REVIEW ARTICLE

Reference Range of Serum Zinc Concentration in Patients with Heart Failure: A Systematic Review and Meta-analysis of Cross-Sectional Studies in the 21st Century

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Abstract

Background: Heart failure (HF) is a clinical disorder and Zinc is an important cofactor in regulating oxidative status. The present study aimed to determine the mean concentration of serum zinc in patients with HF.

Methods: PubMed, Embase, Scopus, and Web of Science were used in the present systematic review and meta-analysis to find relevant cross-sectional studies up to 1st January 2020. A random-effects model was used to pool the effect size (ES) and 95% confidence intervals (CI). In addition, meta-regression analysis was performed to find the sources of statistical heterogeneity among the studies.

Results: Our meta-analysis of 1358 HF patients indicated that their mean serum zinc concentration was 66.24 µg/dl (95% CI: 59.16, 73.33). In sub-analysis, the mean concentration was 75.04 µg/dl and 52.90 µg/dl in patients <65 years and >65 years old, respectively. Subgroup analysis by geographical region showed that mean serum zinc was 70.70 µg/dl, 69.08 µg/dl and 60.91 µg/dl in HF patients from Europe, America, and Asia, respectively. Meta-regression analysis indicated a reduction of 1.42 µg/dl in serum zinc per each year of aging.

Conclusion: In summary, our meta-analysis indicates that serum zinc concentrations have a narrow range in HF patients worldwide that declines with age and varies with geographical region. Additionally, serum zinc concentrations are lower in HF patients, specifically in the elderly.

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Introduction

Heart failure (HF) is one of the leading causes of mortality globally and patients affected by heart failure have a poor prognosis, especially the elderly.[1] Micronutrients have essential roles in protecting the body from various diseases, including cardiovascular system diseases. Zinc is an important micronutrient as it has a role in maintaining cell growth and function as well as regulating gene expression.[2] Moreover, Zinc has cardio-protective effects through regulating the differentiation and regeneration of cardiac muscles and cardiac conductance. Furthermore, zinc has an essential role in maintaining antioxidant status in enzymes such as superoxide dismutase and regulates many metalloproteases, including angiotensin-converting enzyme.[3] In addition, it can have protective effects against acute stress and recovery after heart transplantation,[4]

whereas zinc deficiency induces cellular damage.[5, 6]

Several factors can result in zinc deficiency, including alcoholism, gastrointestinal disorders, and aging.[7, 8] Plasma zinc decrease with age and both intra- and extracellular concentrations are associated with cardiovascular health.[9, 10] It has been suggested that Zinc can be cardio-protective against ischemia/reperfusion injury of the myocardium.[7, 11] Zinc deficiency could contribute to cardiovascular disease due to either low dietary intakes, low absorption, increased excretion, or some medications used in HF patients.[12] Many studies have assessed serum zinc concentration in patients with HF, reporting either lower serum zinc concentrations[13, 14] or no difference compared to healthy populations.[15-17] However, no study has defined the mean concentration of serum zinc in HF patients and its association with age or geographical location. Therefore, we have conducted a comprehensive meta-analysis of the current literature to find a serum zinc concentration reference range in contemporary HF patients.

Methods

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (*PRISMA*) indicate the process of study selection.[18]

Literature Search

A systematic electronic search was undertaken by two independent authors (MJ and MZ) using several online databases, including PubMed, Scopus, Embase, and Web of Science, for all available publications between 1st January 2000 to 1st January 2020. Authors searched Cross-sectional studies investigating serum zinc in patients with HF. Our search terms were designed as follows: ("Zinc"[Title/Abstract] OR "Zink"[Title/Abstract]) AND ("Heart Failure"[Title/Abstract] OR "HF"[Title/Abstract] OR "CVD" [Title/Abstract] OR "Cardiac*"[Title/Abstract] OR "Arterial Fibrillation"[Title/Abstract] OR "Cardio*"[Title/Abstract] OR "AHF"[Title/Abstract] OR "CHF"[Title/Abstract]) AND ("Observational" [Title/Abstract] OR "Cross sectional" [Title/Abstract] OR "Cross-sectional" [Title/Abstract]). The wild-term "*" was used to increase the sensitivity of the search. Our search was augmented through a hand scan of a list of references for included studies and relevant reviews. EndNote X9 was used to simplify the screening process. A discussion between the named authors solved doubts. The corresponding author was consulted if any inconsistencies arose.

