Review

An original discovery: selenium deficiency and Keshan disease (an endemic heart disease)

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This is a review article telling a 50-years old story about the studies on selenium deficiency and Keshan disease in China, an endemic heart disease with high case-fatality, as an example of translational research. Extensive cross-sectional epidemiological studies showed that low selenium concentrations in cereal grains and low selenium status of local residents were associated with the occurrence of Keshan disease. Several large population-based intervention trials using oral administration of sodium selenite tablets showed significant reduction of Keshan disease incidence. Based on the above evidence, it was concluded that selenium deficiency is the major cause of Keshan disease, although other etiological factors could not be ruled out. The implications of the findings include: provided critical scientific evidence for selenium being an essential trace element for humans; as scientific basis for identifying minimum requirement and RDA/RNI for selenium; and as solid reference for the formulation of effective preventive measures for Keshan disease in China.

Key Words: selenium, Keshan disease, translational research, essential trace element

INTRODUCTION

In the present scientific community, the term "translational science" has become more and more popular in any expertise and field. Although it is widely agreed that research outcomes would be much more valuable, if they could be translated into practical means that could benefit the society; in the real world, convincing cases and stories are rare. This overview article aims to tell an old story about selenium deficiency and Keshan disease research conducted in 1960-70 in China, as an example of translational nutritional research based on my personal experience.

A BRIEF DESCRIPTION ON KESHAN DISEASE (KD)[1]

Keshan disease was discovered in the winter of 1935 in northeast China when an outbreak of an unknown disease occurred with sudden onset of precardial oppression and pain, nausea and vomiting and fatal termination. The disease was named Keshan disease (KD), because the outbreak was first occurred in the Keshan county of Heilongjiang province and its cause was unknown. Later on, KD was discovered in other areas of northeast and also southwest China, including Sichuan and Yunnan provinces. It had a very high case fatality, which was greater than 80% in the 1940s and around 30% since. It was at first suspected to be an acute infectious disease, and in 1936 was shown to be a myocardial disease with necrotic lesions of unknown nature. The vulnerable subpopulations were 2-7 year-old children and women of child-bearing age. The disease almost disappeared since 1990.

Clinically, KD showed acute or chronic episode of a heart disease characterized by cardiogenic shock (Figure 1), enlarged heart (Figure 2), congestive heart failure (Figure 3), cardiac arrhythmias and ECG changes. Based on the course and features of KD, it could be divided into 4 types, ie, acute, chronic, subacute and insidious. During autopsy, moderate enlargement with dilation of all heart chambers was found in most cases. Histopathologically, multifocal necrosis and fibrous replacement of myocardium are scattered throughout the heart muscle (Figure 4).

Epidemiology studies revealed that the occurrence of KD was endemic (limited to certain geographical areas), with obvious seasonal variations (peak season: winter in northeast China and spring in southwest China) and yearly variations, and quite interestingly, in the same endemic area, farmer families were affected, but the factory workers and other professional families were not affected.

The etiology was basically unknown, though several hypotheses have been suggested, including infection (virus), intoxication (environmental toxicants, mycotoxins) and nutrition deficiency (monotonous diet cased minerals and vitamins deficiency, eg, Mo, Mg, thiamin). Among them, the selenium deficiency hypothesis was considered as the most convincing one.

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Manuscript received 21 February 2012.Accepted 22 February 2012.

