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Review

Recent advances in the research of an endemic osteochondropathy in China: Kashin-Beck disease

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SUMMARY

Kashin-Beck disease (KBD) is an endemic chronic osteochondral disease, which has a high prevalence and morbidity in the Eastern Siberia of Russia, and in the broad diagonal, northern-east to southern-west belt in China and North Korea. In 1990's, it was estimated that in China 1–3 million people had some degree of symptoms of the disease, although even higher estimates have been presented. In China, the extensive prevalence peaked in the late 1950's, but since then, in contrast to the global trend of the osteoarthritis (OA), the number of cases has been dramatically falling. Up to 2013, there are 0.64 millions patients with the KBD and 1.16 millions at risk in 377 counties of 13 provinces or autonomous regions. This is obviously thanks to the preventive efforts carried out, which include providing millions of people with dietary supplements and clean water, as well as relocation of whole villages in China. However, relatively little is known about the molecular mechanisms behind the cartilage damage, the genetic and the environmental risk factors, and the rationale of the preventive effects. During the last decade, new data on a cellular and molecular level has begun to accumulate, which hopefully will uncover the grounds of the disease.

Introduction

The Kashin-Beck disease (KBD) includes multiple symptoms in the growth and the articular cartilages. It has been known since the sixteenth century, but the first one to describe the disease was I. M. Yurensky in 1849. Some years later (1859–1868), a doctor Nikolai Kashin also investigated the disease, and named it as the Urov disease according to the area where it was abundant. In 1906, a doctor Eugene Beck described his medical cases in a monograph *Osteoarthritis Deformans Endemica*. Later, the disease became known as the KBD. The research efforts on the KBD originated from Russia, then Japanese had an intense period of a research, and finally the research focus has gradually moved to China. Recently, an international collaboration has increased the awareness of the KBD also outside of Asia[1].

In 2013, there were 0.64 millions patients with the KBD and 1.16 millions at risk in 377 counties of 13 provinces or autonomous regions[2]. The major feature of the KBD is a short stature [Fig. 1(A) and (B)]. In contrast to the OA, the clinical symptoms, such as the deformed joints in the fingers and the feet start to appear already at the age 5 years, or even earlier [Fig. 1(C)–(H)]. The patients also suffer from the misshapen legs and OA changes[3]. The short stature is caused by several focal necroses in the growth plates [Fig. 1(J) and (K)], which are not present in the normal growth plate [Fig. 1(I)]. In contrast to the normal cartilage [Fig. 1(L)], the chondrocyte clusters, the necrotic areas and the compressed nuclei become more and more abundant as the disease progresses [Fig. 1(M) and (N)]. The disease not only damages the cartilage, but can also harm the cardiac and the skeletal muscle, the bone marrow, the blood vessel walls, the stomach, the endocrine glands and the peripheral nerves. Disturbances in the cartilage metabolism, the lipid peroxidation, and sulfur and selenium metabolism can also be present[3,4].

More than 50 environmental risk factors have been proposed for the KBD during the past 150 years, including a biogeochemical hypothesis, a cereal contamination by the fungal mycotoxins and the high contents of the humic acids in the drinking

