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KASHIN-BECK DISEASE

by

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Summary. — The article describes the history, clinical picture and anatomopathological changes of Kashin-Beck disease with reference to the stages of the disease which are at present agreed upon. Specific reference is made to the occurrence of the disease in Tibet. An overview is given of the different proposed etiologies.

KEYWORDS: Kashin-Beck Disease; Osteoarthropathy; Selenium; Tibet

Introduction

Kashin-Beck disease (KBD) is an osteoarthropathy of unknown etiology characterised by a focalised destruction of the chondrocytes of the articular cartilage and the growth zone. This results in disturbances in the enchondral ossification and in changes in the articular cartilage with secondary deformities of the affected bones (shortening of the long bones) and joints (enlargement and decreased mobility range). The disease is charaterised by atrophy, degeneration and necrosis of the cartilage.

History

The disease was first described by I.M. Yurensky in 1849 and later by N.I. Kashin around 1860. Kashin described the disease in the South Eastern frontiers of the expanding Czarist empire where Siberia interfaces with China. The Russian outposts were largely Cossack settlements. The Cossacks were largely of caucasian origin and a linguistic group, rather than a racial one. Because the Cossacks settled mainly along the bank of the Urov River the ailment became first known as Urov disease (15).

The next description comes from E. Beck, a physician assigned to the Fourth Medical department of the Transbaikal Cossack Army. Between 1899 and 1902, Beck transferred six affected subjects to the Clinical Military Hospital in St. Petersburg for study. Since his descriptions the disease is known as Kashin-Beck.

Another line of investigations in the disease comes the Japanese T. Takamori, who became Professor of Medicine at the University of Manchuria in Habin during the Japanese occupation. He carried out research on what he

called « Dysostosis enchondralis endemica » until the Japanese were expelled from Manchuria at the end of the Second world war (15, 19, 28).

About 300 years ago, a likely description of this disease appeared in the county records of Anze, Shanshi Province, in North-West China in 1644, a heavy prevalence area of Kashin-Beck disease today. A detailed description was not made until 1934 by Zang Fengshu in Jilin Province, North-East China (28).

Epidemiology

The disease is endemic in Eastern Siberia, Northern Korea and in China, in a belt running from the North-East to the South-West from the most Northern border to Tibet. The disease is most prevalent in Shaanxi province in China. The prevalence ranges widely in different areas with a reported prevalence as high as 96 % in certain communities. In China, it is estimated that about two million people are affected by the disease and that more than thirty million people are living in the endemic areas and subsequently at risk of acquiring the disease (6, 20). A survey made in 1950 in North China indicated that the prevalence generally fell into the range of 30-40 % and mounted to 70 % in certain localities. A more recent survey showed a very high prevalence of 96 % in a village in the South-West of China (28).

The disease is well known in Tibet and has been there « for ever » according to the local population. It is referred to as Big Bone disease. Figures for the prevalence do not exist, and an extrapolation of survey results is not possible due to the very patchy distribution. In endemic regions one can find villages with a very high prevalence (up to 90 %), neighbouring villages with a very low or no prevalence. A survey conducted in the Lhasa prefecture found a prevalence of 13 percent for Nimu county, here again certain villages have a prevalence up to 50 percent (2). New patients can be found in villages where the disease was not known before. In rare cases, the prevalence has been noted to have decreased spontaneously.

In heavily affected areas, new cases of KBD can be detected by the age of 2-3 years by X-ray examination, whereas in mildly affected areas the initial age of onset is usually postponed beyond 10 years of age (3). Generally the vulnerable population are children aged 5-13 years. Very few new cases are seen in adolescents and adults (28, 15). The youngest Kashin Beck patient is three months and seven days old (5). Males and females are equally affected (28). Foetuses, and newborns of affected patients show no signs of the disease.

Epidemiological investigations have led to agreements on only a few aspects of the disease. It occurs in rural (farming and hunting) communities in hilly terrains, particularly in valleys where a poor soil is deposited by the runoff of water (loess). Labourers living in the same area are not, or much less, affected by the disease.