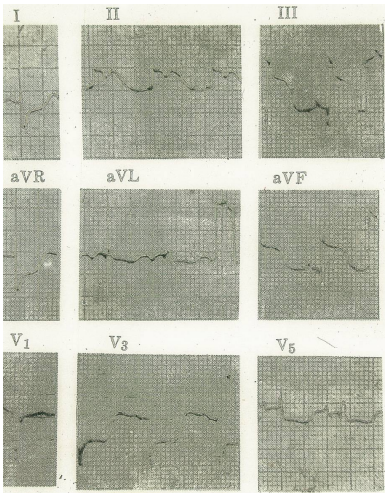

Figure 1. ECG changes of an acute case of Keshan disease patient

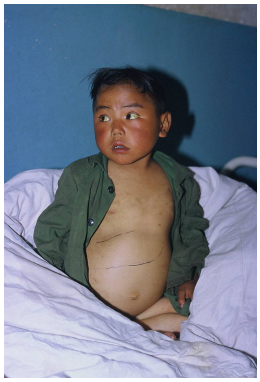

Figure 2. Heart failure of a chronic Kehsan disease patient, showing enlarged liver and ascites

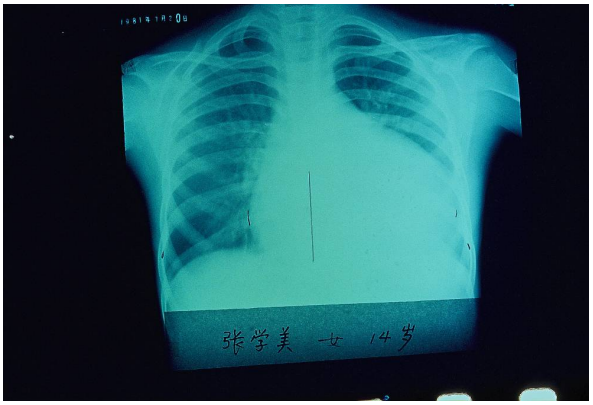

Figure 3. X ray of a chronic Kehsan disease patient showing enlarged heart

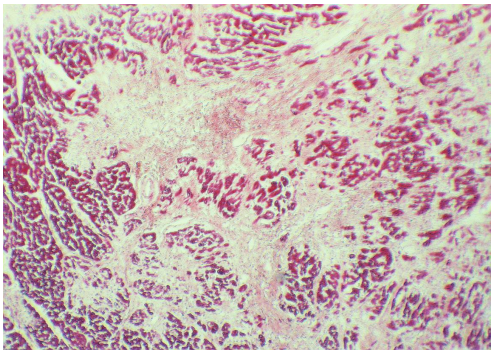

Figure 4. Histopathological changes in heart tissue of a Kehsan disease patient - necrotic and fibrous foci

SELENIUM DEFICIENCY IS THE MAJOR CAUSE OF KESHAN DISEASE

Extensive observational epidemiological studies and population-based intervention trials were conducted in northeast and southwest endemic areas in China from 1960-80s with the Keshan Disease Research Group of the Chinese Academy of Medical Sciences as the leading research force. The causal relationship between selenium (Se) deficiency and Keshan disease was established based on the following research evidence.

Low selenium levels of local foods and low selenium status of local residents were significantly associated with the geographical distribution of KD

Similarities in geographical distribution of KD and Se deficiency

Keshan disease occurred essentially in hilly and mountainous areas with specific focal distribution in a wide belt-like region throughout mainland China, from northeast to southwest (Figure 5), and the low Se area (based on soil Se content) is also located in the same belt region.[2]

Low Se levels of local staple foods in KD endemic, as compared with non-endemic areas

Figures 6 and 7 show that the Se concentrations of maize and rice from the endemic sites were significantly (p<0.01) lower than those from non-endemic sites, with a cut-off point at 0.01 mg/kg of Se for most sites.[1]

Low Se status of local residents in endemic areas, as compared with non-endemic areas

Figures 8 and 9 show that Se concentrations of whole blood and hair collected from residents in endemic sites were significantly (p<0.01) lower than those in non-endemic sites, with a cut-off point at 0.02 mg/L.[1] For further evaluation of Se status in KD patients and healthy local children, whole blood glutathione peroxidase (GSHpx) activities were measured and results[1] (Table 1) show that the GSHpx activities of children in the endemic sites were significantly (p<0.001) lower than those in the non-endemic sites. The GSHpx activity levels of KD patients were a little lower than the healthy children from the same endemic site, but the difference was not significant. After oral administration of sodium selenite as preventive measures, the GSHpx activity levels of healthy