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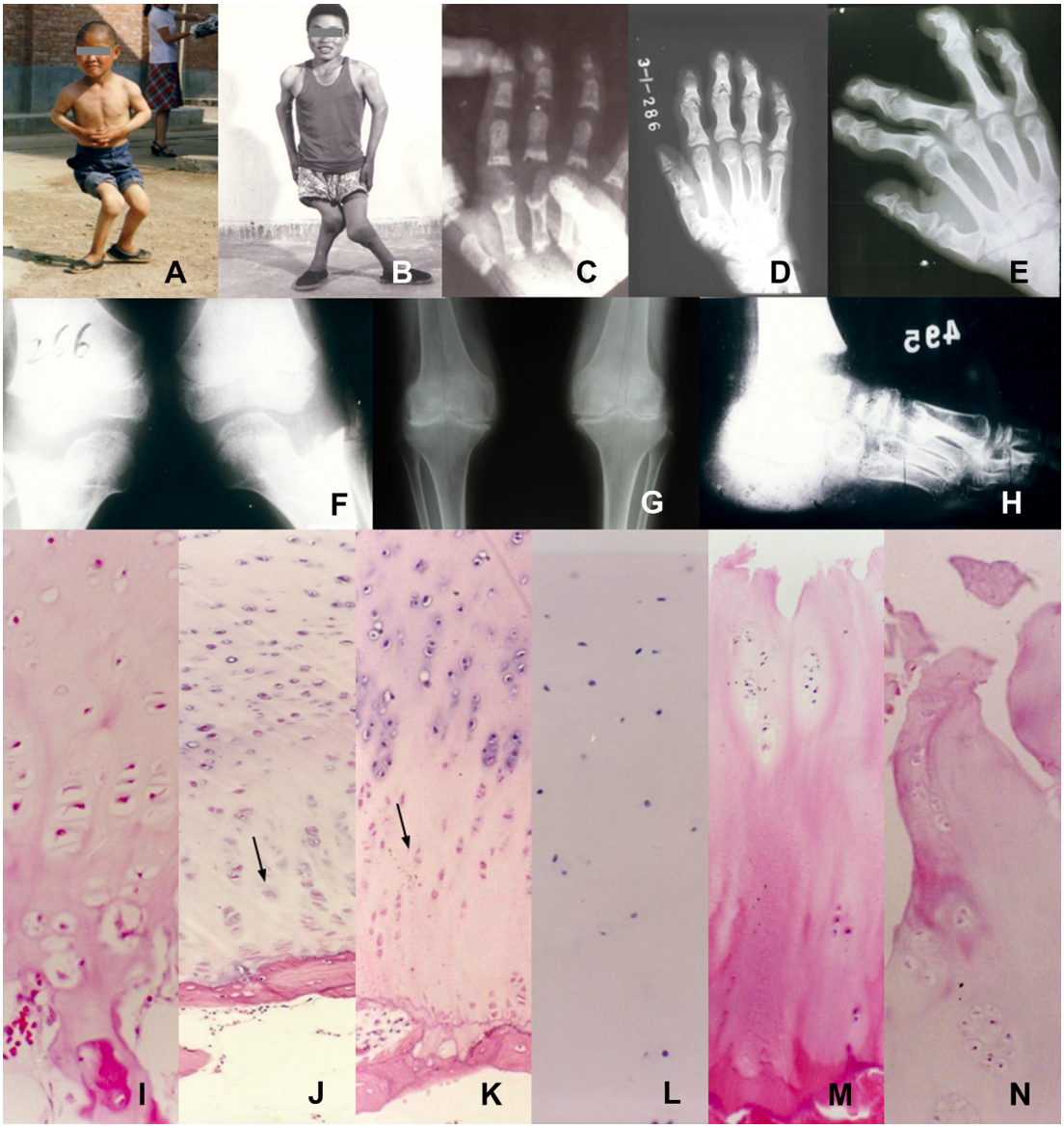

Fig. 1. Two KBD children aged 7 (A) and 15 (B) years old manifested the deformed joints in the limbs, had especially a knee varus deformity and the shortened humeri and the stature. The flexion of the terminal finger joints or the deformed fingers (C–E) was mostly occurring first in the children. The radiographic findings in the right hand of the KBD patients aged 13 (F), and 45 (G), and the feet of 9 years old one (H), respectively. In the growth plate cartilage of the KBD children, the large chondronecrotic areas without cells were typically observed in the deep zone of the cartilage (arrows in J and K). Such findings were not seen in the control cartilage (I). The chondrocyte size was significantly reduced in the KBD (J), but the cell membranes were intact. The nuclei were dissolved, broken and compressed, and associated with a red staining in the chondrocyte cytoplasm (K), and the cellular fibrillated areas (arrowhead) appeared. In contrast to the control cartilage (L), the chondrocyte clusters and the foci of chondronecrosis, the compressed nucleus and the incomplete cell membrane appeared in the upper and the middle zone in the articular cartilage of the KBD adults (M, N). Hematoxylin–eosin staining, 100 × 20.

water[3,4]. Currently, the selenium deficiency and the cereal contamination are regarded as the major environmental risk factors, and a multifactorial model considering the interactions of the multiple environmental and genetic factors has been developed for the KBD. Although the actual mechanism of the disease is still unknown, the recent data collected at a cellular and molecular level has provided important new findings, which hopefully can guide the research to find the cause of the disease. It is typical for the KBD prevalent areas that not all the villages, all the families or everybody in the family suffer from the KBD[5]. It has also been observed that upon an exposure to the same environmental risk factors of the endemic areas, the inhabitants can acquire different types of the endemic diseases, and totally different target organs.

Symptoms of the KBD in the cartilage

The epiphyseal growth plate and the articular cartilage are the most commonly affected anatomical sites in the KBD patients. Microscopically, the degenerative changes in the KBD cartilage are characterized by the chondronecroses in the multiple foci of the deep zone of the cartilage [Fig. 1(J) and (K)]. The focal chondronecroses and an impaired endochondral ossification mostly result in a secondary chronic osteoarthropathy. In the fetal and the juvenile cartilage, most of the KBD changes are located at the zones of the maturing and the hypertrophic cartilage. The necrotic fields can extend to the transitional region between the proliferative and the hypertrophic zones of the growth plate cartilage and, in the advanced KBD, even to all zones of the cartilage[6]. Before the overt

degenerative changes appear in the cartilage extracellular matrix, the chondrocyte necrosis can be visualized under the electron microscope[7]. The chondronecrosis of the growth plate can result in a disturbed endochondral ossification, and even induce the early closure of the epiphyseal growth plate, which will lead to the growth retardation, such as the short fingers, the short limbs, the retarded growth and a disability in the advanced stages[3].

