Rare Osteoarthritis: Ochronosis and Kashin-Beck Disease


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Chapter 185
Rare Osteoarthritis: Ochronosis and Kashin-Beck Disease

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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 osteoarthritis of the spine and large joints, termed ochronotic arthropathies.

KASHIN-BECK DISEASE

Kashin-Beck disease 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 mycotoxins.

The disease is characterized by necrosis and remodeling of cartilage including growth plates.

Clinical features of Kashin-Beck disease include generalized osteoarthritis involving the ankles, knees, interphalangeal joints, wrists, and elbows with foreshortened 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. These rare forms of OA are thought to derive from diverse causes that include genetic determinants (ochronosis), and a combination of genetic, nutritional, and biogeochemical factors (Kashin-Beck disease). 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 (HGO) ([Fig. 185.1](#)). The connection between these two entities was recognized by Albrecht in 1902. Simultaneously, this was the first human disorder found to conform to the principles of mendelian autosomal recessive inheritance. In 1908 the term *inborn errors of metabolism* was first coined by Archibald Garrod to describe this and three other diseases. The absence of the HGO 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 ochrelike pigmentation in the skin, sclera, and cartilages of the body ([Fig. 185.2](#)) 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; the absence of the HGO 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. 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.

Epidemiology

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

Clinical features
The patient with ochronosis is distinguished by the triad of dark urine on addition of alkali, ochronotic pigmentation, and arthritis. 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, and many patients remain undiagnosed until adulthood because 25% do not have the characteristic dark urine staining. 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. 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. 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.

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. The pattern of spine involvement is reported to differ from typical OA in that thoracolumbar changes predominate rather than lumbosacral degeneration, although the severity of lumbar spine involvement had the strongest correlation with disability measures in a study of 53 patients. Narrowing and dense, waferlike calcification of the intervertebral disks are the most characteristic findings in the spine (Fig. 185.3), and osteophytes are said to be usually absent or of small size. The peripheral arthritis closely resembles that of OA; however, hands and feet are usually spared. Arthritis of the peripheral joints is generally observed about 10 years after spinal changes (Fig. 185.4). The main differences between ochronotic arthropathy, primary OA, and ankylosing spondylitis are summarized in Table 185.1. 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. Tendon and ligament ruptures are reported to occur with minimal provocation. Pain, stiffness, crepitation, flexion contractures, and limitation of motion are the most common clinical features. Loose (osteochondral) bodies may cause joint-locking episodes.

Increased bone resorption and osteoporosis have also been documented in association with ochronosis, even in the absence of immobility. Other disease manifestations include renal and prostate stones, aortic valve calcification and stenosis, and coronary artery calcification. Because intense pigment deposition is found in the aortic root and minimal pigmentation is seen in the venous circulation, a role has been posited for blood pressure and hemodynamic factors in
explaining the differential tissue susceptibility to ochronotic pigmentation and pathologic changes.\textsuperscript{23}

Investigations

Noninvasive

The diagnosis of alkaptonuria/ochronosis is suspected when there is bluish black pigmentation of the sclerae and the cartilages of the ears and nose, and darkening of the urine on standing in air or with the addition of alkali (10 drops of 10\% NaOH to 20 mL urine per Zhao\textsuperscript{24}). The diagnosis is confirmed by 24-hour urinary excretion of homogentisic acid, measured by gas chromatography or high-performance liquid chromatography, that is higher than 0.030 to 0.040 mmol/mmol creatinine for children aged 1 to 6 years and 0.017 mmol/mmol creatinine for individuals from age 7 years through adulthood.\textsuperscript{25} In addition, significant laboratory artifacts in alkaptonuria include the following: a false-positive urine Clinitest result for sugars caused by the reduction of copper by homogentisic acid\textsuperscript{18} and a falsely low urinary creatinine level if measured by an enzymatic method due to interference by homogentisic acid.\textsuperscript{26}

The extent of arthropathy is typically documented radiographically, and profound osteoarthritic changes in the large joints and the spine with extensive calcification of intervertebral disks characteristically are seen. Magnetic resonance imaging can readily detect ligamentous lesions.\textsuperscript{27} Bone turnover and bone mass can be determined by quantification of N-telopeptides of type I collagen in the urine and by dual energy x-ray absorptiometry (DEXA) of the femur but not by DEXA of the spine, for which bone mineral density measurements are spuriously overestimated due to intervertebral disk calcification and osteophyte formation.\textsuperscript{22}

