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# Impact of selenium on aging and aging-related diseases-A review

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**Abstract**
Selenium (Se) is an essential dietary trace element that plays an important role in the prevention of inflammation, cardiovascular diseases, infections, and cancer. Selenoproteins contain selenocysteine in the active center and include, i.a., the enzymes thioredoxin reductases (TXNRD1–3), glutathione peroxidases (GPX1–4 and GPX6) and methionine sulfoxide reductase, involved in immune functions, metabolic homeostasis, and antioxidant defense.Ageing is an inevitable process, which, involves an imbalance between antioxidative defense and reactive oxygen species (ROS), changes in protein and mitochondrial renewal, telomere attrition, cellular senescence, epigenetic alterations, and stem cell exhaustion. These conditions are associated with mild to moderate inflammation, which always accompanies the process of ageing and age-related diseases. In the elderly, aging-related diseases include neuropsychiatric diseases, tumors, cardio-vascular diseases, and skin aging, among others. Selenium supplementation is an important strategy for anti-aging and the prevention of aging-related diseases and is of great significance for the elderly. However, with the accumulation of related research, selenium supplementation does not necessarily contribute to the prevention of aging and aging-related diseases. It is believed that a low level of selenium is beneficial to the human body. Thus, the effect of selenium on human aging and aging-related diseases is still controversial.

**Keywords:** selenium, aging-related diseases

## Introduction
Aging occurs throughout the body over time. Although there is no direct relationship between longevity and aging in animals, temporal age is often accompanied by aging in humans. There is a connection between longevity and aging, such that aging may affect lifespan. Thus far, the mechanisms of aging remain to be clarified, and there are several theoretical hypotheses, including the free radical, telomerase and cell division limit hypotheses. The free radical hypothesis, an important aging hypothesis, is closely related to the redox imbalance in cells. Aging is caused by an accumulation of cellular senescence in various organs and tissues. The oxidation–reduction imbalance leads to excessive reactive oxygen species (ROS) production or decreased ROS scavenging, resulting in impaired cellular functions and cell senescence via impaired intracellular biomolecular functions. Additionally, cell senescence is the risk factor for various aging-related diseases includ-ing neurodegenerative, tumor, and cardiovascular diseases, among others. Therefore, the reduction of ROS is the primary goal of anti-aging therapy and theprevention of aging-related diseases.
The trace element selenium (Se), as a significant essential nutritional factor, may remodel biochemical and physiological changes accompanying ageing by improving immune functions, mediating metabolic homeostasis and antioxidant defense, and also in the removal of misfolded proteins. Se deficiency in ageing populations seems to increase the risk of developing age-related diseases. In the EVA study, low levels of Se appeared to decrease human life expectancy by increasing vulnerability to different diseases, suggesting blood Se values to represent a longevity index in an aged population.Maintenance of adequate Se status in the elderly appears to positively affect the self-perception of health, physical activity and quality of life. Adequate Se status has been reported to protect against myocardial infarction. Population-based studies have reported that decreased serum Se and total carotenoid concentrations were related to an elevated risk of death among older women . Of note, it has been observed that fewer individuals with advanced age reside in Chinese counties with endemic Keshan disease, a cardiomyopathy precipitated by Se deficiency, in comparison with counties free of this condition, indicating elevated mortality from chronic diseases in Se-deficient areas. Furthermore, in COVID-19, which seems to be an age-related disease as the lethality increases strongly with age, a low selenium status was associated with an unfavorable outcome. Aside from its role in antioxidant defense, Se is known as an important trace element for alleviating metal toxicity and for adequate immune responses. Its presence within at least 25 selenoproteins in the form of the amino acid selenocysteine (SeC) has attracted attention regarding human health. Several researchers have reported that Se deficiency or inadequate supply is an important issue affecting

millions of people worldwide. In the case of deficiency, supplementation with organic selenium in the form of selenomethioneine, the main dietary form of selenium, has frequently been used.