Since the growth plate cartilage is the growth center of the bone, the developmental deformities of the KBD patients are most likely a result of an impaired chondrocyte differentiation and the endochondral ossification. The younger the symptoms arise, the more serious malformations develop. Additionally, the chondronecrosis of the articular cartilage can induce a scar formation, bony enlargements, osteophytes, loose bodies and a narrowed joint space in the KBD patients[3]. The electron microscopic analyses have confirmed the chondrocyte necrosis and revealed a reduction in the collagen fibril diameter, and a loss of the fibril banding patterns in the cartilage matrix of the KBD patients[7]. The KBD chondrocytes display the swollen mitochondria and a decreased density of the mitochondrial matrix compared to the normal ones [Fig. 2(A) and (B)]. The distended cisternae and a ribosomal detachment from the membrane are present in the swollen endoplasmic reticulum after a cell injury [Fig. 2(C) and (D)]. These endoplasmic reticulum events may coincide in an apoptosis and a necrosis. Besides the distended Golgi apparatus there can be more secretory vacuoles in the KBD chondrocytes [Fig. 2(E) and (F)].

Besides the classical deep zone chondronecrotic changes, the chondrocyte dedifferentiation and an abnormal type X collagen, Parathyroid hormone related protein (PTHrP), transforming growth factor-β (TGF-β), basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) staining patterns have been discovered in the KBD cartilage[8], which suggests that the endochondral ossification and the terminal differentiation disorders of the chondrocytes may be involved in the pathogenesis of the KBD. The degenerative and the hypertrophic changes have also been noticed in the KBD chondrocyte cultures[9]. The excessive apoptosis and the abnormal expression of the apoptosis regulating factors, such as Bcl-2, Bax, Fas and inducible NO synthase (iNOS)[10] are consistent findings with the increased serum levels of NO and the iNOS in the KBD patients[11].

The proteoglycan metabolism is affected by the KBD, since a decreased content of the proteoglycans can be found in the deep zone of the cartilage, particularly in the necrotic areas[12]. The aggrecanase-generated epitopes are present in the KBD cartilage, and also an increased serum content of CD44 and its immunostaining in the KBD cartilage[13]. The potential markers of the joint damage, *i.e.*, cartilage oligomeric matrix protein (COMP) and type II collagen telopeptides, are also increased in the serum[14]. The urine concentrations of the unsaturated glycosaminoglycan disaccharides and the pyridinoline cross-links of the collagens also correlated with the grade of the KBD[15]. The serum levels of the catabolic cytokines interleukin-1β and a tumor necrosis factor-α were high both in the normal and the KBD children in the KBD regions[13], suggesting that some yet unidentified factors may protect certain people from the disease. The markers of an autoimmune and an inflammatory response were also elevated in the KBD patients[16].

Correlation of the soil trace element contents with the KBD

The selenium is well known to associate with the human health and the disease. The incidence of the KBD overlaps strikingly with a Chinese map of the soil poor in the selenium[17]. In the 1970's, the Chinese researchers discovered that a low environmental content of the selenium resulted in a nutritional selenium deficiency of the population via a food chain in the KBD prevalent areas. In human, there are 25 genes encoding the selenoproteins[18], many of which are involved in the redox reactions and the lipid peroxidation of the body, and protect against the oxidative and nitrosative stresses. Thus, it is not surprising that the low blood selenium content in the KBD patients correlates also positively with the glutathione peroxidase enzyme levels. A selenocysteine is the twentyfirst amino acid, which is needed for the function of the selenoproteins[19]. A targeted deletion of tRNA gene for the selenocysteine (Trsp) in the osteo-chondroprogenitor cells causes many features similar to the KBD, suggesting its importance for the cartilage[19]. However, a generalized knockout of the Trsp has a lethal effect at an embryonic stage[20] and, thus, it is still not known whether this gene is involved in the development of the human KBD.

The selenium supplements have been considered a potential way to balance the selenium content of the body. A Chinese intervention study showed that the KBD incidence in 9343 normal children with dietary selenium supplementation (0.45%) was significantly lower than that of 2963 normal children who did not

