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Zinc Deficiency In Heart Patients: Causes, Diagnosis And Management

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I. Introduction

Zinc (Zn^{2+}) An essential trace element in the human body, it plays a vital role in more than 300 enzymatic .reactions and is essential for immune system function, wound healing, protein synthesis, and cell division[1] [2]Zinc is abundant in various human tissues. Adult zinc is typically between 1.4 and 2.3 grams. mostly , concentrated in muscles (60%), bones (30%), liver, prostate, and eyes[2] [3].

So that In developed countries, this delicate element often receives insufficient attention due to the rarity of cases of severe zinc deficiency. However, The Deficiency can play an important role in the aging process and in the causes of many chronic diseases, such as neurodegenerative diseases, immune aging, atherosclerosis, or cancer [4].

Physiology of Zinc

Zinc Absorption and Metabolism

,After iron, zinc is the second most abundant trace element in the human body, as it is found in all organs tissues, and fluids. Plasma zinc makes up only 0.1% of the body's total zinc[5] Dietary zinc is absorbed along . the entire intestinal tract, where the duodenum and jejunum are the main absorption sites. Zinc is transported from the intestinal cavity to the intestinal cells by the 4-like proteinZrt/IRT (ZIP4) which is located on the apical , membrane of intestinal cells. Under normal conditions, the kinetics of intestinal zinc absorption are transport- .mediated and saturated[6] Can be further organized Express . ZIP4 Zinc Carrier 1 (ZnT1) which It's protein. On .the lateral basal membrane, which is Responsible for exporting zinc from intestinal cells to the portal circulation When you are tr[7] ،Zinc aces are low, as in the case of deficiency, these transporters increase their effectiveness while Say Effectiveness When zinc concentrations increase, albumin is the main transporter of zinc in the portal and systemic circulation. and[6] There are many zinc transporters that facilitate its cellular and subcellular movement, as well as its transport within and between tissues [8].

Zinc is excreted from the body mainly through feces. Endogenous zinc is excreted in the digestive tract where some of it is reabsorbed, and the rest is excreted in the stool [9]. Zinc is also lost in the urine, which accounts for less than 10% of zinc loss Natural. Other ways to lose zinc include skin cell regeneration, sweat, hair, semen, and menstruation [10]. In healthy adults, zinc loss is estimated to be around 2 mg per day [11].

Global Epidemiology of Zinc Deficiency:

- ***Global Reach:*** *Zinc deficiency affects about 2 billion people worldwide, or 31% of the populatio[12]*
- ***In developing countries:*** *Zinc deficiency affects 17% of the world's population, and up to 35% in low-income populations, i.e. South Asia and Africa [13]*
- ***In heart patients:*** *Deficiency rates up to 68% in patients with chronic heart failure [14].*
- ***:Seniors****60-40 of Older people with zinc deficiency % [15].*
- ***Economic Cost:*** *The World Health Organization estimates the annual cost For problems caused by zinc deficiency $20.5 billion [16].*

Recent data from a study Framingham Heart Study that low levels of zinc in serum are associated with . an increased risk of coronary heart disease by High[17] Recent cross-sectional studies have also shown that heart failure patients show low zinc levels A large percentage of Cases compared to 10-15% with Healthy people [18] ، [21]Until he stood out The concept of zinc as "21st century calcium . [19].

Zinc is an element Essential Rare Plays a Critical Role in Immune Function, Regulation of Oxidative Stress, and Internal Cardiovascular Balance [20] , and often What Heart Failure Patients Show Excess Zinc in Urine due to the use of diuretics and renin-angiotensin-aldosterone inhibitors, which further exacerbate zinc deficiency. Mechanically, it may contribute [22]Zinc deficiency In the progression of heart failure through

multiple pathways, including increased oxidative stress, systemic inflammation, and endothelial dysfunction Vascular. [23]Found Observational study shows that zinc deficiency He was related Predictions Worse in heart failure patients [24]. In addition, preliminary results indicated that zinc supplementation may improve left ventricular ejection fraction (LVEF), highlighting its potential therapeutic role [25].

