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Original Article

The Influence of Selenium on Telomere Length and DNA Damage as Indicators of Age-Related Changes: A Systematic Literature Review

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ABSTRACT

The study aimed to analyze the relationship of selenium to telomere length and DNA damage that reflect aging-related changes at the genome and cellular level. This study used the Systematic Literature Review method to summarize evidence regarding the potential of selenium as an anti-aging agent. It was conducted in April and May 2023. The initial stage was to identify research questions consisting of PICO (Population, Intervention, Comparator, and Outcome). The population involved adults and intervened with selenium, did not use a comparator, and used non-epigenetic biomarker outcomes, namely telomere length and DNA damage which reflect aging-related changes at the genome and cellular level. The reviews were obtained from various countries, including Sweden, France, the United States, Australia, and Brazil. The research subjects used were also diverse and at wide intervals, ranging from young people (20-30 years) to adults (> 70 years). A total of 4 of the 7 studies used a cross-sectional study scheme, 1 case-control, and 2 used an experimental design. Adequate selenium intake can potentially affect telomere length and telomere length maintenance. However, the relationship between selenium and telomere length can be affected by other factors, such as the individual's age and health conditions. Selenium intake may be an important factor in maintaining telomere length and preventing age-related diseases. Selenium supplementation may be beneficial for people with low selenium levels or who are at risk of age-related diseases. Further research is needed to confirm the findings of this study and to determine the optimal dose of selenium for maintaining telomere length.

Keywords : Selenium, Telomere Length, DNA Damage, Aging

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INTRODUCTION

The aging process is an inevitable natural phenomenon. With increasing age, significant physiological changes occur in the human body, which decreases the quality of life and physical function [1]. Aging increases the risk of chronic diseases such as heart disease, diabetes, cancer, neurodegenerative disorders, and cognitive problems [2].

Research on aging and its role in disease development is an exciting and relevant topic in nutrition and health sciences. One of the interesting ingredients to study is selenium, an essential mineral that is found in various foods and is also widely developed as a supplement. Selenium has an important role in antioxidant selenoproteins for protection against oxidative stress initiated by excess reactive oxygen species (ROS) and reactive nitrogen species (NOS) [3]. Selenium has also been linked to a variety of potential anti-aging effects, including protection against oxidative damage [4], immune system enhancement [5], and regulation of important cellular functions [6].

Previously, a review of articles

reviewing research developments and the role of selenium in aging and aging-related diseases was carried out in 2018 with the conclusion that the effects of selenium on human aging and aging-related diseases are still controversial [7]. The determination and use of biomarkers to assess aging also vary, such as routine laboratory tests, epigenetic, non-epigenetic, also the physical ability and organ function, as well as senescence biomarkers (to assess changes in gene expression, enzyme activity, modifications to proteins, or increases in molecules production associated with oxidative stress and cellular damage) [8]. Based on previous studies' results, non-epigenetic biomarkers are the most frequently used biomarkers, including telomere length, amount of DNA damage, and mitochondrial dysfunction, which can describe aging-related changes at the genome and cellular level[8]. Aging is characterized by telomere shortening caused by oxidative stress (OxS); other factors, such as lifestyle, can also cause damage to biomolecules, apoptosis, or cell aging, which is characterized by the emergence of age-related diseases, one of which is Metabolic Syndrome (MetS) [9].

Previous studies have shown that selenium has potential anti-aging effects, but the findings have been inconsistent. Some studies have found that selenium supplementation can increase telomere length and reduce DNA damage, while other studies have found no effect. This study aims to systematically review the literature on the relationship between selenium and telomere length and DNA damage. The goal is to clarify the role of selenium in aging and to identify the factors that may influence the effectiveness of selenium supplementation.

METHOD

This study used the Systematic Literature Review method to summarize evidence regarding selenium's potential as an anti-aging agent, conducted in April and May 2023. In the early stages of the study, research questions were identified consisting of PICO (Population, Intervention, Comparator, and Outcome). The population was adults with selenium intervention, did not use a comparator, and the outcome used non-epigenetic biomarkers, namely telomere length and DNA damage which reflect aging-related changes at the genome and cellular level.

