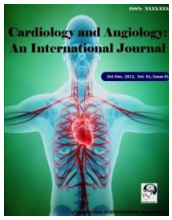

Cardiology and Angiology: An International Journal
3(2): 114-121, 2015, Article no.CA.2015.009
ISSN: 2347-520X

SCIENCEDOMAIN *international*
www.sciencedomain.org

Serum Zinc Levels do not Differ in Type 2 Diabetic Subjects with and without Coronary Artery Disease

Aggelos G. Ioannidis[1*], Athanasia K. Papazafeiropoulou[2], Alexios Sotiropoulos[3], Athanasia Kokkinari[1], Ourania Apostolou[4], Maria Stefanidou[1] and Stavroula A. Papadodima[1]

[1]Department of Forensic Medicine and Toxicology, National and Kapodistrian University of Athens, Greece.
[2]Department of Internal Medicine and Diabetes Center, Tzaneio General Hospital of Piraeus, Greece.
[3]Clinical pathology and Diabetes Center, General Hospital of "St Panteleimonas", Greece.
[4]Curator A΄ of General Hospital of "St Panteleimonas", Greece.

Authors' contributions

This work was carried out in collaboration between all authors. Authors AS, AGI and OA participated in the collection of the data. Authors AS, SAP, AK, AKP and MS participated in the design of the study and performed the statistical analysis and drafted the manuscript. All authors gave final consent for publication.

Article Information

DOI: 10.9734/CA/2015/13760
Editor(s):
(1) Francesco Pelliccia, Department of Heart and Great Vessels University La Sapienza, Rome, Italy.
(2) Anonymous.
Reviewers:
(1) Abdulrahman M Almoghairi, Adult Cardiology Department, Prince Sultan Cardiac Center (PSCC), Riyadh, Saudi Arabia.
(2) Alexander Berezin, Internal Medicine Department, State Medical University, Zaporozhye, Ukraine.
(3) Anonymous, Azienda Ospedaliero - Universitaria di Parma, Italy.
(4) Anonymous, Pad. Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, India.
(5) Anonymous, Henan University of Traditional Chinese Medicine, China.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=841&id=26&aid=7090

Original Research Article

Received 2nd September 2014
Accepted 12th November 2014
Published 6th December 2014

ABSTRACT

Aims: The scope of this study is to investigate zinc levels in type 2 diabetic subjects with and without coronary artery disease (CAD).
Place and Duration of Study: This study was performed in outpatient clinic of General Hospital of Nikaia between December 2009 and May 2010.
Methodology: A total of 100 type 2 diabetic subjects with CAD and 100 diabetic subjects without CAD were enrolled into the study.
Results: There was no difference of serum zinc levels between diabetic subjects with and without

**Corresponding author: E-mail: angelsorrowspath@yahoo.gr;*

CAD (89.53±22.39 vs. 86.97±20.85 μg/dl, *P*= 0.40). Multivariate linear regression analysis showed significant independent associations between zinc and age (beta = -0.23, *P*= 0.01) and alcohol consumption (beta = 0.29, *P*=0.001) in diabetic subjects with CAD. Also, significant independent associations demonstrated between serum zinc and dietary vitamins intake (beta = 0.19, *P*= 0.03) and number of platelets (beta = 0.16, *P*= 0.05) in diabetic subjects without CAD.

Conclusion: Serum zinc levels were not different between diabetic subjects with and without CAD. Age and alcohol consumption were the only determinants of serum zinc levels in diabetic subjects with CAD. Dietary vitamins intake and number of platelets were the only determinants of serum zinc levels in diabetic subjects without CAD.

Keywords: Zinc; diabetes; type 2 diabetes; coronary artery disease.

1. INTRODUCTION

Coronary artery disease (CAD) causes much of the serious morbidity and mortality in patients with diabetes, who have a 2- to 4-fold increase in the risk of CAD [1]. Diabetic patients, who suffered from acute myocardial infarction, are more likely to undergo a new myocardial infarction, heart failure, or even die [2]. In fact, the 5-year mortality rate following MI may be as high as 50% for diabetic patients—more than double that of nondiabetic patients [3]. Such results led the Adult Treatment Panel III of the National Cholesterol Education Program to establish diabetes as a CAD risk equivalent mandating aggressive antiatherosclerotic therapy [4]. Aggressive antiatherosclerotic management strategies, such as blood pressure control, lipid-lowering therapy, angiotensin-converting enzyme inhibition, and antiplatelet drugs have been shown to significantly reduce the risk of cardiovascular events upon diagnosis of type 2 diabetes and minimize the risk of cardiovascular morbidity and mortality [5].