Invasive

Macroscopic inspection of the joint during surgery shows darkened cartilage. Biopsy of affected tissues reveals the characteristic yellow-brown pigment in unstained sections, both free and intracellularly; the pigment typically is seen in macrophages, but researchers have also found pigment in chondrocytes, osteocytes, osteoblasts, osteoclasts, and fibroblasts.\textsuperscript{28,29} In cartilage the ochronotic pigmentation is most severe in the deep layer of cartilage, known to be a region of low protein turnover, whereas the articular surface, the region with the highest level of protein turnover, shows little pigmentation (Fig. 185.5a).\textsuperscript{30} Ochronotic fragments of cartilage are found embedded in synovium where they evoke foreign body reactions with multinucleated giant cells.\textsuperscript{31} Ochronotic fragments of cartilage are also found in the joint cavity where they form a nidus for the development of osteochondral bodies.\textsuperscript{11} 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 cross banding (Fig. 185.5b) 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. This may, at least in part, explain the general lack of osteophyte formation as described earlier. It has recently been demonstrated that ochronotic pigment colocalizes with amyloid in osteoarticular tissues and is associated with high plasma levels of serum amyloid A and P proteins, which suggests that secondary amyloidosis occurs in response to the inflammation invoked by ochronotic pigment. 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. In one report, an aspirate from an affected joint yielded a synovial fluid with a speckled “ground pepper” appearance and dark cytoplasmic inclusions in mononuclear and polymorphonuclear cells. Unlike urine, synovial fluids 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 I stain, originally developed for identification of melanin, and also 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 when oxidized to urobilin. The endogenous form of ochronosis may also be confused with exogenous ochronosis. Exogenous ochronosis refers to ochrelike pigment deposition in the skin, and sometimes in cartilages or other organs, as a result of exposure to a variety of exogenous compounds. Compounds implicated as causative agents of exogenous ochronosis include topical phenol formerly used as an antiseptic, topical hydroquinone bleaching creams, quinine injections, oral antimalarial drugs, amiodarone, cytotoxic drugs, minocycline, and levodopa and methyldopa used in the treatment of Parkinson.
disease. In most cases, long-term exposure to the inciting agent is necessary for the development of hyperpigmentation. Reversal is slow or nonexistent. These cases are distinguished from endogenous ochronosis by lack of urinary homogentisic acid excretion, genetics, and, in some cases, biopsy findings. No clear clinical effects beyond the cosmetic ones have been delineated for exogenous ochronosis. Thus it is necessary to appropriately distinguish exogenous from endogenous ochronosis, both to determine prognosis, which is more favorable for exogenous ochronosis, and to recommend the appropriate therapy, as described later, for an individual with endogenous ochronosis.

Pathogenesis

The tissue accumulation of homogentisic acid and its oxidation byproduct, benzoquinone acetic acid, is believed to be responsible for the clinical manifestations and severe arthropathy of ochronosis. Homogentisic acid can undergo both autoxidation and enzymatic oxidation and polymerization to form an ochronotic pigment in the presence of the enzyme homogentisic acid polyphenol oxidase, present in skin and cartilage (see Fig. 185.1). High levels of homogentisic acid perturb collagen assembly and structure \textit{in vivo} and \textit{in vitro}. The infiltrated cartilaginous tissues become stiff and brittle, and fissure and fragment readily. In addition, benzoquinone acetic acid may inhibit lysyl hydroxylase, thereby reducing cross-linking of types I and II collagen and further impairing the ability of menisci and articular cartilage to resist stress and shearing injury. Finally, homogentisic acid also inhibits cell growth \textit{in vitro} in a dose-dependent manner. The concentrations of homogentisic acid (1 to 5 µg/mL) that proved to be cytotoxic in one \textit{in-vitro} study corresponded to plasma concentrations reported for patients with alkaptonuria (3.0 to 27.8 µg/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 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 HGO enzyme. The HGO enzyme is a hexamer consisting of two trimeric subunits. The proper folding or association of the HGO subunits can be readily abolished by nonsynonymous (affecting a change in an amino acid) point mutations in the HGO gene on chromosome arm 3q, which eliminates
the function of the HGO enzyme at the sites of its tissue expression: liver, kidney, small intestine, colon, and prostate— and, as recently described, chondrocytes, synoviocytes, and osteoblasts. To date, a total of 119 different HGO mutations have been reported. With the exception of several mutations affecting individuals from the high-prevalence areas of Slovakia and the Dominican Republic, most of these HGO 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 HGO gene or founder effects — the consequence of a population arising from a small number of genetically isolated individuals, one or more of whom had the gene mutation. To date, no apparent correlation has been discerned between a patient’s genotype and the level of excreted homogentisic acid, nor have there been clear correlations between specific genotypes and clinical manifestations, including age of onset of symptoms; a functional enzyme assay is believed to be required to accurately predict the pathogenicity of specific HGO variants.