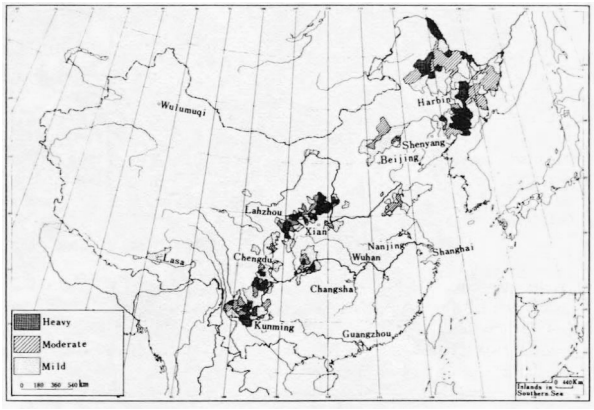

Figure 5. Geographical distribution of Keshan Disease in China

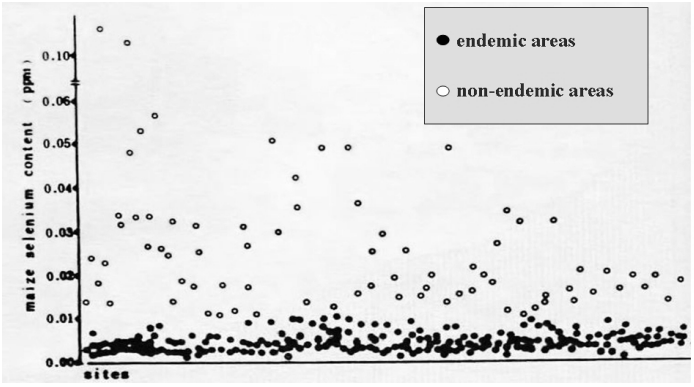

Figure 6. Average selenium level of maize in Keshan disease endemic and non-endemic sites

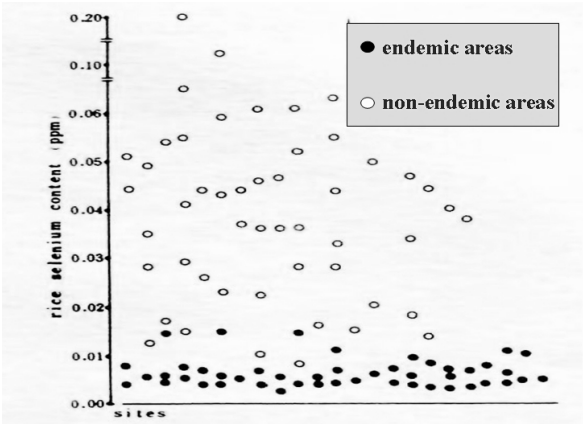

Figure 7. Average selenium level of rice in Keshan disease endemic and non-endemic sites

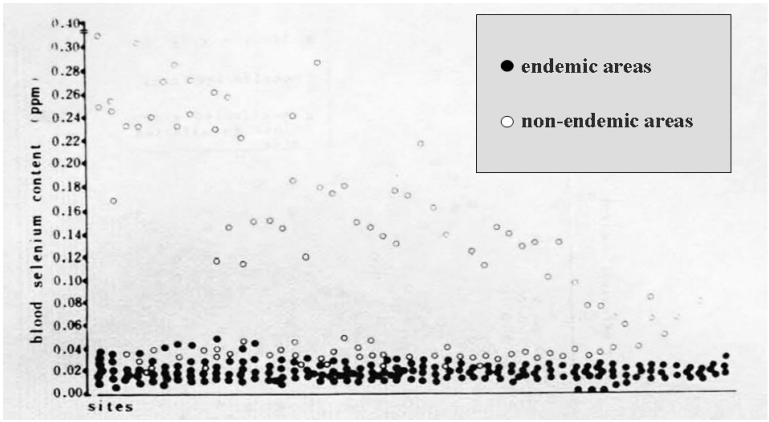

Figure 8. Average blood selenium levels of local residents in Keshan disease endemic and non-endemic sites