Eligibility Criteria

Studies were included if they met the following terms: (1) cross-sectional, (2) published in or after 2000, (3) assessed serum zinc concentration in patients with HF, (4) reported mean serum zinc and at least one of the standard error (SE) or standards deviation (SD) or 95% confidence intervals (CI) for mean serum zinc concentration and (5) had human participants. Exclusion criteria were: (1) reporting unusable or / and unconvertable data for serum zinc or / and SE or / and SD or / and 95% CI, (2) a review article, editorials, patents, conference abstracts, comments, and thesis and (3) non-English language. The inclusion and exclusion criteria were evaluated by two independent reviewers (MJ and MZ), and the corresponding author resolved any disagreements.

Data collection and Quality Appraisal

Two independent reviewers (MJ and MZ) abstracted all eligible references and extracted the following data: first author's last name, publication year, country, sample size, type of HF, age of participants, serum zinc concentration in µg/dl, SD, SE, lower-limit of 95% CI, upper-limit of 95% CI, and quality of studies. The quality assessment of all included studies was appraised using the *Joanna Briggs Institute* (JBI) checklist.[19] If data were presented as a graph, WebPlotDigitizer (*https://automeris.io/WebPlotDigitizer/*) was executed to extract data. Discussion between MJ and MZ resolved any doubt. The corresponding author was asked to solve disagreements, if any.

Statistical Analysis

A random-effects model was used to assess the pooled effect size (ES) and 95% CI, where only SD for mean was published, SE were calculated using the following formula: $(SD/\sqrt{n})$. 95% CI was calculated using (Effect±(1.96×SE). I^2 statistics (>50%) and P-value (<0.05) for chi-square were checked to assess the between-studies statistical heterogeneity. In the presence of heterogeneity among studies, a random-effects meta-regression was undertaken to evaluate its potential sources. Subgroup analysis was performed by region (Europe, America, and Asia) and mean age (less than 65 years old vs. more than 65 years old). Sensitivity analysis was planned to verify the robustness of the ES estimates by excluding each study at a time. Stata computer software v13 was used to analyze all data. A P value<0.05 was assumed as statistically significant.

Results

Systematic Review
Literature Search

Figure 1 shows The *PRISMA* diagram used to demonstrate the study selection process. Initially, 1674 records were retrieved, of which 738 references were excluded as they were duplicate findings. Then, 936 papers were selected for the title and abstract screening,