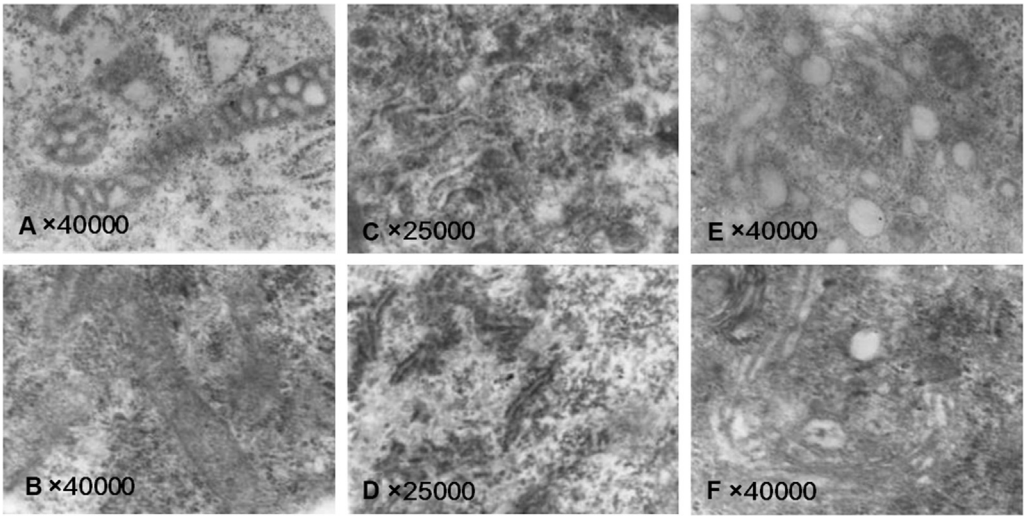

Fig. 2. The ultrastructure of the KBD and the normal chondrocyte shown in the transmission electron microscopic images. The KBD chondrocytes displayed the swollen mitochondria (A) compared to the normal one (B), and had the distended endoplasmic reticulum with detached ribosomomes (C) compared to the normal cells (D). The KBD chondrocytes has the distended Golgi apparatus (E) in contrast to normal ones (F).

have the selenium supplement in the KBD areas (1.9%)[21]. For 2197 KBD patients, the repair rate of the metaphysis pathological changes and the aggravating rate got to 64.8% and 2.8% in the selenium supplement group, in contrast to 19.9% and 11.3% in the non-selenium supplement group, respectively[21]. Still, the selenium supplement cannot fully prevent the incidence of the KBD, which can also decline without any change in the environmental selenium state. Thus, the role of the selenium in the KBD is still uncertain.

Additionally, a concomitant shortage of the iodine usually exists in the KBD area besides the low selenium in the soil. In some KBD areas, the selenium and the iodine deficiency coexist in the soil, the grain and the water, and the low levels of the selenium and the iodine can be measured in the children living in Tibet[22]. However, the low selenium, the low iodine or the low selenium together with the low iodine in the rat food, followed for two generations, failed to generate the characteristic chondrocyte necrosis typical for the human KBD[23]. Although the other elements, such as the fluorine and the zinc, have been considered to associate with the KBD, their contribution has not been further verified. Therefore, it inclines one to think that the selenium deficiency is one of the important environmental risk factors for the onset of the KBD.

Some other elements in an overdose, such as the thallium and the silicon, are also able to cause the deep zone chondrocyte necrosis in the experimental animals, but there is no significant difference in the thallium contents in the hair of the children living in the KBD endemic areas and in the non-endemic ones[24–26].

Toxins as a risk factor for KBD

Since the environmental selenium deficiency is not the sole predictor of the KBD, the onset of the disease likely has some additional epidemiologic characteristics. It has been observed that the dietary fungal toxin contaminations correlate with the risk of the KBD[4]. For instance, the toxic effects of a T-2 toxin have been reported[27]. The T-2 toxin also promoted an increased degradation of the cartilage proteoglycans, which could be partly prevented by the selenium supplementation[28]. In ATDC5 chondrogenic cells, the T-2 toxin activated the catabolism via a reactive oxygen species (ROS)/NF-kB/hypoxia inducible factor(HIF)-2α pathway[27]. Another mycotoxin, butenolide, increased the cytotoxicity via a disturbed antioxidant balance[29].

The studies of the KBD have been complicated due to the lack of a good animal disease model, which would have exactly the similar microscopic symptoms as the human KBD. To verify the environmental pathogenic hypothesis of the KBD, the grain and the water from the KBD prevalent areas have been used to feed animals, in order to obtain similar pathological changes as observed in the human KBD. A feeding of rhesus monkeys with the grain and the water from the KBD areas for 14 months displayed the chondrocyte necrosis similar to the human KBD[30]. The feeding of mini-pigs with a low selenium fodder for 30 days, and then with a fungal toxin fodder for more than 3 months, interfered with the normal metabolism of the cartilage, and the necrosis appeared in the deep layer of the articular cartilage, but not in the epiphyseal growth plate cartilage[31]. Similar results were obtained in the rat experiments using the T-2 toxin combined with a low selenium diet[32]. However, the low selenium in combination with the T-2 or moniliformin toxins were reported to retard the growth in the rats[33]. Also the bone and the metaphyseal plate of Wistar rats fed with the T-2 toxin and the KBD-affected diet had the KBD-type abnormalities[34]. The decreasing antioxidant levels were also observed by the T-2 toxin treatment under the selenium deficiency conditions[35].

Genetic involvement with the KBD

It is known that the KBD mostly attacks the local farmers, and the immigrating populations from the non-endemic areas are affected, too. In a study of 4938 nuclear families with the KBD patients, the KBD families were divided into four categories based on the parental phenotypes: (1) the father affected and the mother not; (2) the mother affected but the father not; (3) the both parents affected; (4) none of the parents affected. The family aggregation was observed in the first offspring generation at the KBD areas with the middle (10–20%) and the high population prevalence (more than 20%), but not in the low prevalence areas (less than 10%). The family aggregation of the KBD appeared in the families with the both parents, and either the father suffering from the KBD, but not in the families with the mother or neither of the parents suffering from the KBD (Fig. 3). This data has been compiled from our previous study[36]. The KBD family aggregation was observed in the first offspring generation, and depended on the types of the KBD areas and the KBD status of the parents.

