Selenium and Its Related Disorders in China

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ABSTRACT

A selenium (Se) deficiency zone was identified in China. The Se content of the top soil in this zone was 0.08-1.12 ppm, while outside this zone was 0.18-0.32 ppm.

Keshan disease (KD), an endemic cardiomyopathy was reported from 309 counties located in the Se poor zone. Se contents of staple cereals were 0.005 to 0.018 ppm in the endemic areas, but were 0.024-0.087 ppm in non-endemic areas. The blood Se level and the GSH-px activities of endemic population were lower than that of the non-endemic populations. Oral supplementation of sodium selenite 1-2 mg/week reduced the prevalence of KD in heavily affected areas.

Kaschin-Beck diseases (KBD), an endemic osteoarthropathy characterized by degeneration and necrosis of the epiphyseal cartilage, was also found in the Se poor zone in China. Epidemiological and clinical studies indicated close correlation between Se deficiency and prevalence of KBD.

Selenosis was observed in limited district in central China. Clinical signs of chronic Se intoxication were seen in inhabitants with an average intake of 1338 ug Se per day. The Se contents in blood, hair, nails and urine were well in association with their Se intakes.

The distribution of selenium (Se) varies widely in soils in China. The epidemiological characteristics of Se deficiency and excess have been extensively investigated in connection with relevant disorders of humans namely Keshan disease, Kaschin-Beck disease and endemic intoxication.

Selenium Distribution

Five categories of ecological landscapes of Se i.e. deficient, marginal, morderate, high and excessive were proposed based on geochemical and epidemiological studies [1, 2]. These landscapes were categorized by the total and watesoluable Se contents in the topsoil, the Se contents in food grains and in human body. The threshold values for these categories are given in Table 1.

The Se-deficient and marginal landscapes illustrated a broad belt zone running from northeast to southwest of China. Separated by the Se-poor belt zone, there are two relatively Se-rich zones, the north-

Table 1. Threshold Value(ppm) for Dividing Se Ecological Landscape

Category	Total Se in topsoil	Water-soluble Se in topsoil	Se in Food grains	Se in Hair (children)
Deficient	< 0.125	< 0.003	< 0.025	< 0.200
Marginal	0.125-0.175	0.003-0.006	0.025-0.040	0.200-0.250
Moderate	0.175-0.400	0.006-0.008	0.040-0.070	0.250-0.500
High	0.400 +	0.008 +	0.070 +	0.500 +
Excessive	>= 3.0	>= 0.02	>= 1.0	>= 3.0

west zone and the southeast zone. Both Keshan Disease (KD) and Kaschin-Beck Disease (KBD) have been recorded exclusively in the Se-poor belt, therefore, it is referred as "endemic zone". The other two zones where are free from these diseases are referred as "non-endemic" zones. The Se contents of staple cereals were significantly lower in the endemic zone than that in the non-endemic zones [2]. Also, the Se content of some non-staple cereals, pulses and tubers showed the same tendency between this different zones [2, 3].

Keshan Disease and Se Deficiency

KD is an endemic cardiomyopathy observed in the Se-deficient zone. Its outstanding clinical features are the acute or chronic episodes of heart disorder characterized by cardiogenic shock and/or congestive heart failure. It can be clinically classified as four types: acute, subacute, chronic and latent. Dilatation of the heart was commonly seen. The main pathological changes are multi focal myocardio necrosis and fibrous replacement.

KD attacks mainly women of child-bearing age and children below 10 years old with very high death rate. The severe outbreak resembled a plague in Keshan county, Northeast China, in 1935, and subsequently attracted great attention in China.

Selenium deficiency and its related disorders in animals were reported in 1960s. Since then, particularly when Se was identified as a component of GSHPx in mammal animal tissues [4], it had been believed that Se deficiency should be existing but hard to identify in humans because signs of deficiency are unknown [5].

White-muscle disease (WMD) a known Se deficiency disorder in young livestock was often observed in KD endemic areas. Some epidemiological and clinical similarities between KD and WMD led the clinicians in endemic areas to use sodium selenite combined with vitamin E for the prevention of KD in early 60s [6]. Some encouraging results were recorded but no conclusion could be drawn due to the limited number of subjects investigated.

In 1973 when the Se concentration of hair, blood and dietary Se intake were reported in the first national symposium on the etiology of KD in China, the extremely poor Se status of the inhabitants in KD endemic area became evident [7].