Where KBD is endemic winters are long and severe, and the summers are warm and humid. Consequently, crops are harvested and stored under conditions that might favour rot (28).

Anatomopathological changes

The disease mainly involves Hyaline cartilage. Epiphyseal cartilage, enchondral cartilage of the growth plates and articular cartilage are the most affected sites. Lesions in the cartilage tissues of the whole skeleton have been described, including vertebrae and cranial base, with the exception of the mandibular joint.

The most important pathological feature is that of multiple localized chondronecrosis in the deep portion of the cartilage tissue. In the necrotic areas chondrocytes die, lose their stainable nuclei, and become cell ghosts. The intercellular matrix may stay for a while. The cell ghosts then disappear and the necrotic areas become gradually homogenized. After the chondrocytes die the surviving chondrocytes adjacent to these necrotic areas soon proliferate and even form chondrocytic clusters. As a result of the reactions of the primordial bone marrow, a process of absorption, remotion, organisation, dystrophic calcification, and ossification gradually takes place in the necrotic cartilaginous mass. Eventually the necrotic areas heal up with the formation of a repaired cicatricial bone tissue, which thereafter, undergoes absorption and adaptive remodelling (14). This scar bone formation results in bony enlargements, osteophyte formation and disfiguration of the joints affected (endemic osteoarthrosis deformans).

Clinical picture

The disease begins gradually and often asymptomatically in children of school age. Sometimes a patient discovers that some joints have become thickened, without having any sensation of illness. Most patients experience slight aching and muscular weakness which increase with walking or other physical exertion, fatiguability, and sometimes general weakness. One half to one year after the onset of the disease thickness and deformity of the joints, most often of the interphalangeal and wrist joints, are found. There is crepitation, but inflammation or effusion are absent. Articular involvement is almost always symmetrical.

The disease progresses slowly and chronically. The earlier in childhood that the first signs of the disease appear the more severe do the arthritic deformities and limitations of the joint function tend to be, and the more commonly does symmetric disability occur. Soviet authors distinguish three degrees of the disease, according to the patients age and the severity of the joint involvement (15).

First degree, i.e. the mild form of the disease, usually corresponds to the initial phase of its development. Although complaints may be absent, objective signs such as thickening and slight deformities of interphalangeal or wrist joints, are demonstrable both clinically and roentgenographically. In this stage patients often complain of tiredness, rapid fatiguability, pain and stiffness of involved joints which increase after exertion and with changes in the weather; sometimes muscular cramps or paresthesias are observed. The most prominent physical finding is enlargement of symmetrical joints of the extremities, most often interphalangeal joints of fingers, wrists and ankles, and minimal atrophy of the muscles adjacent to the affected joints.

The second degree is characterized by the complete clinical and roentgenographic picture of deforming osteoarthrosis. The patients complain of progressive decrease of their capacity to work because of pains in the joints and limitation of mobility in them. These pains become essentially constant, are intensified by exertion and by changes in the weather. The patients also complain of sensations of stiffness in the extremities, paresthesias, coldness of hands and feet, periodic cramping of the affected muscles. Usually the patients are aware of the shortness of their fingers, forearms, and/or legs, resulting respectively, from involvement of the interphalangeal, carpal, radioulnar, ankle and knee joints. At this stage of the disease the extremities are shorter and the joints visibly deformed. The affected joints have a limited range of motion which characterises the pose of these patients; fingers are bend, elbows and/or knees are in varying degrees of permanent flexion (Figure 1). Acute joint pains resulting from the pinching of intra-articular lose bodies often occurs. As a rule effusions do not occur in the uncomplicated cases, nor any other sign of joint inflammation.

Figure 1
A 13 year old boy affected by Kashin-Beck disease holding his arms in maximal extension. Note the thickening of the elbow joints.

