fewer horses raced as 2-year-olds and earnings were less, both at 2 and 3 years of age.[176] In a more recent study in racing Thoroughbreds (flat and hurdle racing) that took into account all radiographic findings related to juvenile osteochondral conditions, fewer horses with radiographic findings raced as 2-year-olds and fewer were placed as 3-year-olds compared to horses without radiographic anomalies.[177]

In sport horses, studies are scarce. In show jumpers, no differences between horses with tarsocrural OC and controls could be established. However, OC of the femoropatellar and MCP/MTP joints significantly affected performance.[178]

Economic Impact

OC has a huge effect on the economics of the equine industry, mainly because of value depreciation of affected horses, and indirectly, through the effect on breeding. Because of the high incidence, elimination of affected horses would mean that a large proportion (in some cases up to 30%) of potentially good breeding stock would be excluded. This would not only directly affect breeders, but it would mean eliminating a significant part of the gene pool. The fact that tens of thousands of horses have to be operated each year means significant costs for the equine industry, but is also an important welfare issue because of the suffering of the animals associated with the surgical intervention.

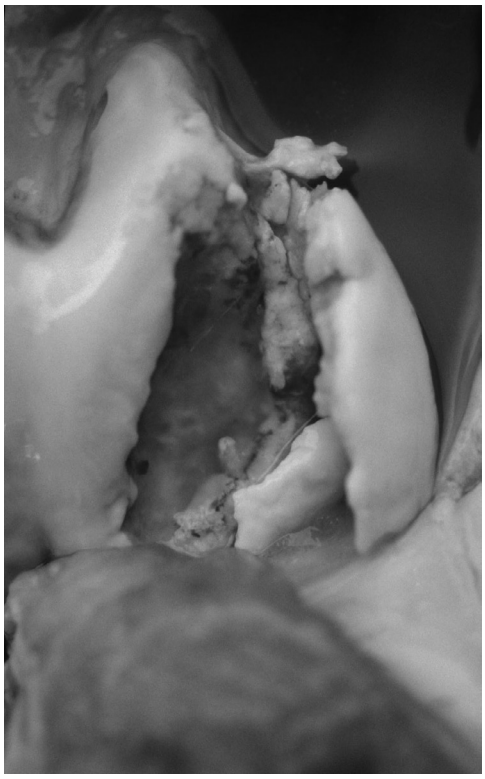

Figure 89-14. Dramatic osteochondral fragmentation of the lateral femoral trochlear ridge in a 7.5-month-old Selle Français foal. The animal had slipped accidentally at an age of 3 weeks. At that moment no direct damage was visible, but the accident had probably prompted the development of a large osteochondrotic lesion. (From Denoix JM, Jeffcott LB, McIlwraith CW, et al. A review of terminology for equine juvenile osteochondral conditions (JOCC) based on anatomical and functional considerations. *Vet J*. 2013;197:29–35.)

CONCLUSION AND SUGGESTIONS FOR FURTHER RESEARCH

OC is a multifactorial and complex disorder that, despite its nonlethal character and the relatively minor effect on athletic performance in the majority of cases, has a huge impact on the equine industry. Much progress has been made since the disorder became a focus of research in the late 1980s and early 1990s.[179] It is now clear that OC can only be understood in the wider framework of the developing musculoskeletal system in the juvenile horse and the genetic and environmental factors acting thereon.[122] Whereas there is still much conflicting data about incidence and heritability, it is now known why this is so. The early pathogenetic mechanisms have been discovered and progress is being made in unravelling the exact molecular pathways and

how they are triggered by numerous etiological factors. The (surgical) treatment of OC has evolved well and generally carries a fair to good prognosis, but better prevention would be much more desirable endpoint.

It is clear that no simple "cure" for OC exists and that it will be impossible to eliminate the disorder while maintaining current management practices and breeding goals regarding performance and esthetics.[180] However, further research will allow the disease to be better managed. Detailed studies at the molecular level will allow a separation of events related to the normal process of endochondral ossification, those related to the primary etiopathogenesis, and those reflecting the secondary repair process. The upcoming "omics" approaches might well prove to be of great use for the better understanding of this complicated and multifactorial disorder, as will be detailed epigenetic studies. More epidemiological studies, taking a more refined approach to allow discrimination between lesions of various types and at different locations will help to develop better selection strategies and result in more accurate prognostication.

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