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Review article

The Actual Benefits of Zinc for Cardiovascular Diseases: Mini Review

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Abstract

The leading causes of death, particularly among the elderly, are cardiovascular illnesses, which are frequently linked to altered lifestyle patterns. Numerous academic research on health and disease have stressed the role of micronutrients like zinc. Furthermore, both healthy and unwell patients are increasingly consuming dietary supplements that contain micronutrients for wellbeing. Cardiovascular disease can be brought on by trace element deficiencies, particularly zinc insufficiency. This study's goal is to analyze current theories regarding the benefits of zinc supplementation for people with cardiovascular problems. We used reliable websites like Google Scholar, PubMed, and Research Gate to find the most recent papers. Preprints, review papers, and studies with meta-analyses were included, and search terms such as "zinc levels," "cardiovascular disorders," and "zinc homeostasis" were employed. In conclusion, decreasing serum zinc levels were associated with increased mortality and decreased physical activity in individuals with cardiovascular illnesses.

Keywords: zinc, cardiovascular diseases, hypertension, atherosclerosis, antioxidant, heart failure.

الفوائد الحقيقية للزنك في أمراض القلب والأوعية الدموية: مراجعة مصغرة

الخلاصة

من الأسباب الرئيسية للوفاة، لا سيما بين كبار السن، هي أمراض القلب والأوعية الدموية، والتي ترتبط في كثير من الأحيان بأنماط الحياة المتغيرة. أكدت العديد من الأبحاث الأكاديمية حول الصحة والمرض على دور المغذيات الدقيقة مثل الزنك. علاوة على ذلك ، يستهلك كل من المرضى الأصحاء والمرضى بشكل متزايد المكملات الغذائية التي تحتوي على المغذيات الدقيقة من أجل حياة صحية. يمكن أن تحدث أمراض القلب والأوعية الدموية بسبب نقص العناصر النزرة، وخاصة قصور الزنك. هدف هذه الدراسة هو تحليل النظريات الحالية المتعلقة بفوائد المكملات الحاوية على الزنك للأشخاص الذين يعانون من مشاكل في القلب والأوعية الدموية. استخدمنا مواقع ويب موثوقة مثل الباحث العلمي من Google و PubMed و Research Gate للعثور على أحدث النشريات. تم تضمين المطبوعات المسبقة وأوراق المراجعة والدراسات مع التحليلات التلوية، وتم استخدام مصطلحات البحث مثل "مستويات الزنك" و "اضطرابات القلب والأوعية الدموية" و "توازن الزنك". وفي الأستنتاج، ارتبط انخفاض مستويات الزنك في الدم بزيادة الوفيات وانخفاض النشاط البدني لدى الأفراد المصابين بأمراض القلب والأوعية الدموية.

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INTRODUCTION

Non-transmissible diseases, involving cardiovascular diseases, chronic respiratory diseases, cancer, and diabetes mellitus, are major sources of morbidity and mortality globally. The most frequent reasons of lifestyle modifications, such as a good diet, regular exercise, and stopping smoking, are still cardiovascular illnesses [1]. Current guidelines state that a variety of trace minerals, including iron, zinc, copper, and selenium, play a significant role in diets that are cardio-protective. They play a significant part in cellular metabolism. These minerals' oxidant or antioxidant functions may have detrimental effects on cardiovascular health [2]. The

