

Systematic review of zinc biochemical indicators and risk of coronary heart disease

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Review Article

Abstract

BACKGROUND: Poor zinc nutritional status is suspected as a risk factor for coronary heart disease (CHD). Since zinc absorption may be influenced by some nutritional and physiologic factors, it would be better to investigate zinc status through biochemical measurements. The objective of the present study was to review recent studies investigating the association of zinc biomarkers with CHD, systematically.

METHODS: The MEDLINE database was used for relevant studies published from January 2009 to December 2013 with appropriate keywords. Articles were included in this study if they were human studies, original articles, and published in English.

RESULTS: Six case-control studies and two prospective cohort studies that measured zinc biomarkers were included in the study. Almost all case-control studies suggest that decreased plasma zinc was associated with increased CHD risk. Cohort studies did not support this relationship.

CONCLUSION: The majority of the evidence for this theory is extracted from case-control studies, which might have bias. Prospective studies and randomized clinical trials are needed to investigate whether poor zinc status is associated with increased CHD risk. Consequently, a protective role of zinc in CHD could not be still established.

Keywords: Zinc, Coronary Heart Disease, Minerals, Systematic Review, Cardiovascular, Myocardial Infarction

Date of submission: 04 Feb 2015, *Date of acceptance:* 23 May 2015

Introduction

Cardiovascular disorders are the most common cause of mortality in the world.¹ Mortality due to cardiovascular diseases has increased from 31.9% in 1990 to 46.8% in 2010, in Iran.² There are several risk factors have been considered to be effective in the pathogenesis of cardiovascular disorders. Among them, nutrition has an important role.^{3,4} High intake of calorie, total fat, cholesterol and processed foods and low intake of fruits, vegetables, and dietary fiber have been associated with higher risk of coronary heart disease (CHD).^{4,6} When micronutrients were investigated, the protective effect of folate, vitamin B₆, vitamin B₁₂, and vitamin E has been shown.⁷ However, the role of minerals is not well-known.

Prior studies indicate that some dietary minerals,⁸⁻¹⁰ such as selenium intake may affect the

risk of CHD and related mortality.¹¹⁻¹³ Although, the prevalence of zinc deficiency is estimated to be high among all population worldwide,¹⁴ and its role in developing some chronic diseases has been shown recently,¹⁵ the role of zinc in developing CHD is not clear.^{8,16,17}

There are different methods for evaluating zinc status in nutritional epidemiology such as nutrient intake assessment through questionnaire and biochemical measurement. Biochemical measures or biomarkers are attractive because they are objective and less suspicious to forgetful and biased human answers to the questionnaire.¹⁸ In addition, within-food variation may occur due to geographical difference in soil zinc content. Consequently, since the concentration of Zn in most foods is not inherent and more important, Zn absorption may be affected by some physiologic and dietary factors

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such as phytate,¹⁹ observational studies of Zn status may benefit from the use of biochemical measures of zinc levels in hair, nail, serum or plasma Zn concentrations more than its dietary intake.²⁰ While, serum and urine zinc usually inhibits recent intake,¹⁴ nails and hairs slow growth have been shown to be a reliable biomarker for trace element status, especially reflecting past year exposure.²¹

Since the role of zinc is not clear in such a common disease and dietary recommendations are cost-effective and safe²² and usually work even in developing countries,²³ the objective of this study was to review the results from studies of the association of Zn biomarkers with CHD, systematically.

Materials and Methods

Database MEDLINE was searched for observational studies and randomized trials investigating the relationship between Zn biochemical measurement and CHD. The following Medical Subject Headings (MeSH) terms were applied (cardiovascular OR myocardial infarction OR peripheral arterial disease OR stroke OR mortality OR coronary); and were combined with each of the terms (“zinc,” “Zn,” “zinc gluconate,” “zinc sulfate,” “zinc acetate,” “zinc oxide”). The articles published in recent 5 years were included. The potentially relevant articles were included if the full paper had been obtained. Studies were restricted to human studies and publications in English. References of identified articles and reviews were also searched for additional relevant articles.