Animal models

The mouse gene homologue of human alkaptonuria was mapped in 1994 through creation of a mutant mouse strain. In another animal model, an arthropathy resembling ochronosis was induced in rats by feeding a diet with 8% L-tyrosine for 9 or more months starting at 1 month of age. In a third animal model, injection of homogentisic acid into the joints of rabbits produced joint lesions that were similar to those of ochronosis, including the deposition of pigment within the synovium, synovial thickening, and granulomatous reaction in response to embedded fragments of damaged cartilage or tendon. This pathologic process could be ascribed directly to homogentisic acid rather than acidity because similar results were observed with both unbuffered and buffered (pH 7) homogentisic acid solutions. Finally, a recent report documented the first histologic evidence for ochronosis of tissues in a murine transgenic model of alkaptonuria; of note, macroscopic and microscopic evidence of ochronosis was first observed at 13 months of age and was most readily identified by Schmorl staining. These animal models, the latter in particular, may be of use for studies of the pathogenesis of this disorder and provide model systems in which to evaluate potential therapies.

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). This study also noted that a history of regular swimming correlated with less kyphosis and scoliosis and a trend toward higher vitality, physical role, and mental health scores on the SF-36 Health Survey. Based on this study, treatments likely to benefit the physical function of these individuals include regular swimming, spine mobilization, and development of good truncal strength initiated early in the disease process. There has been one report of the disappearance of alkaptonuria and the cessation of ochronotic lesions following liver transplantation for hepatitis B–related cirrhosis. Surveillance for aortic dilatation and valvular calcification is recommended, as well as intervention for prostate and renal stones as needed.

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. This drug inhibits the enzyme 4-hydroxyphenylpyruvic acid dioxygenase that produces homogentisic acid (see Fig. 185.1). A prospective randomized clinical trial involving 40 patients who were treated for 3 years with 2 mg nitisinone orally once daily showed a reduction of 95% or more in urine and plasma homogentisic acid levels and few adverse effects (one case each of corneal keratopathy and hepatotoxicity); however, hip range of motion and musculoskeletal function were not significantly different between treated and nontreated groups, although the trend in all these outcome measures favored the nitisinone group at study completion. Of patients lacking aortic stenosis at baseline, none of the 18 nitisinone-treated patients compared with 7 of 17 control patients developed aortic sclerosis or stenosis by study completion. Of note, patients could not be masked as to their treatment group because their urine color revealed the impact of nitisinone. These results suggest that this therapy is worth further study, but a longer trial, different primary endpoints, and/or a younger patient group may be required to demonstrate clinical efficacy. The estimated half-life of nitisinone of 54 hours may ultimately permit even less frequent dosing than once daily. Standardized clinical assessment tools for alkaptonuria have been developed; these are expected to facilitate longitudinal clinical assessments of patients.

Other treatments have included dietary restriction of protein to limit tyrosine and phenylalanine intake, although this was not required in the clinical trial described earlier. Compliance with these restrictions is reported to be difficult for adults, and long-term clinical trials of dietary therapy for alkaptonuria/ochronosis have not been conducted. Low-dose methotrexate was recently suggested to potentially inhibit the secondary production of amyloid in patients with alkaptonuria. Antioxidants have also been proposed for the treatment of
alkaptonuria based on the ability to counteract both the polymerization and accumulation of homogentisic acid, and the deleterious effects of free radicals generated in the course of homogentisic acid oxidation. Antioxidants studied to some extent to date include ascorbic acid (vitamin C), N-acetylcysteine, phytic acid, and vitamin E as well as taurine, ferulic acid, and lipoic acid.