It has also been shown that the parents and the siblings of the KBD have a 3–4 times higher risk of the KBD than the random non-related individuals. The segregation ratio and the heritability of the KBD within the siblings were 0.06% and 28.6%, respectively, estimated from 10,823 inhabitants living in 14 villages of Linyou county, Shaanxi province, China. This result indicates an obvious familial aggregation of the KBD, and the genetic factors account for more than 25% of the risk of KBD. In this context, it has to be realized that it is possible that the KBD development may require mutations in more than one gene. A generalized linear mixed model and a fitted logistic regression model applied to 185 KBD nuclear families and 193 KBD extended families for fitting the genetic variance components model revealed that the KBD family aggregation was mainly attributed to the common environmental risk factors and the relatedness of the offsprings and the offspring-parents[37]. These included the common external environmental factors; the family-shared environmental effects and the additive genetic effects[37]. These findings of the KBD genetics support the individual variation of the susceptibility to the KBD, and suggest that the environment–genome interaction plays an important role in the pathogenesis of the KBD.

The genome analyses of KBD patients

It is well documented that most diseases are associated with the individual's genetic make-up, the environmental agents and the complex interaction between the genetic and the environmental factors. Subtle differences in the individual genetic make-up can cause the people to respond differently to the same environmental exposure. A number of the OA susceptibility genes are known today[38]. To address the role of the genetic factors in the development of the KBD, a number of the short tandem repeat (STR) units on the chromosomes 2, 11 and 12 have been analyzed[39]. Eleven of 63 STRs correlated with the risk of the KBD (Fig. 4), as compiled from previous publications[40–43]. Three of the identified STRs were located at the chromosomal region 12q24.31-q24.33, at the proximity of the region 12q24.33 associated with the hand OA[44]. Single nucleotide polymorphism (SNP) analyses have indicated that the polymorphisms in growth differentiation factor 5 (GDF-5)[45], double von Willebrand factor A (DVWA) and interleukin-1β[46], glutathione peroxidase 1 and 4[47,48], TNF-α and Fas[49], and selenoprotein P[50] genes have associations with the KBD. Some of these genes have been shown to be associated also with the OA, such as GDF-5 and DVWA[38]. In the Tibetan population, the genetic variants of HLA-DRB1 gene were associated with the KBD[51]. Whole-exome sequencing also identified HLA-DR1, but also CD2AP, gene to be

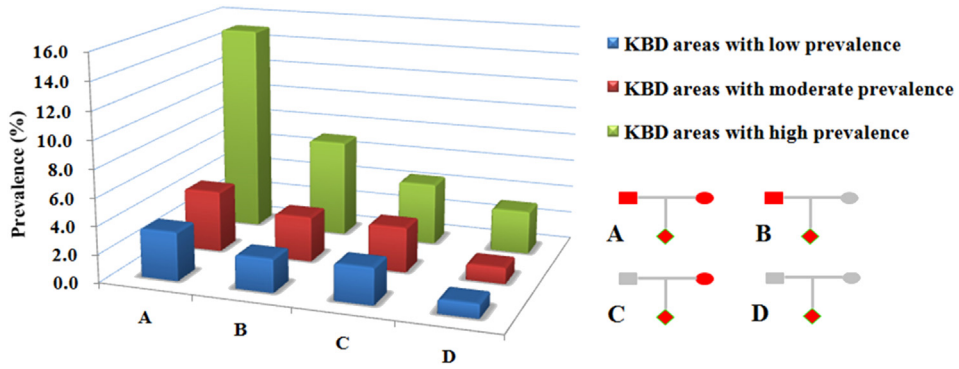

Fig. 3. The prevalence in the first offspring generation of the KBD families depended on the clinical phenotype of parents' status and the types of the KBD areas. In the same KBD area, the first offspring generation from the families whose both parents were the KBD patients (A) displayed a higher prevalence of the disease than the ones from families with a single parent suffering from the KBD (B, C); and higher than the one from families with a non-KBD history (D).