Molecular roles of zinc in the cardiovascular system:

- ***Maintaining the integrity of the lining of blood vessels:*** *Through Regulation of nitric oxide production (eNOS) Prostacycline[26].*
- ***Regulating blood pressure: Through*** *Effect on the renin-angiotensin-aldosterone system(RAAS) [27].*
- ***Protection from oxidative stress:*** *by means of Cofactor of the enzyme Cu/Zn-SOD Catalase [28].*
- ***Regulation of fat metabolism:*** *because Effect on Enzyme 3-hydroxy-3-methylglutaryl-CoA reductase [29].*
- ***Participation in blood clotting: Through*** *Regulating coagulation factors II ،VII ،IX ،X [30].*
- ***Regulate the heart rhythm:*** *Affect Zinc affects the heart rhythm through a range of mechanisms. These mechanisms include modulation of sodium, calcium and potassium ion channels, as well as influencing beta-adrenergic receptors and the enzyme adenylate cyclase[31].*
- ***Inflammation Control:*** *Inhibition of the path NF-kb and inflammatory cytokines [32].*

Mechanisms of Zinc Molecular Homeostasis:

Intracellular zinc is regulated by a complex network of zinc transporters that includes two main families: ZIP (Zrt-Irt-like proteins) which facilitate the entry of zinc into cells, and ZnT (zinc transporters) which facilitates the exit of zinc from cells [33]. In the cells of the heart muscle, ZIP7 And ZIP14 A pivotal role in maintaining zinc balance [34].

The Relationship Between Heart Disease and Zinc Deficiency

Recent studies indicate that Meta-analysis 24 studies included and 15,184 Co-reported a strong inverse relationship between zinc levels and the risk of heart disease. [32]Where he showed Heart failure patients showed low levels of zinc in Serum (Medium 68.2 ± 15.4μg/dL) Compared to people Healthy people ([35] (95.8 ± 12.3 μg/dL.

Scientific evidence from clinical studies:

- *Showed study The results of the meta-analysis indicated that there is a significant association between low .serum zinc levels and heart failure[36]*
- *Zinc deficiency caused 14.4% of diarrhoeal deaths, 10.4% of malaria deaths and 6.7% of pneumonia deaths among children aged 6 months to 5 years[37].*
- *A significant inverse relationship was found between zinc level and ICU admission; as the zinc level decreased, the likelihood of admission to the ICU increased. [38]*

Molecular and biochemical mechanisms of zinc deficiency:

1. ***Effect on Cardiac Muscular Contraction:*** *Zinc deficiency affects contractile proteins (troponin and myosin) and reduces calcium sensitivity to muscle filaments, resulting in decreased systolic strength[39] as Regulates . activity Ca^{2+}-ATPase In the sarcoplasmic reticulum[40].*
2. ***Chronic inflammatory pathways:*** *Zinc deficiency activates a pathway NF-kb and increased production of inflammatory cytokines (TNF-A, IL-1β, IL-6) by 2-4 times, which accelerates the development of atherosclerosis and the accumulation of fatty platelets [41].*
3. ***Oxidative stress and free radicals:*** *Low zinc levels reduce enzyme activity Cu/Zn-superoxide dismutase by increases the accumulation of free radicals ,%60-40 (ROS) and oxidation[42]LDL-cholesterol and also affects , activityglutathione peroxidase And ،[28]catalase.*
4. ***Lipid and glucose metabolism disorder:*** *Zinc deficiency affects the activity of the enzyme HMG-CoA reductase and increases of LDL cholesterol levels [43] (LDL) by 20-30%, and increases insulin resistance and [44] HbA1c.*
5. ***Impact on endothelial functions:*** *Zinc deficiency reduces nitric oxide production by 35-50%، It increases endothelin-1 production, leading to endothelial dysfunction، and increased vascular resistance[45].*
6. ***Electrolysis disorder:*** *Zinc deficiency affects the sodium and potassium channels in the heart muscle, increasing the risk of arrhythmias, especially ventricular tachycardia [31].*

Molecular effects at the gene level:

Zinc deficiency affects the expression of more than 2,000 genes, the most important of which are genes responsible for the synthesis of cardiac proteins such as A-myosin heavy chain and β-myosin heavy chain [46]

It also influences the expression of antioxidant and inflammatory genes, which explains the strong association between zinc deficiency and the development of heart disease [32].