For many years ascorbic acid was considered a potential therapy for ochronosis based on a mechanism of action of inhibition of homogentisic acid polyphenol oxidase responsible for producing the oxidized and polymerized byproducts of homogentisic acid (see Fig. 185.1). Consistent with this proposed mechanism of action, ascorbic acid inhibited the binding of a radiolabel derived from a homogentisic acid precursor to connective tissues in a rat model of alkaptonuria and decreased the excretion of benzoquinone acetic acid in the urine. In one report, transient (about 12-day) enhancement of homogentisic acid urinary excretion was achieved by ascorbic acid (500 mg twice daily) in 2 of 3 patients. On a cautionary note, ascorbic acid may serve as a cofactor for 4-hydroxyphenylpyruvic acid dioxygenase (see Fig. 185.1) and therefore may increase the production of homogentisic acid in alkaptonuria through this mechanism. Clinical outcomes of long-term treatment with ascorbic acid (0.25 to 4 g/day) have varied, and overall it has not been dramatically effective; however, controlled trials have never been conducted.

KASHIN-BECK DISEASE

History

Kashin-Beck disease (KBD) 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. 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. 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. The world’s literature on KBD was summarized in 1994 by Allander. Skeletal remains indicate that it goes back to at least the 16th century.

Epidemiology
KBD 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. According to the 2008 health statistics issued by the Chinese Ministry of Health, there are currently 714,822 individuals affected by KBD in 2253 villages; this represents a KBD prevalence of 0.2% in the endemic villages (www.moh.gov.cn/publicfiles/business/htmlfiles/zwgkzt/ptjty/200805/35671.htm). In nongovernmental reports, the prevalence of KBD is described to be 8% to 43% in heavily affected areas. KBD is mainly a disease of poor farming families, on whom it imposes a severe socioeconomic stress. These endemic regions are known for especially low environmental levels of the essential trace element selenium and, consequently, low selenium levels in the blood and tissues of the native peoples consuming food from these areas. The population mean serum selenium concentration in this region is less than 0.020 mg/L, whereas serum selenium concentrations in healthy persons have been found to average 0.066 to 0.104 mg/L. In China, the geographic distribution of KBD corresponds most closely to the areas of lowest selenium in water, soil, and food grains, and fluctuations in disease status are reported to correspond to fluctuations in serum selenium concentration, the so-called wave character in morbidity. The daily intake of selenium in the Shaanxi KBD endemic area of China was quantified as 4.6 µg/day compared with 10.5 µg/day for nonendemic areas. Both levels are well below the U.S. recommended daily allowance (RDA) of 70 µg for men and 55 µg for women. Within low-selenium areas, the reliance on river water for drinking has been associated with increased risk of disease in KBD areas, although selenium levels of the various water sources under study were not cited. Eating corn, wheat, and barley has also been associated with KBD, whereas 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 apparent 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 socioeconomic 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, selenium deficiency was severe in both KBD-affected and unaffected children, whereas 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 KBD 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 61-fold increase in the odds of KBD.

In China, foodstuffs such as corn have commonly been stored in cave dwellings, where it is believed mycotoxins enter 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 species, and Dreschlera species). The KBD prevalence rate increased dramatically from 13% 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.

Evidence for hyposelenosis in non-KBD areas suggests that other risk factors, in addition to selenium deficiency, contribute to the pathogenesis of KBD. For instance, hyposelenosis exists in non-KBD areas such as Scandinavia, New Zealand, Poland, Central Africa, and the Democratic Republic of the Congo, although the degree of deficiency in these areas may not be as profound as in the KBD-endemic areas. Nevertheless, recent data suggest that milder degrees of selenium deficiency are associated with deleterious musculoskeletal consequences. In a population-based study in Johnston County, North Carolina, low selenium levels have been associated with increased odds of knee and hip OA. 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. In addition, selenium levels were found to be significantly lower in men than in women in this American cohort. As for many essential nutrients, the RDA for selenium is higher for men than for women to compensate for their larger body mass. Thus it is possible that selenium levels in men may more readily fall below a critical level necessary for joint tissue health under conditions of severely limited intake. The possibility that insufficient selenium intake may impact males more readily suggests a possible rationale for the consistent reports of a higher prevalence of KBD in males.

