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**Review Article**

# Preventative role of Selenium in Keshan Disease: A Review

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## ABSTRACT

Mineral deficiencies have caused severe health consequences in developing countries. Among many other minerals, selenium is also an essential nutritional trace mineral element that is critical to the normal physiology of humans. Regional dietary deficiency of selenium caused Keshan and Kashin-Beck diseases (KDs). KD is endemic congestive cardiomyopathy, characterized by cardiac insufficiency, heart enlargement, arrhythmia, and electrocardiographic modifications. This disease is clinically divided into four categories: acute, subacute, chronic, and latent. However, selenium supplementations to the residents of Keshan disease endemic areas significantly reduced the incidence of KD. Thus, the government decided to apply sodium selenite to growing crops, and the incidence of the disease decreased dramatically.

## INTRODUCTION

Human health has been compromised due to inadequate intake of minerals. It has led to dreadful results specifically among developing countries. Amount of minerals in crops is directly related with minerals content present in soil and thus ultimately impacting human mineral levels within the body who incorporate such crops. Even though having such a significant impact of soil on health status, this still needs to be highlighted by nutrition experts and other community health law-givers [1]. Selenium (Se) is one of the many other essential micronutrients, which are absolutely necessary for the maintenance of adequate functioning of human bodies. For example; the incidence of KD is the best depiction of its prime significance [2]. In 1817, a Swedish chemist and physician known as Jons Jacob Berzelius first made the discovery of this element [3]. It is also required for appropriate functionality of biological systems. However, reduced selenium concentrations have been observed and linked with its lower amount in soil and edible food products as well [4]. But toxicity and essential impact of selenium among bacteria and animals has made this mineral to act as a moon with dual-face. It is also known as "essential-poison". The USDA has set fifty-five micrograms of selenium per day as recommended dietary allowances for adults. However, its toxic limit is eight hundred micrograms per day according to WHO for adults [5]. Geographical deficiency of selenium in diet is associated with several diseases. However, KDs are among the most persuasive illnesses explaining the role of selenium deficiency more evidently [6]. In 1979, preventative impact of selenium in KD and endemic congestive cardiomyopathy including the characteristic features i.e. enlarged heart, abnormal/irregular heartbeat was noted. However, Se deficiency has also been linked with long-term parenteral nutrition as well [7]. KD has prevailed for over a decade in China [8]. In 1935, KD was first recognized in

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Keshan County, China. Thus, named as KD, with four different subsequent phases including; acute, sub-acute, chronic-stage and the latent KD. Differences in DNA sequencing and mutations are also associated with KD according to the latest studies [9]. KD has been declared as endemic because of its occurrence in a particular region of China [10]. In the last ten years, many studies have been done on exploring the etiology of KD and pathogenicity is deficiency selenium [11]. In the 1940's, instantaneous occurrence of pain, nausea, vomiting, precordial oppression and end-stage disease has been observed among extreme cases of KD [12]. Regardless of the fact that KD has been explored for a long time but KD still didn't receive much recognition by scientists of western countries [13]. Dietary factors lead to many chronic illnesses raising the death rate. Similarly, protective roles of selenium protein components are significantly associated with preventing various chronic illnesses [14]. Thus, an inadequate diet with low selenium food-sources leads to the damage of heart muscles among humans and animals as well [15]. Intake of nuts, mushrooms and exogenous-cereals are the fundamental food sources [16]. Therefore, sodium-selenite was incorporated by the ruling government into growing crops which reduced the occurrence of KD abruptly. But there still are some cases of chronic or latent stage [17]. WHO considers selenium as the major leading cause of KD. Thus, selenium supplementation must be added into the monitoring process of KD [18]. This paper reviews the significance of selenium, its role in KD from a historical aspect, and the present situation.

**Selenium:** Selenium is an important trace mineral [19]. Moreover, it is the integral element of Glutathione peroxidase enzyme (GPx). GPx is an enzyme which protects from blood-clotting, oxidative damage of lipids and also from occurrence of atherosclerotic-plaque [20].

**Sources of Selenium:** Nuts, mushrooms and exogenous cereal tend to be the most important food sources of selenium [16]. Similarly, vegetables are also rich in selenium however determination of its amount is done on the basis of soil and bio-accessibility [21]. Organ meats including kidney, liver are also rich in selenium. On the other hand, sea-food, muscle meat, and grains contain significant content of selenium in them but it differs from country to country. Animal-food supplementation or plants are also good sources. However, it can be overdosed by incorporating Brazilian nuts [22]. Additionally, cigarette smoke, air-pollutants, combustible elements of coal are sources of selenium as well [23,24].