Figure 2
A 45 year old women with Kashin-Beck disease from Nimu county, Lahsa prefecture, Tibet, standing next to a Tibetan male of the same age and measuring 1.65 m

The third degree is characterized by the combination of chronic deforming osteoarthrosis and general manifestations of chronic disease. These patients complain of severe muscular and general weakness, considerable limitation of mobility of the affected joints and sharply decreased capacity for work. The limitation of articular mobility, pain, muscle atrophy, and often pes planus

cause a characteristic waddling gait. Furthermore, there is a reduction of height, shortening of the fingers, forearms, etc. The vertebral column may be involved. The spondylarthrosis further limits mobility and the capacity to work.

The gross deformities seen are due to osteo-arthrotic processes with the development of osteofytes. In cases of early onset marked deformities of the spine and joints with marked stunting, even dwarfism, can be found. The cases of dwarfism have a typical disproportionate shortening of the extremities (Figure 2).

Chinese authors classify the disease in four stages (30):

Early stage: flexion of the distal part of the fingers, bow like fingers, and pain of the knee and ankle joints.

First degree: enlargement and crepitus of small joints.

Second degree: short fingers, enlargement and dysfunction of medium size joints.

Third degree: enlargement and dysfunction of large joints, underdevelopment of stature.

The basic X-ray signs of the disease were summarised at the IPCS/WPRO (1985) meeting as follows (6):

a) the calcification line becomes blurred, thin, interrupted and disappears, this as a characteristic of chondronecrosis;
b) marginal defects of the metaphyseal plate, end of distal bone, and metacarpal bones following chondronecrosis;
c) deformity of epiphysis, synostosis of epiphyseal plate resulting from necrosis of the whole layer of the epiphyseal plate;
d) enlargement of joints and stubby fingers as the effect of secondary osteoarthrosis.

The etiology

At present no consensus on an etiological factor has been reached. The general consensus is that it is a nutritional problem either due to an unbalanced composition of the food or a contamination of it. Selenium deficiency is most widely hypothesized as a cause and also the deficiency or abundance of other minerals. Contamination of food by funguses is mainly hypothesized by the Russian investigators.

A. *Selenium*

1. *Introduction*

In 1957 it was discovered that Selenium could prevent liver necrosis in vitamin E deficient rats and pancreatic atrophy in vitamin E supplemented chickens. This led to a more vigourous investigation in to the role of selenium

in preventing diseases in animals, and the establishment of its protective role against white muscle disease in lambs and calves, and hepatosis dietetica in pigs (16).

The role of Se in Kashin-Beck disease was accidentally discovered in an experimental feeding of rats. 40 % of the rats fed with cereals and drinking water from KBD affected areas died and 75 % developed muscular dystrophic changes. Analysis of the food used revealed significantly lower vitamin E and Se contents as compared to non affected areas (14).

Given the importance of both Keshan disease (4, 27) and Kashin-Beck disease extensive surveys were set up to examine the Se content of Soil all over China and the Se content in foods and drinking water in diseased and non diseased areas. Human specimens of blood, urine, hair, nails were analyzed for Se and enzyme activities. At the same time trials were set up to examine the influences of Se supplementation on the control of the disease and its prevention (24, 25).

2. *Chemicogeography of Selenium*

The Se distribution in soils takes three different forms: one were the concentration is not associated with any diseases, and considered adequate; another where soils contain high amounts of Se associated with chronic Selenosis is livestock: Wyoming and South Dakota, Alberta, Saskatchwan, and Manitoba in Canada, in Colombia and Venezuela, the South African Karoo, the Huley Valley of Israel and the Hubei province in China. In this last area human Selenosis has also been described. Lastly, areas where the selenium content of the soil is very low; Pacific North-West, the South Atlantic Seaboard, New Zealand, parts of Australia, Scandinavia, Scotland, parts of Europe, western Russia and a zone stretching from the North-East to the South-West in China. Selenium deficiency diseases have been described in livestock in many of those areas, but an association with human diseases only in China.

Investigation in China have shown that in the low selenium zone stretching NE to SW, all the diseases of Keshan and Kashin-Beck can be found (21). Multi element analysis was conducted starting in 1973 in five provinces, which was expanded to the whole of China in 1977. In the Selenium deficient zone one can find areas with Kashin-Beck, Keshan disease and with both. No differences in Se content of the soils, crops and water were found between these different areas, neither was the hair selenium content different.