Serum zinc has also drawn attention concerning its role as a preventive strategy of atherogenesis [6]. Zinc is an important component of biomembranes and an essential cofactor in a variety of enzymes [7], has antioxidant-like properties; thus, it can stabilize macromolecules against radical-induced oxidation in vitro as well as limit excess radical production [8,9] and plays an important role in the synthesis and function of insulin, it is capable of modulating insulin action, and it improves hepatic binding of insulin [10]. As an antioxidant, zinc has membrane-stabilizing properties and is cause of its ability to inhibit the pathways of processes leading to apoptosis, probably by upregulating caspase genes [11,12].

Although several epidemiological studies addressing the role of zinc in atherogenesis in the general population have been conducted, the data regarding diabetic patients are very limited. Because of limited literature data concerning the impact of serum zinc levels to diabetes and its complications, we conducted this study in order to investigate zinc levels in T2D subjects with and without coronary artery disease (CAD).

2. MATERIALS AND METHODS

2.1 Subjects and Procedures

A total of 100 type 2 diabetic subjects with CAD and 100 diabetic subjects without CAD consecutively selected from the diabetes outpatient clinic of General Hospital of Nikaia between December 2009 and May 2010. American Diabetes Association guidelines [13] used for diagnosis of diabetes. A questionnaire was given to the subjects about previous and current diseases, medical treatment, smoking habits, vitamin use, and they were physically examined. As non-smokers were considered those who have never smoked or those who didn't smoke for three years consecutively. During the study, subjects didn't receive zinc supplements or zinc multivitamins. A questionnaire designed in order to list their dietary habits [14]. The zinc concentration in many foods defined from nutritional data of Italian National Institute of Nutrition [15]. Their dietary habits were stable for the last 2 years and didn't change in the duration of our study.

All measurements were performed in the morning, after 10-12 hours fast. Blood samples were obtained for measurement of glucose, glycated hemoglobin, creatinine, total cholesterol levels, LDLc, HDLc, triglyceride levels. Patients received their antidiabetic treatment at the end of the examination. Blood pressure was measured using an appropriate cuff size, three times consecutively, one minute in apart, while subjects were calm and seated. The average of the two last measurements was calculated and

used in the analysis. As hypertensive patients considered those who had systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or when the patients were on antihypertensive treatment, according to the current guidelines [16]. CAD was defined as presence of history of previous myocardial infarction, bypass surgery, positive stress testing, or stenosis > 50% at one or more coronary arteries. Body weight, height and body mass index (BMI) was measured. All subjects were informed about the objective of the study, who then volunteered to participate. Aiming the conduction of the study, an approval of the study was given by ethics committee of the General Hospital of Nikaia and informed written consent was obtained.

2.2 Analytical Methods

Blood samples were collected in the morning from fasting subjects. The determination of zinc was carried out in serum samples by air–acetylene flame atomic absorption spectrometer (Varian model Spectra AA) equipped with D2 lamp background correction system. A Technicon analyzer RA-XT was used for the measurement of fasting serum glucose, lipids and creatinine concentrations. Low density lipoprotein (LDL) cholesterol concentrations were estimated using the Friedewald formula [17]. A high-performance liquid chromatography (HPLC) (Roche Diagnostics, Mannheim, Germany) with a non-diabetic reference range of 4.0-6.0% was used for the measurement of $HbA_{1c.}$ Microalbuminuria was assessed by measuring the albumin-to-creatinine ratio (ACR) in a random urine sample on a DCA 2000 analyzer using the immunonephelometry technique (Bayer HealthCare LLC, Elkhart, USA).

2.3 Collection of Serum Samples and Analytical Methods

Blood samples were collected in the morning from fasting subjects. Serum samples were obtained from the spontaneous coagulation of blood. The blood was then centrifuged at 2500 rpm for 10 min to obtain serum. Hemolyzed samples were excluded.