Clinical features
KBD 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 disease are symmetric and may vary with the time in life of exposure to the endemic environment. The arthropathy progresses to severe joint dysfunction, enlargement, and deformity. The Chinese characters for this disease, when literally translated, mean “big joint disease” (Fig. 185.6). The most distal joints of the upper and lower 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 brachydactyly (Fig. 185.7 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) and 2001 (radiologic W/T 207-2001); their correlation with other features of KBD, including brachydactyly, has been evaluated. In addition, other staging systems have been devised for this disorder based on clinical or radiologic features (see Tables 185.1 and 185.2). A significant correlation has been shown between the clinical classification system of Mathieu and the radiologic classification system of Hinsenkamp. 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.

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 and lead 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, matrix metalloproteinase-1 (MMP-1), interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), cartilage oligomeric matrix protein, and type II collagen. 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 (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 due to inhibition of conversion to the mature collagen II, as well as decreased collagen II levels; increased levels of collagens I, II, and X; increased MMP-13 levels; and increased aggrecanase-generated proteoglycan loss from cartilage. These effects were ascribed to fulvic acid 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. 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 to triiodothyronine. Thus a closer examination of the role of thyroid hormone abnormalities in the pathogenesis of KBD would appear to be warranted.

Pathogenesis

To date, no consensus has been reached on the cause of KBD. Early residents of the Urov 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), and contamination of food by noxious mycotoxins. Cold exposure and occupational microtrauma have also been implicated in disease severity. In this model, low selenium level is an essential but insufficient condition for the development of KBD. 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. Inadequate antioxidant defense derives from a lack of selenoprotein antioxidants such as glutathione peroxidase and thioredoxin reductase. Selenium can partially counteract adverse chondral effects of the fungal toxin T-2 and IL-1, and suppression of the selenoprotein iodothyronine deiodinase-2 (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). These results underscore the key antiinflammatory role performed by selenium in cartilage. In the absence of adequate selenium and antioxidant defense, the final common pathway of pathogenesis is 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 in combination with insulin and transferrin. Selenium bioavailability ultimately depends on both intestinal absorption of selenium and its conversion into a biochemically active form. Selenomethionine is 50% more bioavailable than selenite. Brief (24-hour) exposure of chondrocytes in vitro to selenomethionine (0.5 to 1.0 μmol/L) has been shown to block IL-1-mediated inhibition of cartilage matrix macromolecule (collagen II, aggrecan) synthesis and transforming growth
factor-β2 receptor synthesis, as well as induced nitric oxide synthase and COX-2 expression and nitric oxide and prostaglandin E\textsubscript{2} production.

Some chondrotoxic effects and other pathologic effects have been attributed to mycotoxins and fulvic acid. Nivalenol, a mycotoxin produced by \textit{Fusarium}, inhibits protein synthesis by binding to the ribosome. Added to cartilage grafts \textit{in vitro}, nivalenol inhibits glycosaminoglycan synthesis and retention in the extracellular matrix, overall reducing the chondroitin 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, would be poorly scavenged in a selenium-deficient host with low levels of glutathione peroxidase activity. \textit{In vitro}, fulvic acid stimulates the generation of H\textsubscript{2}O\textsubscript{2} by chondrocytes and increases collagen secretion in a H\textsubscript{2}O\textsubscript{2}-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 in which Chinese villages where KBD was endemic were 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 2006-2007 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% versus 10.2%, respectively; P = .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 environmental risk factors. Given the association of selenium deficiency with KBD, the possibility of genetic variation in the regulation of selenium absorption and metabolism has been of interest. It is estimated that there are 25 selenoproteins in the human genome. Several of these selenium-containing proteins have known and crucial functions in vivo: glutathione peroxidase protects tissues against reactive oxygen damage; iodothyronine deiodinase converts thyroxine to the biologically active form, 3,4,3′-triiodothyronine, and selenoprotein P, produced primarily in the liver, plays a key role in whole-body selenium metabolism and carries 60% to 70% of the circulating selenium. Moreover, selenoprotein P is a negative acute-phase protein, leading possibly to further limitation of selenium bioavailability during periods of acute illness and thus possibly potentiating KBD. To date, genes reported to contain genetic variants associated with KBD have included HLA-DRB1, TNF-α, glutathione peroxidase 4 (GPX4), and glutathione peroxidase 1 (GPX1); preliminary association analysis of one polymorphism in selenoprotein P (SEPP1) yielded negative results.