To obtain the data results according to this stage, it began with a data search on the websites:
https://www.scopus.com,
https://www.mdpi.com/,
https://pubmed.ncbi.nlm.nih.gov/,
https://www.sciencedirect.com/,
https://www.nature.com/,
https://www.hindawi.com/journals/.

The keywords included "Selenium and telomere length and aging" and "Selenium and DNA damage and aging". The article inclusion criteria, such as the result of research published in 2018 – 2023, in English, the population was human, selenium intervention, and the outcome was telomere length and DNA damage associated with aging.

Followed by data screening to filter and select the appropriate data based on the journal abstracts obtained and ended with an assessment of data quality using the website https://rayyan.ai/. The quality of the data was measured by the clarity of the research article methodology, which can provide a good chronological aspect starting from the selection of materials and study results that were in accordance with this article. The next step was to develop a protocol using Meta-analysis (PRISMA/Preferred Reporting Hans for Systematic Reviews and Meta-analysis) [10]. The data extraction process included full-text articles and summarized information by systematic review (Figure 1).

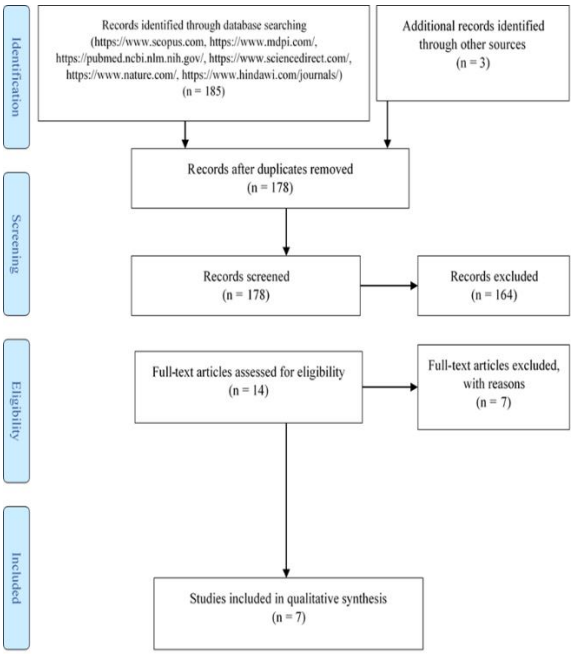

Figure 1. PRISMA Flow Diagram.

RESULTS

This review was obtained from various countries, including Sweden, France, the United States, Australia, and Brazil. The research subjects used were also diverse and at wide intervals, ranging from young people (20-30 years) to older people (> 70 years). A total of 4 of the 7 studies used a cross-sectional study scheme, 1 case-control, and 2 used an experimental design. The main variables observed were telomere length and DNA damage (Table 1).

Table 1. Tabulation of Data Extraction

No	Source	Country	Selenium	Research Subject	Research Design	Main Variabel	Main Finding
1	Opstad et al. 2022 [11]	Sweden	Supplements	Selenium-deficient Swedish elderly people aged over 70 years.	Randomized, double-blind, placebo-controlled clinical trial.	Telomere length	Supplementation with a combination of selenium and coenzyme Q10 for 42 months prevented telomere length reduction in an elderly population in Sweden that is deficient in selenium.
2	Favrot et al. 2018 [12]	French	Supplements	Young age (20 – 30 y.o) Old age (60 -70 y.o)	Experimental	DNA Damage	• Low doses of selenium (30 nM) were effective in protecting keratinocytes in young individuals from damage from UVA exposure, • Higher doses (240 nM) were required to protect keratinocytes.
3	Shu et al. 2020 [13]	United States	Food intake	Middle-aged and elderly people	Cross-sectional	Telomere length	• Increased dietary intake of selenium linked to longer telomeres in adults and elderly Americans. • Every 20 µg increase in dietary intake of selenium was associated with an increase in telomere length of 0.42%. • Dietary intake of selenium might play a role in telomere length maintenance.
4	Dhillon, Deo, and Fenech 2023 [14]	Australia	Selenium level	The 2 groups were prostate cancer patients and	Case-control	DNA Damage	• Increased DNA damage could be caused by low levels of lycopene and selenium