The serum was stored at -18 8C. All glassware and bottles used for the isolation of serum and for analysis were previously soaked in diluted nitric acid (10%) for 3 h and rinsed thoroughly with deionized water. This procedure was followed in order to exclude the possibility of contamination with zinc. All samples were diluted (1:4) using water.

The determination of zinc was carried out in serum samples by air–acetylene flame atomic absorption spectrometer (Varian model Spectra AA) equipped with D2 lamp background correction system. A copper and zinc hollow cathode lamp (Varian) were operated at 10 mA intensity and a spectral width of 0.7 nm which was selected to isolate the 324.7 nm and 213.9 nm lines for copper and zinc, respectively.

All analyses were performed in peak height mode to calculate absorbance rates. All samples were analyzed in triplicate.

2.4 Analytical Characteristics

The detection limit was 0.60 μg/dl for copper and 0.90 μg/dl for zinc. The accuracy and precision of the method were evaluated in six replicate assays with a reference lyophilized serum control (Clin ChekR RECIPE Chemicals, Munich, Germany). The values found for zinc were 93.2±2.5% (μg/dl) (n =6) and 97.6±4.5% (μg/dl) (n =6), respectively, while the recommended zinc concentrations were 92.1 μg/dl and 96.6 μg/dl, respectively. The relative standard deviation was 2.44% for copper and 4.70% for zinc (n =6) in one sample analyzed in this study.

2.5 Statistical Analysis

The SPSS (10.0) statistical package was used for the statistical analysis of data. Unless specifically stated differently, all results are presented in the form of (mean value ± standard deviation of the mean), for a significance level of 5% (P = 0.05, two-tailed). Goodness of fit of the data with the Gauss distribution was tested for all variables involved. Differences between the control group and the sample under examination were assessed using:

a) The t -test for two independent samples in the case of continuous variables and
b) The χ^2- test for homogeneity in the case of categorical variables.

The relationship between serum Zn levels in the blood samples and each variable of interest was examined using univariate linear regression (ULR). Associations between serum Zn levels and the set of variables of interest were examined using multivariate linear regression (MLR). All independent variables included in the

MLR models were selected by stepwise regression, namely backwards elimination and tested for multicolinearity.

The formula used for the sample size calculation for a significance level equal to **a** and a value of acceptable error equal to **d** is:

$$N=1/4 \cdot [Z_{a/2d}/d]^2,$$

where $Z_{a/2}$ is the value of the standardized normal variable Z~N(0,1) for which

$$P(Z>Z_{a/2}) = a/2.$$

For a significance level of a=0.05 and a magnitude of acceptable error equal to d = ±0.1, the above formula yields:

$$N=1/4 \cdot [Z_{a/2d}/d]^2 = ¼ \cdot [Z_{0.025}/0.01\ ]^2 = 96.4$$

hence a sample size of N=100 was implemented for each one analysis.

3. RESULTS AND DISCUSSION

Serum zinc levels were not different between diabetic subjects with and without CAD (89.53±22.39 vs. 86.97±20.85 μg/dl, *P*= 0.40). The anthropometric, clinical and laboratory characteristics of the two study groups are showed in Table 1. In the group of the diabetic subjects with CAD was obtained that 30.8% was on treatment with sulphonylurea, 59.8% on metformin, 8.4% on DPP-4 inhibitors, 3.7% on glitazones, 3.7% on acarbose, 2.8% on megltitinides, and 51.5% on insulin. In the group of the diabetic subjects without CAD was obtained that 47.0% was on treatment with sulphonylurea, 69.7% on metformin, 44.6% on insulin, 13.6% on glitazones, 4.5% on DPP-4 inhibitors, 3.0% on acarbose, and 1.5% on megltitinides. Systolic and diastolic blood pressure values were higher in diabetic subjects without CAD than in diabetic subjects with CAD. Diabetic subjects with CAD had frequently demonstrated retinopathy and lower serum levels of total and LDL-cholesterol than diabetics without CAD. Comparing diabetic subjects without CAD with those with CAD, the first used more often vitamins of the B and C complex. Statin use was not different between the two study groups (Table 1). Additionally, diabetic subjects with CAD were more often smokers than diabetic subjects without CAD (Table 1).

The mean serum zinc concentration was similar in insulin-treated subjects compared with those subjects who did not have insulin included in their treatment (Table 2).

The mean serum zinc level was similar in subjects who received diuretics compared with those who didn't receive diuretics (Table 3).