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. Second-generation rats fed a selenium-deficient diet showed growth retardation, a reduction in pituitary growth hormone and plasma insulin-like growth factor I levels, and impaired bone metabolism and osteopenia. 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. Combined selenium and iodine deficiency in rats significantly impaired the growth of bone and cartilage. Rats developed chondronecrosis when fed a selenium-deficient diet for 2 months followed by a 1-month oral challenge with bacterial A-1 toxin (from a bacterial contaminant of local grain). Conversely, mice prone to OA (the STR/1N strain) were protected from disease while on a diet enriched with vitamins (C, E, A, and B₆) and selenium. The role played by muscle in this disease has also been questioned. Severe white muscle lesions develop in sheep in...
response to low selenium levels. Therefore the possibility has been raised that muscle weakness may contribute directly to the musculoskeletal abnormalities of KBD.\textsuperscript{64}

Strong support for a definitive role of selenium deficiency in KBD has recently been provided by a mouse model in which the gene encoding the selenocysteine transfer RNA, essential for selenoprotein expression, has been deleted from chondrocytes.\textsuperscript{144} The mice manifested a number of pathologic features typical of KBD (chondronecrosis of articular cartilage, ear cartilage, and tracheal cartilage; small spine size; disproportionate widening of the epiphyseal growth plates) and died by 7 weeks of age due to respiratory distress from tracheomalacia.

Management

Individuals with radiologic lesions have more advanced stages of the disease and are expected to be less influenced by selenium treatment than individuals without radiologic lesions.\textsuperscript{110} Therefore the key to managing KBD is to prevent its occurrence. The strategy of selenium supplementation is considered the mainstay of therapy for KBD in China. Daily intakes of selenium below 20 $\mu$g are considered insufficient.\textsuperscript{132} The U.S. RDA is based on optimization of plasma glutathione peroxidase concentrations; however, the amount of selenium needed to optimize selenoprotein P levels may be greater than the current U.S. RDA.\textsuperscript{120} The plasma selenium concentration is often used to assess selenium nutritional status. At plasma concentrations of about 0.08 mg/L (0.4 $\mu$mol/L), the selenoproteins glutathione peroxidase and selenoprotein P are considered optimized.\textsuperscript{120} Selenium supplementation in China has been effected through the distribution of selenium-enriched table salt, the distribution of selenium tablets to children,\textsuperscript{73} and the use of selenium-enriched fertilizer\textsuperscript{64,74} (Table 185.4). Selenomethionine, the major form of selenium found in food, has almost twice the bioavailability of selenium in the form of selenite.\textsuperscript{120} The use of selenium-enriched fertilizer in selenium-deficient areas has been shown to increase the average daily intake of selenium as much as fourfold to 16.8 $\mu$g/day.\textsuperscript{74} Two meta-analyses have summarized the results of the known trials of selenium supplementation for KBD performed to date (5 randomized, 10 nonrandomized), conducted in China from 1982 to 1994.\textsuperscript{66,145} These trials involved more than 2000 participants ranging in age from 0 to 16 years with 10 months to 6 years of follow-up. Based on radiographic and physical examination outcomes (national KBD criteria), selenium reduced the odds of initial KBD manifestations by 80\% (odds ratios of 0.13 and 0.16 for the randomized trials and nonrandomized trials, respectively). Although few of these trials reported adverse effects, one trial that administered 1 to 2 mg/day (rather than per week) for the first week reported nausea and vomiting at the beginning of the trial. Excess selenium is toxic, so dosages
must be carefully regulated. Both selenium-deficient and selenium-excess diets have adverse effects on the mechanical properties of bones.\textsuperscript{105} Other toxic effects of selenium excess include hair and nail loss,\textsuperscript{146} neurologic dysfunction and respiratory distress,\textsuperscript{147} and death.\textsuperscript{72} The toxicity limit is estimated to be 600 to 800 $\mu$g/day.\textsuperscript{132,146}

