Zinc status in Cardiovascular patients in the north of Islamic Republic of Iran

Morteza Rahbar-Taramsari[1] , Marjan Mahdaviroshan[2,*] , Bijan Shad[1] , Mehrdad Sadegi[1] , Maryam Shakiba[3]

[1]Faculty of Medicine ,Guilan university of Medical Sciences ,Rasht,Iran
[2]Students' Research Committee, National Nutrition and Food Technology Research Institute Faculty of Nutrition Sciences and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Faculty of Public Health,Shahid Beheshti university of Medical Sciences, Tehran, Iran

*Corresponding Author: email address: Marjan_Mahdaviroshan@yahoo.com (M. Mahdaviroshan)

ABSTRACT

Studies have demonstrated that zinc plays an important role in development of cardiovascular diseases in Western populations. But there is little data for other racial groups. This study was aimed to investigate the association between serum zinc and coronary artery disease (CAD) in Iranian subjects.This study was conducted on 81 subjects,which referred to Heshmat Hospital of Guilan province , Iran, for routine coronary angiography from June to August 2011. Subjects were assigned into 2 groups; 41 CAD patients.case and 40 healthy subjects in control group. Data about smoking habit,physical activity, dietary intake and anthropometric indices were collected by questionnaire. Serum zinc was measured by atomic spectroscopy.The serum zinc concentrations were significantly lower in case group than control (p<0.05). The mean serum zinc concentration in the case and control group was 73.50±1.61µg/dl and 78.47±1.66µg/dl, respectively. subjects that lives in rural area had 7.11-fold higher CAD risk in compare to subjects lives in urban_ after adjustment for confounder factors,they also had lower zinc concentration than urban (p<0.05). in our study With increasing in serum zinc concentration CAD risk decrease 0.94-fold.Zinc concentration had significant correlation with age (r= -0.23 p<0.05), weight (r=0.26 p<0.05) and Place for living (r=- 0.22 p= 0.04).There were no significant correlation between the dietary intake , Waist circumference ,smoking and serum zinc concentration in our study.Serum zinc concentration was significantly lower in the north of Islamic Republic of Iran patients with abnormal versus those with a normal angiogram. It seems Serum zinc concentration correlate with some risk factors for coronary artery disease.

Keywords: zinc; CAD; weight; smoking habit; Waist circumference; diet

INTRODUCTION

Coronary artery disease (CAD) is a leading cause of morbidity and mortality in developed countries and is emerging as an epidemic in developing countries [1]. The established and proposed risk factors for CAD include age, gender, family history of CAD, dyslipidemia , hypertension , diabetes mellitus, obesity ,cigarette smoking,dietary pattern and increased thrombogenicity[2]. Also there is strong evidence that oxidative free radicals have a role in the development of degenerative diseases including CAD [3]. Studies on the roles of trace elements in health and disease over the past 40 years have led to a good understanding of their mechanism of function and why they are essential to life [4]. Trace element status may be associated directly by cardiovascular disease, through effect on the vascular system, or indirectly through lipoprotein metabolism [5].

Zinc was known as essential trace elements in 1970 [6] that plays a critical role in the stabilization of biological membrane, protein synthesis, nucleic acid metabolism, and as a cofactor of several enzyme systems [7]. Its deficit can also affect the development of multiple organs including the brain, lung, skeleton, kidneys and heart [8].Zinc can protect membrane against unsaturated lipids and inflammatory cytokines [9]. Studies have shown that abnormalities of zinc homeostasis may

be associated with pathogenesis of chronic diseases. Both decrease and increase in zinc serum level were reported in ISCMP patients [10]. Zinc deficiency is associated with susceptibility to oxidative stress, endothelial cell apoptosis, and atherogenesis [11]. Investigators suggest that a decreased serum zinc concentration may increase the risk of cardiovascular disease [5,11].Additionally, zinc deficiency may predispose to atherosclerosis through its effects on glucose intolerance, diabetes mellitus and insulin resistance [12].