We aimed to identify all observational and randomized trials studies that assessed the association of Zn with CHD. Articles met the following criteria were excluded:

- 1- Not original research (reviews, editorials, non-research letters);
- 2- Case reports or case series;
- 3- Ecologic studies;
- 4- Studies lacking a biochemical measurement of Zn status;
- 5- Cellular or molecular studies;
- 6- Studies which their outcomes were a specific risk factor of CHD (for example lipid profile) or total mortality.

Data extraction and quality assessment

One investigator reviewed search results. Abstract of 209 retrieved articles were studied, and articles which met exclusion criteria were excluded. Although the stringent criteria were used for inclusion and exclusion, the studies which were

finally included in the study, had different methodology and biochemical measurements. Therefore, the results were summarized and tabulated. For the included articles, some important information were extracted and tabulated including study design, first author, year of publication, country, patient characteristics (gender and mean age), sample size, case and control definition and the reported Zn status from studies (Tables 1 and 2). All biochemical measurement including hair, nail, urine, serum and plasma were included in the study. Case-control studies were concluded in table 1 and cohort studies were concluded in table 2. The quality of observational studies was assessed according to the criteria used by Flores-Mateo et al.¹¹ to minimize including of articles which have bias (Appendix 1).

Results

Six case-control studies and two prospective cohort studies were included in the study (Figure 1). The studies were published between 2009 and 2013 (Table 1). The number of case subjects varied between 24²⁴ and 457.²⁵ The quality scores varied widely. In almost all studies, serum Zn concentration was less in CHD patients as compared to control subjects, but this difference was not significant in all studies (Table 1). In the study of Islamoglu et al.²⁶ 67 patients with CHD were compared with 26 clinically healthy individuals. The serum Zn was found to be significantly lower in patients than in healthy control ($P < 0.010$). In the study of Bayir et al.²⁷ patients with diagnosed acute coronary syndrome (ACS) ($n = 100$) were compared with their age-matched controls ($n = 100$). Serum Zn concentration was significantly less in the CHD group compared to the control group ($P < 0.010$).

However, in the study of Giannoglou et al.²⁸ 40 patients with diagnosed CHD were compared with 32 controls. Serum Zn was not significantly associated with CHD risk and severity ($P = 0.320$). However, urinary Zn concentration was significantly higher in patients with CHD ($P = 0.030$). In the study of Cebi et al.²⁹ which compared 30 patients with diagnosed CHD with 20 healthy subjects, serum Zn was not statistically different in two groups ($P = 0.650$).

Hair Zn was assessed in two studies with contradictory results.^{24,25} In the study of Afridi et al.²⁵ who investigated Zn status in hair, urine, and blood, 457 male CHD patients were enrolled and compared with 536 healthy individuals.

Table 1. Case-control studies of biochemical measurement of zinc and coronary heart disease (CHD)

Author	Country	Men among control (%)	Mean age of case subjects (years)	Mean age of control subjects (years)	Type of case subjects	Source of control subjects	Number of case subjects/control subjects	Zinc assessment (technique)	Zinc concentration		P
									Case subjects	Control subjects	
Tan et al. ²⁴	China	50	36-81	24-72	ACS	Healthy volunteers	24/100	Hair (ICP-AES)	168.12 ± 69.74 ng/ml	166.60 ± 68.24	NR
Giannoglou et al. ²⁸	Greece	53	66	61	ACS (diagnosed with angiography)	Healthy volunteers (R/O ACS with angiography)	40/32	Serum, urine (AAS)	Serum = 626.5 µg/l Urine = 620 µg/24 h	Serum = 628.5 Urine = 469.4	0.830 0.014
Afridi et al. ²⁵	Pakistan	100	31-60	31-60	ACS (diagnosed with angiography)	Healthy volunteers	457/536	Serum, hair, urine (AAS)	NR	NR	< 0.050
Cebi et al. ²⁹	Turkey	NR	59.1 ± 11.0	57.5 ± 10.0	ACS (diagnosed with angiography)	Healthy volunteers (R/O ACS with angiography)	30/20	Serum (AAS)	0.85 µg/dl	0.90 µg/dl	0.650
Islamoglu et al. ²⁶	Turkey	73	58 ± 12.0	53 ± 12	ACS (diagnosed with angiography)	Healthy volunteer (R/O ACS with angiography)	67/26	Serum (AAS)	0.61 ng/l	0.96 ng/l	< 0.010
Bayir et al. ²⁷	Turkey	56	61.4 ± 12.0	61.6 ± 18.0	ACS	Healthy volunteers	100/100	Serum (AAS)	0.72 ppm	1.3 ppm	< 0.010