The results of the univariate linear regression analysis demonstrated that in diabetic subjects with CAD serum zinc levels were associated significantly with age [standardized regression coefficient (beta) = -0.33, *P*= 0.001], duration of diabetes (beta = -0.19,*P*= 0.04), alcohol consumption (beta = 0.31,*P*= 0.001) and creatinine levels (beta = -0.25,*P*= 0.009). Multivariate linear regression analysis showed, after controlling for duration of diabetes and serum creatinine, significant independent associations between serum zinc and age (beta = -0.23, *P*= 0.01) and alcohol consumption (beta = 0.29, *P*= 0.001) (Table 4).

The results of the univariate linear regression analysis demonstrated that in diabetic subjects without CAD serum zinc levels were associated significantly with dietary vitamins intake (beta=-0.18, *P*=0.03) and number of platelets (beta=0.16, *P*=0.05). Multivariate linear regression analysis showed significant independent associations between serum zinc and dietary vitamins intake (beta=0.19, *P*=0.03) and number of platelets (beta=0.16, *P*=0.05) (Table 4).

The results of the present study showed that serum zinc levels were not different between diabetic subjects with and without CAD. Age and alcohol consumption were the only determinants of serum zinc levels in diabetic subjects with CAD. Dietary vitamins intake and number of platelets were the only determinants of serum zinc levels in diabetic subjects without CAD.

Several epidemiological studies addressing the role of zinc in the prevention of atherosclerosis in the general population have been conducted; however, their results are conflicting. In a large cross sectional survey of 3575 subjects, aged 25 to 64 years, in North India low serum zinc levels were found to be associated with an increased prevalence of CAD and diabetes [18]. On the contrary, in a population in Australia, zinc supplement was shown to decrease lipoprotein (HDL)-c concentrations but the role of zinc in influencing other risk factors for CHD such as antioxidant status and thrombogenesis proved insufficient [19].

Table 1. Anthropometric, clinical and laboratory characteristics of diabetic subjects according to the presence (CAD+) or not (CAD-) of coronary artery disease

	CAD (-)	CAD (+)	*P*
Males/females (%)	52 / 48	52 /48	-
Age (years)	66.68±9.52	65.60±8.16	0.39
Body mass index (kg/m2)	32.66±5.20	33.20±5.53	0.23
Waist (cm)	104.31±12.51	106.62±12.10	0.18
Systolic blood pressure (mm Hg)	148.65±19.34	142.75±18.24	0.02
Diastolic blood pressure (mm Hg)	80.74±9.68	77.70±9.27	0.02
Duration of diabetes (years)	11.83±8.28	13.23±8.27	0.23
Smoking (yes) (%)	22.0	35.0	0.03
Alcohol consumption (yes) (%)	39.0	35.0	0.67
Vitamins (yes) (%)	15.0	5.0	0.02
Hypertension (yes) (%)	87.0	92.0	0.07
Dyslipidemia (yes) (%)	90.0	92.0	0.22
Peripheral artery disease (yes) (%)	7.0	14.0	0.09
Cerebrovascular disease (yes) (%)	6.0	11.0	0.18
Any retinopathy (yes) (%)	15.0	27.0	0.03
Neuropathy (yes) (%)	6.0	9.0	0.67
Microalbuminuria (yes) (%)	49.0	58.0	0.24
Treatment for diabetes	-	-	-
Antidiabetic tablets (yes) (%)	81.0	67.0	0.04
Insulin (yes) (%)	45.0	50.0	0.32
HbA1c (%)	7.58±1.72	7.74±1.74	0.51
Statins (yes) (%)	89.0	95.0	0.15
Glucose (mg/dl)	159.83±53.63	160.74±58.53	0.90
Total cholesterol (mg/dl)	181.56±40.80	168.48±43.85	0.03
HDL cholesterol (mg/dl)	46.52±10.99	43.40±10.38	0.04
LDL cholesterol (mg/dl)	106.13±37.92	94.26±37.25	0.03
Triglycerides (mg/dl)	153.14±82.00	158.08±87.97	0.68
Urea (mg/dl)	44.91±23.34	45.77±21.00	0.78
Creatinine (mg/dl)	1.00±0.55	0.99±0.24	0.88
Uric acid (mg/dl)	5.54±1.61	5.65±1.68	0.64
CRP (mg/dl)	4.32±1.16	3.7±1.8	0.52
Ht (%)	40.16±3.66	40.41±3.55	0.63
WBCs (n)	7,561.68±2,038.28	8,040.91±2,196.38	0.11
PLTs (n)	250,980.20±72,600.54	242,969.07±17,043.47	0.66
Serum Zinc (μg/dl)	86.97±20.85	89.53±22.39	0.40
Dietary Zinc (μg/dl)	120.06±49.33	126.54±46.71	0.34