				healthy people			• Eating foods rich in lycopene and selenium could help reduce the risk of developing prostate cancer and DNA damage caused by ionizing radiation and/or oxidative stress.
5	de Lima-Reis et al. 2022 [15]	Brazil	Food	Subjects were men and women between the ages of 20 and 59 y.o	Cross-sectional	DNA damage	• Oxidative damage to DNA in individuals at cardiovascular risk was influenced by serum levels of vitamin A, selenium, and DTAC independently of other factors [F(6,110)=8,213; P<0.001; R2=0.330]. • Nutritional factors such as total antioxidant capacity in food, vitamin A, and selenium might protect against oxidative damage to DNA in these individuals.
6	Liu et al. 2019 [16]	United States	Food	Adults aged 20 years or older who participated in the National Health and Nutrition Examination Survey (NHANES) 1999-2002.	Cross-sectional	Telomere length	• No significant association was found between dietary intake of selenium and telomere length in adults in the United States. • There was a significant interaction with age (P = 0.02). In individuals aged 20–44 years, the β-coefficient of telomere length log, compared to the group with the lowest intake of dietary selenium, was -0.041 (SE 0.012, P = 0.002) and -0.033 (SE 0.018,

							P = 0.07) for the middle group and the highest intake of selenium, respectively. • The relationship between dietary selenium intake and telomere length differed significantly by age group, suggesting that higher selenium intake may prevent telomere shortening in older adults but not in younger or middle-aged adults.
7	Gong et al. 2023 [17]	United States	Food intake	Age ≥45 y.o and ≤45 y.o	Cross-sectional	Telomere length	• Low (< 50 μg/day) and high (> 250 μg/day) selenium intake did not significantly associate with telomere length in diabetic patients. • Selenium intake in the 0-250 μg/day range was associated with increased telomere length in diabetic patients, especially in the female population.

Selenium, Telomere Length, Aging

Telomere length is related to the aging process. Telomeres are protective structures at the ends of chromosomes that shorten each time somatic cells (body cells) replicate [18]. Short telomeres indicate that the cell has lost its ability to replicate [19]. As a result, cells enter the senescence (aging) stage or experience cell death. Telomere shortening indicates cell aging and can affect cell function and integrity [20]. Telomere length decreases proportionally with age in humans, and fetal cells or tissues have longer telomeres than adult somatic cells [21]. In addition, telomere shortening is also associated with the risk of chronic age-related diseases, such as heart disease, diabetes, cancer, and neurodegenerative conditions [22]. Telomere shortening can accelerate the cellular aging process [23], increases cell susceptibility to damage and stress [24], and interfere with normal cell function [25].

Telomere shortening can be inhibited by lifestyle modifications such as diet and physical activity with the potential to reduce the rate of telomere shortening or at least prevent excessive telomere reduction. An antioxidant-rich diet has been linked to longer telomeres. Antioxidants play an important role because they can slow down the aging process and prevent diseases caused by oxidative stress; besides, various nutrients such as vitamins B12, A, C, and E, selenium, zinc, magnesium, and PUFAs have been linked to DNA protection (telomere integrity). Subjects who followed a diet with higher intakes of fruits, vegetables, nuts, fish, poultry, and whole grains reported

lower markers of inflammation, oxidative stress, and longer telomeres[26].