ACS: Acute coronary syndrome; AAS: Atomic absorption spectrometry; ICP-AES: Inductively coupled plasma atomic emission spectroscopy; NR: Not reported

Table 2. Prospective studies of biochemical measurement of zinc and coronary heart disease

Author	Country	Population	Men (%)	Mean age (Years)	Endpoint ascertainment	Follow-up (years)	Outcome	Number of case subjects/non-case subjects	Zinc assessment (technique)	Unadjusted HR (95% CI)/P	Adjusted HR (95% CI)/P
Bates et al. ³¹	Britain	British National diet and nutrition survey	51	76.6 ± 7.4	Death certificate	14	CHD mortality	1054	Plasma (colorimetric assays)	0.73 (0.61-0.88)/0.001	0.83 (0.65-1.07)/0.150
Lobo et al. ³⁰	Brazil	Brazilian cohort	62	54.6 ± 12.7	Death certificate	2	CHD mortality of hemodialysis patients	45	Plasma (AAS)	NR	NS

HR: Hazard ratio; CHD: Coronary heart diseases; AAS: Atomic absorption spectrometry; NR: Not reported; NS: Not significant; CI: Confidence interval

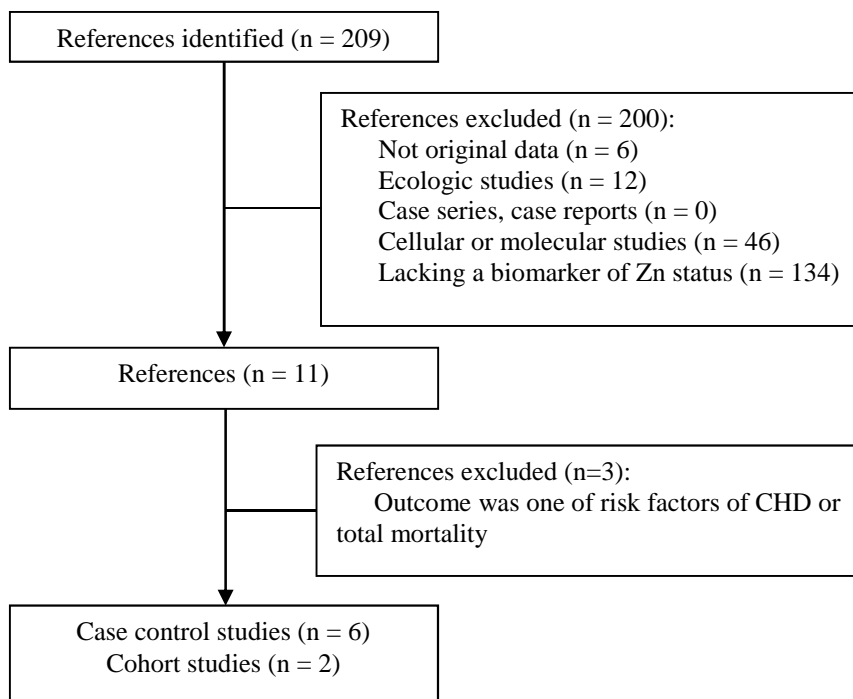


Figure 1. Flow of study selection process
CHD: Coronary heart diseases

The results showed that the concentrations of Zn were lower in CHD patients in both blood and hair samples ($P > 0.001$). However, the excretion of Zn was higher in CHD patients. Tan et al.²⁴ enrolled 24 CHD patients and 100 healthy persons aged 24-72. The concentration of hair Zn was not different significantly in case and control groups. Urine Zn was reported in two studies, and it was significantly higher in CHD patients than controls.^{25,28}