***Selenium Nutrition:Absorption, distribution, metabolism and function of selenium***

Selenium in the diet, in the forms of selenomethionine, selenocysteine, selenite and selenate, is absorbed into the body by Se-related transporters in the lower part of the small intestine. Selenomethine is the main form of selenium in the diet, selenite and selenate are the most common forms of selenium supplementation, and selenocysteine is the inter-mediate product of selenium metabolism. The distribution of selenium in the body after absorption is mainly dependent on liver transport. Selenoprotein P (Sepp), as a carrier-containing selenium, is mainly synthesized in the liver and released into the circulatory system. Finally, Sepp in the circulatory system is distributed into extrahepatic tissues for synthesizing other selenoproteins in which selenium is the essential element for developmental functions. Some mechanisms of selenium uptake by extrahe-patic tissue have been elucidated, such as megalin-mediated uptake of Sepp from the glomerular filtrate in kidneysand apoER2-mediated uptake of Sepp from the systemic circulation in brain and testis, among others. Addition-ally, selenosugar produced by the liver is also thought to be a selenium transporter that is responsible for the distri-bution of selenium in humans. Selenium metabolism depends on the source of selenium and the selenium status in the body. Trimethylselenide and selenosugar, both of which are excreted via the urine, anddimethylselenide, which is excreted via the feces and respiration, are then pro-duced through complicated excretory metabolitesynthesis. Therefore, the dynamic balance of selenium intake and excretion maintains the level of selenium in the human body. Selenium utilization in organisms plays biological roles in the form of selenoproteins, all of which contain sele-nium cysteine residues. The functions of selenoproteins are involved in antioxidant reduction, the synthesis of thyroxine, selenium transport, and anti-inflammatory activities, among others. Antioxidant selenoproteins can be classified into four categories: Gpx1–Gpx6, thioredoxin reductase (TR)1–TR3, methionine sulfoxide reductase1 (MsrB1) and endoplasmic reticulum-selenoproteins, such as Sel15, SelS, SelK, and SelM. It has been demonstrated that theseselenopro-teins have beneficial effects on anti-aging, prolonged lon-gevity, and the prevention of aging-related diseases. It is worth noting that the physiological functions of organs naturally decrease with age. The absorption,distribu-tion, metabolism and function of selenium in theelderly are seriously affected by the impaired function of vital organs such as the intestine, liver, and kidney, among others. Unfortunately, until now, almost all the studies examining selenium and elderly people have been limited to the rela-tionship between dietary selenium, selenium levels and dis-ease. Thus, further studies on the physiological activities of selenium such as the absorption, distribution and metabolism in the elderly are needed.

***Selenium Deficiency—A Role in Diseases in the Elderly***

***Ageing and Inflammation***

The mechanisms of selenium against aging, an increasing number of studies have shown that the mechanisms by which selenium combats aging are related to its antioxidant activity. A weakened antioxidant capacity promotes the production of ROS to impair proteins, genes and others. Cell senescence thus occurs, followed byaging and aging-related diseases.

***Selenium, inflammation, and antioxidation***

The consequences of aging include numerous changes at the cellular and molecular levels. Among the most characteristic features in the ageing process are increased expression of acute phase reactants, such as C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), and interleukin-6 (IL-6).

Mitochondrial injuries appear to be an important factor in cellular senescence. The free radical theory of aging states that the generation and leakage of ROS from the mitochondrial respiratory chain increases with age, leading to cellular oxidative damage. Apparently, oxidative stress, inflammation, and ageing interact with each other in a complex way, and inflammation accompanying ageing is often referred to as “inflammaging”. Inflammation in the elderly is considered to represent a risk factor for several diseases, including CVD, cancer, and dementia. Supplementation of Se in vivo appears to enhance antioxidant capacity and alleviate inflammation. Among inflammatory biomarkers evaluated in a cohort of elderly individuals supplemented with a combination of Se and coenzyme $Q_{10}$ in the Swedish KiSel project, the markers CRP, P-selectin and osteoprotegerin (OPG) were reduced or normalized following a four-year period of supplementation. In another cohort encompassing elderly women, Se supplementation was observed to ameliorate obesity-induced inflammatory responses. Insulin-like growth factor 1 (IGF-1), considered to be a central biomarker in nutrition and inflammation, did increase following selenium supplementation.