**Impact of Selenium Deficiency:** At first, selenium was known to cause selenosis due to its toxic effect among industry workers and selenium rich animal feed [25]. Whereas, diets with inadequate selenium can also create havoc in human health by compromising immunity. Thus, leading towards more vulnerability of getting infections and cancers. Modulation in pathology of chronic anti-inflammatory illnesses of gut and liver can also occur due to Selenium [26]. Similarly, as a result of selenium deficiency a sudden progression in myocardium/ heart muscle diseases was observed in the 80s [27]. Alterations in the bioprocesses and degenerative diseases of various organs and tissues resulted due to low amount of seleno-protein components. This was observed among people and animals who were living in areas with decreased selenium amount in soil. Selenium deficiency primarily impacted cardiac-muscles and joints of both humans and animals. However, its moderate reduction in diet can lead to raised risk of neurological illnesses, nephropathy, male-infertility and prostate-cancer. Furthermore, diet deficit in selenium leads to KD [28].

**Prevalence of Selenium Deficiency:** Inadequate selenium status due to diet insufficiency has been observed in Europe. Similarly, in other regions of Brazil, a decreased amount of selenium found in their agricultural items [29]. Cattles and buffaloes of more than 9 years in Pakistan also have insufficient selenium status. As a result, their health and work output is badly impacted [30].

**Keshan Disease:** Chinese governments have made significant efforts in preventing the KD epidemic. KD then additionally recognized in Finland and New Zealand, in regions with selenium-terrible soil, this being the principal predisposing thing which amplifies the virulence and cardiotoxicity of Coxsackie B virus [31]. Symptoms such as high blood pressure, coronary heart failure and pulmonary oedema, can be relieved with the aid of administering Se supplements [32]. Health situations as a result of excessive Se deficiency consist of Kashin-Beck sickness and KD. Each of these conditions occur more frequently with iodine deficiency or environmental pollution. In KD, viral contamination has been implicated [33]. Keshan sickness is a cardiomyopathic situation characterized by way of heart failure, cardiac enlargement, abnormalities of electrocardiogram ECG, gallop rhythm, or even cardiac surprise. This disorder is reported to arise predominantly in youngsters and women of baby-bearing ages [34].

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| Author/Year | Topic | Clinical signs and symptoms | Sample Size, setting | Findings |
|---|---|---|---|---|
| Sun. Y et al., 2017 [35] | Preliminary quantitative proteomics evaluation in continual and latent Keshan disease by way of iTRAQ labelling technique | Chest radiography exam, all 31 CKD patients confirmed cardiomegaly, pulmonary congestion, and decreased cardiac pulsation. Only 5 of 40 LKD cases showed moderate cardiac growth | 31 CKD affected person's females. Forty LKD sufferers. | Chronic sufferers confirmed extra EGC abnormalities compared to Latent. |
| Liu, et al., 2016 [13] | Progressive Risks of Latent Keshan Disease: a Long Term Follow-up Study | | 448 sufferers with newly diagnosed latent KD were monitored and accompanied up for 10 years. | Older age (> 15 years), male, own family history of KD, smoking, lower degree of blood selenium (< 60 μg/L), main ECG abnormalities, and 18.Five kg/m$^2$ ≤ body mass index (BMI) 23.9 kg/m$^2$ had been associated with a higher cumulative occurrence of chronic KD. |
| Yuanyuanet al., 2016 [36] | Life first-class of Chinese sufferers with chronic Keshan sickness and its influencing elements | | 146 patients having chronic KD | All measurement ratings have been appreciably lower than those of the general population. The HRQOL of patients with chronic Keshan disease is substantially declined compared with the overall population, and the lowest is RP.NYHA purposeful magnificence, course of the disease, and family profits are a relative dominant predictor of sufferers HRQOL among all variables. |
| Lei, C. et al., 2011 [37] | Is selenium deficiency the cause of Keshan disorder? | The primary clinical features had been accelerated cardiac load on ECG and increased CT ratio and Tei index. | 71 KD sufferers and 290 controls. | The essential risk elements located have been low GPx-1 pastime, family history of KD, and dwelling in a pandemic place. |

**Table 1:** Summary table of clinical signs and symptoms of Keshan Disease

**Prevention of Keshan Disease through Selenium-supplementation:** KD is significantly linked with dietary nutrition. The only dietary component, lower nutritional status and lower selenium levels rise the chances of KD [36]. Selenium consumption may be enhanced by intake of Selenium rich foods, selenium supplementation, food