The Se status of endemic inhabitants indicated by Se contents of blood, hair and other tissues, and by the activities of blood GSHPx was so poor that was hardly seen in any other part in the world [8]. The average blood Se level of population in various endemic areas was no more than 0.02 ug/ml. The average hair Se contents were lower than 0.123 μg/g in endemic areas, but higher than 0.2 μg/g in the northwest and southeast non-endemic zones [8]. The Se contents in muscle and other organs of KD patient were extremely low (Table 2). It was also evident that the urine excretion rate of Se after a loading dose was lower significantly in the endemic populations [9].

During 1974-1977, sodium selenite tablets were given to children in randomly selected production teams, and placebo in other teams for control. Along with the increase of blood-Se concentration, the numbers of acute and subacute cases reported in the Se treated group were 17 in contrast to 106 cases in the control group. The eventual death in four years was only one Se-treated subject but 53 controls (Table 3). Data collected in the subsequent years in five counties further affirm the role of Se in prevention of KD. The differences between control and treated groups were significant in each year (Table 4) [10].

Table 2. Selenium Concentration of Human Tissues of KD Patients or Other Patients (μg/g fresh tissue)

	Skeleton muscle	Heart	Liver	Kindney
Fresh cases of KD	0.040[2] (0.039 − 0.041)	0.077[9] (0.026 − 0.129)	0.094[4] (0.047 − 0.149)	0.254[4] (0.184 − 0.388)
Patients from hospital in an endemic area	0.074[4] (0.043 − 0.105)	0.067[5] (0.026 − 0.141)	0.075[5] (0.043 − 0.120)	0.173[5] (0.045 − 0.405)
Patients from hospital in a non-endemic area	−	0.976[3] (0.914 − 1.060)	1.202[3] (1.108 − 1.326)	2.211[3] (2.002 − 3.085)

From Zhou and Yang [1986, unpubl.]
Numbers in brachets are the number of samples.
Numbers in parentheses indicate the range.

Table 3. Se Treatment and Incidence/Prognosis of KD in Children in Mianning County

	Year	No. of Subject	Cases Alive			Turned Chronic	Eventual Deaths
			No. of Cases	Turned Insidiom	Improved		
Control	1974	3985	54	16	9	2	27
	1975	5445	52	13	10	3	26
Treated	1974	4510	10	9	0	1	0
	1975	6767	7	6	0	0	1

Table 4. KD Incidence in Se-treated and Untreated Children in Five Counties During 1976-1980

Year	Treated children			Untreated children		
	No. of Subjects	No. of KD Cases	Incidence (per 1000)	No. of Subjects	No.of KD Cases	Incidence (per 1000)
1976	45,515	8	0.17[a]	243,649	488	2.00[a]
1977	67,754	15	0.22[b]	222,944	350	1.57[b]
1978	65,953	10	0.15[c]	220,599	373	1.69[c]
1979	69,910	33	0.47[d]	223,280	300	1.34[d]
1980	74,740	22	0.29[e]	197,096	202	1.07[e]
Total	323,872	88	0.27[f]	1,107,568	1,713	1.55[f]

[abcde]: ($p < 0.01$; [f]: ($p < 0.00001$).

Epidemiological Characteristics of KD and Se Deficiency

KD endemic areas are all located in the Se-poor belt. Selenium concentration of hair samples collected from 128 KD affected and non-affected counties over the country was ranked in order [1]. No single affected county was found where the hair Se level was fallen outside the range of that of the Se-poor zone.

North part of Shanxi province is mixed up with KD affected and non-affected areas. Corn and human hair were sampled from 25 sites in 16 counties. The average Se contents of corn were 0.019 ± 0.0046 μg/g in non-endemic sites and 0.006 ± 0.001 in endemic foci. The difference between the two groups was highly significant. The hair Se contents were all below 0.11 ug/g, averaged 0.073 ± 0.005 ug/g in 11 sites where KD had been reported [11].

Keshan disease was prevalent in rural population and mostly in peasants. There were few cases reported from staff's or worker's households even residing in the same endemic districts [12]. The non-peasant families obtained their food from the market, thus less affected by the local water/soil conditions, and their diet was relatively manifold as well. The Se nutrition status of children in staff's or worker's families was better than that in peasant's families. The hair-Se level of peasant-children ranged from 0.058 to 0.151 ug/g, significantly lower than that from 0.131 to 0.295 ug/g of non-peasant-children. The difference was further illustrated by blood GSHPx activities [13].