The phenomenon of increased inflammatory response in the elderly may in part be related to reduced expression of sirtuins. The family of sirtuins (SIRT-1–SIRT-7), with different cellular localization (nucleus, mitochondria, cytosol), have been associated with longevity. Sirtuin enzymes belongs to class III of histone deacetylases and deacetylate histones and non-histone substrates in a nicotinamide adenine dinucleotide (NAD+)-dependent manner and are thus implicated in the regulation of numerous cellular events including cell cycle control and apoptosis, mitochondrial biogenesis, gene silencing, and genomic stability, thereby mediating longevity. Sirtuins are also involved in age-related processes such as inflammatory responses, as well as in the control of oxidative stress responses. It has been reported that SIRT-1 and SIRT-6 located in the nucleus, and SIRT1 translocated to

cytosol, exert anti-inflammatory effects by interacting with NF-κB subunits. In a recent study, sirtuin levels in peripheral blood mononuclear cells in a group of elderly individuals with CVD were examined, disclosing downregulated SIRT-1, SIRT-5, SIRT-6, SIRT-7, and increased serum CRP values in subjects with low serum Se (Se < 0.75 μmol/L). However, by which mechanism selenium possibly is linked to sirtuins is not known.

***Selenium, Ageing and Cardiovascular Disease (CVD)***

Cardiovascular disease is a common and high-risk disease in the elderly. Although factors affecting cardiovascular disease include diet, inheritance, smoking and other fac-tors, body dysfunction causedby aging is also an important risk factor for cardiovascular disease. Oxidative stress is animportantmechanism of aging. Decreased levels ofendogenous antioxidants have been found to be directlyassociated with aging and to promote the associationbetween type 2 diabetes and hypertension. Duringthe process of aging, supplementation with antioxidantscontributes to disease management. In a study of revers-ible heart failure, reversible heart failure was considered to be the result of selenium deficiency. Fundamental stud-ies have found that the heartfailure mortality is inverselycorrelated with selenium intake in spontaneously hypertensive rats after selenium supplementation. Protein molecular studies have shown that the activities ofperoxidase and thioredoxin reductase related to seleniumantioxidant activity in myocardial tissue are all increasedafter selenium supplementation. Oxidative stressis associated with hypertension and myocardial remodeling, which is the basis for the development of chronic heart failure. Therefore, selenium reduces the occurrence of heart failure by increasing the expression of antioxidants such as peroxidase, thioredoxin reductase and other factors, thereby reducing heart failure mortality. Brachial–ankle pulse wave velocity is an important risk factor, which is recognized as a parameter of cardiovas-cular function. The higher this value is, the greater is the cardiovascular risk. The protective function of Se against CVD has been debated. Two early studies reported that low Se status represents a risk factor for myocardial infarction, with increased risk at plasma values below 1 μmol/L (about 80 μg/L). According to the EVA study which included an elderly population in France, a plasma selenium level of 1.1 μmol/L exerted a protective action, whereas the suggested optimal plasma selenium for GPX activity is somewhat higher, viz. about 1.2 μmol/L. An inverse association between cardiovascular health and selenium status could be shown in populations with Se intakes below about 60 μg/day, while others did not detect deficient selenium status to be a risk factor for myocardial infarction, when populations with higher Se levels (above about 1.0 μmol/L) were investigated. The observed elevated risk of ischemic heart disease among elderly subjects (mean age 63 years) with low serum Se levels (<1.0 μmol/L) in Denmark, is in agreement with observations on a German population with serum Se levels of about 0.9 μmol/L and a recent study on an elderly population (>70 years of age) performed in Sweden. The latter study reported a significant increase in cardiovascular mortality in the lowest Se quartiles (<0.7 μmol/L). In the EURAMIC study (1997), which was a multicenter case–control study including 10 centers in Europe and Israel in 1991–92, Kardinaal et al. found a remarkable inverse relation between the risk of myocardial infarction and toenail Se levels only for the included European center with the lowest Se levels (Germany). The BIOSTAT-CHF prospective observational cohort study, in which patients with worsening heart failure were included, showed that patients deficient in selenium (<70 μg/L, 20.4% of enrolled patients) had worse New York Heart Association (NYHA) class and more severe signs of heart failure and lower quality of life than those with higher plasma selenium. Selenium deficiency was also associated with a higher rate of hospitalization for heart failure or all-cause mortality. SELENOP was determined in the Malmö Preventive Project, a population-based prospective cohort study including 4366 individuals that were followed up for 9.3 (8.3–11) years. The risk of all-cause mortality, cardiovascular mortality, and a first cardiovascular event were all inversely associated with plasma SELENOP concentration. In the United States, physicians reported no significant relation between Se in the serum and the risk of CVD in subjects with plasma concentrations above about 1.0 μmol/l . These observations are essentially consistent with meta-analyses of coronary heart disease and Se. Thus, Rees et al. concluded in their meta-analysis that Se supplementation did not reduce cardiovascular mortality, but they admitted to have included most of their patients from the Nutritional Prevention of Cancer (NPC) or the Selenium and Vitamin E Cancer Prevention Trial (SELECT) trials, with a mean baseline intake of about 130 μg/day in males and 90 μg/day in females, which is substantially higher than European levels and well above a risk threshold of around 1.0 μmol Se/L (80 μg/L) in plasma, as discussed above This conclusion also agree with the lack of effect on CVD mortality in the French SU.VI.MAX study that supplemented subjects with 100 μg Se/d together with vitamin C and E, beta-carotene, and zinc in a cohort with baseline plasma Se above this threshold (mean 1.1 μmol/L). In contrast, a significantly reduced CVD mortality was obtained in the Swedish KiSel study that supplemented participants with 200 μg Se/d for 4 years in an elderly population (>70 years of age) with mean basic plasma values of about 0.8 μmol/L (67 μg/L). The reduction in CVD mortality was negatively associated with baseline plasma selenium.