Regarding the fact that zinc is a potent antioxidant [13]. zinc deficiency is a cause for the increased oxidative damage in multiple organs including the heart [14], due to the declined cardiac antioxidant capacity [14]. In addition, zinc deficiency exacerbates hypertension in hypertensive rats [15] and it is discussed as a risk factor for atherosclerosis [16]. Although there are strong hypothetical reasons why zinc status may be involved in the etiology of CAD, studies have been inconsistent. In animal experiments, a diet high in zinc leads to hypercholesterolemia and cardiovascular complications [17]. Alissa et al [18] have shown that Saudi subjects with established CAD do not have significant different serum levels of zinc from subjects without CAD.The prevalence of cardiovascular disease is high among Iranian population and association between zinc status and coronary risk factors is controversial. Therefore, this study was aimed to investigate serum zinc status in CAD patients and the association between zinc status and coronary risk factors.

MATERIALS AND METHODS

This descriptive–analytical study was conducted on 81 subjects, aged 30 to 70 years that referred to Dr. Heshmat Medical Educational Hospital of Guilan, Iran, for routine coronary angiography, mainly for stable angina from June to August 2012.

Subjects who take oral contraceptives or hormone replacement therapy or had diabetes, renal disease, hyperlipidemia, overt clinical features of infection, or chronic inflammatory disease , prior history of coronary angioplasty or coronary artery bypass graft (CABG) were excluded from the study. Smoking habit, numbers of smoked cigarettes per day and physical activity data were collected by questionnaire.

This study was Approval by Regional Medical Research Ethic Committee of Guilan university of Medical Sciences .All subjects signed the informed consent for participation in this study. Anthropometric indices including, weight, height, and waist circumference were measured using standard protocols. Waist circumference was measured at the level of the umbilicus (at the level midway between the lower rib margin and the iliac crest). Height, body weight, and waist circumference were measured with subjects dressed in very light clothing after an overnight fast. Body weight of each subject was measured with a standard scale to an accuracy of ± 0.1 kg, and height was measured to an accuracy of ± 0.1 cm. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). In addition, dietary intake was assessed by a food frequency questionnaire (FFQ) and 3 days food records .

Coronary angiograms were performed using routine procedures. Analysis of the angiograms was performed offline by a Specialist Cardiologist. The presence of one or more stenosis in diameter of at least one major coronary artery (Left main, Right coronary artery, Left anterior descending, Circumflex) was considered evidence of significant CAD (case group).

Subjects in whom there is no visible atherosclerotic changes in the coronary arteries were considered to have a normal angiogram (control group). Subjects were assigned into 2 groups according to the coronary angiogram results. The first group included 41 patients with coronary artery disease patients (case group) and the second group included 40 healthy subjects (control group). Blood samples were collected in the morning after an overnight fast and were drawn into acid wash trace mineral free tubes. Samples were centrifuged at 3000 µg for 10 minutes and Serum was stored at -20 C until analysis .Serum zinc concentration was measured using the atomic absorption spectrophotometer (CAT-2000, Chem. Thech Co.,USA)

Statistical Package for Social Sciences version 11.5 was used for all statistical analysis. Data were presented as mean ± SE. Pearson correlation coefficients were used to evaluate the association between zinc concentration and risk

factors for CAD. For calculation adjusted OR logistic regression were used. T-test and Chi-square tests were used for quantitative and qualitative variables.

The mean difference between groups was analyzed using a one-way ANOVA. *P* values of <0.05 was considered statistically significant.

RESULTS

The mean age of subjects in case group was 53.31±1.35 years and in control group was 51.2±1.67 years, that was not different between the groups (p=0.11).

Among the 41 subjects in case group, 29 (70.7%) were male and 12 (29.3%) were female, and of those 40 who were in control group, 24 (60%) were male and 16 (51%) were female. The clinical and biochemical characteristics of subjects are shown in Table 1.