P values for the comparison between groups with and without metabolic syndrome (MS) by independent samples t-test for continuous variables or by Pearson $\chi 2$ for nominal variables.

HbA1c: glycated hemoglobin A1c; HDL: high density lipoprotein; LDL: low density lipoprotein; CRP: high sensitivity C-reactive protein; Ht: Hematocrit; WBCs: white blood cells count; PLTs: platelets.

Table 2. Serum zinc in insulin-treated and non insulin treated subjects

	Insulin +	Insulin -
Diabetics without CAD	87,71±2,54 (μg/dl)	88,05±2,42 (μg/dl)
Diabetics with CAD	90,81±8,15 (μg/dl)	93,59±8,76 (μg/dl)

In a study on Greek population, Giannoglou et al. [20] demonstrated that serum Zn concentration was not associated with the presence and severity of CAD, whereas the amount of Zn excreted daily via urine as well as the serum Zn/24-hour urine Zn ratio were significantly associated with CAD prevalence and severity. They suggested that in individuals with severe

Table 3. Serum zinc in subjects who received diuretics

	Diuretics +	Diuretics -
Control group	97,02±10,05 (μg/dl)	91,01±10,79 (μg/dl)
Diabetics without CAD	86,85±10,62 (μg/dl)	89,40±5,93 (μg/dl)
Diabetics with CAD	88,11±2,24 (μg/dl)	95,04±7,12 (μg/dl)

Table 4. Results of multivariate linear regression analysis

	B	*P*
Diabetic subjects with CAD (Model 1)		
Age	-0.23	0.01
Alcohol consumption (yes vs. no)	0.29	0.001
Diabetic subjects without CAD (Model 2)		
Dietary vitamins (yes vs. no)	0.19	0.03
Platelets	0.16	0.05

β: standardized regression coefficient.
Additional variables tested in Model 1: duration of diabetes and creatinine levels.
No additional variables were assessed in Model 2.

CAD, an increased urinary Zn loss may occur, which may shift Zn from the intracellular compartment to extracellular fluid (plasma) to maintain serum Zn levels within the physiological range. Reduced intracellular Zn could significantly affect Zn-dependent enzymes and subsequent intracellular signaling cascades, and that an individual may be Zn deficient despite serum Zn concentrations remaining within the reference range.

The data concerning the association of zinc with atherogenesis in diabetic patients is also conflicting and limited. Soinio et al. [21] in their large prospective study of a population consisted of 1,059 patients with type 2 diabetes and showed that zinc acts as an independent risk factor for CHD events in type 2 diabetic patients.

On the other hand, Seet et al. [22] found that zinc supplementation may not be beneficial in patients with type 2 diabetes as they did not show any improvement on oxidative damage and vascular function.

In our study, no correlation was found between zinc serum concentration and coronary disease in Greek patients with diabetes type 2. None of the patient included in the study had abnormal zinc serum value. In other words, our results show that when serum zinc concentration is within the normal limits, no difference exist between Greek diabetic patients with and without coronary disease. Consequently, it may be suggested that even if zinc deficiency promotes atherosclerosis, zinc supplementation may not be helpful when administered to people with serum values within normal limits. Besides, the effects of diabetes on vascular components may be so detrimental that the protective role of zinc is almost eliminated.

The present survey has its limitations. First of all, no power sample calculation was performed that could eliminate possible error type II in the study. Furthermore, zinc urinary excretion, presence of metabolic syndrome, energy intake and physical activity were not examined for possible associations with zinc levels in the two groups. Finally, use of insulin and diuretics may have influenced zinc levels, and as a consequence, have confused our results. The mean serum zinc level, however, was similar in subjects who received diuretics compared with those who didn't receive diuretics. The same applied concerning the use of insulin.