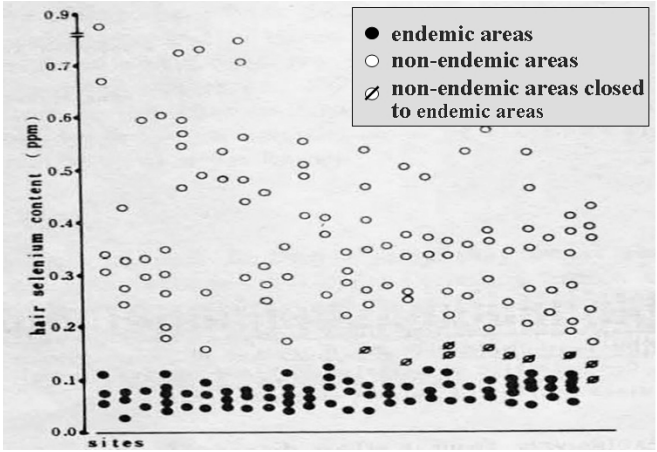

Figure 9. Average hair Selenium levels of local residents in Keshan Disease endemic and non-endemic sites

Table 1. Blood glutathione peroxidase (Se-GSHpx) activities and selenium status of children from Keshan disease endemic and non-endemic sites

Sites	SeGSHpx activity †	Blood Se (mg/kg)	Hair Se (mg/kg)
Non-endemic	73.6±3.1 ‡,¶ (20)	0.065 ¶ (11)	0.237 ¶ (18)
Endemic, healthy children	60.5±0.7 ¶,††,‡‡ (63)	0.023 ¶,††,‡‡ (16)	0.058 ¶,††,‡‡ (22)
Endemic, KD patients	57.1±1.3 †† (22)	0.020 †† (8)	- §
Endemic, healthy children treated with Na2SeO[3]	76.1±1.1 ‡‡ (58)	0.050 ‡‡ (15)	0.233 ‡‡ (21)

† Oxidation of GSH determined with 5,5'-dithio-bis (2-nitro-benzoic acid) after incubation for 5 minutes with 8 µl of whole blood. The nonenxymatic oxidation has been subtracted;
‡ Mean; sample number is indicated in parentheses;
§ Not determined;
¶,†† Means with same superscripts are significantly different (p<0.001);
‡‡ Means with same superscript are not significantly different (p>0.05).

Table 2. Hair selenium levels (mg/kg) of children from farming and non-farming families in the same endemic area

Province	Non-farming families	Farming families
Heilongjiang, Site 1	0.295±0.23 ‡ (11) †	0.151±0.11 ‡ (20)
Heilongjiang, Site 2	0.357±0.021 § (22)	0.146±0.013 § (21)
Shandong	0.238±0.011 ¶ (7)	0.128±0.009 ¶ (14)
Sichuan	0.161±0.007 †† (16)	0.058±0.003 †† (22)

† Numbers in parentheses are the number of samples analyzed; ‡, §, ¶, ††Means with same superscripts are significantly different (p<0.01).

Table 3. Effects of sodium selenite in the prevention of Keshan disease in children

Groups	Year	N	New KD cases	Death cases
Control	1974	3,985	54	27
	1975	5,445	52	26
Intervened	1974	4,510	10*	0*
	1975	6,767	7*	1*

* p<0.01, intervened vs. control in both 1974 and 1975.

children in the endemic sites increased to levels comparable to those of children in the non-endemic sites. Significant correlations were found between Se levels of blood and hair and GSHpx activity levels (r=0.57 and 0.64, respectively).[1]

Hair Se levels of children from farming families, as compared with children from non-farming families in the same endemic area

As indicated earlier, one of the epidemiological characteristics of KD is its prevalence among children of farming families, but not of non-farming families (eg, factory worker, other professionals) in the same endemic area. Results in (Table 2) show that in all four study areas the vulnerable sub-population had lower hair Se levels than the children from non-farming families.[1] The possible interpretation was that non-farming families had access to more sources and varieties of food, in particular animal foods.