***Selenium andcentral nerve system diseases***

Aging inevitably leads to a decline in the function of tissues and organs. The degeneration of the nervous system causes a weakening of nervous functions such as poor learning and memory abilities, among others. Oxidative stress causes aging, which further leads to neurodegenerative diseases such as Alzheimer’s disease and Parkinson’s disease. Sele-nium is a necessary trace element in the human body, and its distribution in human organs is hierarchical. In the case of selenium deficiency, the brain tissue guaranteesselenium protein synthesis

by consuming other selenium-containing proteins, and the brain, reproductive andendocrine organs are preferentially supplied with selenium, which depends on selenoprotein P as a selenium transporter to ensure a sufficient supply of selenium in the brain. Therefore, selenium plays an important role in the maintenance of brain function.Red blood cells (RBCs) reflect the long-term status of nutrition in the body. The selenium in RBC gradually decreases in normal elderly people, patients with Alzheimer's disease and elderly people with mild cognitive impairment. A study with a 9-year followup has shown that a low selenium status was a risk factor for cognitive decline because cognitive ability decreased synchronously with the plasma selenium level. Oxidative stress is an important factor in aging-related neurodegenerative diseases. δ-Aminolevulinate dehydratase (ALA-D) is a biomarker of oxidative stress and is inhibited to promote the production of ROS. The impaired cognitive function is associated with reduced activity of ALA-D and a reduced level of selenium. The reduced selenium status impairs anti-oxidation ability and indirectly promotes oxidative stress leading to cognitive impairment. The APOE ε4 allele is one of the highest risk factors for Alzheimer's disease. In the brain, the selenium level is not only related to Alzheimer's disease, but it is also associated with the APOE ε4 allele. It has been speculated that a low level of selenium is related to the occurrence of Alzheimer's disease via the APOE ε4 allele. Parkinson's disease is a common neurodegenerative disorder in the elderly. Thedegeneration occurs in the nigrostriatal system. Although the cause has not been fully clarified, oxidative damage is an important causal factor. Selenium, as an antioxidant, has been shown to protect the nigrostriatal system in animal models, and the plasma sele-nium level has been found to be significantly associated with decreased neurological coordination in elderly Parkinson's patients in clinical studies. The elderly are prone to depression because of family, social, psychological, disease and other factors. The selenium level in the elderly has been shown to be negatively correlated with the depression scale score, suggesting that a low level of selenium can aggravate depression. Mutations in GPX1 affect the protective effect of
selenium and are associated with the risk of depression, sug-gesting that mutations in GPX1 cause a failure of sufficient selenium to exert antidepressant effects via the antioxidant ability of GPX1. These clinical findings suggest that selenium levels in the body may lead to the occurrence of aging-related degenerative diseases and clinical symptoms such as memory and reading loss through oxidative stress. In addition to the above clinical studies, basic research has further confirmed the relationship between selenium andcentral nerve system diseases and elucidated some of the mechanisms. Compared with young rats, the activity