Type of Medication	Typical dosage	Mechanism	Degree of Impact	Duration of Effect
Lug diuretics (Furosemide)	40-240 mg/day	Increase the excretion of zinc in the urine by 3-5 times [47] .	High	4-6 hours after each dose
Loop diuretics (Bumetanide, Torsemide)	1-10 mg/day, 10-mg/day 200	Discourage NKCC2 and increased zinc loss [48].	Very high	6-8 hours
Thiazide diuretics (HCTZ, Indapamide)	25-50 ,mg/day mg/day 2.5-1.25	Discourage NCC and increased Zn^{2+} loss[49].	Medium to High [50].	12-24 hours
ACE inhibitors	5-40 mg/day depending on) (the type	Complex compounds with zinc and reduced absorption [51].	Medium	8-24 hours
Angiotensin receptor blockers (ARBs)	25-320 mg/day	Indirect effect on zinc distribution [47].	Low to medium	12-24 hours
Digital (Digoxin)	0.125-0.25 mg/day	Interference with Zinc Transporters [52].	Low to medium	36 Hours
Beta-blockers (Metoprolol, Carvedilol)	50-400 mg/day	Effect on Zinc Metabolism in the Liver [47].	Low	6-12 hours
) Beta-blockersAtenolol)		Decreases the level of zinc in the plasma [53]		
Calcium Channel Blockers	5-20 mg/day (amlodipine)	Interference in the absorption of intestinal zinc [54].	Low	24-36 hours
Statins (Atorvastatin, Simvastatin)	10-80mg day/	Effect on Zinc Metabolism Enzymes [55].	Low (9%)	12-24 hours

**: Thiazide diuretics increase urine excretion by 50-60%, although serum zinc levels are often maintained through an unknown compensatory mechanism [50].*

Causes of Zinc Deficiency in Heart Patients

Cardiac Drugs and Diuretics: Pharmacokinetic Effects

The effects of certain groups of antihypertensive drugs on the links between mineral, lipid and glucose metabolism are often overlooked and remain unstudied. Therefore, although loop diuretics are valuable medications, doctors should be aware of their potential impact on zinc secretion and consider monitoring zinc levels, especially in individuals at risk of deficiency.

Heart failure HF is a common syndrome that leads to a high mortality rate. Heart failure may be associated with zinc deficiency through reduced food intake, reduced absorption due to gastroedema edema, impaired motility, or loss of intestinal zinc. Diseases associated with heart failure, such as diabetes DM and high blood pressure, due to zinc deficiency. Medications given for heart failure may affect zinc metabolism in different ways. Thiazides have been shown to cause abandon zinc urine and low concentration of zinc in the tissues. There is conflicting evidence about the impact of furosemide, because that patients receiving chronic furosemide treatment showed low levels of zinc in the tissues in autopsies. Treatment with ACE inhibitors ACE and angiotensin receptor blockers ARBs to abandon Zinc In the urine and lack of zinc in the serum, but this finding was not consistent across all studies. as for Beta blockers It It did not change the concentration of zinc in plasma. If Metalloproteinase matrix MMPs and angiotensin-converting enzyme ACE is Zinc-containing enzymes play a role in the rebuilding process in heart failure. ACE inhibitors have been shown to It can Inhibits the activity of various types of matrix metalloproteinase that. The exact relationship between heart failure, zinc-containing enzymes, zinc deficiency, and clinical symptoms of heart failure should be studied [56].

A study has shown that Loop diuretics such as furosemide in doses>80 mg/day may cause zinc loss of up to 2-3 mg/day, which is equivalent to 20-30% of the recommended daily intake [57]. Also, Long-lasting useMore Who is it 6 months in high doses it may lead to severe deficiency within 3-6 months [58].

Other causes of zinc deficiency in heart patients:

- ***Malnutrition:*** *decreased appetite in patients with advanced heart failure, restriction Sodium It affects the taste .of food, lack of animal protein[59]*
- ***Malabsorption:*** *Intestinal congestion reduces zinc absorption، Intestinal mucositis[60].*
- ***Increased metabolic need:*** *Oxidative stress increases zinc consumption by 2-3 times, chronic inflammation leads to the redistribution of zinc to tissues[61].*
- ***Age (>65 years):*** *The kidneys may lose their ability to effectively reabsorb zinc with age, leading to an increase in levels of zinc excreted in the urine [62].*
- *Lack of dietary diversity and low total nutrient intake may lead to lower zinc levels in older adults[15].*