In KBD-affected areas of Tibet, where both selenium and iodine deficiency are endemic, supplementation of iodine over 12 months was primarily responsible for stimulating the growth of a population of 10-year-old children.\textsuperscript{110} As described earlier, a 12 month study of Tibetan children showed the beneficial effects of repleting iodine in cases of KBD associated with both iodine and selenium deficiency. Since selenium repletion may aggravate hypothyroidism,\textsuperscript{110} iodine must be administered before selenium in cases in which both are deficient.\textsuperscript{110} This study has suggested the importance of iodine deficiency as an etiologic factor for KBD manifestations in some areas. In this study, new radiologic lesions occurred only in the group given placebo and iodine group and not in the group given both selenium and iodine, which suggests a potential role for selenium therapy as well.

Other preventive efforts include providing better storage of crops, drying corn, shifting to other crops less susceptible to fungal contamination and with greater bioavailability of selenium (e.g., from corn to rice),\textsuperscript{64,91} and improving the quality of drinking water.\textsuperscript{65} Standard treatments for OA, including physical therapy, nonsteroidal antiinflammatory agents, glucosamine, and intraarticular hyaluronan, can also be of benefit in cases of established KBD.\textsuperscript{148-151} Some individuals undergo osteotomy\textsuperscript{152} or extraction of loose bodies and joint lavage by arthroscopy,\textsuperscript{153} but currently joint replacement is uncommon due to cost barriers.

ACKNOWLEDGMENTS

The author wishes to thank Dr. Christopher McCudden for his invaluable assistance with graphics. She also wishes to thank Dr. Adam Taylor for providing photographs illustrative of ochronosis and Drs. Bruce Caterson, Junling Cao, and Xiong Guo for providing photographs illustrative of KBD.

References


Fig. 185.1
Ochronosis. Pathways leading to pathologic manifestations of ochronosis (alkaptonuria).
(Adapted from references 2, 8, and 19.)

Fig. 185.2
Ochronosis. Black-gray pigmentation of the ear cartilage in a patient with ochronosis.

Fig. 185.3
Ochronosis. Radiographs of the spine showing narrowing and calcification of the intervertebral disks.

Fig. 185.4
Ochronotic arthritis of the shoulder. Radiograph demonstrating characteristic osteoarthritis pathologic features including narrowing of the joint space, marked subchondral sclerosis, and small osteophytes.

Fig. 185.5
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-eosin, ×4). Inset: Chondrocytes located on the border between dense and light extracellular pigment. Chondrocytes show intracellular pigmentation and in some instances signs of necrosis (hematoxylin-eosin, ×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, post-stained using lead citrate and uranyl acetate, ×60,000).
(Courtesy Dr. Adam M. Taylor, findAKUre project, University of Liverpool.)

Fig. 185.6
Kashin-Beck disease manifested as bony enlargement of the elbows (a) and knees (b) exemplifying the characteristic for which the disease is named large joint disease in China.
(Courtesy Drs. Virginia Byers Kraus and Junling Cao.)

Fig. 185.7
Kashin-Beck Disease of the hand. (a) Photograph of a hand with the brachydactyly of Kashin-Beck disease (on left) compared with a reference hand of a Chinese individual without Kashin-Beck disease (on right). (b) Radiograph of the hand of an individual with Kashin-Beck disease demonstrating shortened middle and distal phalanges, cone-shaped metaphyses, and "pumice stone" deformity of carpal bones. (a, Courtesy Dr. Junling Cao; b, courtesy Dr. Xiong Guo.)
### TABLE 185.1
Characteristics of ochronotic arthropathy versus primary osteoarthritis and ankylosing spondylitis

