Osteochondrosis: Etiologic Factors

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ABSTRACT: Osteochondrosis is a disease of articular cartilage development and is a major source of lameness in young horses, leading to decreased athletic potential. Osteochondrosis involves abnormal differentiation and ossification of articular cartilage during development, resulting in a weakened cartilage matrix and subsequent cartilage flap formation within the joint. This disease is multifactorial, with nutrition, growth rate, hereditary factors, and trauma playing important roles. In addition, aberrant local signaling to the chondrocytes in the deep layer of the articular-epiphyseal cartilage complex is believed to underlie the development of this disease.

Osteochondrosis constitutes a complex of cartilage aberrations, collectively known as *developmental orthopedic diseases* in horses, including osteochondritis dissecans of the joints (Figure 1), physitis, collapse of cuboidal bones in the carpus and hock, and cervical vertebral malformation.[1] Osteochondrosis develops as the result of focal or multifocal defects in cartilage differentiation and endochondral ossification. *Dyschondroplasia* is used synonymously with *osteochondrosis* to describe the disease in horses,[2] but dyschondroplasia really represents a more generalized metabolic disorder of endochondral ossification that affects the entire skeleton from the early stages of development.[3] The definitive cause of osteochondrosis has not been identified, despite many studies of this disease in horses and other species. The consensus is that osteochondrosis is multifactorial and likely the result of a combination of metabolic derangements. Nutrition, hereditary factors, biomechanical trauma, and molecular aberrations have all been implicated in the etiopathogenesis of osteochondrosis.[2]

NUTRITION

The impact of nutrition on the development of osteochondrosis has been studied extensively during the past 15 years. High planes of nutrition coupled with rapid growth rates are associated with an increased incidence of osteochondrosis.[4–6] In addition, weanlings with a high glucose and insulin response to concentrates may be predisposed to osteochondrosis,[7] and weanlings that have adapted to high glycemic feeds may show changes in insulin sensitivity.[8] Other nutritional factors that may be involved in the etiopathogenesis include low copper, calcium, or selenium levels and high phosphorus, zinc, or molybdenum levels.[9–13] Copper supplementation of mares during pregnancy may help decrease the prevalence of osteochondrosis.[13,14]

As a result of altered nutritional practices to reduce growth rates and balance the mineral content of feed, the incidence of osteochondro-

sis in foals and yearlings has been significantly reduced. Despite these altered practices, however, the disease complex remains at an incidence plateau of approximately 10%.[15] In addition, osteochondrosis has been identified in feral horses not receiving high levels of nutrition.[16]

GENETIC INFLUENCE

The possibility of a familial tendency for osteochondrosis has been described, particularly in Standardbreds and Swedish Warmbloods.[17–19] In these breeds, the incidence of osteochondrosis is significantly greater in offspring of stallions with osteochondrosis of the hock than in offspring of stallions without the disease.[19] Heritability estimates of up to 0.52 also support genetic influence as an important factor in osteochondrosis.[20] In further support of heritability as an etiologic factor, research[21] shows that inherent growth rate is a major determinant in the development of femoropatellar osteochondrosis in horses. Based on this study,[21] greater weight gains during the third and fifth months of life appear to have the most influence on the development of osteochondrosis. The same study[21] did not report a gender influence on the prevalence of osteochondrosis. However, others have reported[22] a male predominance: twice the number of males underwent surgery for femoropatellar osteochondrosis than did females.

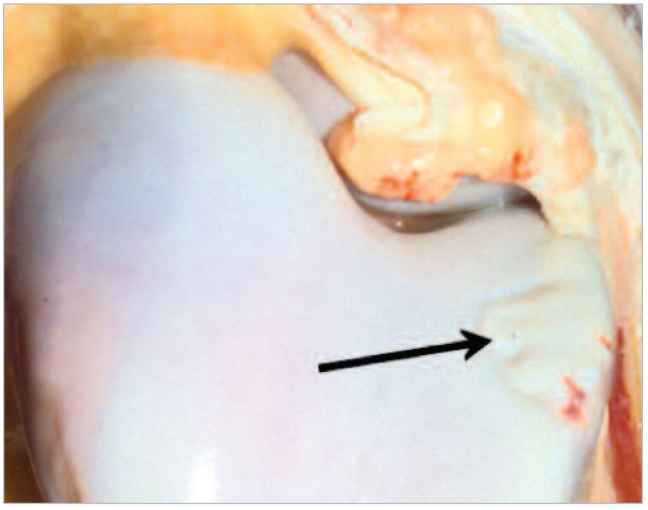

Figure 1. Osteochondrotic lesion (*arrow*) of the femoropatellar joint in a yearling quarter horse. The cartilage of the lateral trochlear ridge of the distal femur remains attached to adjacent cartilage but has partially separated from the underlying subchondral bone.