- *Certain medications, especially those that work on Lose Stomach acid (such as proton pump inhibitors or blockers H2), also affect the absorption of zinc. [63]*
- ***Affective comorbidities:***
- *Diabetes: 2-4 times increased kidney loss, and chronic kidney disease: Disturbance in reabsorption, as well as Liver disease: Deficiency of zinc-transporting albumin synthesis[64].*
- *Zinc deficiency to be accompanied by Hypothyroidism [65].*
- ***Nutritional factors:*** *Vegan diet, excessive intake of phytes and fiber, low meat intake[66].*
- ***Environmental factors:*** *Exposure to heavy metals (lead, cadmium), heavy alcohol intake [64].*

Genetic and Genetic Factors

Genetic basis of zinc metabolism:

Zinc homeostasis is controlled by a complex network of specialized genes, which includes 24 genes for zinc transporters from the ZIP and . ZnT Mutations in these genes may lead to a disturbance in the uptake, distribution, or excretion of zinc [34].

Key influencing genes:

Gene	*Function*	*Impact on the heart*	*Spread of the surge*
SLC39A4 (ZIP4)	*Intestinal Zinc Absorption*	*Early heart failure[67].*	*1:500,000*
SLC30A8 (ZnT8)	*Regulation of Zinc in the Pancreas [68].*	*Increased risk of diabetes and heart*	*15-20% in some races*
SLC39A8 (ZIP8)	*Transport of Zinc and Manganese*	*Cardiomyopathy [69].*	*Rare <1:1,000,000*

Genetic mutations and associated diseases:

- ***Acrodermatitis Enteropathica****Mutation in gene* ***:*** *SLC39A4 leading to severe zinc absorption and premature , heart complications[70].*
- ***Syndrome Ehlers-Danlos*** *They are associated with mutations that affect zinc metabolism and lead to* ***:*** *connective tissue disorders in the heart [71].*
- ***Genetic variation in CYP2E1:*** *Affects zinc metabolism and increases the risk of heart disease [72].*

Available genetic tests:

- ***Complete exome sequencing:*** *To detect zinc transporter mutations [73].*
- ***analysis SNPs:*** *To detect genetic variation in zinc metabolism genes [74].*

Clinical Symptoms and Signs

Clinical symptoms in severe cases of zinc deficiency include pustular bullous dermatitis, alopecia, diarrhea, emotional disturbances, weight loss, recurrent infections, and male hypogonadism, in mild cases of zinc deficiency, spermatomy observed and increased ammonia level in the bloodandModerate zinc deficiency is characterized by delayed growth and puberty in adolescents, male hypogonadism, rough skin, poor appetite, mental lethargy, delayed wound healing, taste disorders, and difficulty adjusting to dark colorsAs for severe zinc deficiency,It can lead to fatal results if not detected and treated. Zinc is an important element for growth, and lack of Negatively affects T cell function and chemotaxis, commonly observed in cellular immune function in zinc deficiency patients. Studies have shown that thymopoietin, a hormone necessary for the maturation of T cells, is dependent on zinc [75].

General and systemic symptoms detailed:

- ***Weakened immune system:*** *3-4 times increase in respiratory infection, decrease in lymphocyte count [76]*
- ***Slow wound healing:*** *Increased healing time by 50-70%, especially surgical wounds[77].*
- ***Hair loss:*** *Loss of 20-30% of hair density, brittle and weak hair[70].*
- ***Sensory disturbances:*** *Loss of taste (hypogeusia) . In 70% of cases, the lack of sense of smell is 50%[78]*
- ***Skin problems:*** *Dermatitis around the mouth and extremities, dry and cracked skin [79].*
- ***Celiac disorders:*** *Chronic diarrhea in 40% of cases, malabsorption [80].*
- ***Neuropsychological changes:*** *Depression (45% of patients), mood disorders, difficulty concentrating [81].*
- ***Developmental and developmental disorders:*** *In children - delayed physical and mental development [82].*

Cardiovascular symptoms caused by zinc deficiency:

- ***Increased severity of heart failure symptoms:*** *Deterioration of the classification NYHA Who is it II into III-IV In 65% of patients [83].*
- ***Irregular heartbeat:*** *2.3 times increased risk of atrial fibrillation, ventricular tachycardia in 15% of cases[61].*
- ***High blood pressure:*** *Increase by 10-15 mmHg At systolic pressure, It may be Resistant to conventional treatment[84]*