elderly typically has poor zinc homeostasis as a result of age-related changes. Due to its function in the immune system, metabolic functions, and antioxidant defense systems, zinc is a crucial dietary component. Additionally, zinc deficiency promotes apoptosis, increases oxidative stress, and is linked to the etiology of cardiovascular and renal illnesses [3]. There is currently much emphasis on the function of tissue formation of reactive oxygen species in the inflammatory process associated with obesity, diabetes, and CVD. Metal homeostasis is connected with oxidation status, an imbalance of redox metabolism. For instance, magnesium is anti-inflammatory but iron tends to be pro-oxidative [4]. The significance of tissue levels of specific trace elements, including copper and iron, in the production of reactive oxygen species (ROS) during inflammatory processes linked to obesity and various chronic diseases, including diabetes and cardiovascular disease, is currently the focus of research. For instance, zinc is a crucial trace element whose deficiency is associated with cardiovascular diseases. Iron, on the other hand, is a general pro-oxidant, whereas magnesium and zinc have an anti-inflammatory effect. The enormous number of proteins that need zinc ions as part of their structures is thought to be the reason for zinc's significance. In addition, zinc has constitutional and adjuvant activity in tens of thousands of enzymes in addition to regulatory roles in an increasing number of proteins [5].

Physiological Functions of Zinc

The human body needs zinc for growth and development. About 60% of zinc is contained in the muscles, 30% in the bones, and 5% is available in the skin [6]. Numerous studies have demonstrated that zinc is crucial for a variety of biological and physiological processes that take place within the biological system. Over 300 enzymes that control the creation of macromolecules including DNA, RNA, and proteins as well as cell development, proliferation, and other types of metabolism have been shown to depend on zinc to function [7]. Additionally, the data demonstrate that over 300 proteins and transcription factors need zinc to retain their tertiary structures. By binding proteins, DNA, and RNA, these zinc finger-print domain proteins with Cys2-His2 (C2H2) are known to regulate the gene expression of a number of growth factors, steroid receptors, and immunological response mediators [8]. Zinc has a crucial role as a vital nutrient for human health, as low zinc levels in cells have an impact on the structures of zinc-dependent proteins and lead to anomalies in protein action [9].

Role of Zinc in the Immune Functions

The physiological function of the immune system depends on the element zinc. Zinc has anti-inflammatory and antioxidant capabilities, as well as the ability to stabilize membranes. The survival of immune cells is decreased by zinc deficiency, and critical processes including phagocytosis, target cell death, and cytokine synthesis are also compromised. Zinc deficiency results in thymus and lymphoid tissue atrophy, as well as a reduction in the helper T cell activation machinery and cytotoxic CD8+ T-cell responses, according to preclinical prototype studies. Immune system weakening is specifically brought on by zinc deficiency [10]. Due to zinc's direct effects on immune system cells, there is a clear correlation between zinc deficiency and reduced immunological function, particularly during respiratory tract infections [11].

Zinc as an Antioxidant and Anti-inflammatory Element

Minerals and other necessary elements that have the capacity to scavenge free radicals are together referred to as antioxidants. Selenium, zinc, and vitamins A, C, and E are some of them. These nutrients have been proven to lower cardiovascular disease morbidity and mortality and may also aid in the activation of innate antioxidant defenses [12]. The catalytic activity of copper/zinc superoxide dismutase, compensation of membrane structure, stability of the sulfhydryl groups in the protein, and overexpression of metallothionein, which has the ability to bind metals and express antioxidant functions, are all reasons why zinc, a redox-inactive mineral, functions as an antioxidant. Zinc also reduces anti-inflammatory reactions, which can occasionally lead to an increase in oxidative stress. In biological systems, zinc is involved in a variety of biological processes, including the control of various metabolic pathways. It has been demonstrated that excessive cellular oxidative stress is caused by an increase or decrease in zinc levels [13,14]. Additionally, zinc has anti-inflammatory qualities. The production of inflammatory cytokines such TNF-α, IL-1β, IL-2, and IL-6 was elevated along with declining plasma zinc levels in aged participants; these effects were changed by zinc supplementation. Zinc also produces A20, which inhibits NF-κB activation and lowers the generation of inflammatory cytokines, according to research utilizing cell culture [15].