Rapid growth rates and factors that lead to rapid growth, including genetic and environmental influences, predispose young horses to osteochondrosis.

BIOMECHANICAL FACTORS

Environmental conditions such as access to exercise have been investigated to determine their effects on the manifestation of osteochondrosis. In one study, three groups of foals were compared: those confined in stalls, those turned out to pasture, and those confined in stalls but galloped daily.[23] Although the addition of exercise did not significantly affect the number of osteochondrotic lesions, it did affect their location and severity. Compared with other affected foals, foals confined in stalls tended to have more severe lesions, and the femoral condyles were more often affected. In contrast, exercised foals tended to have lesions involving the lateral trochlear ridge of the femur. The results of this study[23] indicate that the number of osteochondrotic lesions per foal decreases significantly from 5 to 11 months of age, suggesting that lesion healing may occur naturally during this 6-month period. Based on this study,[23] biomechanical forces appear to play an important role in the location and severity of osteochondrotic lesions. Other investigators[24] also suggest that biomechanical forces play an important role in causing the detached cartilage flaps associated with osteochondritis dissecans by initiating separation at the chondro-osseous junction, where the matrix is already weakened.

MOLECULAR ALTERATIONS

The biochemical phenomena that precede the weakened matrix associated with osteochondrosis have only recently been studied.[25–28] There is little doubt that some abnormality in matrix production and assembly is at the core of the development of osteochondrosis. It is likely that aberrant signaling to the chondrocytes of the prehypertrophic or hypertrophic layers of the articular–epiphyseal cartilage complex may result in delayed chondrocytic differentiation and matrix calcification and the subsequent development of osteochondrosis. Figure 2 depicts the

Factors that Stimulate or Inhibit Terminal Differentiation of Chondrocytes

Factors that Stimulate
- Indian hedgehog
- Bone morphogenetic protein 6
- Bone morphogenetic protein 2

Factors that Inhibit
- Parathyroid hormone–related peptide
- Transforming growth factor–β1
- Bone morphogenetic protein 7

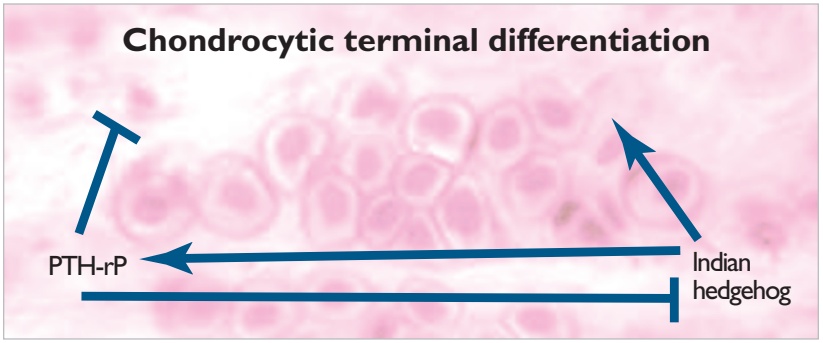

Figure 2. Negative feedback loop of the paracrine factors parathyroid hormone–related peptide (PTH-rP) and Indian hedgehog and their effect on terminal differentiation of growth cartilage. PTH-rP inhibits terminal differentiation of chondrocytes and expression of Indian hedgehog. Indian hedgehog stimulates terminal differentiation of chondrocytes but also increases expression of PTH-rP, causing a negative feedback on itself and, ultimately, a delay in differentiation.

basic negative feedback loop of paracrine factors that control the rate of terminal differentiation of cartilage. The box on this page lists cell-signaling factors that affect terminal differentiation of chondrocytes. Increased expression of factors that inhibit terminal differentiation or decreased expression of factors that promote terminal differentiation can delay endochondral ossification and cause osteochondrosis. Altered vascular invasion, at least in physeal manifestations of osteochondrosis, may also contribute to the delay in endochondral ossification.[29]

