Rare osteoarthritis: ochronosis and Kashin-Beck disease
Virginia Byers Kraus

Key Points

**OCHRONOSIS**
- Ochronosis is a rare autosomal recessive disorder resulting from a constitutional lack of homogentisic acid oxidase.
- In ochronosis, homogentisic acid undergoes autoxidation as well as enzymatic oxidation and polymerization to form an ochronotic pigment that accumulates in cartilage and connective tissues.
- The endogenous form of ochronosis may be confused with exogenous ochronosis, a limited hyperpigmentation of skin caused by various drugs and chemicals.
- Clinical features of ochronosis include homogentisic aciduria, pigmentation of cartilages and other connective tissues, and in later years, generalized ochronosis of the spine and large joints, termed ochronotic arthropathies.

**KASHIN-BECK DISEASE**
- Kashin-Beck disease (KBD) is a severe, progressive osteoarthropathy of unknown cause endemic to China and Tibet, with onset in childhood.
- Three interacting causal mechanisms have been proposed, including a deficiency in trace elements (selenium and iodine), exposure to organic matter in contaminated drinking water, and contamination of food by noxious fungal and bacterial toxins.
- The disease is characterized by necrosis and remodeling of cartilage, including growth plates.
- Clinical features of KBD include generalized osteoarthropathy involving the ankles, knees, interphalangeal joints, wrists, and elbows with shortened phalanges; more severe involvement of distal and lower limbs; and an association with short stature.

INTRODUCTION

Osteoarthritis (OA) comprises a heterogeneous group of joint diseases, some of common and some of rare occurrence. Although the rare forms discussed here impact individuals infrequently or in specific and circumscribed geographic regions, nevertheless an understanding of these rare forms of OA may provide useful insights into the nature and pathogenesis of the more common varieties of OA. (Other rare hereditary disorders of cartilage and bone, some of which can lead to OA, are described in Chapter 215.) These rare forms of OA are thought to derive from diverse causes that include genetic, nutritional, and biogeochemical factors (Kashin-Beck disease [KBD]). This diversity of causes is itself illustrative of the multiple pathways to the syndrome of joint failure that we recognize as OA. Although each of these diseases presents clinically as a form of OA, there are differentiating manifestations by which these arthropathies can be distinguished from one another. An appreciation of these subtleties is key to the recognition and management of these disorders.

OCHRONOSIS

**HISTORY**

Ochronosis and alkaptonuria are two names that refer to different manifestations of the same condition resulting from an inborn error of tyrosine metabolism—a deficiency of the enzyme homogentisate 1,2-dioxygenase (HGD), also known as homogentisate oxidase, or HGO) (Fig. 212.1). The connection between these two entities was recognized by Albrecht in 1902. 1 Simultaneously, this was the first human disorder found to conform to the principles of mendelian autosomal recessive inheritance. 1 In 1908, the term *inborn errors of metabolism* was first coined by Archibald Garrod to describe this and three other diseases. 2 The absence of the HGD enzyme, normally highly expressed in hepatocytes, leads to the accumulation of metabolites of homogentisic acid in the connective tissues of individuals who are affected; this deposition causes an ochre-like pigmentation in the skin, sclera, and cartilages of the body (Fig. 212.2) and is the characteristic for which the disease was named ochronosis by Virchow. Only a small proportion of the homogentisic acid formed endogenously is normally retained in the body because of its high renal clearance 6; the absence of the HGD enzyme leads to abundant urinary excretion of homogentisic acid, which darkens slowly upon oxidation by prolonged exposure to air. The darkening is hastened by the addition of alkali to the urine and is reflected in the original term for homogentisic acid, alkapton, which refers to its avidity for alkali. The distinctiveness of alkaptonuria accounts for reports of dark urine, including urine “as black as ink,” dating as far back as the Middle Ages. 7 There has even been biochemical confirmation that ochronotic pigment in the bone and articular hip cartilage of an Egyptian mummy originated from homogentisic acid, which demonstrates that this disorder has afflicted humans since ancient times. 7

**EPIDEMIOLOGY**

Alkaptonuria or ochronosis is one of the rare diseases that affect human beings on a worldwide scale. 6 In the United States, alkaptonuria has a prevalence of 1 case per 250,000 to 1 million live births. 3 The highest frequencies are reported in Slovakia and the Dominican Republic, in which the prevalence approaches 1 case per 19,000 inhabitants, 8 and in a single village in southern Jordan with a large number of cases (40 individuals in 17 families) considered a probable consequence of the high rates of consanguineous marriages in Jordan. 9 10

**CLINICAL FEATURES**

Patients with ochronosis are distinguished by the triad of dark urine on addition of alkali, ochronotic pigmentation, and arthritis. 3 11 Alkaptonuria is present at birth and is often diagnosed by discoloration of the diapers. This is the only sign of the disorder in the pediatric age group, 11 and many patients remain undiagnosed until adulthood because 25% do not have the characteristic dark urine staining. 12 It is possible that many of the early manifestations of this disorder may go unnoticed by the patient, including dark urine and dark cerumen at birth, axillary pigmentation at puberty, and earlobe skin and scleral pigmentation at 20 to 40 years of age. 12 Cases that escape detection in childhood are usually diagnosed on the basis of chronic joint pain, which typically develops in the third decade of life. 1 The delay in appearance of the ochronotic arthropathy until after midlife is often ascribed to a waning efficiency of the renal clearance of homogentisic acid, leading to an accelerated accumulation of homogentisic acid oxidation byproducts with aging. 13