A comparison study indicated that Se status coincide with the severity of KD. Hair samples of inhabitants residing in heavily prevalent sites and their nearby mildly prevalent sites were collected from both north and south part of China. The result (Table 5) showed that the severity of KD in population was in line with the extent of their Se deficiency. Coordinately, the Se content of cereals was lower as well in the KD heavily prevalent sites [14].

In association with the improvement of farmers' diet and increase of Se intake, the incidence of acute and subacute KD has been declining dramatically in the last decade. For example, Huanglong county and Luochuan county, Shaanxi province [15] are two heavily affected sites. The hair Se contents in these two

Table 5. Hair Se Content of Residents in Neighboring Districts with Different Severity of KD Incidence

Mildly Affected Sites	Hair Se(ppm)	Nearby Heavily Affected sites	Hair Se(ppm)
Gaojian Commune Xichang, Sichuan (1973)	0.112 ± 0.006	Hebian Commune Mianing, Sichuan (1973)	0.071 ± 0.003
Gaojian Commune Xichang, Sichuan (1974)	0.106 ± 0.007	Xianfung Commune Mianing, Sichuan (1974)	0.088 ± 0.006
Dungfung Commune Chuxiung, Yunnan (1974)	0.096 ± 0.007	Shaqiao Commune Nanhua, Yunnan (1974)	0.068 ± 0.004
Tanjiaying Commune Ansai, Shaanxi (1974)	0.113 ± 0.006	Xiho Commune Ansai, Shaanxi (1974)	0.080 ± 0.004
Woniuho Commune Puteha, Heilongjiang(1974)	0.106 ± 0.007	Zilaojing Commune Arunqqi, Heilongjiang(1974)	0.047 ± 0.004

Mean ± SEM

counties increased obviously from 0.081-0.095 μg/g in 1976 to 0.161-0.218 μg/g in 1985. Meanwhile, the chronic cases observed in 1981, 1983 and 1985 were 25, 19 and 11 per thousand population in Huanglong, and 12, 6 and zero per thousand in Luochuan respectively. There were no acute cases reported in these years.

Other possible pathogenic factors of KD

It is clear that the prevalence of KD is closely related to Se deficiency. Some epidemiological characteristics, however, can not be explained by Se deficiency alone. Many other factors including some biological factors may be also involved in the pathogenesis of KD. Injection of Coxsackie B4 virus induced heavy myocardial lesions in Se deficient mice. Increasing Se intake of the animals decreased the heart damage [16]. Insufficiency of dietary vitamin E [17, 18], and sulfur amino acids [19, 20] may play some role as well. Inadequate amount of Zn or Mo, excessive amount of Mn, Ba or Pb were also proposed. Mycotoxin, other organic toxins and compounds also have been studied. Recent studies suggested that the widespread myocardionecrosis is probably resulted from the damage to the bio-membrane [21, 22], and the damage to the intracellular macromolecule substances in the myocardiocytes [23].

Kaschin-Beck Disease and Se Deficiency

KBD is an endemic osteoarthropathy recorded in 303 counties in 15 provinces and autonomous re-

gions in China [24]. It was distributed predominantly in hilly and mountainous areas in the Se-poor zone. The total number of patients was over two million, and the incidence rate may as high as 30-40% in heavily affected sites [25]. Clinically, weakness is followed by joint stiffness and pain. The major pathological changes are the degeneration and necrosis of the joint and epiphyseal plate cartilage of the four limbs. Enlargement of joints and deformity of limbs and the typical signs of the advanced cases [26].

Epidemiology of KBD and Se Deficiency

Many hypotheses have been suggested, such as calcium deficiency, sulfur deficiency, strontium (Sr) excess/Ca deficiency and bio-substance intoxication etc.[27]. However, extensive analysis of minerals and trace elements in water, soil, food grains and human hair revealed that the prevalence of KBD was most closely related to the low-Se environment [28-31].

The distribution of KBD coincided with that of KD in the low-Se environment [24], and no KBD has been reported from the relatively Se-rich zones. The incidence rate in children diagnosed by X-ray examination in Yongshou county, Shaanxi province was negatively correlated with the Se content in soil, water cereals and human hair (Table 6) [24].

