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REVIEW ARTICLE

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Major clinical outcomes of nutrology and lifestyle in the metabolic processes of healthy aging: a systematic review

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Abstract

Introduction: Centenarians exemplify the concept of healthy aging and therefore provide an invaluable resource for identifying novel host-intestinal microbiota relationships concerning aging. Approximately 18 micronutrients, composed of minerals and vitamins, facilitate the optimal utilization of macronutrients through their role in catalyzing numerous biochemical processes, increasing their bioavailability and absorption, and balancing the microbiome. In the context of aging, a major challenge to maintaining health in old age is unbalanced nutritional intake, resulting in nutritional deficiency or malnutrition. **Objective:** The main clinical outcomes of nutrology and lifestyle in the metabolic processes of healthy aging were listed through a systematic review. **Methods:** The systematic review rules of the PRISMA Platform were followed. The search was carried out from July to August 2024 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 118 articles were found. A total of 39 articles were fully evaluated and 29 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 21 studies with a high risk of bias and 15 that did not meet the GRADE and AMSTAR-2 criteria. Most studies showed homogeneity in their results, with X^2=82.7%>50%. Zinc and copper govern many functions that characterize the so-called "oxy-aging". Selenium (Se) is a fundamental cofactor in many redox functions, the role of vitamin C in aging has been investigated particularly for skin health and immunity, particularly in inflammatory and degenerative diseases. Retinoids, which represent a synthetic form of vitamin A, appear effective in preventing skin degeneration due to aging. The role of vitamin E in the prevention and reduction of ROS-induced lesions has been well described. Supplementation with selenium and coenzyme Q10 influenced the analyzed biomarkers in a way that

indicated an anti-aging effect. It was concluded that an adequate plasma level of trace elements, such as Zn or copper (Cu), promotes an optimal function of the immune response. Selenium (Se) is a key cofactor in many redox functions, which reduces ROS-induced degeneration in the senescent phenotype. The role of vitamin C in aging has been investigated particularly for skin health and immunity, particularly in inflammatory and degenerative diseases. Vitamin A acts in the prevention of skin degeneration due to aging. The role of vitamin E in the prevention and reduction of ROS-induced lesions has been well described, as well as it has been associated with the prevention of cognitive decline during senescence, particularly in Alzheimer's disease. Good fats, vitamins, minerals, or polyphenols can have antioxidant and anti-inflammatory activities, with anti-aging effects. Recent studies have shown that vitamin K is a vital cofactor in the activation of several proteins, which act against age-related syndromes.

Keywords: Healthy aging. Nutrients. Vitamins. Metabolism.

Introduction

Centenarians exemplify the concept of healthy aging and thus provide an invaluable resource for identifying novel host-gut microbiota relationships concerning aging. The global increase in the number of elderly individuals has stimulated extensive health and social concerns, presenting emerging clinical challenges regarding chronic conditions such as diabetes mellitus, kidney disease, neurological disorders, cardiovascular disease, and neoplasia in an aging population. A deeper understanding of aging processes and the mechanisms underlying age-related diseases may lay the foundation for the development of more effective health strategies for older adults **[1,2]**. In this scenario, the three essential macronutrients that provide the basic materials for the construction of biological structures and for the production of energy required for all physiological and biochemical processes are proteins, carbohydrates, and lipids. Furthermore, approximately 18 micronutrients, composed of minerals and vitamins, facilitate the optimal utilization of macronutrients through their role in catalyzing numerous biochemical processes, increasing their bioavailability and absorption, and balancing the microbiome **[2]**.

In the context of aging, a major challenge to maintaining health in old age is unbalanced nutritional intake, resulting in nutritional deficiency or malnutrition. Among the various reasons for this condition is the age-related decline in digestive and metabolic activities, exacerbated by reduced taste and smell and worsening oral health, including the ability to chew and swallow. In addition, older adults' greater dependence on medications for the management or treatment of various chronic conditions may be antagonistic to certain essential nutrients. For example, long-term use of metformin, the most frequently prescribed medication for type 2 diabetes, reduces the levels of vitamin B12 and folate in the body **[3,4]**.