Soil Se in the non diseased belt was consistently above 0.125 ppm, whereas in the diseased belt it was found to be less than 0.125 ppm. The mean difference in content was highly significant (21).

Se content in grains in diseased and non diseased areas were found to be significantly different, with wheat, corn, rice and potatoes having Se concentrations below 0.02 ppm. In non endemic areas this was consistently above 0.02 ppm (9).

The geographic distribution of hair selenium shows the same correlation with the distribution of selenium in topsoil and foodgrains. Hair selenium levels are below 0.200 ppm in the endemic disease belt (21, 9).

The Se concentration of hair of children 3 to 6 years old was examined in Sichuan province where Keshan disease is very prevalent and in non diseased areas. In diseased areas the Se concentration was consistently lower than 0.12 ppm. Between people living in the same areas the farmer population showed significantly lower hair selenium levels than labourers, or otherwise employed people. The explanation given is that of greater access to diversified food for the non farming population, where the farmers tend to live off their own land entirely and have a more monotonous diet (18). The adult farming population had also significantly higher hair selenium levels than their children (9). This could be related to the changing Selenium requirements with age, where the period of highest demand is between 11 and 15 years (5).

Some authors mention a seasonal variation in selenium (Se) concentration in hair and urine samples. Higher concentrations were found during summer and autumn and lower in winter and spring. The selenium content of the soil and of drinking water was higher in spring and summer than in autumn and winter (6).

It is estimated that in endemic areas of Kashin-Beck disease the average daily selenium intake of adults is around 10 mcg or less, and meets therefore only one fourth to one seventh of the daily recommended intake as suggested by the US National Research Council (28).

3. *Treatment and Prevention of Kashin-Beck Disease*

Following the hypothesis of low Selenium intake and low Vitamin E intake, a trial was set up by Li in 1979 to test the therapeutic effects of Selenium. Patients were treated with oral administration of 0.5-2.0 mg sodium selenite weekly associated with vitamin E injections over a period of 3-6 months. Out of 224 cases, 187 (83 %) showed improvement of the metaphyseal lesions on X-ray films (8, 9).

From 1977 till 1983 children 3-10 years old were given Sodium Selenite supplements in Gansu Province. The author reports that the percent of normal X-rays increased during the observation period from 57 % to 95 % in 1983. The numbers are however too small to be able to test the data from significance (17).

Studies in Shaanxi province strongly suggest a therapeutic effect of selenium supplementation in a group of 3-10 year old children after oral sodium selenite supplementation. From 1980 to 1981 and from 1981-1983, children aged 3-10 received a one mg tablet per week. X-rays were taken at regular intervals and rated according to their severity. Follow up pictures were rated to their degree of improvement. In 82 % of the cases X-rays showed improvements as compared with controls where 40 % improved and 19 % deteriorated (10).

Prevention trials with fortified salt were also conducted in Shaanxi Province from 1981-1985. The incidence dropped from 66 % to 46 % as compared with a drop from 75 % to 54 % in the control group. No significance could be shown (11).

Spraying blossoming wheat crops with sodium selenite elevated the grain selenium three fold. The X-ray detection rate of abnormal metaphysis in

children who had consumed the Selenium-fortified wheat for two years reduced from 63 to 42 %, and the abnormal metaphyseal detection rate from 59 to 32 %. In the control group, changes of both rates were not significant (30).

4. *Selenium and the chondrocyte*

An experiment designed to detect minimal survival requirements of chondrocytes for selenium failed to show an idiosyncratic requirement of chondrocytes for selenium. Cultured human chondrocytes were grown in artificial media containing different concentration of selenium. Selenium concentrations much lower than possibly those found in human tissues failed to produce death of the cultured chondrocytes (23).

5. *The possible role of Selenium*

Selenium is an integral part of glutathione peroxidase, which together with Superoxide dismutase and catalase neutralises free radicals and hydrogen peroxide. Other seleno proteins exist, like the seleno protein P which is a plasma protein containing Se-cysteine, but their role have not yet been defined (17, 3, 13).