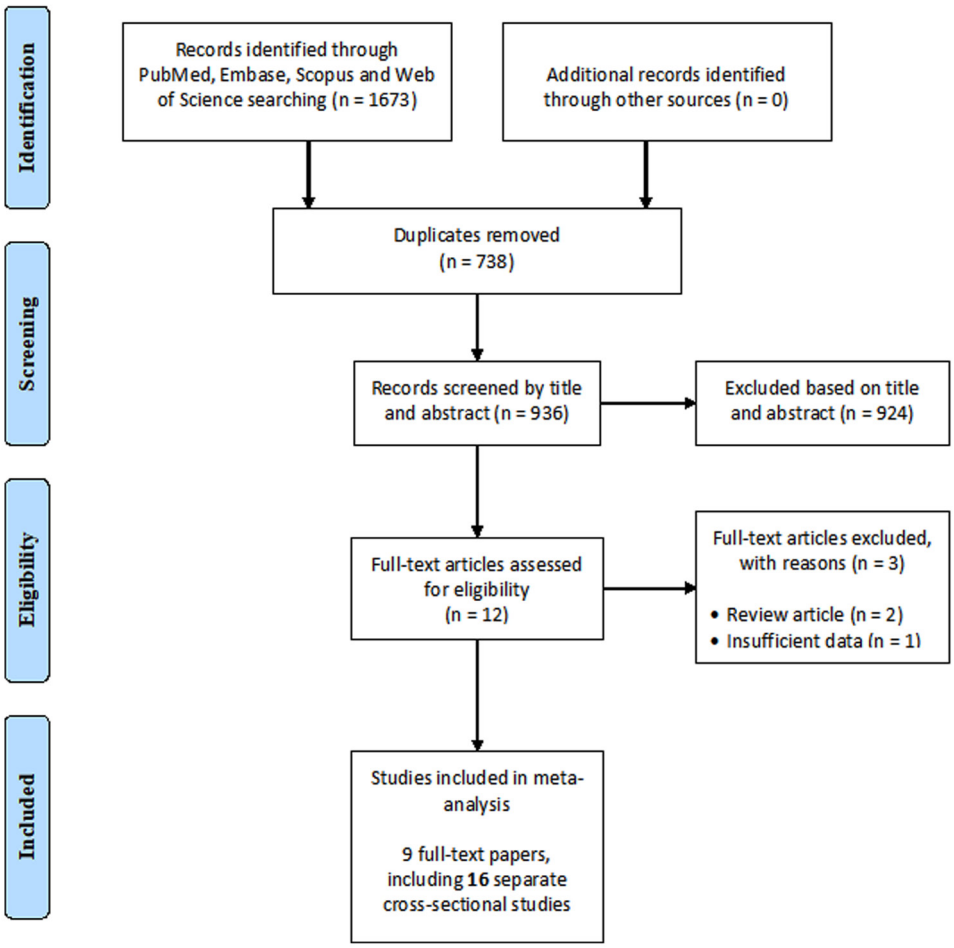

Figure 1: Flowchart of the data selection process

Table 1: Demographic characteristics of the included studies

First author	Year	Country	Sample size	Age	HF type
de Lorgeril et al.[20]	2001	France	21	27 – 76	Chronic HF
Topuzoglu[21]	2003	Turkey	24	18 – 75	Idiopathic dilated cardiomyopathy
Arroyo et al. 1 [22]	2006	USA	10	52	Compensated HF
Arroyo et al. 2 [22]	2006	USA	15	56	Decompensated HF
Arroyo et al. 3 [22]	2006	USA	15	50	Decompensated HF
Kosar et al. 1 [23]	2006	Turkey	26	62	Idiopathic dilated cardiomyopathy
Kosar et al. 2 [23]	2006	Turkey	28	62	Ischemic cardiomyopathy
Salehi et al. [16]	2008	Iran	18	49.06	Idiopathic Dilated Cardiomyopathy
Shokrzadeh et al.[17]	2009	Iran	30	57.17	Ischemic cardiomyopathy
Ghaemian et al. 1 [14]	2011	Iran	40	66.7	HF with arterial fibrillation
Ghaemian et al. 2 [14]	2011	Iran	38	70.1	HF without arterial fibrillation
Alexanian et al. 1 [3]	2014	Greece	81	69.22	Acute HF
Alexanian et al. 2 [3]	2014	Greece	44	67.5	Chronic HF
Yoshihisa et al. 1 [1]	2018	Japan	323	62.4	Decompensated HF
Yoshihisa et al. 2 [1]	2018	Japan	322	65.9	Decompensated HF
Yoshihisa et al. 3 [1]	2018	Japan	323	71.4	Decompensated HF

and 924 were omitted. At the next step, 12 full-text articles were assessed for eligibility, and finally, 9 full-text papers comprising 16 separate cross-sectional studies were included in the meta-analysis.[1, 3, 14, 16, 17, 20-24]