The average hair Se levels of the endemic and non-endemic residents were 0.094 ± 0.03 ppm and 0.380 ± 0.179 ppm [8]. The blood GSHPx activities measured in Henan province, were 74.0 ± 12.8 units of the endemic and 95.6 ± 8.9 of the non-endemic group. The difference between the two groups was highly signigicant ($P < 0.001$). Oral supplementation of sodium selenite 1-2 mg per week for two months elevated the enzyme activity of the endemic group to the level of the non-endemic group [31].

Comparative study on the Se concentration of food grain and human samples showed a regular variation among KBD affected sites, non-affected sites within the endemic zone and the non-endemic zones (Table 7) [32].

The preventive and therapeutic effect of Se on KBD

Oral supplementation of Se for prevention and treatment of KBD has been trialed in verious endemic areas. As observed in Yingchi county, Henan province, the X-ray diagnosed incidence rate in children of

Table 6. The Correlation Coefficient Between KBD incidence and Se Status in Yongshou County

	Total Se in Soil	Water-soluble Se in Soil	Se in Drinking Water	Se in Corn	Se in Wheat	Se in Hair
Incidence Rate +	− 0.266**	− 0.388**	− 0.187*	− 0.336**	− 0.563**	− 0.487**

diagnosis by X-ray examination

* $P < 0.05$

** $P < 0.01$

3-10 years old reduced significantly from 39.6%, to 10.7% in 3 years in the Se treated group (sodium selenite 1 mg per week), but showed little change (from 42.1% to 38.6%) in the control group [33].

KBD children of 3 to 13 years old were treated with sodium selenite 1-2 mg/week in Yongshou county, Shaanxi province. The therapeutic effect became evident in 6 months and progressed continuously in the following months (Table 8). The hair Se concentration increased accordingly from 0.041 to 0.293 ppm in the treated group, while it remained unchange in the controls [34].

The prevalence of KBD has been decreasing steadily in the last decades. In Hulin county, Heilongjiang Province, for example, the morbidities were 43.6, 23.2, 13.6 and 1.1 percent respectively in the year 1970, 1975, 1980 and 1986 [35]. Presumably, this is associated with the overall improvement of diet including more Se intake of the rural population in China.

There are plenty of evidences indicating a multi-factoral causes of KBD. In addition to Se deficiency, mycotoxin, environmental inorganic and organic substances were also proposed as causal factors. More reseaches are needed to explore the roles played by these factors.

Endemic Se intoxication

During the years of 1961-1964, an outbreak of hair and nail loss of the inhabitants was discovered in

Table 7. Se Content of Staple Food and Se status of Adolescent

	Corn Se*	Wheat Se*	Hair Se*	Blood Se*	GSH-Px**
KBD Affected Area	5 ± 2(6)	13 ± 3(5)	33 ± 14(73)	17 ± 2(14)	73 ± 12.5(10)
Non-affected sites in the Affected Zone	19 ± 5(4)	24 ± 4(3)	156 ± 20(20)	25 ± 3(20)	74.9 ± 9.3(19)
Non Affected Zone	46 ± 17(7)	80 ± 16(6)	363 ± 15(21)	65 ± 4(10)	95.7 ± 8.7(20)

* Mean ± SD (ppb)

**activity units

Table 8. The Relationship Between the Duration of Se-treatment and the Curative Effect

	3 Months	6 Months	9 Months	12 Month
Cases of Inprovement(%)				
Se-treated group	27.9	68.3	79.8	81.9
control group	18.7	41.4	40.3	39.6
Cases of deterioration(%)				
Se-treated group	4.4	3.4	0.6	0.0
control group	6.6	18.3	18.2	18.9

Enshi County, Hubei Province, central China. The average incidence was about 50% in five heavily affected villages, and the extreme one reached 82.5%. Livestock poisoning and plant injury were also observed in the affected villages [36].

Endemic Se toxicity of humans with loss of hair and nail had already been reported by Rosenfeld et al in 1936 [36], and more studies conducted in South Dekota and Venezuela, however, failed to reveal any public health problems that can be linked to Se over exposure [38, 39, 40, 41].

The most common symptoms of chronic selenosis in Enshi county were loss of hair and deformation of the fingernails, and the skin, the nervous and digestive systems may also be affected in severe cases. Patients recovered gradually after being transferred to nearby unaffected places as their high Se diets were changed [42].