Investigations in low soil selenium areas have found that not only plasma selenium is significanty lower but also the glutathione peroxidase activity of the investigated subjects (26). Glutathione peroxidase activity increased after supplementation with selenium selenite.

Chicken chondrocytes incubated with fulvic acid and free radicals where inhibited in their growth and decreased their deposition of proteoglycans and secreted mainly type I collagen instead of type II, which in turn caused abnormal mineralisation (22).

B. *Other possible etiologies*

In their review articles Sokoloff (9), Levander (7) and Yin (29) discuss other possible etiologies for Kashin-Beck disease i.e. mycotoxines, other minerals, drinking water and miscellaneous compounds.

1. *Mycotoxines*

The possible role of mycotoxines in Kashin-Beck disease was proposed by Russian researchers. Fusarium sporotrichella is mentioned as the main contaminant by Nesterov (15). This has led the Soviets to import bread and flour from disease free regions to in the endemic areas, or to migrate entire populations out of the endemic areas, with success. Investigations in China have led to the isolation of *Fusarium* species particularly *F. oxysporum* and *F. moniliforme* from corn.

Evidence to support the role of mycotoxines is the observation that rice eating communities are spared from the disease. However it should be noted that rice generally contains more Selenium than corn in a given area and thus provides an alternative explanation.

2. *Other minerals*

Soviet investigators compared the mineral content of bones from cadavers of Kashin-Beck patients and non-diseased patients. The bones of KBD patients showed significant lower levels of calcium, and increased levels of strontium, iron, lead, manganese, zinc and silver. Copper content did not change. The bone mineral with the greatest relative change was silver, which increased more than ten fold. This is an intriguing finding because silver has been show to exacerbate selenium and/or vitamin E deficiency experimentally in a variety of species, including rats, swine and turkeys, presumably by decreasing the glutathione peroxidase activity. Thus one has to entertain the possibility that environmental silver exposure might have particular damaging consequences in persons with poor selenium status.

Ivanov and Voshchenko of the Chita Medical Research Institute, Russia, recently proposed that excessive intake of phosphate and manganese may play a role in the etiology of Kashin-Beck disease. They found that the diet in areas endemic with Kashin-Beck disease furnished 2.5 times more manganese and 1.8 times more phosphorus than diets from non-endemic areas. The mechanism by which this mineral imbalance might contribute to the development of Kashin-Beck disease was thought to involve the inhibition of bone growth via the increased parathormone production (high phosphate) and osteoclast activation (high manganese).

Another element of possible interest in Kashin-Beck disease is thallium, which, when injected into the yolk sack of chick embryos, causes a severe cartilage necrosis. This chondrocytic effect of thallium is decreased substantially by the injection of selenium into the yolk sac (12).

3. *Drinking water*

Differences in prevalence between farmers and other occupations in endemic areas have also been related to the drinking water sources. It was found that farmers collect rainwater and store it in under the houses, whereas the other people used water from deep wells. Changing the water source to deep wells for everyone didn't affect the incidence.

Inorganic and organic constituents of drinking water have also been incriminated. For example the water in endemic areas is poorer in calcium, magnesium, chloride and sulphate but richer in iron, manganese and barium than the unaffected areas.

In certain Kashin-Beck areas, the drinking water may be contaminated with organic matter where the water is stagnant with a thick layer of humus soil. The incidence of the disease as diagnosed by X-ray examination is positively correlated with the concentration of humic acid in the drinking water.

4. *Miscellaneous compounds*

Beta-Cyanoalamine, an unusual toxic amino acid that occurs in certain legumes, has been tested as a possible etiologic agent in cultured chondrocytes. It did not have selective chondrocytic properties in concentrations up to 1 mM, nor did nalidixic acid and cinoxacin, two antimicrobials known to damage articular cartilage of young puppies (20).

Conclusions

Most of the publications that have been researching Kashin-Beck disease agree that neither of the possible etiological factors alone can explain the epidemiological characteristics, nor the clinical and anatomopathological picture of the disease. It is probable that a multifactorial etiology is responsible for the disease. The selenium deficiency might be the underlying determinant that renders the body more susceptible to other acting factors, like toxins, other minerals, viruses, contaminants, etc.