Demographic Characteristics

Table 1 outlines the demographic characteristics of all included studies between 2001 – 2018. Three studies were conducted in Iran,[14, 16, 17] two in Turkey,[21, 23] one in the USA,[22] France,[20] Greece,[3] and Japan.[1] They included 998 participants with decompensated HF, 81 with acute HF, 68 with idiopathic dilated cardiomyopathy, 65 with chronic HF, 58 with ischemic cardiomyopathy, 40 with HF plus atrial fibrillation,

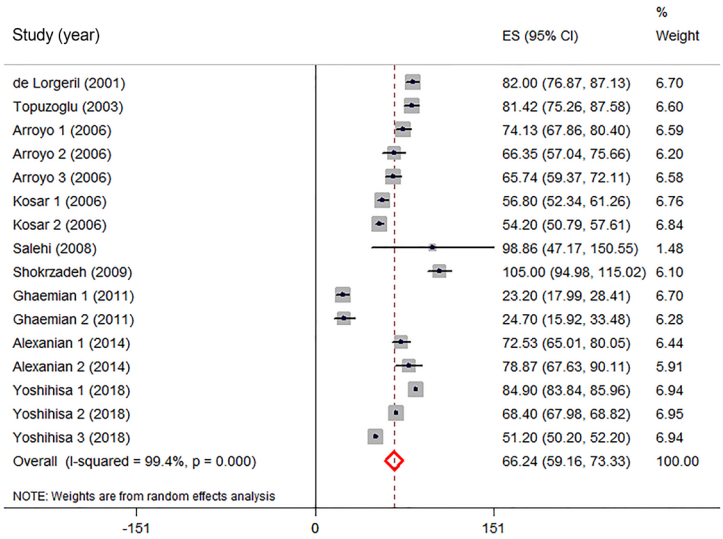

Figure 2: Overall ES with 95 % CI of mean serum zinc concentration

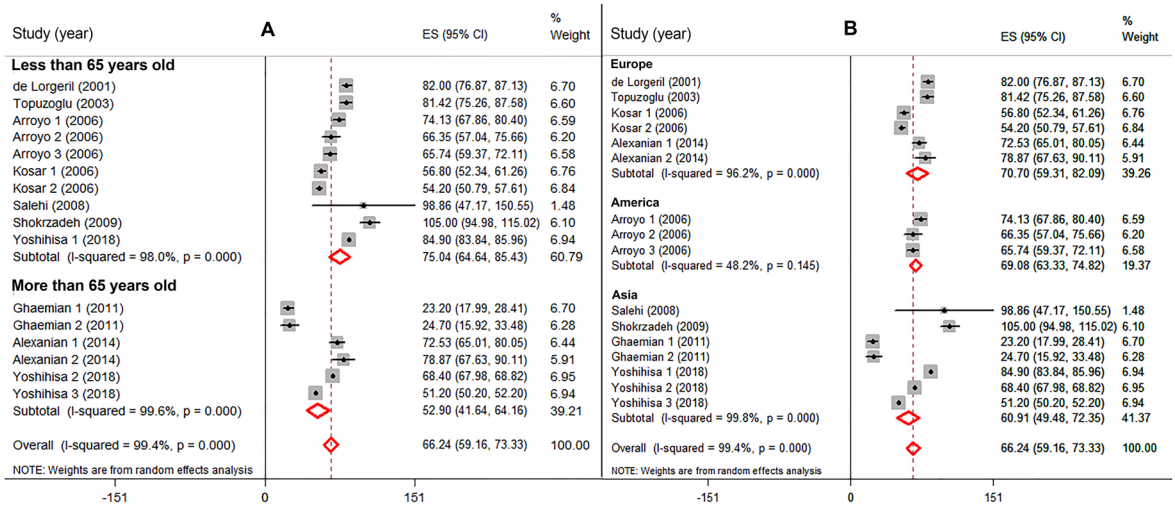

Figure 3: Subgroup analysis of mean age (less than or more than 65 years old) (A) and geographical regions (Europe, America, and Asia) (B)

38 with HF without atrial fibrillation, and 10 with compensated HF with an age range of 18 – 71 years.