The above results showed a clear relationship between Se deficiency and KD. Although these are based on cross-sectional studies and the results could not be used as evidence for a causal relationship, considering the large amount of data from both food and human samples and in particular the characteristics of relying on local foods by the study subjects in that period, the chance of mere coincidence is small. At least, the results gave a strong clue that Se deficiency is very likely to be one of the major etiological factors for KD.

Oral administration of selenite significantly reduced the incidence of KD in a number of large population-based intervention trials[1,3]

Based on a pilot intervention trial in Heilongjiang endemic area using sodium selenite, a double-blind placebo controlled oral administration trial was conducted in children (1-9 year-old) in Mianning county, Sichuan province in 1974 and 1975 using oral administration of sodium selenite tablets (0.5 mg Se for 1-5 yr and 1.0 mg for 6-9 yr., once a week). Se tablets and placebo were delivered to the study subjects once a week by village health workers. The results (Table 3) showed significant reduction of KD (acute and subacute types) incidence in the intervention group and the results from both years are consistent.

The success of the 2-year trials established the foundation for expanded non-blind large scale intervention trials

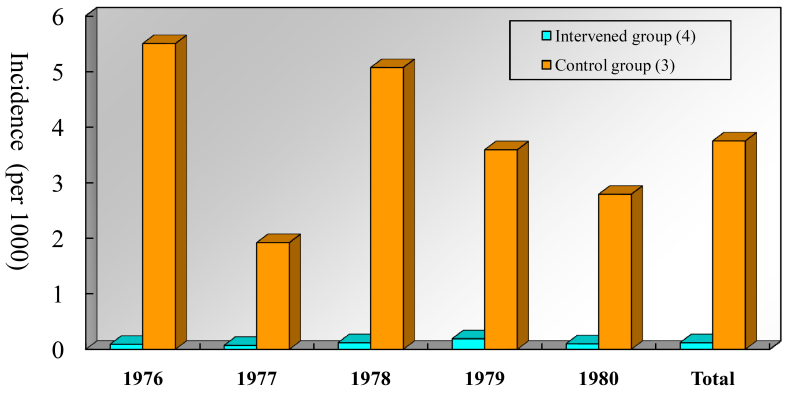

Figure 10. Keshan disease incidence in control and sodium selenite intervened communes in Mianning county (1976-1980). Numbers in parentheses are the number of communes; Intervened group consisted of approximately 41,000 subjects and control group consisted of approximately 6,000 subjects per year; intervened vs. control, $p<0.01$ in each year.

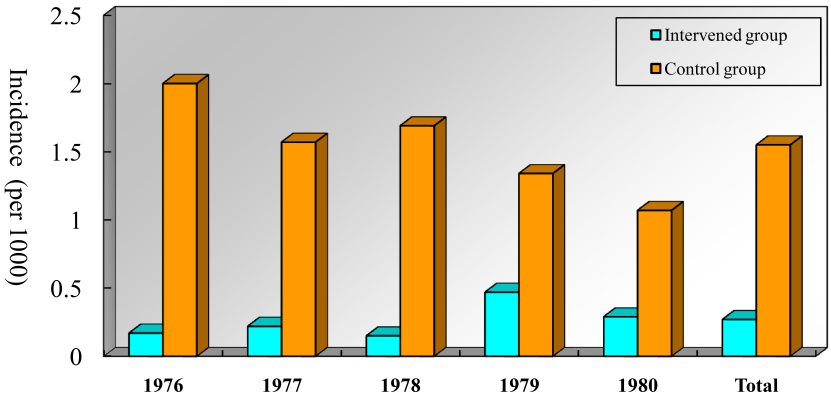

Figure 11. Keshan disease incidence in the control and sodium selenite intervened population in 5 endemic counties of Sichuan province (1976-1980)