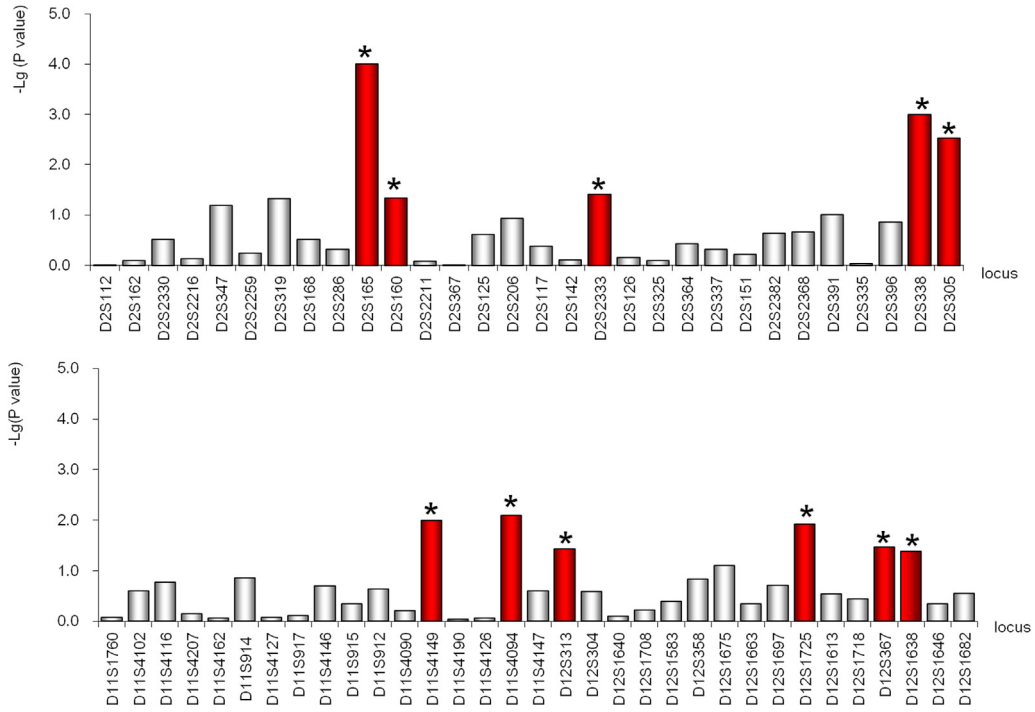

Fig. 4. An analysis of the allele frequencies of 63 STR loci in the chromosomes 2, 11 and 12. * There were significant differences in the allele frequencies between the KBD patients and the normal residents living in the KBD areas, marked with *.

among the susceptibility genes for the KBD[52]. A genome-wide copy number variation study identified ABI3BP gene a novel susceptibility gene for the KBD[53].

The gene expression profiling

To understand the mechanism underlying the necrosis, the dedifferentiation and the apoptosis of the chondrocytes in the KBD cartilage, the gene expression profiles of the KBD, the OA and the normal controls were compared using a human whole genome microarray chip[54]. In the cultured articular chondrocytes, 55 up-regulated and 24 down-regulated genes were identified in the KBD vs the normal donors. These 79 genes participate in various cellular processes, mainly including the metabolism, the apoptosis, the proliferation and the matrix degradation[54]. Recently, nuclear magnetic resonance-based metabolomics analysis confirmed the metabolism alterations in the glucose, lactate and citrate in the sera of the KBD patients[55]. Additionally, 83 up-regulated and 14 down-regulated genes were identified in the peripheral blood mononuclear cells of the KBD, which were involved in the metabolism, the apoptosis, the adaptive immune defense, the cytoskeleton, the cell movement and the extracellular matrix[56]. The above gene expression profiles of the KBD cartilage and the peripheral blood mononuclear cells suggest that the chondrocyte metabolism and the apoptosis contribute greatly to the cartilage lesions of the KBD. A recent finding suggests that the c-Jun N-terminal kinase (JNK) and the p38 signal transduction pathways may be involved in apoptotic events by phosphorylating activating transcription factor 2 (ATF2)[57].

Because many individual genes have distinctive functions in various cellular processes, the knowledge of the individual genes, which are differently expressed, is usually inadequate for the understanding the pathogenesis of the KBD. To reveal the mechanism behind the disease, a gene set expression analysis (GSEA) was

applied to analyze the gene expression profile data of the KBD cartilage vs the healthy cartilage. This analysis found that the apoptosis-, hypoxia- and mitochondria-related pathways were significantly up-regulated in the KBD patients compared to the healthy controls[58,59]. For instance, the pathways related to various types of the intracellular stress, including the growth factor withdrawal, the DNA damage, the unfolding stresses in the endoplasmic reticulum, and the death receptor stimulation were affected by the disease, in addition to the adaptive immunity-associated gene expressions in the peripheral blood mononuclear cells[60]. Nine mycotoxin-related genes were also differentially expressed in the KBD samples compared with the normal ones[61].