Meta-analyses

The pooled effect of the 16 datasets showed that mean serum zinc concentration was 66.24 µg/dl (95% CI: 59.16, 73.33) in HF patients (Figure 2). It was 75.04 µg/dl (95% CI: 64.64, 85.43) and 52.90 µg/dl (95% CI: 59.16, 64.16) in patients younger than 65 and older than 65 years old, respectively (Figure 3A). In addition, after sub-grouping for different geographical regions, serum zinc levels were 70.70 µg/dl (95% CI: 59.31, 82.09), 69.08 µg/dl (95% CI: 63.33, 74.82), and 60.91 µg/dl (95% CI: 49.48, 72.35) in HF patients of Europe, America and Asia, respectively (Figure 3B).

Meta-regression

Meta-regression analysis by mean age indicated that serum zinc concentration decreased 1.42 µg/dl (95% CI: -4.73, -0.96, P=0.03) for each year, and mean age was assessed as the source of between-study statistical heterogeneity (Figure 4).

Sensitivity Analysis

Sensitivity analysis showed that mean serum zinc concentration was not affected by removing each study one at a time (Figure 5).

Discussion

Our meta-analysis showed that mean serum zinc concentration in HF patients was 66.24 µg/dl and had a narrower range than in healthy adults (70-120 ug/dl),[25] confirming zinc deficiency was prevalent. This findings agreed with other studies.[13,14] Pro-inflammatory cytokines including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are increased in HF patients,[26] and these can increase metallothioneins (MTs) which bind Zinc in plasma and tissues. Lower bioavailability of Zinc may, therefore, occur.[27]