4. CONCLUSION

In conclusion, the present study showed that serum zinc levels were not different between diabetic subjects with and without CAD. These results showed that zinc supplementation does not seem to have any protective role on CAD in diabetic subjects. However, the role of serum zinc levels in T2D and CAD need to be examined in further, longitudinal trials.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

REFERENCES

1. Feskens EJ, Kromhout D. Glucose tolerance and the risk of the cardiovascular disease: The Zutphen Study. J Clin Epidemiol. 1992;45:1327-1334.
2. Malmberg K, Yusuf S, Gerstein HC, et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: Results of OASIS (Organisation to Assess Strategies for Ischemic Syndromes) Registry. Circulation. 2000;102:1014-1019.
3. Herlitz J, Karlson BW, Lindqvist J, Sjolin M. Rate and mode of death during five years of follow-up among patients with acute chest pain with and without a history of diabetes mellitus. Diabet Med. 1998;15:308-314.
4. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. 2001;285:2486-2497
5. Beckman J, Greager M, Libby P. Diabetes and atherosclerosis Epidimiology, Pathophysiology, and Management. JAMA. 2002;287:2570-2581.
6. Powell SR. The antioxidant properties of zinc. J Nutr. 2000;130:1447-54.
7. Bettger W, O'Dell B. A critical physiological role of zinc in the structure and function of biomembranes. Life Sci. 1981;28:1425–1438.
8. Bray T, Bettger W. The physiological role of zinc as an antioxidant. Free Rad Biol Med. 1990;8:281–291
9. Hennig B, Meerarani P, Toborek M, Mc-Clain C. Antioxidant-like properties of zinc in activated endothelial cells. J Am Coll Nutr.1999;18:152–158.
10. Arquilla E, Packer S, Tarmas W, Miyamoto S The effect of zinc on insulin metabolism. Endocrinology.1978;103:1440–1449
11. Meerarani P, Ramadass P, Toborek M, Bauer H-C, Bauer H, Hennig B. Zinc protects against apoptosis of endothelial cells induced by linoleic acid and tumor necrosis factor. Am J Clin Nutr. 2000;71:81– 87.
12. Hennig B, Meerarani P, Ramadass P, Toborek M, Malecki A, Slim R, McClain CJ. Zinc nutrition and apoptosis of vascular endothelial cells: Implications in atherosclerosis. Nutrition. 1999;15:744–748.
13. Chobanian AV, Bakris GL, Black HR, et al. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42:1206–1252.
14. Sieri S, Pala V, Brighenti F, Pellegrini N, Muti P, Micheli A, Evangelista A, Grioni S, Contiero P, Berrino F, Krogh V. Dietary glycemic index, glycemic load, and the risk of breast cancer in an Italian prospective cohort study. Am J Clin Nutr. 2007;86:1160–6.
15. Salvini S, Parpinel M, Gnagnarella P, Maisonneuve P, Turrini A. Italian food composition database for epidemiologic studies. European Institute of Oncology; 1998.
16. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499–502.
17. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 1997.20:1183–1197.
18. Singh RB, Niaz MA, Rastogi SS, Bajaj S, Gaoli Z, Shoumin ZJ. Current zinc intake and risk of diabetes and coronary artery disease and factors associated with insulin resistance in rural and urban populations of North India. Am Coll Nutr.1998;17:564-70.
19. Hughes S, Samman S. The effect of zinc supplementation in humans on plasma lipids, antioxidant status and thrombo-genesis. J Am Coll Nutr. 2006;25:285-91.
20. Giannoglou G, Konstantinou D, Kovatsi L, Chatzizisis Y, Mikhailidis D. Association of reduced zinc status with angiographically severe coronary atherosclerosis: A pilot study. Angiology. 2010;61(5):449-455.
21. Soinio M, Marniemi J, Laakso M, Pyorala K, Lehto S, Ronnemaa T. Serum zinc level

and coronary heart disease events in patients with type 2 diabetes. Diabetes Care. 2007;30:523–528.

22. Seet RC, Lee CY, Lim EC, Quek AM, Huang H, Huang SH, Looi WF, Long LH, Halliwell B. Oral zinc supplementation does not improve oxidative stress or vascular function in patients with type 2 diabetes with normal zinc levels. Atherosclerosis. 2011;219(1):231-9.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=841&id=26&aid=7090