In cohort studies included into this review study, serum Zn was not associated with CHD. Lobo et al.³⁰ followed 45 hemodialysis patients for 2 years to investigate the risks for CHD mortality. During the 24 months, 24.4% of the patients died, all due to CHD. In Lobo et al.³⁰ study, decreased plasma Zn was associated with increased tumor necrosis factor alpha (TNF- α) levels and oxidized low-density lipoprotein (LDL) in patients, but analysis by the Cox model showed that plasma Zn was not a significant predictor of mortality. In Bates et al.³¹ prospective study, mortality status and its underlying causes were studied in 1054 subjects aged more than 65 years in the British National Diet and Nutrition Survey in 1994-2008. Primary vascular disease mortality comprised about 26% of all mortality. Model adjustment for sex and age, plasma Zn was suggested to be protective against vascular mortality, but after adjusting for all known risk factors (body

mass index, systolic blood pressure, smoking, number of prescribed drugs, health score, physical activity score, and poverty) it was not significant.

Discussion

According to our knowledge, this study is the first systematic review evaluating the association between Zn status and CHD. Eight studies were included in this study, and the majority of the case-control studies showed an inverse association between Zn status through different indicators and CHD. This inverse association was observed in populations with different baseline Zn concentrations and in persons from different countries. Prospective cohort studies did not protect this association. However, we found no intervention studies to summarize.

In almost all studies, serum Zn concentration was less in CHD patients as compared to control subjects, but this difference was not significant in all studies (Table 1). Zn deficiency may have a roll in CHD risk. This theory is consistent with cellular and molecular findings. There are evidences that Zn may suppress apoptosis.^{28,32-34} Therefore, Zn depletion may affect myocardial reperfusion injury by induction of apoptosis.³⁵ Zn deficiency can alter angiotensin-conversion enzyme activity adversely and cause hypertension due to vasoconstriction.³⁶ In addition, Zn may affect inflammatory response in humans

thorough affecting the production of inflammatory cytokines such as interleukin-1 (IL-1) and TNF- α .³⁷ Poor Zn status has been shown to be associated with inflammation.^{38,39} Inflammation has been shown to play a role in the pathogenesis of myocardial ischemia^{40,41} and anti-inflammatory strategies which reduce myocardial tissue damage are challenges in interventional cardiology.⁴²⁻⁴⁶ Inflammation response will be initiated after releasing of inflammatory cytokines and absorbing neutrophils to the injury site, which lead to injury to the endothelial cells by the production of reactive oxygen species.^{41,47} Moreover, the gene IL-6 which regulates the amount of circulating proteins involved in inflammatory responses, may be influenced by zinc status.⁴⁸ This gene has been shown to be associated with CHD.⁴⁹

Although Zn deficiency could be a risk factor for CHD, decreased serum Zn in these patients could be caused by CHD. Evidence has shown that plasma Zn is a negative acute-phase reactant and after ACS plasma Zn may decrease in response to inflammation. Plasma Zn is affected by metallothioneins homeostasis, which is itself influenced by proinflammatory cytokines. Metallothionein which is expected to be increased in chronic inflammation causes low Zn availability in inflammatory conditions.³⁷ Thus, impaired Zn homeostasis in CHD patients may be due to chronic inflammation in these patients versus a risk factor of CHD. Therefore we could not determine which one comes first based on case control studies which is a limitation of case control studies. However, ignoring which comes first, CHD patients have poor Zn status and it is recommended to investigate if improving Zn status in these patients could improve their survival.

Urine Zn was reported in two studies and it was significantly higher in CHD patients than controls^{25,28} which indicate zinc excretion and it is in consistent with studies shows lower level of zinc in serum. Hair Zn was assessed in two studies with contradictory results.^{24,25} The Afridi *et al.* study is limited to men and this difference may be related to sex.²⁵ Tan *et al.* study might have not enough power to detect the difference between two groups because of low sample size in this study (only 24 cases).²⁴

Careful consideration of choice of biochemical indicators will be valuable. All biochemical indicators of Zn, such as hair, urine, nails or plasma may reflect Zn exposure to some degree.^{14,50,51} However, the interpretation of biomarkers is not simple because circulating plasma or serum Zn concentrations respond to conditions such as inflammation, infection, and time of last meal. Nails

are susceptible to soil contamination. Contamination by coloring dyes and anti-dandruff shampoos may limit the suitability of hair.