One of the diet choices to inhibit the rate of telomere shortening is selenium intake. Several studies show a link between selenium and telomere length, namely: 1) Seleme supplementation research in an elderly population in Sweden shows that supplementation with a combination of selenium and coenzyme Q10 for 42 months prevents a decrease in telomere length in a population that is deficient in selenium [11]. Dietary intake of selenium in adults and the elderly in America found that increased intake of selenium in the diet is associated with longer telomeres, and this study also suggests that adequate dietary intake of selenium may contribute to the maintenance of telomere length [16]. Additionally, other studies have shown that higher selenium intake appears to be more associated with telomere length maintenance in older adults but not in younger or middle-aged adults [17]. However, low (< 50 µg/day) and high (> 250 µg/day) selenium intake did not have a significant association with telomere length in diabetic patients [17]. Later, other studies have shown that proper selenium levels in the body can help reduce the risk of inflammation and improve adult survival [27]. The average dietary intake of selenium in the United States ranges from 93 micrograms in women to 134 micrograms in men, compared to only 40 micrograms per day in Europe (the recommended daily amount for adults in the United States is 55 micrograms per day) [28].

Thus, telomere shortening is linked to cellular senescence and the risk of age-related diseases. Lifestyle modifications, including adequate selenium intake, can affect telomere length and maintenance. However, the relationship between selenium and telomere length can be affected by other factors, such as the individual's age and health conditions.

Selenium, DNA Damage, Aging

DNA damage is one factor contributing to the aging process, both natural aging and/or aging influenced by external factors. DNA damage can cause mitochondrial dysfunction, impaired autophagy, altered metabolism, and trigger cell aging [29]. One mechanism related to DNA damage with aging is oxidative stress. Oxidative stress occurs when the balance between free radical production and the ability of cells to fight free radicals is disturbed. In aging, the body's antioxidant system tends to decrease so that the level of free radicals that damage DNA increases.

Figure 2 shows that selenium is required for the synthesis of selenoproteins, which are included in the cellular antioxidant system. Selenoprotein acts as an antioxidant enzyme that can inhibit the production of free radicals, thereby helping to protect cells from oxidative damage caused by free radicals. Adequate selenoprotein levels, selenium can help reduce the level of free radicals in cells, thereby reducing the risk of DNA damage caused by free radicals [30]. Thus, selenium acts as a nutrient that protects DNA from oxidative damage.

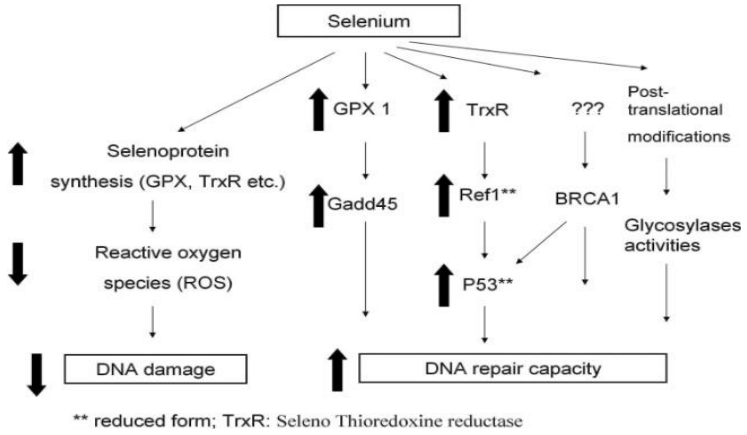

Figure 2. Mechanisms of selenium in DNA damage repair [30]

The results showed that low doses of selenium (30 nM) were effective in protecting young keratinocytes from UVA damage, whereas higher doses (240 nM) were needed to protect aged keratinocytes[12]. Selenium supplementation is a strategy to fight aging and

signs of aging on the skin by protecting skin cells from DNA damage. Then, a deficiency of selenium and lycopene (carotenoids in tomatoes) can exacerbate DNA damage and increase the risk of prostate cancer [14]. In addition, there is a relationship between selenium levels in the body and the level of DNA damage caused by oxidative stress in individuals with different cardiovascular risks [15].