From a discussion on the known epidemiological characteristics of the disease, Allander concludes that more epidemiological studies could help eliminate a number of possible etiologies and clarify some of the gaps in the knowledge about the population affected and its characteristics (1).

Even with the likelihood of a multicausality in the etiology, selenium supplementation is widely practised, particularly in Tibet. In this last region Iodine deficiency is still widely prevalent (it ranged from 13-30 % for stages Ia-III in women of childbearing age in four counties of the Lhasa prefecture (2)). Supplementing Selenium, when not controlling Iodine deficiency could have important negative effects on the iodine deficiency prevalence, since thyroxine catabolism seems to be decreased in situations of a combined iodine and selenium deficiency, decreasing iodine needs (Dr. Chanoine, personal communication at the Workshop for Iodine deficiency in Europe, Brussels 1992). Selenium supplementation in these situations worsens the degree of hypothyroidism.

REFERENCES

1. Allander E: The Epidemiology of Kashin-Beck Disease. Some Reflections on Possibilities for International Cooperation. AIN Symposium Proceedings, 1987. American Institute of Nutrition Annual Meeting, Washington DC, 1987, pp. 72-75.
2. Atkinson S, Kolsteren P, Maskall K: Nutrition, Health, Water and Sanitation Assessment, Lhasa prefecture. Save the Children Fund (UK), 1990.
3. Burk R: Recent developments in trace element metabolism and function: newer roles of selenium in nutrition. J. Nutr., 1989; **119**, pp. 1051-1054.
4. Cheng Yun-Yu: Selenium and Keshan disease in Sichuan, Province, China. In: Selenium in Biology and medicine (G.F. Combs Jr., J.E. Spallholz, O.A. Levander, J.E. Oldfield, Eds), Van Nostrand Reinhold Company, New York, 1986, pp. 877-891.
5. Hou Shao-fan: The relationship between selenium dynamics in the course of human body growth and the Kashin-Beck epidemiology. Acta Geographica Sinica, **39**, 1984, pp. 75-85.
6. IPCS/WPRO/PROC Meeting on Kashin-Beck Disease. Summary report.
7. Levander OA: Etiological Hypotheses Concerning Kashin-Beck Disease. AIN Symposium Proceedings, 1987. American Institute of Nutrition Annual Meeting, Washington DC, 1987, pp. 67-71.