<table>
<thead>
<tr>
<th></th>
<th>Ochronosis</th>
<th>Osteoarthritis (primary)</th>
<th>Ankylosing spondylitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Joints involved</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Knees</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Hips</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Shoulders</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Knees</td>
<td>++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Hips</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hands</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Distinguishing spine features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacroiliac joints</td>
<td>Spared</td>
<td>Spared</td>
<td>Involved</td>
</tr>
<tr>
<td>Osteophytosis</td>
<td>Sparse</td>
<td>Prominent</td>
<td>None</td>
</tr>
<tr>
<td>Disk calcification</td>
<td>Dense/waferlike</td>
<td>Mild-moderate</td>
<td>Mild-moderate</td>
</tr>
<tr>
<td>Multiple vacuum disks</td>
<td>Common</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Syndesmophytes</td>
<td>Broad</td>
<td>None</td>
<td>Thin + vertical</td>
</tr>
<tr>
<td>Apophyseal facet joint disease</td>
<td>Mild</td>
<td>Mild-severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Ligamentous ossification</td>
<td>Prominent</td>
<td>Scarce</td>
<td>Scarce</td>
</tr>
</tbody>
</table>

### TABLE 185.2
Staging systems for Kashin-Beck disease

<table>
<thead>
<tr>
<th>Clinical staging system based on the Chinese National Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
</tr>
<tr>
<td>Early</td>
</tr>
<tr>
<td>First stage</td>
</tr>
<tr>
<td>Second stage</td>
</tr>
<tr>
<td>Third stage</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical staging system of Mathieu</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical staging criteria of Beck</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
</tbody>
</table>
*Associated symptoms are tiredness, muscle weakness, inability to work, pes planus, waddling gait, and dwarfism.

### TABLE 185.3
Radiologic staging systems for Kashin-Beck disease

<table>
<thead>
<tr>
<th>Grade</th>
<th>Basis for grade (features scored below)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0 points</td>
</tr>
<tr>
<td>Mild</td>
<td>1-4 points</td>
</tr>
<tr>
<td>Moderate</td>
<td>5-7 points</td>
</tr>
<tr>
<td>Severe</td>
<td>8-10 points</td>
</tr>
</tbody>
</table>

Possible points 3

<table>
<thead>
<tr>
<th>Radiologic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteophyte: absent = 0; &lt;2 mm = 1; 2 to &lt;4 mm = 2; ≥4 mm = 3</td>
</tr>
<tr>
<td>Joint space narrowing: absent = 0; narrowed by &gt;1/2 normal joint space = 1; &lt;1/2 normal joint space but joint surfaces did not contact = 2; joint surfaces contacted or loose bodies found in the joint = 3</td>
</tr>
<tr>
<td>Sclerosis of bony margins: absent = 0; present = 1</td>
</tr>
<tr>
<td>Depression of bony margins: absent = 0; present = 1</td>
</tr>
<tr>
<td>Transverse deformation of joint: absent = 0; present = 1</td>
</tr>
<tr>
<td>Cysts under bony articular surface: absent = 0; present = 1</td>
</tr>
</tbody>
</table>

### Radiologic staging system of Hinsenkamp*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Radiologic feature</th>
<th>Total score</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>No radiologic change</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Radiologic changes of the epiphysis or metaphysis</td>
<td>1-10</td>
<td>I</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Radiologic changes of the epiphysis or metaphysis without fusion</td>
<td>11-20</td>
<td>II</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Local fusion of the metaphyseal growth plate</td>
<td>21-36</td>
<td>III</td>
</tr>
</tbody>
</table>

*In the Hinsenkamp system, six sites (hands/wrists, elbows, shoulders, ankles, knees, and hips) are graded on the 0-3 scale yielding a total score of 0-36 and then a stage of disease is assigned.

<table>
<thead>
<tr>
<th>Form of selenium</th>
<th>Dose or concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium selenite (oral)*</td>
<td>1 mg/wk for children aged 3-10 yr</td>
</tr>
<tr>
<td></td>
<td>2 mg/wk for children aged 11-13 yr</td>
</tr>
<tr>
<td>Selenized table salt</td>
<td>16.7 mg/kg salt, which provided a calculated average intake of 50 μg selenium/day</td>
</tr>
<tr>
<td>Sodium selenite (fertilizer spray)</td>
<td>15 g/hectare</td>
</tr>
</tbody>
</table>

*Representative of the most common selenium dosage regimen of the clinical trials performed to date in China for Kashin-Beck disease per Zou et al.\(^66\). The U.S. recommended daily allowance of selenium for adults is 70 μg/day for men and 55 μg/day for women. Adapted from references 64, 66, and 120.