The arthropathy that develops affects the spine and large joints. The low back is frequently the signal anatomic site. The spine involvement resembles ankylosing spondylitis but differs in sparing the sacroiliac joints. 1 The pattern of spine involvement is reported to differ from typical OA in that thoracolumbar changes predominate rather than lumbar sacral degeneration, 16 although the severity of lumbar spine involvement had the strongest correlation with disability measures in a study of 53 patients. 12 Narrowing and dense, wafer-like calcification of the intervertebral disks are the most characteristic findings in the spine (Fig. 212.3), and osteophytes are said to be usually absent or of small size. 16,17 The peripheral arthritis closely resembles that of OA; however, the hands and feet are usually spared. 17 Arthritis of the peripheral joints is generally observed about 10 years after spinal changes (Fig. 212.4). The main differences among ochronotic arthropathy, primary OA, and ankylosing spondylitis are summarized in Table 212.1. Tendon involvement is typically symmetric and involves traction tendons and their insertion sites with characteristic changes of enthesopathy, in general sparing tendons with synovial sheaths. 20 Tendon and ligament ruptures are reported to occur with minimal provocation. 124 Pain, stiffness, crepitation, flexion contractures, and limitation of motion are the most common clinical features. 125 Loose (osteochondral) bodies may cause joint-locking episodes. 20 Synovial effusions are reported in about half of cases, with cell counts of 100 to 700 cells/mm 3 and a predominance of mononuclear cells. 20,21

Increased bone resorption and osteoporosis have also been documented in association with ochronosis, even in the absence of immobility. 22 Other disease manifestations include renal and prostate stones, aortic valve...
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**BIOCHEMICAL PATHWAYS LEADING TO OCHRONOSIS**

![Diagram of biochemical pathways leading to ochronosis](image)

**FIG. 212.1** Ochronosis. Pathways leading to pathologic manifestations of ochronosis (alkaptonuria). (Adapted from references 3, 9, 19.)

**FIG. 212.2** Ochronosis. Black-gray pigmentation of the ear cartilage in a patient with ochronosis.

**FIG. 212.3** Ochronosis. Radiographs of the spine showing narrowing and calcification of the intervertebral disks.
calcification and stenosis, and coronary artery calcification. Because intense pigment deposition is found in the aortic root and minimal pigment deposition is seen in the venous circulation, a role has been posited for blood pressure and hemodynamic factors in explaining the differential tissue susceptibility seen in the venous circulation, a role has been posited for blood pressure and hemodynamic factors in explaining the differential tissue susceptibility seen in alkaptonuria comparing patients with healthy control participants included metallocollagenase (MMP)-mediated degradation of Tirin (TIM) and mimocollagen (MIM) reflecting cardiovascular remodeling, MMP-mediated collagen type VI (C6M) degradation reflecting cartilage remodeling, and collagen type I degradation (CTX-I) reflecting bone resorption. Notably, whereas MMP-mediated collagen type II degradation was the only biomarker reduced in alkaptonuria compared with control participants, it is usually elevated in OA; this was attributed to the extensive pigmentation of cartilage that could make it resistant to remodeling and proteolysis. This supposition is supported by direct analyses of cartilage revealing a very low turnover state and low levels of extractable matrix proteins in alkaptonuria. Further studies are required to determine if these biomarkers will facilitate monitoring of treatment responses.

### Invasive

Macroscopic inspection of the joint during surgery shows darkened cartilage. Biopsy of affected tissues reveals the characteristic yellow-brown pigment in subchondral bone. Similar findings have been reported in macrophages and osteoblasts. The pigment is also found in chondrocytes, osteocytes, and fibroblasts. Ochronotic fragments of cartilage are found embedded in synovium, where they evoke foreign body reactions with multinucleated giant cells. Ochronotic fragments of cartilage are also found in the joint cavity, where they form a nidus for the development of osteochondral bodies. Although the molecular basis for this is unclear, by electron microscopy, ochronotic pigment has been observed deposited on collagen fibrils of joint capsule and cartilage, often in a distinctive pattern with some association with the periodicity of collagen crossbanding (Fig. 212.5, b) as well as pigment invasion and disordering of collagen structure. This distinct pattern of ochronotic pigment deposition can be reproduced by 5 to 7 days of in vitro culture of osteosarcoma cell lines and chondrocytes in a culture medium supplemented with homogentisic acid. Interestingly, bone collagen is largely unaffected, which indicates that mineralization of the collagen fibers in vivo prevents deposition of ochronotic pigment. Homogentisic acid, the toxic agent in alkaptonuria, was recently identified as a member of a new chemical group of fibroblast growth inhibitors, which suggests that the pigment itself may have some antianabolic characteristics that would inhibit the ability of joint tissue to respond to the pathologic insult induced by the deposition of pigment. The antianabolic characteristics of the pigment may, at least in part, explain the general lack of osteophyte formation as described earlier. It has recently been demonstrated that ochronotic pigment co-localizes with amyloid in osteoarticular tissues and is associated with high plasma levels of serum amyloid A and P proteins. This suggests that secondary amyloidosis occurs in response to the inflammation invoked by ochronotic pigment. In one report, an aspirate from an affected joint yielded a synovial fluid with a speckled “ground pepper” appearance and dark chromatinic inclusions in mononuclear and polymorphonuclear cells. Unlike urine, synovial fluid reportedly have low concentrations of homogentisic acid and fail to darken upon addition of alkali. Homogentisic acid and its oxidation byproduct, benzoquinone acetic acid, react positively with Nile blue sulfate variant 1 stain, originally developed for identification of melanin and turn black when stained with methylene blue or cresyl violet.

