

Serum zinc levels in diabetic patients with and without dyslipidaemia and cardiovascular diseases

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Abstract

Introduction: Diabetes mellitus (DM) is a major health problem which increases the risk of cardiovascular diseases (CVDs). Zinc (Zn) has a number of antioxidant functions which neutralize the reactive oxygen species (ROS) generated in patients with diabetes. ROS stimulate oxidation of low density lipoprotein (LDL), cholesterol, cholesterol derived species in atherosclerotic plaques in arteries in dyslipidaemia patients. The oxidized LDL (Ox-LDL) has been identified as a major cause of endothelial dysfunction leading to CVDs.

Objective: In this study, the serum Zn levels, anthropometric and clinical parameters of diabetes patients with and without dyslipidaemia and CVDs were investigated.

Method: The serum samples of 116 subjects which include 42 patients with Type 2 Diabetes Mellitus (T2DM) alone, 55 patients with T2DM and dyslipidaemia and 19 patients with T2DM, dyslipidaemia and CVD from diabetes and endocrinology clinic were analysed.

Results: The serum Zn levels of diabetes patients (944.69 ± 241.53 ppb), diabetes with dyslipidaemia (991.45 ± 265.50 ppb) and diabetes, dyslipidaemia and CVD ($1,000.97 \pm 295.17$ ppb) were not statistically significant {significance value of the ANOVA test was 0.619 ($p=0.619 > \alpha =0.05$)}. Zinc deficiency was 27.27% among male patients and 16.00% among female patients. Zinc concentration among Type 2 diabetes patients was not affected by, gender, body mass index (BMI) and duration of diabetes.

Conclusion: Serum zinc levels were not statistically different among diabetic patients with and without dyslipidaemia and CVD. The role of serum zinc levels in T2DM and CVDs need to be examined further in long term longitudinal trials. (SJDEM 2020/Vol 10/No 2)

Keywords: Diabetes Mellitus, Cardiovascular diseases, Serum Zn, ROS, oxidized LDL.

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Introduction

Atherosclerotic cardiovascular disease is a leading cause of death with estimated 31% of all deaths worldwide⁽¹⁾. Diabetes mellitus (DM) and dyslipidaemia are some of the main risk factors for it. In DM, increased plasma glucose in turn causes the generation of ROS and the excess generation of ROS causes oxidative stress, which further develops the progression of diabetes and its complications. Oxidative stress is currently the unifying factor in the development of diabetes complications⁽²⁾. With the development of diabetes, oxidation of lipids, proteins and deoxyribonucleic acid (DNA) increase with time. Recent research shows oxidative stress is a primary or secondary cause of many CVDs⁽³⁾. Further in vivo and ex vivo studies have provided evidence supporting the role of oxidative stress in a number of CVDs such as atherosclerosis, ischemia, hypertension, cardiomyopathy, cardiac hypertrophy and congestive heart failure⁽⁴⁾. Further, pancreatic β -cells are particularly sensitive to oxidative damage by free radicals⁽⁵⁾. In a study conducted by Sarita & Afreen showed that increased production of free radicals is an important trigger for insulin resistance⁽⁶⁾.

ROS and other free radicals are detoxified by natural antioxidant mechanisms such as glutathione, catalase, superoxide dismutase (SOD) and more recently described metallothionein (MT)^(7&8). Superoxide radicals are reduced to hydrogen peroxide by SOD in the presence of copper and zinc cofactors⁽⁹⁾. Zinc is second to iron as the most abundant trace element in the body. Zinc ions exist primarily in the form of complexes with proteins and nucleic acids and participate in all aspects of intermediary metabolism, transmission and regulation of the expression of genetic information, storage, synthesis and action of peptide hormones and structural maintenance of chromatin and biomembranes. Zinc is an essential cofactor in a variety of enzymes. It can stabilize macromolecules against radical-induced oxidation in vitro as well as limit excess radical production⁽¹⁰⁾. Zinc also 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⁽¹¹⁾. Most of the complications of diabetes may be related to increased intracellular oxidants and free radicals associated with a decrease in intracellular zinc and zinc dependent antioxidant enzymes⁽¹²⁾.

In non-diabetic subjects, serum Zn is associated with increased incidence of CVDs⁽¹³⁾. However, the enhanced risk of CVDs of T2DM patients is not completely explained by traditional risk factors^(14&15). Previous studies have shown that serum zinc level is lower in diabetic patients than in non-diabetic subjects, increased urinary zinc excretion being the main reason⁽¹⁶⁻¹⁹⁾. In another study Zn deficiency was found to be a risk factor for cardiac oxidative damage and supplementation with Zn provides.

Significant prevention of oxidative damage to the heart⁽²⁰⁾. Further, there is very little information on the zinc status of populations worldwide due to the lack of appropriate biochemical indicators of Zn status. So, serum Zn content is not usually analyzed as an investigation in routine clinical practices. Therefore, sufficient information is not available for zinc levels for patients with T2DM, patients with T2DM with dyslipidaemia and patients with T2DM with dyslipidaemia and CVDs. Hence this study was carried out to investigate the serum Zn levels of patients with T2DM, patients with T2DM with dyslipidaemia and patients with T2DM with dyslipidaemia and CVDs and to determine whether there are any similarities among the serum Zn levels of the above groups.