using nearby villages, communes or counties in the area as natural controls. The same dosage scheme was used, ie, 0.5 mg Se (1-5 yr-old) or 1 mg Se (6-9 yr-old) once per week in the form of sodium selenite. Again, the Se intervened population had significantly less new cases of KD than the natural controls (Figures 10 and 11).

Conclusions and possible mechanisms

It was concluded from the above observational epidemiological study and population based intervention trial results that Se deficiency is the key etiological factor for KD. On the other hand, it is believed that Se deficiency may not be the only etiological factor, because it could not explain the seasonal and yearly variation of the KD epidemic. The role of virus infection in the KD epidemic could not be ruled out.

The possible mechanisms of Se in KD prevention are: antioxidative effects – protect membranes from lipid peroxidation; improve the transport and utilization of oxygen, hence protect myocardium from hypoxic damage; and anti-infection effects (the virus etiology).[1] However, further studies to support these hypotheses are needed.

TRANSLATION OF THE SCIENTIFIC FINDINGS

Selenium is a well recognized essential trace element for animals based on its roles in white muscle disease in sheeps,[4] liver necrosis in rats [5] and exudative diathesis in chicks.[6] However, the evidence to support Se as an essential trace element for humans was lacking, until the studies on Se deficiency and KD were published. It was the first time that Se deficiency was proven as a cause of a human disease.

The studies on Keshan disease have provided valuable data for determining the minimum Se requirement for humans and the RDA of Se. By using the relationship between the plateau of blood Gpx and the dietary Se intake of local residents as well as the Se intake of residents in the non-endemic areas of KD, the Chinese Nutrition Society set up the daily minimum requirement for Se (30 μg/day for adults) and RNI (50 μg/day for adults).[7] The same study results have been used as the scientific basis to establish RDA/RNI for Se in other countries, such as USA.[8]

The study results were used as the basis for the formation of preventive and control strategies for KD by the Ministry of Health of China, including the oral administration of sodium selenite tablets and selenized salt (sodium selenite fortified salt) in KD endemic area. No significant outbreaks of KD occurred since these preventive and control measures were implemented in the late 1970s.

CONCLUSIONS

It was a unique opportunity to study the relationship between selenium deficiency and Keshan disease. The studies were successful because the diet of rural residents in China in the 1960-1970s was monotonous and mainly comprised of cereal grains and vegetables (very little animal food) produced locally.

This story on selenium deficiency and Keshan disease provides an example that nutritional research results

could be translated into effective, feasible and sustainable nutrition improvement measures, in addition to scientific achievements. However, to achieve overall success, joint efforts amongst the government, academia, industry and media are required.

AUTHOR DISCLOSURES

There is no conflict of interest.

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Review

An original discovery: selenium deficiency and Keshan disease (an endemic heart disease)

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原始發現：硒缺乏與克山病(一種高致死率的地方性心臟病)

本文報告 50 年前中國的一項硒缺乏與克山病(一種高致死率的地方性心臟病)的研究，作爲營養學轉化研究的一個實例。大量横斷面流行病學研究表明，糧食硒含量低和人群硒營養狀況低下與克山病發病相關。數個用口服亞硒酸鈉片的大型人群干預實驗，見到克山病發病明顯下降。根據上述證據，得出硒缺乏是克山病主要病因的結論；儘管不能完全排除其他致病因素。這些研究發現有以下意義：提供了硒為人體必需微量元素的重要證據；確定硒的人體最低需要量並為 RDA/RNI 提供了科學依据；爲制定中國有效防治克山病的措施提供了堅實的參考信息。

關鍵字：硒、克山症、轉化研究、必需微量營養素