### Differential Diagnosis

Alkaptonuria may be confused with several other conditions that cause dark urine, including porphyrias, the ingestion of indole compounds, myoglobinuria, hemoglobinuria, hematuria, bilirubinuria, and the presence of urobilinogen in urine, including porphyrias, the ingestion of indole compounds, myoglobinuria, hemoglobinuria, hematuria, bilirubinuria, and the presence of urobilinogen in.
and brittle, and they fissure and fragment readily. In addition, benzoquinone acetic acid may inhibit lysyl hydroxylase, thereby reducing cross-linking of types I and II collagen, further impairing the ability of menisci and articular cartilage to resist stress and shearing injury. Finally, homogentisic acid also inhibits cell growth in vitro in a dose-dependent manner. The concentrations of homogentisic acid (1–5 \( \mu \text{g/mL} \)) that proved to be cytotoxic in one in vitro study corresponded to plasma concentrations reported for patients with alkaptonuria (3.0–27.8 \( \mu \text{g/mL} \)). Injected in high concentrations into joints of rabbits, homogentisic acid caused swelling, limitation of motion, and articular cartilage necrosis.

**GENETICS**

In 1901, Garrod suggested an inherited cause of alkaptonuria based on observation of a family with two affected siblings and consanguinity of the parents. In 2007, clinical images of the eye, ear, and spine were published, showing the progression to ochronosis by age 60 years of the infant with alkaptonuria originally identified by Garrod. It is now well established that the accumulation of homogentisic acid and its oxidation products occurs through a deficiency of the HGD enzyme. The HGD enzyme is a hexamer consisting of two trimeric subunits. The proper folding or association of the HGD subunits can be readily abolished by nonsynonymous (affecting a change in an amino acid) point mutations in the HGD gene on chromosome arm 3q, which eliminates the function of the HGD enzyme at the sites of

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**FIG. 212.5** Ochronosis. (a) Photomicrograph showing the presence of ochronotic pigment in the cartilage from a femoral condyle of a patient with alkaptonuria. Pigmentation appears as a gradient and is most severe in the deep layers of cartilage; the articular surface shows little pigmentation (hematoxylin and eosin [H&E] stain, \( \times 4 \)). *Inset:* Chondrocytes located on the border between dense and light extracellular pigment. Chondrocytes show intracellular pigmentation and, in some instances, signs of necrosis (H&E stain, \( \times 10 \)). The evidence suggests that pigmentation occurs initially at the deep layers of cartilage before progressing toward the articular surface. (b) Transmission electron micrograph showing collagen fibers of ligamentous capsule from a patient with alkaptonuria. Collagen fibers have numerous electron-dense deposits of ochronotic pigment located along the fiber body. Deposits show some association with collagen cross-banding. Not all fibers have deposits (stained using 1% aqueous osmium tetroxide solution and 5% alcoholic uranyl acetate; poststained using lead citrate and uranyl acetate, \( \times 60,000 \)). (Courtesy of Dr. Adam M. Taylor, findAKUre project, University of Liverpool.)

**FIG. 212.6** Exogenous ochronosis in a patient treated for more than 10 years with minocycline. Widespread pseudo-ochronosis with black and blue-gray pigmented areas of the skin on the face (a), leg (b), plantar surface of foot (c), and dorsal surface of foot (d). (Courtesy of Dr. Virginia Byers Kraus.)
its tissue expression: liver, kidney, small intestine, colon, and prostate—and, as recently described, chondrocytes, synoviocytes, and osteoblasts. A mutation database, founded on the Leiden Open (source) Variation Database (LOVD) system, is available for online submissions of alkaptonuria-causing mutations and variants of the HGD gene (http://hgdatabase.criver.se).7 To date, more than 100 different HGD mutations have been reported.39,40 With the exception of several mutations affecting individuals from the high-prevalence areas of Slovakia and the Dominican Republic, most of these HGD mutations are unique and specific to particular families with the disorder. The occurrence of a few specific mutations in the high-prevalence areas is taken as evidence for mutational hot spots within the HGD gene or founder effects39—that the consequence of a population arising from a small number of genetically isolated individuals.39,40 The excretion of homogentisic acid in urine was first observed at 13 months of age and was most readily identified by Schmorl staining. These animal models may be of use for studies of the pathogenesis of this disorder and provide model systems in which to evaluate potential therapies.