In cohort studies included into this study, serum Zn was not associated with CHD. Lobo *et al.* have evaluated the association of plasma Zn and oxidized LDL and TNF- α .³⁰ It was concluded that decreased plasma Zn were associated with increased TNF- α levels and oxidized LDL in patients who undergone hemodialysis. It can be concluded that there is a relationship between Zn deficiency with inflammation and lipid peroxidation in hemodialysis patients, but serum zinc was not a predictor of CHD mortality. It should be mentioned that the follow-up for mortality was 2 years in this study, and it could be not enough for evaluating the effect of this mineral. Small sample size (45 hemodialysis patients) could be another reason for failure in finding significant relationship. Large prospective studies with enough sample size are needed for strong conclusion.

In another prospective study, it was suggested plasma Zn could be protective against vascular mortality, but after adjusting for all known risk factors it was not significant.³¹ In this study, four model were used, and the protective effect of Zn was significant in all models except the full model which all confounders were entered into the model. However, the hazard ratio was very similar to other three models and paying attention to a confidence interval (0.65-1.07) shows the protective effect of zinc. The Bates *et al.* study investigated risk factors in elderly. However, the predictive value of risk factors for disease and mortality appears to decrease with age.⁵² Moreover, the association between Zn and CHD might be underestimated in this study.

The discrepancy between most case-control studies and prospective studies may be related to the fact that this is inflammation of post-CHD which causes low plasma Zn which could be detected in case-control studies.

In assessing the association between Zn and CHD, different confounders should be considered. Zinc depletion could be due to a strict vegetarian diet (a diet which is limited to plant products)⁵³ or alcohol or drug addiction which all of them have relation with CHD and may confound the relation between Zn and CHD. Moreover, physical activity and age may affect Zn absorption and Zn loss.¹⁴ They should be also taken into account because they may also confound this relationship.

The competency for absorption among nutrients and such interactions should be considered too, as they may affect Zn utilization.

Conclusion

In conclusion, the results from observational studies evaluating the association between Zn status and risk of CHD are controversial; however, case-control studies with sufficient sample size could find a significant inverse association between serum Zn concentration and CHD risk. None of the prospective studies confirmed this association. More cohort studies with CHD mortality endpoint and appropriate biologic samples which have collected in the beginning of the study are needed to be able to conclude about this association in future.

Acknowledgments

The authors thank Dr. Reza Malekzadeh and Dr Nizal Sarrafzadegan for their critical review of this paper.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Hashemian M, Poustchi H, Mohammadi-Nasrabadi F, Hekmatdoost A. Systematic review of zinc biochemical indicators and risk of coronary heart disease. *ARYA Atheroscler* 2015; 11(6): 357-65.

Appendix 1. Quality criteria for observational studies on zinc and CHD (coronary heart disease)

Reference number	24	28	25	31	29	26	30	27
All observational studies								
Exposure was assessed at the individual level	√	√	√	√	√	√	√	√
Outcomes were based on objective tests or standard criteria in 90% of study participants	√	√	√	√	√	√	√	√
The authors presented internal comparisons within study participants		√	√	√				√
The authors controlled for potential confounding risk factors in addition to age	√	√		√				√
Prospective cohort studies								
Loss to follow-up was independent of exposure								
The intensity of search of disease was independent of exposure status				√				
Case-control studies								
Data were collected in a similar manner for all participants	√	√				√	√	√
The same exclusion criteria were applied to all participants		√				√		√
The selection process for Non-cases was described		√						
Samples were collected ≤ 24 hour after the onset of symptoms for all cases				√				√
The study was based on incident cases of disease	√							√
Non cases were persons who would have been excluded if they had developed CAD								

CAD: Coronary artery diseases