Some other well-known examples of medications used to treat age-related diseases include statins, and cholesterol-lowering drugs, which can cause coenzyme Q10 levels to become too low. Several diuretics (water pills) can cause potassium levels to become too low, and antacids can decrease vitamin B12, calcium, magnesium, and other minerals. Thus, medications used to treat chronic diseases in old age can also be "nutrient wasters" or "antinutrients" and can cause decreased absorption, bioavailability, and utilization of essential micronutrients and may have deleterious health effects **[4,5]**.

In contrast, many nutritional components have the potential to interact with various medications, leading to reduced therapeutic efficacy of the medication or increased adverse effects of the medication, which can have serious health consequences. For example, calcium in dairy products such as milk, cheese, and yogurt can inhibit the absorption of tetracycline and quinolone antibiotics, thus compromising their ability to effectively treat infections **[1,5]**. In the context of nutrology, lifestyle, and longevity, aging promotes a senescent phenotype with tissue degeneration, telomere shortening, dementia, cognitive deficits, functional impairments, and chronic pathologies **[1-3]**. There is a theory of genetically programmed longevity, showing that aging is the consequence of the initiation or interruption of certain genes and the shortening of telomeres **[1]**. Furthermore, there is an endocrine theory that aging is governed by a biological clock whose function is regulated by endocrine mechanisms, among which the insulin-like growth hormone IGF-1 plays an important role. And there is a theory about immunity, stating that the immune system is programmed to decrease its functionality (immunosenescence), increasing susceptibility to infectious diseases and inflammatory pathologies **[4]**.

In this scenario, reactive oxygen species (ROS) are probably the most important free radicals, with major implications for the destruction and aging of cells and the body. It has been shown that mitochondria are the main site of chemical reactions that generate free radicals. Considering aging as a gradual decrease in the functional regulation of complex multifactorial biological processes, the individual's genotype certainly impacts the rate of aging **[4-7]**.

Given this, the main ways to increase healthy life expectancy include lifestyle modifications and pharmacological (or genetic) manipulations **[1,2]**. Adequate diet and caloric restriction are crucial for healthy aging **[5]**. One of the main goals of anti-aging medicine, however, is not only to extend life expectancy but, in particular, to sustain a healthy life for longer. Rattan proposed to change the approach in this field from "anti-aging" to "healthy aging", thus reinforcing health-oriented research **[6-8]**.

Therefore, the present study listed the main clinical outcomes of nutrology and lifestyle in the metabolic processes of healthy aging through a systematic review.

METHODS

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 07/18/2024. The AMSTAR-2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 07/18/2024.

Data Sources and Search Strategy

The literature search process was carried out from July to August 2024 and developed based on Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following descriptors (MeSH Terms) were used: "Nutrition. Healthy aging. Nutrients. Vitamins. Metabolism", and using the Boolean "and" between MeSH terms and "or" between historical findings.

Study Quality and Risk of Bias

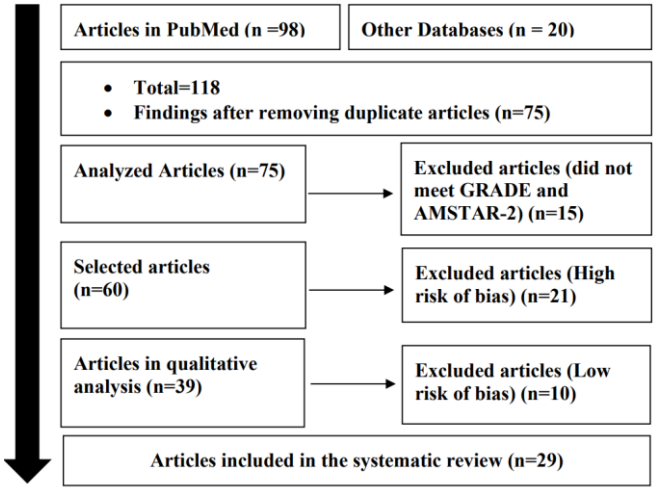
The quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analysis of randomized clinical trials, followed by randomized clinical trials. Low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument through the analysis of the Funnel Plot graph (Sample size versus Effect size), using Cohen's d test.

Results and discussion

Summary of Findings

A total of 118 articles were found that were submitted to eligibility analysis, and 29 final studies were selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with X^2=82.7%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 21 studies with a high risk of bias and 15 studies that did not meet GRADE and AMSTAR-2.

