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Review Article

Selenium Deficiency and Keshan Disease Mechanism and Management

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Abstract

Selenium (Se) is a trace element for humans. It has important functions for the body, primarily to play a role in anti-oxidant reactions. In addition to its antioxidant effects, Se is known to be necessary for thyroid hormone metabolism and the healthy functioning of the immune system. Se deficiency disrupts many metabolic systems and causes diseases that can be mortal. Infertility, susceptibility to viral infections, myodegenerative, and cardiovascular events may occur. The most lethal of these is the fatal cardiomyopathy known as Keshan Disease (KD). In this article, we will discuss the mechanism of development of KD, which stands out with the diseases and mortality seen in selenium deficiency, and the management of Se deficiency in general.

Introduction

Selenium deficiency affects 500 million to 1 billion people worldwide due to insufficient intake [1]. Dietary Se intake is highly dependent on the Se content in the soil and the bioavailability of the crops [2]. However, factors affecting global soil Se concentrations and Se distributions are largely unknown [3]. The trace element selenium (Se) is needed for regular biosynthesis of selenoproteins, which can contribute to antioxidative defense systems and affect redox-regulated signaling [4]. For example, glutathione peroxidase (G-Px), a selenoprotein, performs antioxidant activities that protect against reactive oxygen and nitrogen species. Iodothyronine deiodinases, which convert inactive thyroxine (T4) to triiodothyronine (T3), the active thyroid hormone, are selenium dependent. One of the interesting properties of selenium is that it plays a role in immune system functioning and the progression of HIV to AIDS [1] and therapeutically, it is recommended that people ingest selenium (200 µg / day), and research has shown that this reduces the viral load and reduces the rate of HIV-1 infection of monocytes [5]. Selenium deficiency has been associated with

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cardiovascular disease, infertility, myodegenerative diseases, and cognitive impairment [1]. Although there is no high evidence value, a study has shown that excessive selenium intake is associated with a high cure rate for COVID-19 disease [6]. In this article, we will talk about the development mechanism of CH, which stands out with the diseases and mortality seen in selenium deficiency, and the management of Se deficiency.

Studies in Chinese seniors report an association between low Se levels in nails and poorer cognitive performance, and Apolipoprotein E4 carriers have significantly lower Se nail content than non-carriers [7].The study by Jiahui Ma et al [8] showed that decreased Se concentration in serum is significantly associated with the risk of schizophrenia, consistent with previous studies, and this study showed that Se supplementation improves the appetite and memory of patients with schizophrenia.

In selenium deficiency, problems arise in bone development as a result of increased oxidative stress. Selenium deficiency is the main cause of endemic Kashin-Beck disease (CBD), which has been reported mainly in low selenium regions of China, North Korea and Siberia of Russia [9]. This disease is a chronic, multi-joint, deformative osteoarthropathy characterized by necrosis and remodeling of cartilage, including growth plates, and often impairs the growth and development of children and adolescents. Clinically, it presents with short fingers and limbs, delayed growth and disability in advanced stages [10]. In the study by Y. Jirong et al. [11], Sodium selenite is effective in preventing and treating CBD.

Selenium deficiency has negative effects on both female and male reproductive systems. Se is important for both the oocytes and the sperm to mature and fertilize and existing evidence shows that although routine Se level assessment during infertility research is not beneficial yet, Se supplementation positively affects fertility, especially in men [12].

Keshan disease (KD) is an endemic and highly motal cardiomyopathy first reported in 1935 in the Keshan county of northeastern China [13]. KD can be categorized in four different ways as acute, subacute, chronic and latent (Table 1) [14]. Although the etiology of KD is not fully explained, genetic and viral infections, especially selenium deficiency, are held responsible for the pathogenesis. For example, epidemiological studies by Junshi Chen [15] revealed that KD formation is endemic and occurs in the same endemic region with marked seasonal variations (peak season: winter in northeast China and spring in southwestern China) and annual variations, and quite interestingly. In the study conducted by Li-Qun Ren et al. [16], It was shown that the positive rate of coxsackievirus B3 RNA with in situ hybridization was 83%, 67% and 80% in acute, subacute and chronic Keshan patients, respectively. These results support that enterovirus, especially CVB3, may play an important role in the pathogenesis of Keshan disease. Also, the area, range, and distribution of the positive signal of CVB3 have been associated with the development of Keshan disease. In addition, selenium deficiency can lead to increased T4 and decreased peripheral T3, largely due to inactivation of type I deiodinases [17]. Decreased T3 concentration can impair the activity of innate immune cells, including natural killer cells and dendritic cells (DC), which can reduce the effectiveness of virus clearance [18]. This supports viral etiologies in KD by creating a predisposition to viral infections as a result of selenium deficiency.