of GPX and the level of selenium in the pineal gland of aged rats is significantly decreased. It has been speculated that the decreased selenium level is closely related to the degeneration of the pineal gland. After supplementation with selenium, serum levels of inflammatory factors, such as TNF-α, IL-1β and IL-4, are reduced and the activity of GPX increased to induce protective effects against experimental dementia. Additionally, selenium supplementation combined with swimming training also further increases the expression of neuroprotective proteins such as mature brain-derived neurotrophic factor (mBDNF), neuronal nuclear protein, and Bcl-2, among others, to reduce the apoptosis of neural cells and activities of neural inflammatory proteins in aged rats. Neuron cell survival is the key point in preventing degeneration of the nervous system. The accu-mulation of amyloid plaques, amyloid beta-protein and Tau protein lead to brain degeneration. Supplementation with selenium in the form of sodium selenate improves spatial learning and memory abilities in the hippocampus by reduc-ing the accumulated Tau protein. Glial fibrillary acidic protein (GFAP) and ionized calcium-binding adaptor mol-ecule-1 (ICBAM1) are activation biomarkers of gliacytes. In aged rats, supplementation with selenium was found to be beneficial for promoting the expression of GFAP and ICBAM1. Selenium contributes to the decrease in apoptosis anddegeneration of microglial cells in the hypothalamus and has significant neuroprotective effects. At the molecular
level, excessive calcium leads to an accumulation of calcium in mitochondria and cell death. TRPM2 and TRPV1 can be activated by oxidative stress and promote calcium influx. Selenium inhibits the activation of TRPM2 and TRPV1 by regulating oxidative stress via enhancing GPX activity, thereby preventing the development of neurodegenerative disorders such as Alzheimer's disease.

***Selenium, Ageing and Cancer***

Several epidemiological studies conducted in Europe, the USA, Japan, and China have indicated a significant protective role of Se in malignancies. A recent meta-analysis concluded that Se at recommended daily intakes above 55 μg/day decreased the risk of cancer. In Finland, the implementation of a state program for the elimination of micronutrient deficiencies, including Se fertilizer supplementation, was accompanied by a reduction in cancer mortality. An American study, referred to as the NPC study, including 1312 patients (mean age 63 years) taking 200 μg Se/day decreased the risk of cancer incidence in general by 37%, colorectal cancer by 58%, prostate cancer by 63%, and lung cancer by 48%. Later, the SELECT study, involving 35,500 people (mean age 63 years), did not report these outcomes and intervention with 200 μg Se/day combined with 400 IU vitamin E/day for 5.5 years did not show a positive effect on cancer incidence in general. However, baseline Se levels were above about 1.4 μmol/L (110 μg/L), reflecting baseline intakes above 120 μg/day, presumably explaining that supplementation with extra Se was without protective effect. Among those with a high selenium status, an increased risk of high-grade prostate cancer was even found. Although supplementation was not protective at such high baseline intakes, a recent meta-analysis concluded that Se at recommended daily intakes above 55 μg/day was associated with reduced cancer risk. This study revealed a significant inverse relationship between the risk of cancer after adjusting for body mass index, smoking, age, and Se intake. A reasonable