The mean of weight in case and control group was 72.53±1.47 and 70.52±1.57, respectively. The number of smokers (p=0.03), means of body mass index (p=0.01) and waist circumference (p=0.04) were significantly higher in case group compared to the control (table 1). With increasing body mass index, subjects had a 1.35-fold higher CAD risk , also subjects that lives in rural area had 7.11-fold higher CAD risk in compare to subjects lives in urban_ after adjustment for confounder factors (table2). Table 3 presents dietary factors for both groups. Patients with CVD had lower intake of fruits,nuts and fish and higher intake of total grains than control group and 73.2% of CVD patients was eating frying foods .

Table.1. Clinical and biochemical characteristics of subjects with CAD and without CAD

Clinical and biochemical characteristics	**Group**		**P**
	Case (n=41)	**Control (n=40)**	
Age (yrs)	53.31±1.35	51.20±1.67	1.53
BMI(kg/m^2)	28.33±0.54	26.15±0.58	0.01
Waist circumference (cm)	99.46±1.58	95.21±1.34	0.04
Male/female(%)	70.7/29.3 %	60/51 %	0.31
Smokers(%)	39%	17.5%	0.03
Activity(%)	29.3%	27.5%	0.86
Live in city/rural area(%)	52.2/48.8%	85/15%	0.001

Table.2. Regression analysis for defining the independent determinants of CAD

Clinical and biochemical characteristics	**Adjusted OR**	**95%CI**	**P**
Serum zinc level	0.94	0.88-0.99	0.03
Waist circumference	1.35	1.04-1.74	0.02
Smoking	3.12	0.87-11.16	0.35
Live in city	7.11	1.84-27.51	0.004

R^2 =51%

Table.3.dietary factors of subjects with CAD and without CAD

dietary factors	**Group**		**P**
	Case (n=41)	**Control (n=40)**	
Total grains(servings/d)	4.13±0.07	3.86±0.07	0.09
Whole grains (servings/d)	0.34±0.03	0.31±0.02	0.58
fruits(servings/d)	0.71±0.05	0.85±0.03	0.03
vegetables(servings/d)	1.08±0.11	0.98±0.09	0.85
fish(servings/d)	0.21±0.02	0.34±0.02	0.02
nuts(servings/d)	0.19±0.04	0.35±0.04	0.01

The mean of serum zinc concentration was 73.51±1.61µg/dl in the case group that was lower than normal range (75-125 µg/dl) and the mean serum zinc concentration was 78.47±1.66µg/dl in the control group.

The mean serum zinc concentration was significantly lower in case group than the control group (p=0.03), this difference between case and control group remains significant after adjustment for confounding factors including body mass index, waist circumference, smoking and the place of living (table 2). With increasing in serum zinc concentration CAD risk decrease 0.94-fold.

But this association did not correlate with the number of the stenosed coronary arteries in CAD subjects (Figure 1).

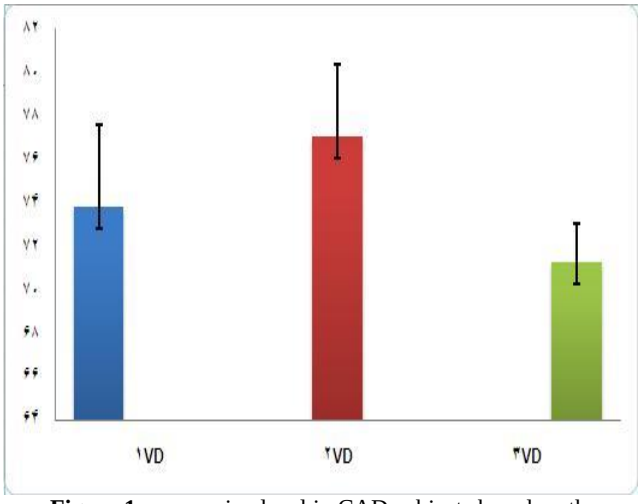

Figure 1: serum zinc level in CAD subjects based on the number of the stenosed coronary arteries .Each value is expressed as Mean±SEM