To address the pathogenetic differences between the KBD and the OA, the gene expression profile comparison of the articular chondrocytes identified 195 up-regulated and 38 down-regulated genes in the KBD, such as CSGALNACT, PIM2, EFNA1, SMAD-9, STK11, AQP, T-cell factor/LEF, PTN, APCDD and CAV[62]. These 233 differently expressed genes were linked to the cartilage metabolism, the ion channel proteins and the apoptosis. The immunohistochemical and the protein analyses confirmed the reduced contents of the CSGALNACT, but also the link protein Hapln-1, in both the KBD and the OA cartilages[63]. In line, the proteoglycan synthesis-associated enzyme contents were shown to be lower in the KBD cartilage, while proteoglycan catabolism-associated ones were higher[64]. Additionally, the GSEA analysis of the KBD cartilage vs the OA cartilage found that the apoptosis- and the NO-related pathways were significantly up-regulated in the KBD cartilage, while the ROS and the VEGF-A-related pathways were significantly up-regulated in the OA cartilages[65]. These results are consistent with the excessive chondrocyte apoptosis, the abnormal expression of Bcl-2, Bax, Fas, iNOS in the KBD cartilage, and the increased levels of NO and iNOS in the KBD patients' serum[11]. Especially the Myc-mediated apoptosis signaling pathway became apparent in further pathway analyses[66]. These results also support the idea that the ROS-induced cartilage damages play an important role in the pathogenesis of the OA, while the NO-mediated chondrocyte apoptosis contributes greatly to the development of the KBD. A recent study also indicated a relation of oxidative stress with the pathomechanism of the KBD[67].

Further studies have been conducted to understand the roles of mitochondria-mediated caspase activation and the apoptosis in the KBD cartilage damages. The reduced activities of the complexes II, III, IV and V, and an increased mitochondrial mass were observed in the KBD articular chondrocytes compared with the healthy chondrocytes[68]. The cultured KBD chondrocytes had reduced cellular ATP levels and a higher proportion of cells with de-energized mitochondria, and involved a mitochondrial cytochrome c release and an activation of caspases 9 and 3. The percentage of the apoptosis-positive chondrocytes from the KBD patient group was larger than that of the healthy controls[68]. These findings suggest that the dysfunction of the mitochondria and the mitochondria-mediated cell death contributed to the pathophysiology of the KBD.

The proteomic analyses of KBD samples

There is a need of biomarkers useful in the screening KBD-affected people from the normal healthy ones. Use of a surface-enhanced laser desorption ionization mass spectrometry (SELDI/TOF-MS) analytics found eleven protein peaks, which were differentially expressed in the KBD patients[69]. A protein peak with m/z 15,886 was significantly lower, while the protein peaks with m/z 2952 and 3400 were significantly higher in the KBD patients than in the normal controls. Additionally, 13 differentially expressed protein peaks were identified between the KBD patients and the OA patients. A classification tree screening identified three potential protein biomarkers at 5336, 6880 and 4155 m/z, the sensitivity and specificity of which were 86.4% and 88.9% for distinguishing the KBD samples from the normal controls.

A proteomic analysis comparing the protein profiles in the chondrocytes cultured from the KBD patients and the normal controls *in vitro* identified 27 differentially expressed proteins by a matrix-assisted laser desorption ionization time-of-flight tandem mass spectrometry[70]. These included 10 up-regulated and 17 down-regulated protein spots, representing 16 proteins. The enzymes involved in the carbohydrate metabolism (phosphoglycerate kinase 1, phosphoglycerate mutase 1, enolase and UTP-glucose-1-phosphate uridylyltransferase), as well as prolyl 4-hydroxylase, manganese superoxide dismutase and protein disulfide-isomerase were at lower levels in the chondrocytes obtained from the KBD cartilage. On the other hand, heat shock protein beta-1, peroxiredoxin 1, actin, cofilin-1, calponin and proto-oncogene C-crk were more abundant in the KBD chondrocytes[70]. This information supports the presence of an abnormal biosynthesis, the metabolism, the subcellular localization and the molecular functions of the differentially expressed proteins in the KBD chondrocytes. These findings hopefully help to develop novel clinical methods for the early diagnosis of the KBD.

The preventive measures against the KBD

The incidence of the KBD has greatly declined from the eastern to the western parts of China. For instance, the damage incidence on the hand radiographs in the children aged 7–12 years was 44.8% in 1990, but only 0.3% in 2010 at Cuimu town of Linyou county of the Shaanxi province. The greatly declined prevalence is mainly attributed to the implementation of comprehensive preventing measures of the KBD, including the selenium supplement in the salts[71,72], and the improved nutrition, water and living environment of the KBD areas. The effect of the selenium supplement has increased the selenium contents in the hair samples in the KBD area, with a simultaneous decrease in the prevalence of the KBD (Fig. 5)[73]. It is anticipated that the continuation of these preventing measures may help to eliminate the KBD cartilage damages in the children in the near future, which is in contrast to the difficult prevention of the OA globally. Although the KBD among the children is today under control and has almost disappeared, the adult KBD is still a serious problem due to its high incidence in China during the last century. At present, there are no effective clinical measures to repair the cartilage damages or defects of the KBD, due to the poor self-renewal ability of the cartilage. Tissue engineering

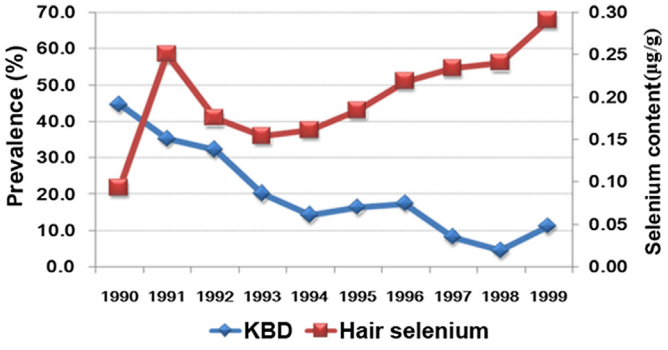

Fig. 5. The relationship between the hair selenium content and the KBD prevalence with the X-ray positive rate in the children aged 7–12 years old in the Shaanxi province of China. The rate of the X-ray positive for the KBD decreased, while the selenium content increased in the hair during years 1990–1999.