Unusually high Se levels were found in food, hair, blood, and urine of inhabitants in the chronic selenosis areas in Enshi, even after the peak prevalence had subsided (Table 9, 10). As shown in Table 9, blood and hair Se concentrations of residents in chronic selenosis areas were tens and hundreds times more than in Se-adequate and Keshan disease areas respectively. The average daily Se intake in the chronic selenosis area was 4.99 mg, which was about 40 and 450 times more than that in the Se-adequate and Keshan disease areas (Table 11). Stony coal was proved to be the source of Se, of which the highest content was 84 mg/g. Weathering process released the Se from the coal to the soil, where it can be absorbed by plants and came into the food chain. There is a positive correlation between total and water soluble Se in the soil ($r = 0.985$, $p < 0.01$), and the Se contents of cereals and soybean are significantly related to the water soluble Se level of the soil ($r = 0.830$, $p < 0.01$).

The outbreak of Se intoxication in Enshi county was owing to a severe drought. Rice was short in sup-

Table 9. Selenium levels of hair, blood, and urine of residents living in high-, adequate- and low-selenium areas*

Place	Hair		Blood		Urine	
	n	Se content μg/g	n	Se content μg/g	n	Se content μg/g
High selenium area of chronic selenosis	65	32.2 (4.1 − 100)	72	3.2 (1.3 − 7.5)	17	2.68 (0.88 − 6.63)
High selenium area without selenosis	14	3.7 (1.9 − 8.2)	14	0.44 (0.35 − 0.58)	14	0.14 (0.04 − 0.33)
Selenium adequate areq	1745	0.36 ± 0.17	111	0.095 ± 0.091	19	0.14 ± 0.012
Low selenium area	40	0.16 ± 0.04	40	0.027 ± 0.009		
Low selenium area with Keshan disease	1478	0.074 ± 0.050	173	0.021 ± 0.010	43	0.007 ± 0.001

* Mean ± SD or range shown in parentheses.

Table 10. Selenium contents of cereals and soybean grown on soils in areas with excess, adequate, and deficient selenium*

Place	Corn		Rice		Soybean	
	n	Se content μg/g	n	Se content μg/g	n	Se content μg/g
High selenium area of chronic selenosis	44	8.1 (0.5 − 28.5)	22	4.0 (0.3 − 20.2)	17	11.9 (5.0 − 22.2)
High selenium area without selenosis	2	0.57	2	0.97	2	0.34
Selenium adequate area	82	0.036 ± 0.056	76	0.035 ± 0.027	31	0.069 ± 0.076
Low selenium area	10	0.009 ± 0.005	32	0.022 ± 0.009		
Low selenium area with Keshan disease	195	0.005 ± 0.003	49	0.007 ± 0.003	150	0.010 ± 0.008

* Mean ± SD or range shown in parentheses.

Table 11. Daily selenium intake of residents living in high-, adeguate-, and low-selenium areas

Place	n	Daily selsmium intake Min. (mg)	Max. (mg)	Aver. (mg)	Se intake from staple cereals as % of total daily intake
High Selenium area of chronic selenosis	6	3.20	6.69	4.99	28 − 70
High Selenium area without selenosis	3	0.24	1.51	0.75	25 − 45
Selenium adequate area (Beijing)	8	0.042	0.232	0.116	Various sources
Low selenium area with Keshan disease	13	0.003	0.022	0.011	Mainly from cereals

ply at that time, and people consumed more corn and vegetables which containing much more Se In addition, in an attempt to increase crop yield during those years, peasants used to apply large amount of lime and plant ash as fertilizer, which promoted the absorption and accumulation of Se by plants.

The exact magnitude of seleniferous areas in china is unkown. In 1980, another seleniferous area not far from Enshi was discovered in Ziyang county, Shanxi Province. Coal seems to be the source of the excessive Se. The distribution of the isolated seleniferous foci likely follows the location of the coal bed in this region.

In the period of 1986-1988, a more comprehensive survey was conducted again in Enshi, and the influence of Se intake on tissue Se levels was studied in detail. Sighificant correlations were observed be-

tween daily intake and the Se in blood, milk and urine. Highly significant correlations were also seen between the Se level of various organs. A relation between the chinical signs of chronical selenosis and Se level in blood and Se-intake was obtained [43, 44].

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