Many studies[25–28,30–34] have revealed changes in the collagen and proteoglycan content of osteochondrotic cartilage compared with normal cartilage. The different collagen types that have been investigated in osteochondrosis are listed in Table 1. In early osteochondrotic lesions in 5- and 11-month-old foals, total collagen and hydroxylysyl pyridinoline cross-linking of collagen are significantly decreased.[30] In contrast, lysyl pyridinoline cross-linking and proteoglycan content are decreased in more advanced osteochondrotic lesions.[30] Trends for altered expression of collagen types I and II occur in osteochondrotic lesions of the femoropatellar and shoulder joints in horses,[25,31] and altered type VI collagen expression is found around chondrocyte clusters and in accumulations of small, rounded chondrocytes in osteochondrosis.[26] Transcription of mRNA for type X collagen, a marker of cellular hypertrophy, is increased in tibial dyschondroplasia of chickens,[28] but there is no increase in equine osteochondrosis.[25] In distal tibial intermediate ridge lesions of horses, the proteoglycan content of osteochondrotic cartilage is decreased by both qualitative and quantitative determinations.[27,30] These matrix changes illustrate the potential for structural weakness in osteochondrotic cartilage that may predispose it to biomechanical damage.

Matrix metalloproteinases and other matrix enzymes are implicated in the structural alterations that occur in osteochondrosis.[35–37] In osteochondrosis samples, gelatinase activity is significantly increased, mostly from the deep layer and along vertical clefts within the cartilage.[35] Gelatinase activity is primarily mediated by matrix metalloproteinases 2 and 9, which are enzymes that break down unwound collagen and gelatin. However, because matrix metalloproteinase activity is not increased in synovial fluid from joints affected by osteochondrosis, other investigators[36] suggest that increased expression of these enzymes may be due to age-related differences rather than osteochondrosis.

In early osteochondrosis, biomechanical factors stressing the abnormal cartilage matrix may ultimately determine whether healing or osteochondritis dissecans flap formation ensues.

Alterations in expression levels of specific growth factors have been identified in osteochondrosis in several species and may be responsible for initiating widespread abnormalities in cartilage development. Specifically, the transforming growth factor (TGF)–β1 mRNA expression level is lower in osteochondrotic cartilage (prima-

rily in the hypertrophic region) of chickens and pigs.[38,39] In horses, protein expression of TGF-β1 is decreased in affected cartilage but increased in adjacent cartilage.[40] Overall mRNA expression of TGF-β1 is increased in equine osteochondrosis, as assessed by quantitative polymerase chain reaction testing.[25]

Insulin-like growth factor (IGF)–I levels may be involved in the development of osteochondrosis, as alterations of IGF-I levels have been identified in osteochondrotic lesions in several species.[25,41–43] In horses, mRNA expression of IGF-I is increased in osteochondrotic lesions compared with normal cartilage from age-matched controls, as assessed by quantitative polymerase chain reaction testing.[25] Given the anabolic effects of IGF-I, increased expression of it may be associated with an attempt to repair the cartilage defect rather than playing a specific causal role in osteochondrosis.[44,45]

Local expression of parathyroid hormone–related peptide (PTH-rP) and Indian hedgehog is also altered in osteochondrosis.[46–49] By regulating the terminal differentiation of chondrocytes, these paracrine factors form an important negative feedback loop in growth-plate cartilage (Figure 2). In mice, overexpression of PTH-rP or Indian hedgehog produces chondrodysplasia and short-limbed dwarfism resulting from delayed endochondral ossification.[47] In horses with osteochondrosis, expression of these two peptides is increased in the deep articular layers of affected cartilage,[46,50] suggesting a possible link to delayed endochondral ossification, which is central to the pathogenesis of osteochondrosis. The focal nature of osteochondrosis in horses suggests that increased expression of these two peptides occurs as a local alteration in cartilage gene expression rather than as a widespread occurrence in all joints.

Bone morphogenetic proteins and their inhibitors are also being investigated[51] in equine osteochondrosis. Normally, bone morphogenetic proteins play an important role in regulating cartilage differentiation and may act as intermediaries in the PTH-rP and Indian hedgehog feedback cycle, controlling the synthesis of these peptides.[52–54] Bone morphogenetic protein 6 stimulates cartilage maturation, and most of the evidence supports its function in the PTH-rP and Indian hedgehog feedback cycle. Bone morphogenetic protein 2 participates in cartilage differentiation by stimulating chondrocyte proliferation and hypertrophy as well as inducing apoptosis.[55,56] No significant differences in mRNA expression of bone morphogenetic proteins 2 or 6 or an inhibitor of bone morphogenetic proteins are identified in osteochondrosis and normal cartilage,[51] suggesting that bone morphogenetic proteins are not involved in the disease process of osteochondrosis, despite the important roles they play in cartilage differentiation.