Table 4. Correlations between serum zinc and individual coronary risk factors

coronary risk factors	r	P
Age	- 0.23	0.03
Weight	0.26	0.02
Place for living	- 0.22	0.04
Waist circumference	- 0.16	0.88
Smoking	0.13	0.24
sex	- 0.13	0.23
Activity	- 0.13	0.23

Pearson's correlation coefficients were calculated for each group separately

There was a positive correlation between serum zinc concentration and weight (p=0.02), and negative correlation between serum zinc and age (p=0.03). Subjects that their home were located in rural area had lower serum zinc concentration than subjects inhabited in urban area (p=0.04).There were no significant correlation between the dietary intake , other coronary risk factors and serum zinc concentration (P>0.05)(table 4).

DISCUSSION

The prevalence of CAD is high in Iran [19].The present study demonstrated that serum zinc concentration was significantly lower in Iranian subjects with CAD basis on angiography test compare to subjects without CAD. Relationship between zinc status and incidence of CAD, are conflicting. Islamoglu et al [5] have reported that serum level of zinc was significantly lower in patients with atherosclerosis than in the control group. Kazemi et al [20] and Ford et al [21] also have found that serum Zn level is significantly lower in patients with coronary disease than in healthy subjects.

Shokrzadeh et al. [22] have determined the level of Zn in 30 patients with ischemic cardiomyopathy diagnosed with coronary angiography, they have indicated that zinc level of patients was not significantly different in comparison with the healthy volunteers.

Alissa et al [19] also have reported that Serum zinc concentrations did not differ between Saudi males with and without CVD. These data are consistent with some previous studies in Caucasian subjects [23,24].

Besides, in animal experiments, a diet high in zinc leads to hypercholesterolemia and cardiovascular complications [8]. There are several mechanisms by which zinc may inhibit heart disease. Nitric oxide synthase (NOS) is a family of mtalloenzymes involved in blood pressure regulation and in cardiovascular function that use zinc as cofactor [8]. NO is an important factor in the regulation of blood flow, arterial blood pressure and heart rate in mammals [25]. Zinc has antioxidant-like properties; thus, it can stabilize macromolecules against radical-induced oxidation in vitro as well as limit excess radical production, also as an antioxidant, zinc stabilizes

membranes and preserve endothelial function through inhibit apoptosis, probability by up regulating caspase genes [26].

In contrast, some studies have reported a positive association between serum zinc and cholesterol concentrations [27,28]. It was found an inverse relationship between age and serum zinc concentration. A fall in serum zinc concentration with age has been reported and attributed to a decline in rate of absorption [29]. There have also been other reports of changes in zinc metabolism with age [21].

A positive relationship has reported between weight and serum zinc concentration. It was noted that zinc was involved in fat metabolism and obesity [30] .Some investigators have reported that serum zinc concentration is lower [31,32] in obese subjects while other studies have reported no significant difference [21].

An inverse association between consumption of fish because of its omega-3 fatty acids and nuts because of its monounsaturated fat with CAD was reported in studies.also higher consumption of vegetables,fruits and whole grains was associated with a lower risk of cardiovascular disease [33,34] .In the study serum zinc was not significantly correlated to dietary intake , because serum zinc can be affected by physiologic factors and diseases [35]. In the present study, subjects in rural area had lower serum zinc than subjects in urban; that is maybe related to social and economical factors.

In the current study, it can be easily observed that there is no significant difference in serum zinc concentration between smokers and non-smokers. That is similar to the result of other studies [36].

CONCLUSION

In conclusion serum zinc concentration is significantly lower in the north of Islamic Republic of Iran patients with established CAD compare to subjects without CAD, and some of risk factors for CAD such as age, weight and place of living are associated with altered zinc status. Present study does not elucidate whether the lower levels of serum zinc in CAD, is causal or the consequence of CAD. Prospective studies would be necessary to confirm a causal relationship.