Zinc Deficiency and Cardiovascular Diseases

Zinc and hypertension

A global health concern, high blood pressure, also referred to as hypertension, raises the risk of many diseases like dementia, ischemic heart disease, chronic renal disease, and stroke. In the entire world, high blood pressure is thought to be the main cause of death. According to estimates, HT will result in 7.5 million fatalities annually. Additionally, in 2025, 1.56 billion individuals are anticipated to have HT. The World Health Organization (WHO) set a target to reduce the prevalence of hypertension by about 25% by 2025 by lowering salt intake and altering other lifestyle factors [16]. With each 10 mmHg rise in systolic blood pressure, observational studies showed that people aged 55 to 64 had a 45% increased chance of having ischemic heart disease and stroke [17]. Community-based screening

makes it feasible to diagnose and treat hypertension early, and lifestyle adjustments like reducing alcohol consumption, salt intake, stress, and obesity can help control the condition [18]. Numerous contradicting conclusions have been drawn from studies on the connection between high serum zinc levels and hypertension. Contrary to previous studies that identified conflicting relationships between serum zinc and blood pressure, a meta-analysis demonstrated that the level of zinc in serum was considerably lower in hypertensive patients than in controls [19]. After adjusting for parameters including caloric intake, sodium intake, and body weight, a different South Korean study discovered that there is an opposing association between zinc intake and systolic blood pressure in obese Korean women [20]. This shows that in this subgroup, zinc deficiency is a unique risk factor for hypertension. The risk of hypertension in men may be independently correlated with greater serum zinc concentrations, according to a prospective study [21], although in hypertension, zinc levels are higher in the heart, kidney, liver, and suprarenal glands and lower in the serum, bones, and lymphocytes. Due to these differences, the zinc level equilibrium is lost, which causes varying degrees of failure that cannot be fully reversed by dietary changes or enhanced GI absorption. Deterioration of the zinc balance can both cause and result in high blood pressure [22]. Zinc's anti-oxidant qualities and function in controlling calcium ion mobility in smooth muscle cells of the heart and blood arteries are related to its proposed influence on blood pressure regulation [23]. Animal experiment findings suggested a potential mechanism for how zinc controls blood pressure. This method proposes that Na^+-Cl^- cotransporter (NCC), a zinc-dependent transporter that is overexpressed in zinc-deficient mice, elevates blood pressure by inducing sodium reabsorption from the kidney [23].

Zinc and atherosclerosis

According to predictions, atherosclerosis will rank among the world's leading causes of mortality and morbidity. Atherosclerosis is thought to be the main risk factor for ischemic heart disease (IHD). According to research, smoking, high blood pressure, diabetes, obesity, dyslipidemia, and family history are the key risk factors for atherosclerosis [24]. Atherosclerosis can lead to a variety of problems, such as coronary artery disease, peripheral artery disease, and cerebrovascular disease. Plaque formation, substantial necrosis or apoptosis, and fibrosis of the surrounding tissues signal the start of the atherosclerosis process. It takes place inside the artery's vessel walls. If the weak plaque is removed, the affected vessels, especially tiny ones like coronary arteries, may become clogged. Typically, these heart or brain intrusions cause immediate mortality, long-term heart or brain damage, or both [25]. In an effort to better understand how zinc contributes to atherosclerosis, numerous studies have been carried out. One prospective longitudinal study discovered a negative correlation between blood zinc levels and the frequency of stroke (ischemic type), particularly in women. Low zinc levels may be a risk factor for ischemic stroke, as evidenced by the inverse relationship between serum zinc concentration and ischemic stroke incidence, particularly in women [26]. An inverse correlation was found between the incidence of hemorrhagic stroke in adult patients with hypertension and the basal level of zinc in plasma in another population study from China that used a nested case-control design [27]. According to the results of a meta-analysis, a zinc supplement had a beneficial effect on the level of plasma lipid indicators in patients with atherosclerosis. In fact, taking zinc supplements lowers total cholesterol, LDL cholesterol, and triglycerides. Additionally, giving patients who have a high risk of developing atherosclerosis zinc supplements raises their HDL cholesterol levels. Therefore, especially in people who are susceptible, it may be able to lower the incidence of atherosclerosis-related disability and death [28]. Due to zinc's crucial function in the immune system, where it serves as an antioxidant and an anti-inflammatory, there may be a connection between the two conditions. In order to prevent these conditions, zinc may be used [29]. It does this by lowering oxidative stress and inflammation. Some chronic conditions, including atherosclerosis and stroke, are accompanied with zinc deficiency, which may enhance the production of inflammatory cytokines and make endothelium cells more susceptible to oxidative stress-related harm. Therefore, increased zinc levels offer protection from stroke, and zinc may play a role in the disease process that results in stroke [26]. The results of studies conducted on lab rats and in cell culture to explain the potential mechanisms of zinc's influence on atherogenesis showed that cellular decline of zinc level led to an overexpression of NF-κB action in endothelial cells, and it has been shown that the smooth muscle cells of the atherosclerotic lesion contain high concentrations of NF-κB. The atherogenesis-related toll-like receptor (TLR) interferes with NF-κB signal transduction, a step in the process of adhesion molecule overexpression, and contributes to the activation and proliferation of smooth muscle cells. TLR is essential for the induction of the immune system response.