Table 1. Collagen Types Investigated in Osteochondrosis

Collagen Type	Description
I	• Major collagen type in fibrous connective tissue and bone • Forms principal molecule of collagen fibrils • Not normally found in articular cartilage
II	• Major collagen in hyaline cartilage • Forms main molecule of collagen fibrils in cartilage
VI	• Small-chain collagen in mammalian articular cartilage • Forms microfibrils that may link type II collagen to cells • May have a cell-signaling function
X	• Small-chain collagen that is found only in hypertrophic growth cartilage and the deep zone of adult articular cartilage • Unknown function • Considered a marker for hypertrophic cartilage

There is currently much interest in the potential use of serum and synovial biomarkers as indicators of osteochondrosis and joint disease in horses.[34,36,57–59] Biomarkers are molecules that can serve as early indicators of metabolic abnormalities in specific tissues of the body.[58] A study[34] on synovial fluid biomarkers revealed differential alterations in aggrecan and collagen turnover in young horses with osteochondrosis. Another study[58] showed that serum biomarkers of collagen degradation and bone mineralization are positive indicators of the severity of osteochondrosis at 5 months of age. However, by 11 months of age, several of these biomarkers become negatively correlated with the severity of osteochondrosis. The ability of biomarkers to indicate the severity of osteochondrotic lesions is apparently strengthened by the inclusion of radiographic evaluation of the hock and stifle.[58] Although no one biomarker or combination of biomarkers is currently known to specif-

ically predict osteochondrosis, continued research on serum and synovial fluid molecular biomarkers may someday allow accurate prediction of the occurrence and severity of osteochondrosis in horses.

CONCLUSION

Given the large number of factors that influence the development of osteochondrosis, it has been difficult to define an exact cause of this disease. However, the evidence supports its multifactorial nature, and several conclusions regarding its pathogenesis can be made. First, rapid growth rates and factors that lead to rapid growth, including genetic and environmental influences, predispose young horses to osteochondrosis. Second, alterations in local cartilage regulatory peptides most likely lead to the abnormal cartilage matrix and weakened osteochondral junction apparent in osteochondrotic lesions. Finally, biomechanical factors that stress the weakened osteochondral junction play an important role in the clinical manifestation of osteochondrosis and may ultimately determine whether healing or osteochondritis dissecans flap formation ensues.

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ARTICLE #2 CE TEST

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1. Which factor(s) has/have been associated with osteochondrosis in horses?
a. trauma to a weakened cartilage matrix
b. a low copper level
c. sire–offspring hereditary influence
d. all of the above

2. Stall confinement during the first 5 months of life tended to have the following effect(s) on foals and the development of osteochondrosis:
a. more severe lesions.
b. less severe lesions.
c. lesions of the femoral condyles.
d. a and c

3. A genetic tendency for osteochondrosis has been found in
a. Standardbreds.
b. American saddlebreds.
c. ponies.
d. none of the above

4. What trace mineral should be supplemented in mares during pregnancy to help reduce the incidence of osteochondrosis in foals?
a. copper
b. zinc
c. molybdenum
d. iron

5. Which cartilage matrix molecules are increased in osteochondrosis?
a. type II collagen
b. proteoglycans
c. polysulfated glycosaminoglycans
d. none of the above

6. Which factors form an important feedback loop in growth cartilage by regulating the rate of hypertrophy and have been shown to be increased in osteochondrosis?
a. bone morphogenetic proteins 2 and 6
b. IGF-I and TGF-β1
c. PTH-rP and Indian hedgehog
d. matrix metalloproteinases and gelatinases

7. Which factors break down unwound collagen and gelatin and have been shown to have increased activity in osteochondrotic cartilage?
a. bone morphogenetic proteins 2 and 6
b. IGF-I and TGF-β1
c. PTH-rP and Indian hedgehog
d. matrix metalloproteinases and gelatinases

8. Which factors are increased in osteochondrotic cartilage but probably play a secondary role by promoting lesion healing?
a. bone morphogenetic proteins 2 and 6
b. IGF-I and TGF-β1
c. PTH-rP and Indian hedgehog
d. matrix metalloproteinases and gelatinases

9. Which statement(s) regarding biomarkers as indicators of osteochondrosis in horses is/are correct?
a. Radiographic evaluation of the hock and stifle may strengthen the ability of biomarkers to predict the severity of osteochondrosis.
b. Alterations in synovial fluid aggrecan and collagen turnover have been found in young horses with osteochondrosis.
c. Serum biomarkers of collagen degradation and bone mineralization may be positive indicators of the severity of osteochondrosis at 5 months of age.
d. all of the above

10. Which etiologic factor(s) is/are most important in the development of osteochondrosis in horses?
a. rapid growth rate
b. biomechanical stress
c. changes in cartilage regulatory peptides
d. all of the above