**ANIMAL MODELS**

The mouse gene homologue of human alkaptonuria was mapped in 1994 through creation of a mutant mouse strain.3 In another animal model, an arthropathy resembling ochronosis was induced in rats by feeding a diet rich in 3,4-trifluoromethyl-2-benzoyl-1,3-cyclohexanedione and was approved by the U.S. Food and Drug Administration in 2002 for the treatment of hereditary tyrosinemia.4 The primary side effect of nitisinone is a rise in blood tyrosine concentrations; tyrosine is poorly soluble and aggregates into needle-shaped crystals potentially causing secondary pigmentation.5 A function enzyme assay is required to accurately predict the pathogenicity of specific HGD variants.50

**MANAGEMENT**

The current approach to the treatment of musculoskeletal manifestations of alkaptonuria consists of standard therapy for OA with judicious use of joint replacement when warranted. In one prospective study of the natural history of the ochronotic disease process, the average age of joint replacement in patients was lower (53 years) than the national mean (67 years) for patients with OA.5 Whether this is due to an earlier age of onset is not proven. This study also noted that a history of regular swimming and maintenance of joint function is associated with a lower average age of joint replacement.6 These findings suggest that regular swimming may improve maintenance of joint function and delay the need for joint replacement surgery, and reduce the large direct patient health care costs (estimated to be as high as £100,000 depending on disease stage and needs for surgery and patient care).6 A completed prospective randomized clinical trial of nitisinone (2 mg/day for 3 years) in humans (40 patients) reduced plasma and urine homogentisic acid by at least 95%; there were few adverse effects (one case each of conical keratopathy and hepatotoxicity); however, the trial failed to demonstrate a conclusive difference in the primary endpoint of hip rotation.55 Nevertheless, among patients lacking aortic stenosis at baseline, none of the 18 nitisinone-treated patients compared with 7 of 17 control patients developed aortic sclerosis by the end of the study.55

An international, multicenter, randomized open-label dose-finding trial called Suitability of Nitisinone in Alkaptonuria 1 (SONIA 1) demonstrated that a 4-week treatment with nitisinone (1–8 mg/day) decreased urinary homogentisic acid to low levels in a dose-dependent manner56 and below the threshold (<10 μmol/L) shown in mice to prevent ochronosis. Based on these results, a long-term study, SONIA 2 (138 patients now fully recruited) was initiated to evaluate the ability of nitisinone (10 mg/day) versus placebo to reduce homogentisic acid, reduce signs and progression of alkaptonuria, and monitor adverse effects over 4 years (http://www.developakure.eu). A longitudinal observational trial, Subclinical Ochronotic Features in Alkaptonuria (SOFA), is currently enrolling patients aged 16 years and older to determine the age of onset of ochronotic pigmentation of cartilage (based on ear biopsies) and joint damage to determine the age when it would be advantageous to institute nitisinone to avoid joint damage. Of note, patients in nitisinone trials cannot be fully blinded to their treatment group because their urine color can unblind them to their treatment allocation, but the ability to quantify homogentisic acid excretion provides a strong objective trial outcome measure. The estimated 34 hours needed to completely eliminate homogentisic acid may ultimately permit even less frequent dosing than once daily. Standardized clinical assessment tools developed for alkaptonuria57,58 are expected to facilitate standardized longitudinal clinical and clinical trial assessments of patients.

The primary side effect of nitisinone is a rise in blood tyrosine concentrations; tyrosine is poorly soluble and aggregates into needle-shaped crystals potentially causing secondary pigmentation.5 A function enzyme assay is required to accurately predict the pathogenicity of specific HGD variants.50 Although no specific pharmacologic therapy yet exists, the compound nitisinone (Orfadin), which has the chemical name 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione and was approved by the U.S. Food and Drug Administration in 2002 for the treatment of hereditary tyrosinemia, has been investigated for use in ochronosis.5,7-9 This drug inhibits the enzyme 4-hydroxyphenylpyruvic acid dioxygenase and reliably reduces serum and urine homogentisic acid concentrations (see Fig. 212.1).10 Lifetime treatment of alkaptonuric patients with genetic disorders associated with tyrosinemia also have some neuropsychological disorders, it is suggested that a strict low-protein diet be maintained to block elevations of blood tyrosine in the context of nitisinone use in children.65 Compliance with these restrictions is reported to be difficult, and long-term clinical trials of dietary therapy for alkaptonuria and ochronosis have not been conducted. Allied treatments include low-dose methotrexate, suggested to potentially inhibit the secondary production of amyloid in patients with alkaptonuria,71 and antioxidants,2,64,65 including ascorbic acid. Such recommendations appear to have merit based on recent proteomic analyses demonstrating oxidative stress and inflammation in alkaptonuria.66 On a cautionary note, ascorbic acid may serve as a cofactor for 4-hydroxyphenylpyruvic acid dioxygenase (see Fig. 212.1) and therefore may increase the production of homogentisic acid in alkaptonuria through this mechanism.67