- ***Reduced ejection fraction:*** *Back off EF within 6 months of deficiency %10-5 [85].*
- ***increase BNP and NT-proBNP*** *Biomarkers rise by 40-60 :% [86].*
- ***Increased cardiovascular events:*** *Increased risk of myocardial infarction [87].*

diagnosis

Laboratory tests and diagnostic criteria:

Updated Zinc Deficiency Diagnostic Criteria (WHO 2023):

1. ***Normal Level:*** *70-120 µg/dL (10.7-18.4 µmol/L) In healthy adults [88].*
2. ***Spurious deficiency:*** *65-70 µg/dL, requires follow-up*
3. ***Mild deficiency:*** *50-65 µg/dL, requires nutritional intervention*
4. ***:Moderate deficiency*** *30-50 µg/dL requires supplementation ,*
5. ***Severe Deficiency:*** *Less than 30 µg/dL-requires immediate treatment [89].*

Standard Sampling Protocol:

1. ***Optimal timing:*** *8-10 am, 8-12 hours fasting, avoid supplementation for 24 hours [90].*
2. ***Sampling Criteria:*** *Rare Metal-Free Plastic Tubes, Avoid Silicone Rubber Tubes [90].*
3. ***Laboratory Interventions:***

- *Acute infections: temporary decrease 20-40%. [91]*
- *. Pregnancy: Physiological low 15-25%[92]*
- *Medications: diuretics, antacids, steroids[93].*
- *Phyte-rich meals: effect for 4-6 hours [94].*

Necessary accompanying tests: *Copper, Iron, Albumi CRP-Total Protein, Magnesium، Vitamin D level 25 , OHIn the serum، Folic acid in serum [95].*

Measuring plasma zinc levels helps confirm the diagnosis. A level of less than 70 µg/L in the case of fasting or less than 65 µg/dL in the case of non-fasting is considered diagnostic. However, you should use sufficient caution while testing zinc levels for accurate values. Using contaminated tubes, catheters, needles, or ,rubber plugs may lead to incorrectly high levels of zinc. Zinc levels may vary depending on the time of day stress, or inflammation. The sample should be withdrawn in the morning using specially acid-washed glass tubes or vials. Low albumin levels may lead to low zinc levels, so serum albumin should also be measured. Measuring alkaline phosphatase, a zinc-based enzyme, may also be helpful in some cases. In cases where the diagnosis is doubtful, a histological examination of the affected skin may be helpful but not diagnostic. Characteristic changes include psoriatic hyperplasia with necrolysis, a term used to describe cytoplasmic paleness, spongiform keratosis and focal keratosis[70].

To obtain accurate serum zinc measurement, samples should be collected using zinc-free vacuum tubes and stainless steel needles, avoiding rubber plugs and hemolysis. Plasma or serum should be separated within 45 minutes, using anticoagulants with low zinc concentrations, preferably as morning samples on an empty stomach. Zinc levels in the urine and zinc concentrations in hair vary widely and cannot be relied upon to assess acute deficiency [96].

Additional diagnostic tests:

- ***Measurement of zinc in urine (24 hours):***
- *Normal Values: 0.3-0.7 mg/24h*
- *Zinc deficiency: less than 0.2 mg/24h*
- *Excessive loss: > 1.5 mg/24h (with diuretics)*
- ***Measurement of zinc in white blood cells:***
- *More refined than serum zinc [97].*
- *Normal Values: 10-14 µg/g protein*
- *Reverses long-lasting zinc stores*
- *Less than* ***Measuring zinc in hair:*** *Useful for assessing chronic deficiency (More than 2-3)Values70 ppm Indicates deficiency [98].*
- ***Zinc Taste Test (Zinc taste test):*** *85% sensitivity in detecting deficiency [99].*
- ***Measurement of Zinc Enzymes:***
- *Alkaline phosphatase decreases with zinc deficiency [100].*
- *Cu/Zn-SOD)Copper/Zinc Superoxide Dismutase Indicator Important Career ([101].*
- *Carbonic anhydrase: Affected by Zinc Deficiency [102].*

Tiered Diagnostic Algorithm:
Phase I - Initial Examination:
1. Serum Zinc Measurement + Medical History
2. If more than 70 µg/dL Periodic follow-up
3. If between 50-70 µg/dL phase II
4. If less than 50 µg/dL Immediate treatment + stage II