interpretation is that Se levels somewhat higher than the average intakes in Europe could protect against some cancers. Of note, the protective effect in the American NPC trial of Se (200 μg as Se-enriched yeast) was confined to the lower tertile of the cohort that had a pre-treatment plasma Se below 1.3 μmol/L (106 μg/L). In contrast, no cancer-protective effects were seen in subjects with baseline plasma concentrations above 1.5 μmol/L. A nested case–control study of Japanese-American menfound that the inverse association between prostate cancer and serum Se was significant particularly in current and past smokers. In contrast, no association between selenium concentration in plasma and prostate cancer risk—neither stage nor grade—was seen in a nested case–control study using the large European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. In a nested case–control study using the EPIC cohort it was found that low selenium status and low SELENOP in plasma were associated with an increased risk of colorectal cancer. Accordingly, in a recent case cohort study using the EPIC Potsdam cohort (mean age about 50 years), plasma selenium and SELENOP were associated with a decreased risk of colorectal cancer. Additionally, hepatobiliary cancer risk was inversely associated with selenium status and SELENOP concentration in the EPIC cohort.

Protection against cancer by supplementation with Se compounds is not expected in populations with an adequate Se status, i.e., blood plasma levels definitively above 1.0–1.2 μmol/L. Thus, the early studies from Finland that disclosed associations between fatal cancers and prediagnostic low blood plasma Se were performed on populations with blood plasma levels as low as 0.6 μmol/L. A review of prostate cancer studies supports the observation of an association between inadequate or low Se status and risk of advanced prostate cancer, with the strongest association being seen in smokers.

It seems likely that a deficient intake of selenium is associated with an increased risk of certain cancers in elderly people, possibly due to less protection against oxidative stress and inflammation. However, the mechanisms of protection are not known, and other explanations have been suggested, based, i.a., on experimental evidence. Hence, the observed anti-carcinogenic effects of some Se species, when supplemented to populations with levels below the threshold of selenoproteome saturation, have been discussed by Rayman et al. [99], who suggested that some methylated metabolites might exert a chemo-preventive action against cancer, presumably by acting through epigenetic mechanisms. Another epigenetic mechanism is the formation of α-keto acid selenium metabolites that effectively inhibit some histone deacetylases, targets which have also been used in the pharmaceutical industry. Protection against age-associated inflammation is presumed to play a role in anti-carcinogenic effects.

***Selenium and immunologic function***

Nutrition is one of the important factors affecting immune function. Selenium contributes to the up-regulation of genes related to improving immune status and innate immunity,

including major histocompatibility class I, arginase I, inte-grin β1 subunit and Toll-like receptors. Selenium sup-plementation delays the atrophy of the thymus and spleen, significantly increases levels of IgG, IgM, complement C3, C4, IL 2, and IL 6, reduces TNF-a, affects the proportion of T-cell subsets, and thus playsan important role in improving immune function. In addition, it also enhances delayed hypersensitivity, promotes the production of specific anti-bodies IgG, IgG1 and IgG2a to enhance the response to antigen and increases the number of CD4+ cells to promote the immune response, demonstrating an important role in improving immune aging and antioxidant capacity. Mesenteric lymph nodes can reflect the degree of human aging, and studies have shown that a lack of selenium and other trace elements is related tochanges in lymph node structure and immune function. However, in studies on the relationship between health care-related infections and nutrients in the elderly, although health care-related infections in the elderly have been associated with nutri-tional deficiencies and immune aging, results suggest that the reductions of selenium and zinc levels in the elderly are associated with health care-related infections. How-ever, based on flow cytometry detection of T-cell subsets, the above nutrients arenot related to T-cell subsets though. Thus, selenium is not associated with immunity. There-fore, althoughmany basic studies have shown that supple-mentation with selenium enhances the immune system, there are conflicting results in clinical studies, and the detailed relationship between selenium and immunefunction needs to be further clarified.