**KASHIN-BECK DISEASE**

**HISTORY**

Kashin-Beck disease was first reported in Siberia in 1849 by a Russian surveyor, M. Jurenskij, who noted that some residents of the Urov River Valley of Russia had shortened fingers, showed a characteristic gait, and could neither walk nor work properly.10 In 1859, the physician Nikolai Kashin, assigned to a Cossack brigade, was ordered to investigate the disease-causing deformities that prevented a segment of the local population from serving in the army.10 He concluded that “goiter, rheumatic pain, and cretinism” was an endemic disease, and it came to be known as Urov disease. Evgeny Beck later added a systematic epidemiologic survey of this disorder in 1906, noting a prevalence of 6% to 46% (mean, 32%). KBD was first reported in China in 1908.69 The world’s literature on KBD was summarized in 1994 by Allan.72 Skeletal remains indicate that it goes back to at least the 16th century.7odcast

**EPIDEMIOLOGY**

Kashin-Beck disease is endemic in a region extending diagonally from northeastern China to Tibet in the southwest, with additional endemic regions in neighboring areas of Russia and some regions of Vietnam and Korea.26 Although no specific pharmacologic therapy yet exists, the compound nitisinone (Orfadin), which has the chemical name 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione and was approved by the U.S. Food and Drug Administration in 2002 for the treatment of hereditary tyrosinemia, has been investigated for use in ochronosis.5,7-9 This drug inhibits the enzyme 4-hydroxyphenylpyruvic acid dioxygenase and reliably reduces serum and urine homogentisic acid concentrations (see Fig. 212.1).10 Lifetime treatment of alkaptonuric patients with genetic disorders associated with tyrosinemia also have some neuropsychological disorders, it is suggested that a strict low-protein diet be maintained to block elevations of blood tyrosine in the context of nitisinone use in children.65 Compliance with these restrictions is reported to be difficult, and long-term clinical trials of dietary therapy for alkaptonuria and ochronosis have not been conducted. Allied treatments include low-dose methotrexate, suggested to potentially inhibit the secondary production of amyloid in patients with alkaptonuria,71 and antioxidants,2,64,65 including ascorbic acid. Such recommendations appear to have merit based on recent proteomic analyses demonstrating oxidative stress and inflammation in alkaptonuria.66 On a cautionary note, ascorbic acid may serve as a cofactor for 4-hydroxyphenylpyruvic acid dioxygenase (see Fig. 212.1) and therefore may increase the production of homogentisic acid in alkaptonuria through this mechanism.67

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Goiter secondary to iodine deficiency was found more often in villages affected by mycotoxins. Binding globulin values were associated with an increased risk of KBD in children, low urinary iodine, high serum thyrotropin, and low serum thyroxine-binding globulin values associated with increased risk of disease in KBD areas, although selenium levels of the various water sources under study were not cited. Whereas eating corn, wheat, and barley has also been associated with KBD, eating rice appears to be protective; interestingly, rice grown in KBD-endemic areas has a higher selenium content and selenium bioavailability than corn or wheat, which possibly accounts for its apparently protective effect.

Although a geographic association between KBD and selenium deficiency has been reported, KBD does not occur in every selenium-deficient area of China. Therefore, to gain a comprehensive understanding of risk factors for KBD, a cross-sectional epidemiologic study was conducted in 12 rural villages in Tibet in which 575 children aged 5 to 15 years were examined. The variables independently associated with KBD were found to be higher age, male gender, low socioecononmic status, a poorly diversified diet, iodine deficiency, and the use of smaller water containers. Individuals were also at greatest risk of KBD if they had a sibling with the disease. In this study, whereas selenium deficiency was severe in both KBD-affected and unaffected children, low urinary iodine, high serum thyrotropin, and low serum thyroxine-binding globulin values were associated with an increased risk of KBD. Goiter secondary to iodine deficiency was found more often in villages affected by mycotoxins than in control villages. In general, selenium deficiency is closely associated with iodine deficiency in KBD areas. In one KBD-endemic area of China, urinary iodine levels were found to be 40% lower in KBD-affected children than in unaffected children. Although iodine deficiency doubled the odds of KBD in this Chinese cohort, selenium deficiency was associated with a 6-fold increase in the odds of KBD.

In China, foodstuffs such as corn were commonly stored in cave dwellings, where it is believed mycotoxins entered the food chain. In Tibet, too, a striking association was found between KBD and moldy grain from storage in a tent out of doors, which further suggests a pathogenic role for mycotoxins. Fungal contamination of barley grain was related to the highest percentage of KBD cases (65%). Three fungal taxa isolated from barley samples were independently associated with KBD (Trichothecium roseum, Alternaria spp., and Drechslera spp.). The KBD prevalence rate increased dramatically from 1% if none of these taxa was isolated to 51% if one taxon was found and 89% if two or more taxa were isolated. This study provided strong support for a multifactorial cause of KBD in Tibet. Since then, numerous in vitro and animal studies have documented the deleterious effect of mycotoxins on cartilage. The consequences of selenium deficiency may be exacerbated by the oxidative stress resulting from the fungal exposures.