ACKNOWLEDGMENTS

This research project has been supported by Guilan University of Medical Sciences Research Council.

REFERENCES

1.Cebi A, uksel Y, Gungor H, Demir H. Trace Elements, Heavy Metals and Vitamin Levels in Patients with Coronary Artery Disease. *Int. J. Med. Sci*. 2011; 8:456.

2. Parikh P, Gruberg L , Jeremias A, Chen J. Association of health insurance status with presentation and outcomes of coronary artery disease among nonelderly adults undergoing percutaneous coronary intervention. *Am Heart J* 2011;162:522-7.

3. Ames BN, Shigenaga MK, Hagen TM. Oxidants, antioxidants, and the degenerative diseases of aging. *Proc Natl Acad Sci*. 1993; 90: 7915–7922.

4. Yavuz B, Ertugrul DT, Cil H, et al. Increased Levels of 25 Hy-droxyvitamin D and 1,25-Dihydroxyvitamin D After Rosuvas-tatin Treatment: A Novel Pleiotropic Effect of Statins? *Cardio-vasc Drugs Ther*. 2009; 20: 312-320.

5. Islamoglu Y, Evliyaoglu O , Tekbas E, Cil H, Elbey M.The Relationship Between Serum Levels of Zinc and Cu and Severity of Coronary Atherosclerosis. *Biol Trace Elem Res* 2011;011:9123-9.

6. Sadighi A, Roshan MM, Moradi A, Ostadrahimi A. The effects of zinc supplementation on serum zinc, alkaline phosphatase activity and fracture healing of bones.*Saudi Med J*. 2008 Sep;29(9):1276-9.

7 .ZUO X,. CHEN J, ZHOU X . Levels of Selenium, Zinc, Copper, and Antioxidant Enzyme Activity in Patients with Leukemia. *Biol Trace Elem Res.* 2006 Winter;114(1-3):52-53

8.Tomat AL, Costa Mde L, Arranz CT. Zinc restriction during different periods of life: influence in renal and cardiovascular diseases. *Nutrition.* 2011 Apr;27(4):392-8.

9. Hennig B, Toborek M, Mcclain CJ .Antiatherogenic properties of zinc: implications

in endothelial cell metabolism. *Nutrition* 1996; 12(10):711–717.

10.Kosar F, Sahin I, Taskapan C, Kucukbay Z, Gullu H, Taskapan H .Trace element status (Se, Zn, Cu) in heart failure. *Anadolu Kardiyol Derg* 2006; 6(3):216–220.

11.Perry DK, Smyth MJ, Stennicke HR et al .Zinc is a potent inhibitor of the apoptotic protease,caspase-3. A novel target for zinc in the inhibition of apoptosis. *J Biol Chem* 1997; 272:18530–18533.

12. Ghayour-Mobarhan M,.Shapouri-Moghaddam A,Azimi-Nezhad M.The relationship between established coronary risk factors an serum copper and zinc concentrations in a large Persian Cohort. *J Trace Elem Med Biol* 2009; 23:167–175 .

13. Prasad AS, Bao B, Beck FW, Kucuk O, Sarkar FH. Antioxidant effect of zinc in humans. *Free Radic Biol Med* 2004;37: 1182–1190.

14.Ho E, Ames BN. Low intracellular zinc induces oxidative DNA damage, disrupts p53, NFkappa B., and AP1 DNA binding, and affects DNA repair in a rat glioma cell line.*Proc Natl Acad Sci, USA* 2002;99: 16770–16775.

15.-Sato M, Yanagisawa H, Nojima Y, Tamura J, Wada O. Zn deficiency aggravates hypertension in spontaneously hypertensive rats: possible role of Cu/Zn-superoxide dismutase.*Clin Exp Hypertens* 2002;24:355–370.

16.Beattie JH, Kwun IS. Is zinc deficiency a risk factor for atherosclerosis. *Br J Nutr* 2004;91: 177–181.