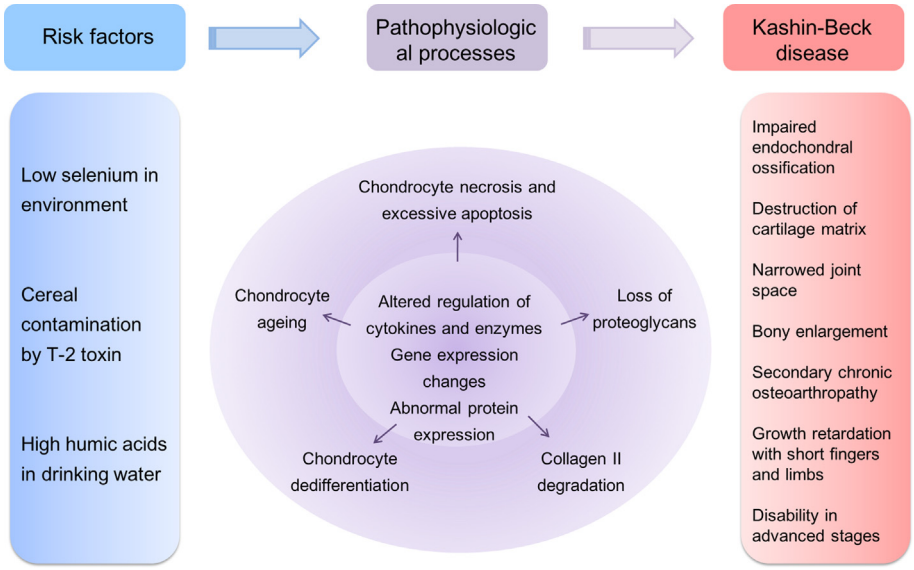

Fig. 6. The scheme of the environmental risk factors, the pathophysiological processes and the cartilage damage linked to the development of the KBD.

and gene therapy approaches have not yet been applied to the treatment of the KBD cartilage damages.

With an arthroplasty, the damaged articular cartilage can be completely removed and replaced by artificial joints, which improves the joint function and reduces the pain of the KBD patients. However, the KBD patients live in poor remote mountainous and rural areas, and cannot afford the high cost of the arthroplasty. Attempts to releave the pain and the symptoms have included, for instance, meloxicam, hyaluronan, chondroitin sulfate and glucosamine treatments[74–76]. The knee joints of 1380 adult KBD patients were injected with sodium hyaluronate intra-articularly in Shaanxi province over the period from year 2003 to 2010[74]. The subsequent clinical evaluation by the The Western Ontario and McMaster Universities Arthritis Index (WOMAC) and the Lequesne grading showed significant improvement of the knee joint dysfunction, the joint pain and the morning stiffness in the KBD. After 6 months of the intra-articular sodium hyaluronan injections, the efficiency rate was 93.6%, in contrast to the C-vitamin control group[74]. A recent 1-year follow-up revealed an improvement in the symptoms for at least 52 weeks[77]. A meta-analysis study also supported intra-articular hyaluronan treatment to be safe and efficient for the KBD[78].

Conclusions

In summary, the KBD is a complex endemic osteoarthropathy closely related to the environmental low selenium nutritional status and the environment-responsive genes and proteins (Fig. 6). The lesions of the articular cartilage and the growth plate cartilage in the KBD mainly include the focal chondronecroses of the cartilage deep zone, the chondrocyte dedifferentiation and the excessive apoptosis, which result in the enlarged, deformed and shortened joints in the extremities. Researchers have identified a set of abnormally expressed genes, proteins and pathways in the KBD, mainly involved in the cartilage structure, the cartilage metabolism, the ion channels, the oxidative stress, the mitochondrial function and the apoptosis. The identified abnormally expressed genes, proteins and pathways provide a new insight for the understanding the pathogenesis of the KBD. Through the improved nutritional diets, the living environment and the drinking water in the KBD areas, the children's KBD has been effectively prevented.

Author contributions

All the authors were involved in the drafting the article and the revising it critically for the important intellectual contents, and all the authors approved the final version to be published. Professor Guo has the full access to all of the data in the study, and takes the responsibility for the integrity of the data and the accuracy of the data analysis.

Role of the funding source

The funding source did not contribute to the design, the interpretation of data, the drafting or the final approval of the manuscript.

Conflict of interests

None.

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