Stage II - Advanced Assessment:
1. Measurement of zinc in WBCs or urine
2. Assessment of causative factors
3. Zinc Taste Test
4. Evaluation of response to experimental treatment

Complications and clinical outcomes
Non-cardiac complications:
- ***Recurrent infections:*** *3.2x increase in pneumonia, surgical wound infections [106].*
- ***Wound healing disorder:*** *Delayed recovery after heart surgery [107].*
- ***Depression and cognitive impairment:*** *2.5 times increased rate of depression, decreased cognitive function [108].*
- ***Osteoporosis:*** *1.8 times increased risk of fractures, especially in older people [109].*

Short-term cardiovascular complications:
- ***Worsening of heart failure:*** *Hospitalization rate increased by 45% in 6 months [18].*
- ***Irregular heartbeat:*** *2.1 times increased risk of new atrial fibrillation [103].*
- ***Reduced ejection fraction:*** *Average decline of 8-12% in 3-6 months [104].*
- ***Resistant hypertension:*** *Control failure despite 3 medications in 60% of cases [84].*

Available evidence suggests that the use of ACE inhibitors, angiotensin-2 receptor antagonists, or thiazide diuretics may lower zinc levels in hypertensive patients [105].

Risk assessment tools andforecasts:
Cardiac Zinc Deficiency Severity Scale *[110]* ***(Cardiac Zinc Deficiency Risk Score):***
Scoring Factors
✓ *Age over 65 years (1 point)*
✓ *Lug Diuretics > 80 mg (2 drops)*
✓ *Heart failure NYHA III-IV (2 points)*
✓ *Diabetes (1 point)*
✓ *Glomerular filtration eGFR less than 60 ml/min/1.73m2 (1 drop)*
- ***Low-risk (0-2 points):*** *follow-up every 6 months*
- ***Moderate risk (3-5 points):*** *3-month follow-up + preventive supplementation*
- ***High-risk (6+ points):*** *Monthly follow-up + active treatment*

Management and prevention
Treatment protocols listed by severity of deficiency *[111]:*

The severity of the shortage	*Preferred*	*Daily Dose*	*Duration of treatment*	*Follow-up*
Mild deficiency (50-65 µg/dL)	*Zinc Gluconate*	*15-25 mg elemental*	*3-6 months*	*Every 6-8 weeks*
Moderate defect (30-50 µg /dL)	*Zinc Sulfate*	*50-75 mg Elemental*	*6-12 months*	*Every 4 weeks*
Severe defect (<30 mb/dL)	*Zinc Picolinate*	*75-100 mg Elemental*	*12-24 Months*	*Every 2 weeks*
Acute deficiency (severe symptoms)	*Zinc Sulfate IV*	*2-5 mg/day IV for 5-7 days*	*Then oral.*	*Daily and then weekly*

Alternative oral therapy is the primary treatment for zinc deficiency. Adults typically need 20 to 40 mg of elemental zinc per day, with symptoms expected to disappear within one to two weeks. The recommended daily dose of elemental zinc to prevent deficiency includes: [112]
- *3 mg/day for children under four years of age*
- *5 mg/day for children four to eight years of age*
- *8 mg/day for children nine to thirteen years of age*
- *9 mg/day for non-pregnant and non-breastfeeding women*
- *11 mg/day for men*

- *11 to 12 mg/day for pregnant and lactating women*

Absorption Improvement Protocol and Intake Guidelines:
- ***Optimal timing:*** *One hour before breakfast or 2-3 hours after the last meal, avoid taking with coffee and tea [112].*
- ***Avoid interference:***
- *Milk and dairy products: Spacing 2 hours [113].*
- *Iron and copper: Spacing 3-4 hours [114].*
- *Antacids: Spacing 4 Hours [115].*
- *Antibiotics (fluoroquinolone): Spacing 6 Hours[116].*
- *Iron and phytate supplements found in cereals and legumes can inhibit the absorption of zinc and should be .taken at least two hours apart from zinc supplements [117]..*
- ***Improved Absorption:*** *Take it with vitamin C (250-500 mg) Avoid rich foods In the Futures [118].*
- ***Split dose:*** *Split the daily dose into two times to reduce side effects such as nausea.*