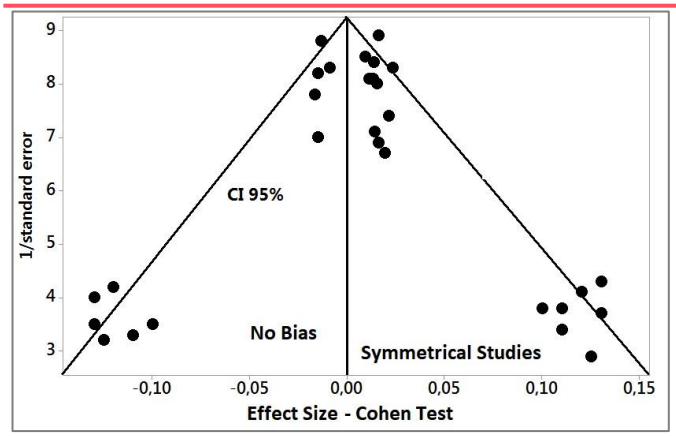
Figure 1. Flowchart showing the article selection process



Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both among studies with small sample sizes (lower precision) that are shown at the bottom of the graph and in studies with large sample sizes that are shown at the top.

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (n=29 studies).



Source: Own Authorship.

Major Clinical Findings

Based on the results found, it was evident that the role of zinc (Zn) in aging and immunosenescence was reviewed and that elderly individuals present deficiency. Zn governs many functions that characterize the so-called "oxy-aging", at least through the functions mentioned above at the biochemical level **[9,10]**. An adequate plasma level of trace elements, such as Zn or copper (Cu), promotes an optimal function of the immune response. High levels of copper, for example, have been associated with cognitive impairment **[11]**.

Furthermore, selenium (Se) is a fundamental cofactor in many redox functions, which reduces ROS-induced degeneration in the senescent phenotype. Cofactors of the main enzymes involved in the elimination of oxidative stressors are certainly beneficial in preventing agingrelated damage **[12,13]**. In the case of Zn, its role in the optimal functioning of immune responses seems particularly crucial, since elderly individuals with reduced zinc levels have been reported to have an increased profile of pro-inflammatory cytokines, such as MCP1 and IL6 in serum, and also to have increased Th1/Th17/inflammatory cytokines (IFNγ, IL17, TNFα, respectively) and decreased naïve CD4 T cells in mesenteric lymph nodes (MLN) **[14–21]**.

Vitamin C (L-ascorbic acid) is a very important water-soluble antioxidant and probably the most common water-soluble vitamin known to date. This vitamin is recommended for dietary intake and topical applications on the skin, as it stimulates collagen synthesis in the dermal layer and contributes to protection against UV-induced damage **[22]**. According to the nationally recommended levels of energy and nutrient intake, the optimal daily intake of L-ascorbic acid ranges from 35 mg/d (6 months to 3 years of age) to 105 mg/d (men) or 85 mg/d (women), except during lactation (130 mg/d). Furthermore, the role of vitamin C in aging has been investigated particularly for skin health and immunity, particularly in inflammatory and degenerative diseases **[22-26]**. In addition, vitamin A can be found in nature as vitamin A (retinol) and provitamin A (carotene) which is found in animal and plant products. Retinol is a highly effective antioxidant. Retinoids, either natural or synthetic, such as tretinoin and tarazotene. Retinoids, which represent a synthetic form of vitamin A, appear effective in preventing skin degeneration due to aging **[27]**. Another antioxidant synthesized by plants is vitamin E, the main sources of which are nuts, grains, extra virgin olive oils, corn, etc. Vitamin E (α-tocopherol) is an essential nutrient derived from a plant lipid antioxidant. The role of vitamin E in preventing and reducing ROS-induced lesions has been well described **[28]**. Tocopherol can prevent UV lipid peroxidation and has a very positive impact on dermal protection. The role of vitamin E in aging is well known, and it has also been associated with the prevention of cognitive decline during senescence, particularly in Alzheimer's disease **[28]**.

Also in this context, vitamin E deficiency causes enzymatic alterations, such as the decreased activity of the cytochrome P450-dependent oxidase system of the microsomal fraction, increased cAMP-phosphodiesterase activity, decreased level of cellular respiration, preventing the conversion of cyanogen amine into its active enzymatic form, etc. **[28]**.