Zinc and heart failure

Heart failure (HF) is a serious and well-known health issue that affects more than 23 million individuals worldwide [30]. The myocardium is a target for therapeutic therapies, particularly those that rely on zinc supplementation because it is implicated in the pathogenesis of CVD [5]. A meta-analysis that clarified the connection between zinc and HF revealed a strong correlation between heart failure and a low blood zinc level [31]. According to another study looking at the connection between serum zinc levels and the prognosis of people with heart failure, low blood zinc levels are connected to high mortality and low physical activity [32]. Studies show that patients with ischemic heart failure produce more pro-inflammatory cytokines and free radicals than patients with non-ischemic heart

failure, and that these factors have a greater role in the development of chronic inflammation and oxidative stress. This implies that people with ischemic heart failure may have worse zinc homeostasis than those with non-ischemic heart failure [33]. There are numerous explanations for the association between zinc level and HF, including low desire for food and early satiation, which are general aspects of heart failure and may demonstrate the depressed level of Zn and other trace minerals [5]. These are also ongoing conditions that cause an edema of the GI tract, diminished motility, or intestinal loss of zinc. The metabolism of zinc is also affected by drugs used to treat heart failure, which leads to a lack of zinc. These drugs are the source of diuretics, in particular thiazide, which are commonly used to treat edema and hypertension. They increase the excretion of zinc in the urine, which reduces the amount of zinc in tissue. Furthermore, zinc insufficiency can be brought on by loop diuretics used to treat CHF, especially furosemide, ACEI, and ARBs [5]. On the other hand, the CHF-related compensation involves activation of the neuro-hormonal system, which causes a persistent increase in aldosterone levels and a subsequent increase in parathyroid hormone levels, affecting the homeostasis of largely linked Zn^{2+} and Ca^{2+}. This degradation could lead to extreme excretory losses of Zn2+ and Ca2+ as well as a decrease in the concentrations of both zinc and ionized calcium in the serum. The mitochondriocentric signal-transducer-effector pathway, PTH-mediated Ca^{2+} overloading, oxidative stress-induced cardiac cell necrosis, and antioxidant defense are all inhibited by a Zn^{2+} deficit [34]. Zinc losses are also made worse by ACEI medication and a reduction in Zn^{2+} dietary consumption [35].

Conclusion

Oxidative stress and immunological dysfunction can help to partially explain the connection between zinc and cardiovascular diseases. Zinc supplements had favorable effects on plasma lipid indicators; they considerably decreased total cholesterol, LDL cholesterol, and triglycerides and are useful for ischemic heart conditions. In patients with cardiovascular illnesses, lower serum zinc levels are linked to greater mortality and lower levels of physical activity. Less data supports zinc's actual effect on CVD, hence more studies and clinical trials are required to provide a clearer picture of zinc's role in CVDs. In order to determine a safe and effective Zn supplementation dose, it is also advised to carefully assess Zn supplementation during the course of CVD.

Conflict of interests

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