8. Li Ji-Yun: Distribution of Selenium in the Microenvironment Related to Kashin-Beck disease. In: Selenium in Biology and medicine (G.F. Combs Jr., J.E. Spallholz, O.A. Levander, J.E. Oldfield, Eds.), Van Nostrand Reinhold Company, New York, 1986, pp. 911-923.
9. Li Chong-Zheng: Sodium Selenite as a Preventive Measure for Kashin-Beck Disease as Evaluated in X-Ray Studies. In: Selenium in Biology and medicine (G.F. Combs Jr., J.E. Spallholz, O.A. Levander, J.E. Oldfield, Eds.), Van Nostrand Reinhold Company, New York, 1986, pp. 934-937.
10. Lian Shu-Tang: Effects of Selenium Supplementation in Prevention and Treatment of Kashin-Beck Disease. In: Selenium in Biology and medicine (G.F. Combs Jr., J.E. Spallholz, O.A. Levander, J.E. Oldfield, Eds.), Van Nostrand Reinhold Company, New York, 1986, pp. 938-946.
11. Liang Shu-Tang: The prophylactic and curative effect of Selenium in combatting Kashin-Beck disease. Proc. IPCS/WPRO Meet, on Kashin-Beck disease, Beijing 1985.
12. Liu Guang-Lin: Investigation of the Protective Effect of the Trace element Selenium on the Chondrocyte. In: Selenium in Biology and medicine (G.F. Combs Jr., J.E. Spallholz, O.A. Levander, J.E. Oldfield, Eds.), Van Nostrand Reinhold Company, New York, 1986, pp. 393-400.
13. Lockitch G: Selenium: Clinical significance and analytical aspects. Crit. Rev. Clin. Lab. Sci., 1989, **27**, pp. 483-541.
14. MO, DX: Pathology of Selenium Deficiency in Kashin-Beck Disease. In: Selenium in Biology and medicine (G.F. Combs Jr., J.E. Spallholz, O.A. Levander, J.E. Oldfield, Eds.), Van Nostrand Reinhold Company, New York, 1986, pp. 924-933.
15. Nesterov I: The clinical course of Kashin-Beck disease. Arthritis Rheum, 1964. **7**, pp. 29-40.
16. Oldfield JE: Contribution of animals to Nutrition Research with Selenium. In: Selenium in Biology and medicine (G.F. Combs Jr., J.E. Spallholz, O.A. Levander, J.E. Oldfield, Eds.), Van Nostrand Reinhold Company, New York, 1986, pp. 33-46.
17. Selenium. In: Present Knowledge in Nutrition, Sixth Edition. International Live sciences Institute, Nutrition Foundation, 1990 (Chapter 30).
18. Shusheng Zhai, Kimborough R, Bo Meng: Kashin-Beck disease: a cross sectional study in seven villages in the People's Republic of China. J. Tox. Env. Health, 1990, **30**, pp. 239-259.
19. Sokoloff L: Kashin-Beck: Historical and Pathological Perspectives. AIN Symposium Proceedings, 1987. American Institute of Nutrition Annual Meeting, Washington DC, 1987, pp. 61-63.
20. Sokoloff L: Kashin-Beck Disease: Current Status. Nutrition Reviews, 1988, **46**, pp. 113-119.
21. Tan Jian-An: Selenium ecological chemiogeography and endemic Keshan disease and Kashin-Beck disease in China. In: Selenium in Biology and medicine (G.F. Combs Jr., J.E. Spallholz, O.A. Levander, J.E. Oldfield, Eds.), Van Nostrand Reinhold Company, New York, 1986, pp. 859-876.
22. Wang kui: Free radicals induced abnormal chondrocytes, matrix and mineralization. Chinese Med. J., 1991, **104**, pp. 307-312.
23. Wei X, Wright G, Sokoloff L: The effect of sodium selenite on chondrocytes in monolayer culture. Arthritis Rheum., 1986, **29**, pp. 660-664.
24. Wen Zhi-Mei: Effect of long term Selenium supplementation on the incidence of Keshan Disease. In: Selenium in Biology and medicine (G.F. Combs Jr., J.E. Spallholz, O.A. Levander, J.E. Oldfield, Eds.), Van Nostrand Reinhold Company, New York, 1986, pp. 902-904.
25. Wen Zhi-Mei: Effect of long term Selenium supplementation on the incidence of Keshan Disease: In: Selenium in Biology and medicine (G.F. Combs Jr., J.E. Spallholz, O.A. Levander, J.E. Oldfield, Eds.), Van Nostrand Reinhold Company, New York, 1986, pp. 902-904.
26. Xia, Hill K & Burk R: Biochemical studies of a selenium-deficient population in China: measurement of selenium, glutathione peroxidase and other oxidant defence indices in blood. J. Nutr., 1989, **119**, pp. 1318-1326.
27. Yang Guang-Qi: Research on Selenium-Related Problems in Human Health in China. In: Selenium in Biology and medicine (G.F. Combs Jr., J.E. Spallholz, O.A. Levander, J.E. Oldfield, Eds.), Van Nostrand Reinhold Company, New York, 1986, pp. 9-32.
28. Yang G, Ge K, Chen J: Selenium-related endemic diseases and the daily selenium requirement of humans, World Rev. Nutr. Diet., 1988, **55**, p. 58.
29. Yin Pei-Pu: The concept of Kashin-Beck disease, AIN Symposium Proceedings, 1987. American Institute of Nutrition Annual Meeting, Washington DC, 1987, pp. 64-66.
30. Yin P: A comparative study of comprehensive method and Se-fortifief wheat for the prevention and therapy of Kashin-Beck disease. IPCS/WPRO Meet. on Kashin-Beck disease, Beijing, 1985.