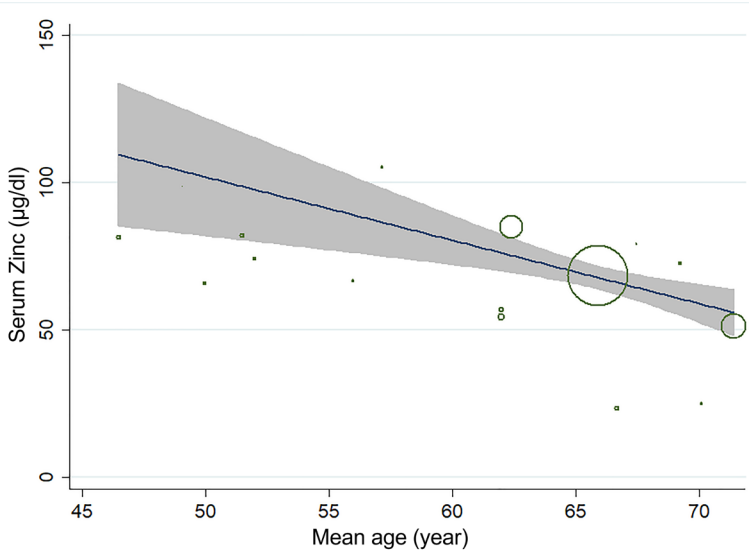

Figure 4: Meta-regression analysis by mean age (year) of patients

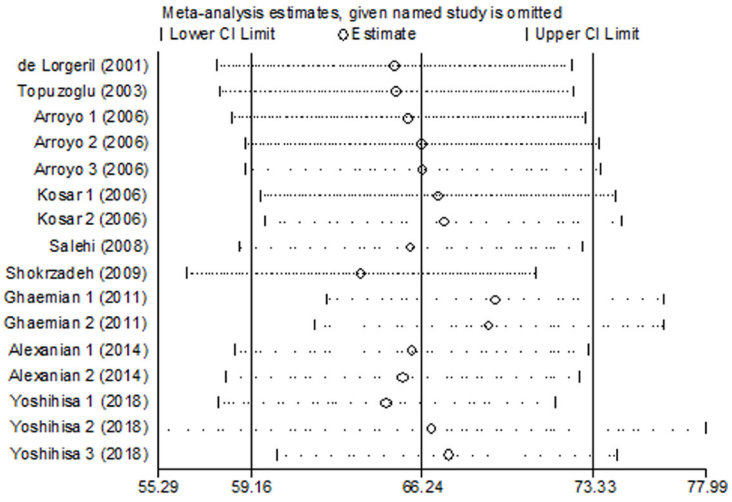

Figure 5: Result of the sensitivity analysis

Other adaptations also occur in HF patients, including raised catecholamines and parathyroid hormone (PTH), which induce calcium accumulation. These may then elevate intracellular zinc concentrations in HF patients.[3, 28] HF patients also tend to have a lower dietary intake due to a reduced appetite, nausea, vomiting, and sense of fullness at the beginning of their meals,[29-31] with lower absorption rates and higher loss from the gut.[32] Furthermore, the use of diuretics raises urinary zinc excretion[12] and activates the renin-angiotensin system.[33] Other comorbiditiesinclude diabetes mellitus and hypertension, whichfurther impair zinc homeostasis, especially in older patients.[34, 35]

Zinc is present in the antioxidant enzyme, superoxide dismutase, and any decrease in zinc concentration can cause oxidative stress, which is an important cause of HF.[13] The zinc concentration decreases with age[8, 36] and persists in HF patients. Any effects may be exacerbated by a decreased Zn/Cu ratio with aging[37] and hospitalization,[38] which results in oxidative stress and atherosclerosis,[39] together with the elevated inflammatory status and poor nutritional status.[13, 40]

After subgrouping studies by geographical locations, mean serum zinc was higher in Europeans, followed by the Americans and Asians (70.70 µg/dl, 69.08 µg/dl, and 60.91 µg/dl, respectively). This finding aligns with a recent study by Yu et al.[13] On a population-wide basis, zinc deficiency is most common in some areas of Asia, especially Iran[41] (included in the current study). A reduced bioavailability causes this issue due to lower animal protein intakes and higher phytate consumption,[41] which is also the case for Japan, especially the elderly.[36] However, high-income countries, including those in Europe and the USA, are less likely to experience zinc deficiency.[41]

Another important point that should be considered in future studies is that there might be a circadian variation in serum zinc measurement (high in the morning and low in the afternoon).[42] **Conclusion**

This is the first systematic review and meta-analysis to define the mean serum zinc concentration in HF patients to the best of our knowledge. This study enjoyed a sufficient number of studies and assessed different age groups and geographical locations . However, one limitation is the lack of control groups, as we only assessed cross-sectional studies, so we cannot determine any causal relationships. Another limitation is that serum zinc concentration may not be an appropriate marker for body zinc status, and zinc serum depletion can occur regardless of body stores. It seems that there might be a vicious cycle between serum zinc concentration and HF, as one can cause the other and vice versa. In addition, it is suggested to conduct more studies to better define the mean concentration of Zinc in healthy and unhealthy populations in different geographical areas to clarify the relationship between zinc concentration and disease progression.

Therefore, standardizing the time of zinc assessment in the serum may be beneficial. A reference range of serum zinc concentration in HF patients could be adopted, which differs from normal or healthy groups.

In summary, serum zinc concentrations are lower in HF patients and have a narrow range, specifically in the elderly. A decrease in zinc concentration while the age increase may increase the prevalence of HF in older patients. Lower Zinc might be more prevalent in some regions such as Asia, especially in Iran, suggesting dietary modifications in these areas.

Author Contribution

MJ contributed to the study concept and design. MJ, MZ, and ZS contributed to literature search, data collection, and analysis. MJ, ZS, and MES contributed to drafting and reviewing the final manuscript. All authors read and approved the final manuscript.

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Ethics approval and consent to participate: Not applicable.

Conflicts of interest: None declared.

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