Clinical Features

Kashin-Beck disease usually becomes evident in children between 5 and 15 years of age. Joint pain is the earliest symptom. For purposes of epidemiologic studies, a diagnosis of KBD has required symptom onset before the age of 30 years to clearly differentiate it from primary OA. An increasing number of joints are involved from childhood to the age of 25 years in a slowly progressive osteoarthropathy. The particular manifestations of the arthropathy are symmetric and may vary with the time in life of exposure to the endemic environment. In this regard, it is interesting to note an observation attributed to Kravencho in 1959 that an inordinate degree of OA developed in individuals who moved into endemic areas of KBD after the age of 25 years. The arthropathy progresses to severe joint dysfunction, enlargement, and deformity. The Chinese characters for this disease, when literally translated, mean “big joint disease” (Fig. 212.7). The most distal joints of the lower and upper limbs (lower more than upper) are most often and most severely affected, including the ankles, knees, interphalangeal joints, wrists, and elbows. The foot and ankle are involved in 90% of cases. In fact, it is said that the absence of talus involvement in an adult is cause to reject the diagnosis of KBD. The hand develops enlargement of interphalangeal joints reminiscent of Heberden and Bouchard nodes; however, the middle and distal phalanges are shortened, termed brachyactly (Fig. 212.8 shows a photograph and a radiograph of a hand with KBD), resembling the foreshortened distal and middle phalanges caused by frostbite injury in children. The carpal bones, in particular the capitate and hamate, are more likely to be involved with worsening severity of KBD involvement of the hand. Short stature is one of the main features of the disease, and dwarfism is sometimes marked, involving a disproportionate shortening of the extremities.

Standardized national clinical and radiologic diagnostic criteria for KBD have been available in China since 1995 (clinical GB16003-1995) (Table 212.2) and 2001 (radiologic WF/2001) (Table 212.3); their correlation with other features of KBD, including brachyactly, has been evaluated. In addition, other staging systems have been devised for this disorder based on clinical or radiologic features (see Tables 212.1 and 212.2). A significant correlation has been shown between the clinical classification system of Mathieu and the radiologic classification system of Hinsenkamp.
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urine OA-related biomarkers have been shown to be associated with the presence or severity of KBD, including chondroitin sulfate and proteoglycan-related epitopes, pyridinoline, serum nitric oxide, CD44, MMP-1, interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), cartilage oligomeric matrix protein, and C-telopeptide of type II collagen (CTXII). Proteomic studies comparing KBD and control sera are ongoing to identify diagnostic biomarkers for KBD.112,113

Invasive

The initial pathologic change in KBD is necrosis of cartilage and secondary repair and remodeling of cartilages of the metaphyses, bone ends, epiphyses, and carpal bones, leading to disturbed mineralization, impaired skeletal development, disfiguration of joints, and chronic deforming OA. Because the metaphyseal side of the growth plate is the most active site of bone growth and development during childhood, it is the site affected earliest and most frequently with cartilage necrosis (termed chondronecrosis). Apoptotic chondrocytes are found more frequently in KBD than in control cartilage.

Table 212.2

Staging systems for Kashin-Beck disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Signs</th>
<th>Clinical staging system based on the Chinese National Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>Flexion of the terminal part of the fingers or crooked fingers and arthritis pain in knee and ankle joints without enlarged finger joints</td>
<td></td>
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<tr>
<td>First stage</td>
<td>Enlarged finger joints and clinical symptoms of the early stage</td>
<td></td>
</tr>
<tr>
<td>Second stage</td>
<td>Shortened fingers and clinical symptoms of the first stage</td>
<td>Rotated growth or dwarfism and clinical symptoms of the second stage</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Age</th>
<th>Severity</th>
<th>Joint enlargement (caused by metaphyseal widening)</th>
<th>Joint pain</th>
<th>Severity of motion restriction of most affected joint</th>
<th>Associated symptoms*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&lt;15 yr</td>
<td>Mild</td>
<td>Deformation or thickening of fingers two to four</td>
<td>+ (and with activity)</td>
<td>Grade 0</td>
<td>–</td>
</tr>
<tr>
<td>I</td>
<td>All ages</td>
<td>Moderate</td>
<td>Deformation or thickening of all fingers, elbow, knee, ankle, wrist, and one or two large joints; brachyphalangy</td>
<td>+</td>
<td>Grades 1–2</td>
<td>–</td>
</tr>
<tr>
<td>II</td>
<td>All ages</td>
<td>Severe</td>
<td>Marked deformation or thickening of finger joints; distinct brachyphalangy</td>
<td>+</td>
<td>Unable to make a fist; very limited motion or fused large joints</td>
<td>Platypodia (splayfoot); short or deformed sole</td>
</tr>
</tbody>
</table>

*Associated symptoms are tiredness, muscle weakness, inability to work, pes planus, waddling gait, and dwarfism.