Previous studies [19,20] have shown that KD cluster in certain families. Familial predisposition has also prompted the medical community to investigate conditions that create genetic predisposition for KD. In the study of Wei J et al. [21], The DR15 allele of the HLA-DRB1 gene was found to be significant in KD and interestingly, they showed that the DR7 allele of the HLA-DRB1 gene could be protective against KD. The study by H.L. Wei et al. [22] showed that blood selenium level and GPx activity were lower in KD patients than healthy controls in the KD endemic region, and also showed that there were significant results between the GPx1 exon 474 mutation and Keshan disease. The SCN5A gene, which encodes the human cardiac sodium channel α-subunit, is responsible for the fast depolarization upstroke of the cardiac action potential. SCN5A gene mutations are associated with various cardiac disorders, including arrhythmogenic syndromes, namely, long QT, Brugada syndrome, familial atrial fibrillation, sick sinus syndrome, paroxysmal familial ventricular fibrillation, progress familial heart block type IA, and dilated cardiomyopathy [23].Genetic epidemiological study by S. Jiang et al [24] showed

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Table 1: Clinical types of KD

KD types	Clinical feature
Acute KD	Charactized by cardiogenic shock, arrhytmia and acut heart failure
Subacut KD	With a slower onset than acute KD and a more rapid one than chronic KD
Chronic KD	Cardiac dilatation, a slow onset, and a long course, with most patients having a cardiac function range ofNYHA II-IV
Latent KD	Develop in either previously unaffected individuals or those with the other three types of KD, featuring myocardial injury and usually arrhytmia, but with normal heart function

Table 2: Selenium dose to be taken daily according to age groups

Age	Selenium [µg/day]	
	Male	Female
Infants		
0 to under 4 months	10	10
4 to under 12 months	15	15
Children and adolescents		
1 to under 4 years	15	15
4 to under 7 years	20	20
7 to under 10 years	30	30
10 to under 13 years	45	45
13 to under 15 years	60	60
15 to under 19 years	70	60
Adults		
19 to under 25 years	70	60
25 to under 51 years	70	60
51 to under 65 years	70	60
65 years and older	70	60
Pregnant women		60
Lactating women		75

that the H558R polymorphism of the SCN5A exon 12 region was significantly associated with KD. Although many factors result for KD, selenium deficiency is the most emphasized factor. In the study of Yan-he ZHU et al. [25], They showed that chronic KD patients with low selenium levels at baseline were more likely to have a cardiovascular event. They showed that selenium replacement from the very beginning resulted in reduced cardiac death in patients with chronic KD who received ACEi + BB compared to the group of patients with chronic KD who without selenium replacement.

It is most useful to supply the selenium deficiency with a daily diet. For example, egg yolk is rich in selenium. Apart from this, using selenium-rich fertilizers and enriching drinking water with selenium can be another method. In severe deficiency, inorganic forms of Se rather than organic selenium, selenite and selenate, can be used, but the risk of toxicity with inorganic Se is higher [1]. The average amount of Se replacement for each age group is shown in the table (Table 2) [26]. When performing Se replacement, the dose should be calculated carefully, otherwise it may cause type 2 diabetes [13]. In acute intoxication due to Se, symptoms include stomach symptoms such as vomiting, pain, and nausea, as well as garlic breath and heart symptoms, and mortality has been associated with blood / plasma levels between 300 and 30,000 µg / L (normal level: 100 µg / L) [27] .

As a result, selenium is essential for the normal function of the antioxidant system. In its deficiency, it can cause mortal diseases by affecting many organs. Here KD stands out with its high mortality rate. Although genetic factors such as HLA gene polymorphism and viral infections are blamed, it can still be said that the most important etiological factor is Se deficiency. Of course, it cannot be denied that KD pathogenesis needs further clarification. We have no doubt that diagnosis and treatment will advance as pathogenesis emerges.

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