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fortification and Selenium fertilization of crops [38]. KD along congestive cardiac failure by follow-up of 10 years. A retrospective long-term follow-up study was undertaken on a controlled group of 32 chronic KD cases aged 40.811.4 years. Out of 32 chronic KD cases, 172 (56.3%) received Se-supplementation till the completion of follow-up treatment. Cox proportional hazards regression methods were used to find the freed heart disease suspects. During follow-up, 101 individuals died of chronic KD with Se treatment and 98 died without Se supplementation. A retroactive long-term follow-up studies were conducted on controlled cohort comprising of three hundred and two chronic KD cases of average age of 40.8±11.4 years. Out of three hundred and two chronic KD cases, one hundred and seventy (56.3%) were administrated Se-supplementation till the end of follow-up treatment. Cox proportional hazards regression models was utilized to figure out the liberated suspected individuals of cardiac diseases. Our findings revealed while in follow-up, one hundred and one patient died with chronic KD of Se-supplementation category and ninety-eight died in Non Se-supplementation category. There was no evidence that Se supplementation decreased the risk of cardiac mortality after adjusting for borderline sex, smoking, age and family history of KD. Studies showed that selenium supplementation, especially when combined with beta-blocker therapy and angiotensin-converting enzyme inhibitors, increased life expectancy in those with chronic KD and congestive cardiac failure [39]. Similarly, four different techniques are recommended for practical supplementation of selenium to the individuals in KD areas. They are given in form of selenite tablets, utilization of foliar sprays on crops, fortification of table salt with sodium selenite and selecting particularly selenium-high foods in affected territory. Selenium value of rice and corn can be increased to level of around 0.07 and 0.05pprn respectively by applying foliar sprays. It has been observed that individuals who were given selenite table salt for up to 3 years and 3 months showed that enriched salt of 10 ppm sodium selenite is adequate to regulate the individuals' hair Se content up to level of around 0.2ppm if around 15g salt is taken from daily meals consumed by adult. Through calculations comprising of 10ppm of sodium selenite amount recommended or by dietary survey, selenium consumption of almost 60µg is needed to regulate such as hair selenium content. Almost around half-year's consumption is needed in regard to increase the hair Se content above 0.2 ppm, an extraoral selenite tablet may be required in initial times of Selenium table salt therapy. No hazardous components were diagnosed during the production of dishes as proved by animal analysis. The researchers suggest that one can choose any methodology given above and in mean time ask individual to include more high selenium foods in diets; So, individuals from KD territories would have adequate selenium to protect them from having selenium deficiency [40]. The major cause of Keshan illness is oxidative stress caused by a deficiency of se and vitamin E. Dehydroepiandrosterone DHEA, a naturally occurring adrenal androgen with antioxidant properties, indicates that a diet low in selenium and vitamin E caused KD wounds in rats. DHEA reduced oxidative stress and extracellular matrix buildup in the left ventricles of rats lacking Selenium and Vitamin E. Deficient Selenium and Vitamin E caused an increase in Transforming Growth Factor TGF-1 and connective tissue growth factor CTGF. DHEA protects against oxidative stress and may help alleviate Selenium and Vitamin E deficiency-related KD. In the left ventricles, it reduced extracellular cell matrix formation and antioxidant activity [17].The preventive effects of Se-supplemented table salt for KD, an endemic myocardiopathy, were found in 1.05 million people with a control group of 0.6 million. The annual incidence of acute and sub-acute illness decreased from 25.23 to 2.7 per 100,000 in Selenium-fed populations, and from 19.76 to 7.36 per 100,000 in control populations. Moreover, the Selenium-supplemented group had a lower diagnostic rate of a latent variety of Keshan illness (0.18%) than the control group [10]. The research purpose is to see if se-supplementation reduces cardiac mortality in chronic KD with congestive heart failure over a decade. A retrospective long-term follow-up study on a controlled group of 32 chronic KD patients aged 40.811. Until the end of the follow-up, 170 chronic KD patients (56.3%) received se-supplementation. During the study period, 101/170 people died of chronic Keshan illness (59.4%), whereas 98 people died of chronic Keshan disease (74.2%). Several studies have connected Se supplementation to a lower risk of cardiac mortality. These trials demonstrated that Se supplementation, together with beta-blocker medication and angiotensin-converting enzyme inhibitors, dramatically increased the life expectancy of those with chronic KD and congestive heart failure [39].

## CONCLUSIONS

On the basis of above evidence and our analysis on possible factors associated with etiology of KD, selenium deficiency is the most evident among worldwide. However, the exact cause of KD is still unknown according to some studies. We have come to the conclusion that critical scientific evidence supports selenium being an essential trace element for humans Moreover the diet rich in selenium should be consumed on regular basis. Its supplementation has been an effective preventive measure for KD in China and some other

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countries.

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