Nutritional interventions:
Foods rich in zinc *[120]:*
- ***Animal sources:*** *red meat, poultry, fish, shellfish*
- ***Plant sources:*** *legumes, nuts, seeds, whole grains*
- ***Dairy products:*** *cheese, milk, yogurt*

Treatment Monitoring:
1. Measuring the serum zinc level 4-6 weeks after starting treatment
2. Assessment of clinical response (improvement of symptoms)
3. Copper and iron levels monitoring
4. Liver and kidney function monitoring
Warning: *Doses higher than 50 mg/day may cause gastroinconutal side effects, including nausea, abdominal upset and diarrhea. Doses above 150 mg/day may impair function Device immunosuppression, altered lipid levels, and impeded the absorption of iron and copper, which can lead to complications in the genitourinary .system [119] [120]*

Taking long-term or high-dose zinc supplements requires monitoring serum copper levels, as zinc ,competes with copper for absorption. Available formulations include zinc sulfate, zinc acetate, zinc aspartate zinc orotate, and zinc gluconate[119].

Must be monitored Clinical Response toFor patients and serum zinc levels after 3 to 6 months of treatment. If the response is inadequate, the dose can be increased, with careful monitoring of toxicity. In enteropathic dermatitis, lifelong zinc supplementation is required, with dosage determined based on sequential zinc levels. Long-term treatment may also require copper monitoring and taking zinc supplements to prevent zinc-induced deficiency [121].

Prevention
Reviewing the guidelines for mineral supplements will be helpful during the treatment of high blood pressure.

Daily need

The World Health Organization (WHO) (WHO) in its recommendations on zinc on bioavailability. In diets with high zinc bioavailability, men need 4.2 mg per day Women to 3 mg per day. In moderately bioavailable diets, the recommended amount increases to 7 mg per day for men and 4.9 mg per day for women. Low-bioavailability diets require the highest doses of zinc at 14 mg per day for men 9.8 mg per day For Women. [122]

Overdose poisoning

Excessive intake of zinc can lead to poisoning and serious health complications. Among the symptoms of acute zinc poisoning, intestinal problems such as nausea, vomiting, abdominal cramps and diarrhea appear [123] Chronically high zinc consumption increases health risks, such as a weakened immune system and an . impact on copper absorption. Zinc competes with copper in the digestive tract, which can lead to copper ,deficiency when zinc is consumed in large amounts for long periods. This entails problems such as anemia neutropenia, and neurological symptoms such as ataxia and peripheral neuropathy. In addition, other symptoms of zinc poisoning include headaches, fatigue, and lipid metabolism disorders[124].

To reduce these risks, various organizations have set maximum limits on zinc intake. The 25 mg limit may be the most appropriate for zinc intake.[122]

Zinc deficiency prevention strategies are essential to reduce cardiovascular complications, including:

- ***Primary Prevention:*** *Promoting dietary zinc intake in vulnerable populations, especially in developing countries [125].*
- ***Secondary Prevention:*** *Monitoring zinc levels in heart patients receiving diuretics and cardiac medications [87].*
- ***Community-based interventions:*** *Zinc immunization, awareness campaigns, and supplementation in health centers[125].*
- ***Cost and Effectiveness****Studies show that zinc supplementation reduces healthcare costs by Good In heart patients [126].*

II. Conclusion

The exact role of zinc deficiency in the development of cardiovascular disease is still not fully determined. The effect of baseline zinc level on the effectiveness of zinc interventions in addressing cardiovascular disease risk factors is vital and should be comprehensively evaluated and documented. Research suggests that zinc balance changes in the early stages of these diseases, reinforcing the importance of zinc-related therapeutic interventions as a potential means of achieving significant health benefits. Recent biomarkers of zinc status should be taken into account, and there are promising possibilities for the use of zinc-based therapies as a treatment strategy for cardiovascular disease.

III. Recommendations:

Studying the biological properties of zinc with a focus on its role in cardiovascular physiology and disease, conducting large-scale and well-designed randomized clinical trials to study the effect of zinc intake on cardiovascular health, and conducting extensive research on the effectiveness of zinc supplementation in the recovery process from cardiovascular disease. These recommendations contribute to advancing scientific understanding of the role of zinc in heart health, and more effectively guide future treatment strategies and .interventions

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