CONCLUSION

Adequate selenium intake can potentially affect telomere length and telomere length maintenance. However, the relationship between selenium and telomere length can be affected by other factors, such as the individual's age and health conditions. Then, intake of selenium through food or supplementation is one effort to protect DNA from oxidative damage, slow the aging process, and reduce the risk of related diseases.

Selenium intake may be an important factor in maintaining telomere length and preventing age-related diseases. Selenium supplementation may be beneficial for people with low selenium levels or who are at risk of age-related diseases. Further research is needed to confirm the findings of this study and to determine the optimal dose of selenium for maintaining telomere length.

REFERENCE

1. Amarya S, Singh K, Sabharwal M. Ageing Process and Physiological Changes. In: Gerontology [Internet]. IntechOpen; 2018 [cited 2023 May 18]. Available from: https://www.intechopen.com/chapters/60564
2. Franceschi C, Garagnani P, Morsiani C, Conte M, Santoro A, Grignolio A, et al. The Continuum of Aging and Age-Related Diseases: Common Mechanisms but Different Rates. Front Med (Lausanne). 2018 Mar 12;5:61.
3. Tinggi U. Selenium: its role as antioxidant in human health. Environ Health Prev Med. 2008 Mar;13(2):102–8.
4. Ruggeri RM, D'Ascola A, Vicchio TM, Campo S, Gianì F, Giovinazzo S, et al. Selenium exerts protective effects against oxidative stress and cell damage in human thyrocytes and fibroblasts. Endocrine. 2020 Apr;68(1):151–62.
5. Huang Z, Rose AH, Hoffmann PR. The Role of Selenium in Inflammation and Immunity: From Molecular Mechanisms to Therapeutic Opportunities. Antioxid Redox Signal. 2012 Apr 1;16(7):705–43.
6. McKenzie RC, Arthur JR, Beckett GJ. Selenium and the regulation of cell signaling, growth, and survival: molecular and mechanistic aspects. Antioxid Redox Signal. 2002 Apr;4(2):339–51.
7. Cai Z, Zhang J, Li H. Selenium, aging and aging-related diseases. Aging Clin Exp Res. 2019 Aug 1;31(8):1035–47.
8. Hartmann A, Hartmann C, Secci R, Hermann A, Fuellen G, Walter M. Ranking Biomarkers of Aging by Citation Profiling and Effort Scoring. Frontiers in Genetics [Internet]. 2021 [cited 2023 May 18];12. Available from: https://www.frontiersin.org/articles/10.3389/fgene.2021.686320
9. Gavia-García G, Rosado-Pérez J, Arista-Ugalde TL, Aguiñiga-Sánchez I, Santiago-Osorio E, Mendoza-Núñez VM. Telomere Length and Oxidative Stress and Its Relation with Metabolic Syndrome Components in the Aging. Biology. 2021 Apr;10(4):253.
10. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21;6(7):e1000097.
11. Opstad TB, Alexander J, Aaseth JO, Larsson A, Seljeflot I, Alehagen U. Selenium and Coenzyme Q10 Intervention Prevents Telomere Attrition, with Association to Reduced Cardiovascular Mortality—Sub-Study of a Randomized Clinical Trial. Nutrients. 2022 Jan;14(16):3346.
12. Favrot C, Beal D, Blouin E, Leccia MT, Roussel AM, Rachidi W. Age-Dependent Protective Effect of Selenium against UVA Irradiation in Primary Human Keratinocytes and the Associated DNA Repair Signature. Oxidative Medicine and Cellular