***Selenium, Ageing, and Other Age-Related Diseases***

Associations between low levels of Se in serum or blood and several other diseases in elderly people have been observed. Ageing increases the incidence of pathological conditions such as neuropathy, and infectious and rheumatic diseases. The elderly often suffer from glomerular or tubular dysfunction and manifest renal failure, and there seems to be a close relationship between renal function and Se status. Peritoneal dialysis as well as hemodialysis can lead to a decrease in Se levels in the body, and low SELENOP levels appeared to be associated with reduced renal function. In hemodialysis patients, supplementation with Se significantly increased GPX and plasma Se levels, and normalized IL-6.

***The risk of ・excessive selenium***

Trace elements play an irreplaceable role in normal physi-ological functions, but excessive trace elements have an adverse effect on the body. For example, excessive mercury and lead in the body cause damage to the nervous system, manifesting as sensory,motor and other functional disorders. It has been suggested that selenium poisoning, a syndrome characterized by loss of teeth, hair and nails, and disorders of the nervous system, are due

to the produc-tion of ROS leading to DNA damage, lipid peroxidation and premature protein degradation in cells. Addition-ally, excessiveselenium not only ensures the expression of selenoproteins, but it is also nonspecifically incorporated into other proteins in the form of selenomethionine, thereby affecting the protein functions via changing their structures. Surprisingly, it has been reported that normal daily selenium supplementation has harmful effects on organisms. A lower level of selenium can even prevent disease and prolong life by stimulating stress reactions. Under the condition of selenium deficiency, selenoproteins with a low hierarchy are preferentially degraded and selenoproteins with a high hierarchy are reserved to play a beneficial role in the body. Not all selenoproteins in the body are beneficial. Some selenoproteins that cause harm to body, such as Gpx1 and Gpx3 in the kidney and Txnrd1 and Selenium in the liver, are degraded during selenium deficiency. However, others, such as iodothyronine deiodinase 2 (Dio2) and selenoprotein N, are upregulated and have a positive effect on the body. In summary, the roles of selenium in aging and health are very complicated. The average sele-nium level in the population likely cannot be used as a reference index to guide daily normal selenium intake. The form of selenium supplementation, genetic polymorphisms, and life behavioral factors, among other factors, should be fully taken into consideration to ensure the effectiveness of improving the level of selenium in the body. The dose of selenium supplementation to achieve optimal SeIP with sele-nium yeast was found to be remarkably different from that supplemented with selenomethionine. Similarly, with respect to genetic polymorphisms, people with the GPx1 rs1050450 CC polymorphism require selenium supplementation at 116 ng/ml to achieve the beneficial effects on DNA stabilization, while others with GPx4 rs713041 TT polymor-phism require selenium supplementation at 149 ng/ml. Interestingly, smokers need more selenium supplementation than those who do not smoke. We believe that sele-nium supplementation should be combined with the actual demand for selenium to play a positive role in the body.

## Conclusions

Until now, most studies have found that selenium deficiency is closely related to aging and aging-related diseases. The mechanisms include oxygen ROS-mediated damage such as inflammation and gene and telomere alterations. However, further research has provided many contradictory conclusions, such as the promotion of longevity by a low level of selenium and the absence of a relationship between selenium deficiency and aging-related diseases such as prostate cancer. In addition, problems such as, e.g., whether the selenium level detected in tissues reflects the general selenium level, the mechanism of selenium supplementation in aging and aging-related diseases via selenoprotein, the aging-related diseases that are benefited by selenium supplementation, and the types and functions of selenoproteins, remain to be further clarified. Although most studies have shown that selenium supplementation has anti-aging properties and prevents aging-related diseases.

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