In this scenario, aging is associated with cardiovascular disease (CVD). Since no biomarker reflects the complete aging process, a randomized clinical trial conducted by Alehagen et al. (2023) **[27]** investigated five markers related to cardiovascular disease and age and the effects of selenium and coenzyme Q10 intervention to elucidate the mechanisms that may influence the course of aging. A total of 441 individuals with low selenium status (mean age 77 years, 49% women) were included. The active treatment group (n = 220) received 200 µg/day of selenium and 200 mg/day of coenzyme Q10, combined. Blood samples were collected at enrollment and after 48 months for measurements of intercellular adhesion molecule (ICAM-1), adiponectin, leptin, stem cell factor (SCF), and osteoprotegerin (OPG). Correlation analyses of biomarker values at enrollment concerning age and relevant markers related to inflammation, endothelial dysfunction, and fibrosis demonstrated the association of biomarkers with these pathological processes; however, only ICAM-1 and adiponectin were directly correlated with age. SEM analyses showed, however, that the biomarkers ICAM-1, adiponectin, SCF, and OPG, but not leptin, had significant associations with age and formed two independent structural factors, both significantly related to age. Although no differences were observed at enrollment, biomarkers changed differently in the active treatment and placebo groups (decreasing and increasing levels, respectively) at 48

months ($p \leq 0.02$ in all, adjusted), and in the SEM model, they showed an anti-aging impact.

Scientific evidence has revealed that healthy diets, including good fats, vitamins, minerals, or polyphenolics, can have antioxidant and anti-inflammatory activities, with antiaging effects. Recent studies have shown that vitamin K is a vital cofactor in the activation of several proteins, which act against age-related syndromes. Thus, vitamin K can carboxylate osteocalcin (a protein capable of transporting and fixing calcium in bones), activate matrix Gla protein (an inhibitor of vascular calcification and cardiovascular events), and carboxylate Gas6 protein (involved in brain physiology and cognitive decline and neurodegenerative diseases). By improving insulin sensitivity, vitamin K reduces the risk of diabetes. It also exerts antiproliferative, pro-apoptotic, and autophagic effects and has been associated with a reduced risk of cancer. Recent research shows that protein S, another vitamin K-dependent protein, can prevent the cytokine storm observed in COVID-19 cases. Reduced activation of protein S due to pneumonia-induced vitamin K depletion has been correlated with increased thrombogenicity and possibly fatal outcomes in patients with COVID-19 **[29]**. Furthermore, vitamin K is a multifunctional micronutrient implicated in age-related diseases such as cardiovascular disease, osteoarthritis, and osteoporosis. Although vitamin K-dependent proteins (VKDPs) have been described as playing a crucial role in the pathogenesis of these diseases, new roles have emerged for vitamin K, independent of its role in VKDP carboxylation. Vitamin K has been shown to act as an anti-inflammatory, suppressing nuclear factor-κB (NF-κB) signal transduction and exerting a protective effect against oxidative stress by blocking the generation of reactive oxygen species. Available clinical evidence indicates that high vitamin K status may exert a protective role in the inflammatory and mineralization processes associated with the onset and progression of age-related diseases. Furthermore, the involvement of vitamin K as a protective super micronutrient in aging and "inflammation" is emerging, highlighting its future use in clinical practice **[29]**.

Conclusion

It has been concluded that adequate plasma levels of trace elements such as Zn or copper (Cu) promote optimal immune response function. Selenium (Se) is a key cofactor in many redox functions, which reduces ROS-induced degeneration in the senescent phenotype. The role of vitamin C in aging has been investigated particularly for skin health and immunity, particularly in inflammatory and degenerative diseases. Vitamin A acts in the prevention of skin degeneration due to aging. The role of vitamin E in the prevention and reduction of ROSinduced lesions has been well described, as well as it has been associated with the prevention of cognitive decline during senescence, particularly in Alzheimer's disease. Good fats, vitamins, minerals, or polyphenolics, may have antioxidant and anti-inflammatory activities, with anti-aging effects. Recent studies have shown that vitamin K is a vital cofactor in the activation of several proteins, which act against age-related syndromes.

CRediT

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