Data for Chinese National Criteria–based staging system from document GB16003-1995; data for Mathieu staging system; data for Beck criteria (1906).

Although the clinical criteria are more sensitive, the radiologic criteria are more specific for KBD. An instrument for assessing quality of life has recently been developed and validated for use in KBD patient populations.

### PATHOLOGY INVESTIGATIONS

**Noninvasive**

The abnormalities of growth and development and the radiographic appearance of this disease have been ascribed to pathologic endochondral growth at epiphyseal and acrophyseal sites. The radiologic features of KBD have been reported to resemble the lesions of osteochondrosis, a group of diseases of children and adolescents that are caused by insufficient blood supply to the epiphyses that leads to localized tissue necrosis at the growing ends of bones during the years of rapid bone growth. The radiologic joint features deemed diagnostic of KBD include irregularities of bony margins; sclerosis; and a cone-shaped, fused, or fragmented metaphysis. Several serum and urine OA-related biomarkers have been shown to be associated with the presence or severity of KBD, including chondroitin sulfate and proteoglycan-related epitopes, pyridinoline, serum nitric oxide, CD44, MMP-1, interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), cartilage oligomeric matrix protein, and C-telopeptide of type II collagen (CTXII). Proteomic studies comparing KBD and control sera are ongoing to identify diagnostic biomarkers for KBD.

**Invasive**

The initial pathologic change in KBD is necrosis of cartilage and secondary repair and remodeling of cartilages of the metaphyses, bone ends, epiphyses, and carpal bones, leading to disturbed mineralization, impaired skeletal development, disfiguration of joints, and chronic deforming OA. Because the metaphyseal side of the growth plate is the most active site of bone growth and development during childhood, it is the site affected earliest and most frequently with cartilage necrosis (termed chondronecrosis). Apoptotic chondrocytes are found more frequently in KBD than in control cartilage.
and at a rate comparable to that in OA. The histologic features of KBD lesions have included the absence of vascularization within the proximal cartilage endplate. In vitro studies of cartilage or chondrocytes have demonstrated increased hydroxyproline content, decreased thermal stability of collagen II, and increased levels of precursor collagen (procollagen II) thought possibly caused by inhibition of conversion to the mature collagen II, as well as decreased collagen II, increased collagen I, III, X, and X, increased MMP-13, and increased aggrecanase-generated proteoglycan loss from cartilage. These effects were ascribed to agglutic toxicity and possibly other environmental exposures.

**DIFFERENTIAL DIAGNOSIS**

Selenium and iodine deficiency are linked geographically. Distinguishing between the radiologic features of hypothyroidism and KBD can be difficult, requiring expert radiographic opinion. It has been thought possible that some of the musculoskeletal abnormalities of KBD may be related to thyroid dysfunction early in life because hypothyroidism in children is associated with epiphyseal dysgenesis, delay of bone development, and reduced endochondral ossification. Of note, selenium plays an indispensable role in thyroid hormone synthesis because it is required for iodothyronine deiodinase activity that converts thyroxine (T4) to the more active triiodothyronine (T3).

**PATHOGENESIS**

To date, no consensus has been reached on the cause of KBD. Early residents of the Ural River Valley associated it with “bad” drinking water and had a notion that the disease could be passed down from generation to generation in “diseased families.” Three causal mechanisms have been proposed to interact to cause KBD:

- A deficiency in trace elements (selenium and iodine).
- The presence of organic matter in drinking water (fulvic and humic acid produced by chemical and microbial decomposition of plants and animals).
- Contamination of food by noxious mycotoxins, bacterial toxins, or both.

Cold exposure and occupational microtrauma have also been implicated in disease severity. In this model, a low selenium level is an essential but insufficient condition for the development of KBD. Low selenium blood concentrations have been documented in endemic KBD areas of China; this has many adverse biological effects. For instance, suppression of the selenoprotein iodothyronine deiodinase-2 (DIO2, responsible for conversion of thyroid hormone to its active form) results in strong proinflammatory effects with increased expression of inflammatory mediators, IL-1β, and cyclooxygenase-2 (COX-2). In addition, low selenium results in inadequate antioxidant defense caused by a lack of selenoprotein antioxidants such as glutathione peroxidase and thioredoxin reductase. It is posited that free radicals, generated by mycotoxins and fulvic acid or other environmental factors, damage chondrocytes under conditions of inadequate antioxidant defense, iodine deficiency, and possible protein-calorie malnutrition. This is supported by results showing that selenium can partially counteract adverse chondrocyte effects with the fungal toxin T-2 or IL-1. Taken together, these results underscore the key chondroprotective and antiinflammatory role performed by selenium. In the absence of adequate selenium and antioxidant defense, the final common pathway of pathogenesis is chondrocyte apoptosis and necrosis of the hypertrophic chondrocytes at the base of the articular and growth plate cartilages.