17.Klevay L. Interactions of copper and zinc in cardiovascular diseases. *Ann NY Acad Sci* 1980;355:151–52.

18. Alissa E , Bahjri S, Ahmed W.Trace element status in Saudi patients with established atherosclerosis. *J Trace Elem Med Biol* 2006; 20:105–114.

19.Sarraf-Zadegan N, Sayed-Tabatabaei FA, Bashardoost N, Maleki A, Totonchi M, Habibi HR, et al. The prevalence of coronary artery disease in an urban population in Isfahan, Iran. *Acta Cardiol* 1999;54:257–63.

20. Kazemi-Bajestani M, Ghayour-Mobarhan M.Serum copper and zinc concentrations are lower in Iranian patientswith angiographically defined coronary artery disease than in subjects with a normal angiogram. *Journal of Trace Elements in Medicine and Biology* 2007;21: 22–28.

21.Ford ES .Serum copper concentration and coronary heart disease among US adults. *Am J Epidemiol* 2000; 152:1182–1188.

22. Shokrzadeh M, Ghaemian A,Salehifar E.Serum Zinc and Copper Levels in Ischemic Cardiomyopathy. *Biol Trace Elem Res* 2009;127:116–123.

23.Mielcarz G, Howard AN, Mielcarz B, et al. Leucocyte copper, a marker of copper body status is low in coronary artery disease. *J Trace Elem Med Biol* 2001;15:31–5.

24. Mikkelsen SL, Bottner RK, Paoli C. Selenium and other plasma element Concentrations in coronary heart disease. *Lab Med* 1992;23:122–4.

25.Mount PF, Power DA. Nitric oxide in the kidney: functions and regulation of synthesis. *Acta Physiol (Oxf)* 2006;187:433–46.

26. Soinio N, Marniemi J, Laakso Kh. Serum Zinc Level and Coronary Heart Disease Events in Patients With Type 2 Diabetes. *Diabetes Care* 2007;30:523–528.

27.Hiller R, Seigel D, Sperduto RD, Blair N, Burton TC, Farber MD, Gragoudas ES, Gunter EW, Haller J, Seddon JM, Sowell AL, Yannuzzi LA and The Eye Disease Case-control Study Group: Serum zinc and serum lipid profiles in 778 adults. *Ann Epidemiol*1995;5:490–496,.

28. The Age-Related Eye Disease Study Research Group: The effect of five-year zinc supplementation on serum zinc, serum cholesterol and hematocrit in persons randomly assigned to treatment group in the age-related eye disease study: AREDS Report No. 7. *J Nutr* 2002;132:697–702.

29.Bales CW, Steinman LC, Freeland-Graves JH, Stone JM,Young RK. The effect of age on plasma zinc uptake and taste acuity. *Am J Clin Nutr* 1996;44:664–9.

30.Tallman D,Taylor C.Effect of dietary fat and zinc on adiposity,serum leptin and adipose fatty acid composition in C57BL/6J.*J Nutr Biochem* 2003;14:17-23.

31.Ghayour Mobarhan M, Taylor A, New S, Lamb DJ, Ferns G. Determinants of serum copper, zinc and selenium in healthy subjects. *Ann Clin Biochem* 2005;42:
364–75.

32.Tungtrongchitr R, Pongpaew P, Phonrat B, et al. Serum copper, zinc, ceruloplasmin and superoxide dismutase in Thai overweight and obese. *J Med Assoc Thai* 2003;86:543–52.
33.Willett W.Optimal diets for prevention of coronary heart disease.*JAMA*;27:2569.
34. Kottke E. What is the optimal diet for cardiovascular health? *BMJ* 2003;327
35.Hyun T,Barrett E.zinc intakes and plasma concentrations in men with osteoporosis.*Am J Clin Nutr*;80:715-21.
36.Kocyigit A,Erel D.Effect of tobacco smoking on plasma selenium ,zinc,copper concentrations and related antioxidant enzyme activities .*Clin Biochem* 2002;34:629-633.