Longevity. 2018;2018:1–9.
13. Shu Y, Wu M, Yang S, Wang Y, Li H. Association of dietary selenium intake with telomere length in middle-aged and older adults. Clinical Nutrition. 2020 Oct;39(10):3086–91.
14. Dhillon VS, Deo P, Fenech M. Effect of Selenium and Lycopene on Radiation Sensitivity in Prostate Cancer Patients Relative to Controls. Cancers (Basel). 2023 Feb 3;15(3):979.
15. de Lima-Reis SR, Silva TA, Costa LSA, Volp ACP, Rios-Santos F, Reis ÉM, et al. Serum levels of vitamin A, selenium, and better dietary total antioxidant capacity are related to lower oxidative DNA damage: A cross-sectional study of individuals at cardiovascular risk. The Journal of Nutritional Biochemistry. 2022 Sep 1;107:109070.
16. Liu B, Sun Y, Xu G, Rong S, Bao W. Association Between Dietary Selenium Intake and Leukocyte Telomere Length in a Nationally Representative Sample of US Adults (OR11-06-19). Current Developments in Nutrition. 2019 Jun 1;3:nzz044.OR11-06-19.
17. Gong H, Yu Q, Guo D, Wang Y, Duan L, Huang W, et al. The relationship between dietary selenium intake and telomere length among diabetes. British Journal of Nutrition. 2023 Feb;129(4):610–6.
18. Shammas MA. Telomeres, lifestyle, cancer, and aging. Curr Opin Clin Nutr Metab Care. 2011 Jan;14(1):28–34.
19. Maestroni L, Matmati S, Coulon S. Solving the Telomere Replication Problem. Genes (Basel). 2017 Jan 31;8(2):55.
20. Ridout KK, Ridout SJ, Goonan K, Tyrka AR, Price LH. Chapter 18 - Telomeres and Early Life Stress. In: Fink G, editor. Stress: Neuroendocrinology and Neurobiology [Internet]. San Diego: Academic Press; 2017 [cited 2023 May 22]. p. 185–93. Available from: https://www.sciencedirect.com/science/article/pii/B9780128021750000188
21. Purwaningsih E. Telomer, Aging Dan Karsinogenesis. YARSI medical Journal. 2010 Aug;18(2):137–43.
22. Rossiello F, Jurk D, Passos JF, d'Adda di Fagagna F. Telomere dysfunction in ageing and age-related diseases. Nat Cell Biol. 2022 Feb;24(2):135–47.
23. Lin J, Epel E. Stress and telomere shortening: Insights from cellular mechanisms. Ageing Res Rev. 2022 Jan;73:101507.
24. Barnes RP, Fouquerel E, Opresko PL. The impact of oxidative DNA damage and stress on telomere homeostasis. Mech Ageing Dev. 2019 Jan;177:37–45.
25. Ruiz A, Flores-Gonzalez J, Buendia-Roldan I, Chavez-Galan L. Telomere Shortening and Its Association with Cell Dysfunction in Lung Diseases. Int J Mol Sci. 2021 Dec 31;23(1):425.
26. Ojeda-Rodriguez A, Morell-Azanza L, Alonso-Pedrero L, Del Moral AM. Aging, Telomere Integrity, and Antioxidant Food. In: Obesity [Internet]. Elsevier; 2018 [cited 2023 May 29]. p. 241–61. Available from: https://linkinghub.elsevier.com/retrieve/pii/B978012812504500012X
27. Giovannini S, Onder G, Lattanzio F, Bustacchini S, di Stefano G, Moresi R, et al. Selenium Concentrations and Mortality Among Community-Dwelling Older Adults: Results from ilSIRENTE Study. J Nutr Health Aging. 2018 May 1;22(5):608–12.
28. Daniells S. Higher dietary selenium intakes linked to younger 'biological age': Telomere study [Internet]. nutraingredients-usa.com. 2022 [cited 2023 May 29]. Available from: https://www.nutraingredients-usa.com/Article/2022/06/27/higher-dietary-selenium-intakes-linked-to-younger-biological-age-telomere-study
29. Yousefzadeh M, Henpita C, Vyas R, Soto-Palma C, Robbins P, Niedernhofer L. DNA damage—how and why we age? Simon M, Tyler JK, editors. eLife. 2021 Jan 29;10:e62852.
30. Bera S, Rosa VD, Rachidi W, Diamond AM. Does a role for selenium in DNA damage repair explain apparent controversies in its use in chemoprevention? Mutagenesis. 2013 Mar;28(2):127–34.