Selenium is necessary for the growth of cells in tissue culture and is commonly used (in the form of selenite) as a supplement for chondrocyte culture. Selenium bioavailability ultimately depends on both intestinal absorption of selenium and its conversion into a biochemically active form. Selenomethionine, the major form of selenium found in food, has almost twice the bioavailability of selenium in the form of selenite. Brief (24-hour) exposure of chondrocytes in vitro to selenomethionine (0.5–1.0 μmol/L) has been shown to block IL-1–mediated inhibition of cartilage matrix macromolecule (collagen II, aggrecan) synthesis, transforming growth factor-β2 receptor synthesis, and inducible nitric oxide synthase and COX-2 expression responsible for nitric oxide and prostaglandin E2 production, respectively.

Some chondrotoxic effects and other pathologic effects have been attributed to mycotoxins and fulvic acid. Nivalenol, a mycotoxin produced by Fusarium spp., inhibits protein synthesis by binding to the ribosome. Added to cartilage grafts in vitro, nivalenol inhibits glycosaminoglycan synthesis and retention in the extracellular matrix, overall reducing the chondroitic acid sulfate content of cartilage. It has been hypothesized that mycotoxins may inhibit angiogenesis, block thyroid hormone function, and bind thyroid receptors in bone cells. When added to the diet of rats, fungal extracts inhibit glutathione peroxidase and superoxide dismutase activities and accelerate lipid peroxidation. Similarly, it is hypothesized that organic matter in the form of fulvic acid may accumulate in musculoskeletal tissues and induce superoxide production via its semiquinone radicals and lipid peroxidation. These, in turn, may be potent proinflammatory and chondrotoxic stimuli. Selenium-deficient hosts with low levels of glutathione peroxidase activity. In vitro, fulvic acid stimulates the generation of H₂O₃ by chondrocytes and increases collagen secretion in a H₂O₃-dependent manner. Fulvic acid has also been shown to inhibit the conversion of procollagen II to mature collagen II. However, the levels used in these experiments have not been equated to blood or tissue levels of affected individuals in endemic areas. Finally, this family of organic acids may interfere with selenium absorption from the intestine.

**GENETICS**

As described earlier, hyposelenosis may be necessary but not sufficient to cause disease. Within the low-selenium belt in China, there are some places and individuals without KBD even though selenium concentrations in the soil, food grains, and hair are low. The mosaic character of disease prevalence (affected villages next to healthy ones) was noted as early as 1939. In his extensive review of the KBD literature from 1849 to 1992, ALLANDER noted instances of Chinese villages where KBD was endemic within 30 to 50 miles of villages where KBD was nonexistent. This suggests that other environmental or as yet unknown genetic factors are required for full manifestation of the syndrome. Clustering within families has been noted. Genetic factors, common environmental risk factors, or a combination of both could account for this clustering. A 2006 to 2007 survey of 212 case and 212 control families (total of 3848 individuals) reported that use of river water as the main source of drinking water clustered in KBD families and accounted for a sixfold increase in the odds of KBD. The proportion of KBD-affected relatives among the probands’ families was substantial and significantly higher than that in the control families (55.4% vs 10.2%, respectively; P = 0.0001). Neither drinking river water alone nor other dietary factors fully explained the familial aggregation of KBD. In a companion study, the heritability of KBD was estimated to be 29% in Linyou County, China. These observations suggest that other factors influence the development of disease. Nevertheless, until recently, the possibility of a genetic component of disease susceptibility has generally been overlooked in favor of...
of environmental risk factors. To date, reported genetic variants associated with KBD have included those shown in Box 212.1.

**ANIMAL MODELS**

Mice fed for two generations on a selenium-deficient diet supplemented with fulvic acid in the drinking water demonstrated disturbed development of the articular space and meniscus, disturbed subchondral ossification, overly hydroxylated collagens I and II with less thermal stability, and low bone formation activity.1,15-16 Second-generation rats fed a selenium-deficient diet showed growth retardation, a reduction in pituitary growth hormone and plasma insulin-like growth factor 1 levels, and impaired bone metabolism and osteopenia.1,15-16 Chronic selenium deficiency in rats was also associated with abnormalities of chondrocytes in the deep cartilage layers consisting of nuclear degeneration and ballooning of the endoplasmic reticulum.1,15-16 Combined selenium and iodine deficiency in rats significantly impaired the growth of bone and cartilage.1,15-16 Rats developed chondronecrosis and features of KBD when fed a selenium-deficient diet followed by oral challenges with A-1 toxin (bacterial contaminant of grain)1,15-16 or T-2 mycotoxin (fungal contaminant of grain).1,15-16 Conversely, mice prone to OA (the STR/1N strain) and A-1 toxin (bacterial contaminant of grain)1,15-16 or T-2 mycotoxin (fungal contaminant of grain)1,15-16 were protected from disease while on a diet enriched with vitamins (C, E, A, and B₃) and selenium.15-16 The role played by muscle in this disease has also been questioned. Severe white muscle lesions develop in sheep in response to KBD.70

**REFERENCES**