Methodology

This is a cross sectional study conducted among subjects attending to diabetes clinic National Hospital Kandy, Sri Lanka. The study was carried out from 16 Nov 2016 to 30 March 2017. All the protocols used were in accordance with the guidelines for the protection of human subjects. Patients with T2DM, T2DM with dyslipidaemia and T2DM with dyslipidaemia and recent CVDs were recruited for the study. Patients with Inflammatory bowel disease including Crohn's disease, ulcerative colitis, cancers, renal failure, thyroid dysfunction, liver disease, human immunodeficiency virus (HIV), strict vegetarians & patients who are on any treatment with Zn or drugs affecting Zn level in the four weeks prior to enrolment were excluded from the study. The selected patients were categorized into 3 groups namely group A, B and C. The group A contained patients with only T2DM. American Diabetes Association guidelines were used for diagnosis of diabetes⁽²¹⁾. This group subjects were considered as the control group. The group B contained patients with T2DM & dyslipidaemia. The group B subjects had LDL cholesterol (LDL-C) values above 100 mg/dL. The group C contained patients with T2DM, dyslipidaemia and prior history of cardiovascular event. CVD was defined as presence of history of previous myocardial infarction, coronary artery bypass surgery, positive stress testing, stenosis > 50% at one or more coronary arteries & ischaemic stroke. The LDL-C values of the patients of this group were also more than 100 mg/dL. In this study none of the participants were on a special diet. There were no any cigarette smokers or alcoholics. The serum samples were digested by Ethos Easy –Milestone microwave digestion system and serum Zn concentrations were determined by Microwave Plasma Atomic Emission Spectrometer (Agilent 4200 MP-AES).

Results and Discussion

In this study, there were 116 subjects (50 women and 66 men). Mean age was 51.78 ± 8.84 years for female patients (range 27-69 years) and 53.39 ± 8.99 for male patients (range 32- 78 years). Baseline patient characteristics are shown in Table 1.

Table 1: Baseline patient characteristics

	DM patients	DM + Dyslipidaemia	DM + Dyslipidaemia + CVD
Male/Female (%)	62/38	49/51	68/32
Age(Years)	47.57±8.05	54.16±7.91	59.8±7.29
Body Mass Index (kg/m ²)	24.34±3.26	24.39±3.71	24.55±2.59
Duration of diabetes (Years)	8.6	7.7	21.78
Hypertension (Yes %)	76.19 %	41.81%	100%
Insulin (yes %)	9.52%	25.45%	31.57%

Serum zinc levels among three groups of patients

There were no any differences in the serum zinc levels among three groups of patients {the significance value of the ANOVA test was 0.619 ($p=0.619 > \alpha =0.05$)}. The mean serum zinc level was also lower in patients with only diabetes

(944.69±241.53) compared to the other two groups (Table 2). Several studies showed that heart failure patients had lower serum zinc level⁽²²⁻²⁴⁾ while others claims that there is no any significant difference in the serum zinc among heart failure subjects and control group^(25&26).

Table 2: Mean serum levels of the three groups

	n	Serum Zinc (ppb) Mean ± SD	95% Confidence Interval for Mean		Minimum	Maximum
			Lower Bound	Upper Bound		
DM + Dyslipidaemia	55	991.45±265.50	919.67	1,063.23	500.00	1,549.00
DM	42	944.69±241.53	869.42	1,019.95	421.00	1,432.00
DM + CVD	19	1,000.97±295.17	858.71	1,143.24	542.00	1,575.00

As per the Pearson correlation analysis, there was no any association with age, gender, BMI and duration of diabetes and serum zinc concentration. The study conducted by Masood N et al also showed that there was no association between age, gender, BMI and the duration of diabetes on the serum zinc concentration in type-2 diabetic patients⁽¹⁷⁾. Analysis of serum zinc levels in patients with and without hypertension showed that the mean serum zinc levels in diabetes patients with hypertension (1022.5 ± 277.4) were higher than the patients without hypertension (942.5 ± 242.2) irrespective of gender. Analysis of serum zinc levels in patients with and without insulin treatment showed that the mean serum zinc level was similar in insulin-treated subjects (992.70 ± 250.78) and who did not have insulin included in their treatment ($910.22 \pm$

307.41). Moreover, mean serum zinc level was not different among female (976.6 ± 249.8 ppb) and the male (975.7 ± 271.0 ppb) patients. Similar results were seen in a study done by Chooi et al. ⁽²⁷⁾.

Evaluation of serum zinc levels and possible biological conditions showed that 22.41% of the total population had zinc deficiency due to physiological fluctuations. A higher percentage of zinc deficiency due to physiological fluctuation was found in male patients (27.27%) than female patients (16.00%). However, the prevalence of Zn deficiency was similar among female (8.00%) and male (7.57%) patients.

Table 3: Possible conditions and the population based zinc levels

Serum zinc level ppb= $\mu\text{g}/\text{dm}^3$ (parts per billion) conditions	DM Possible	DM + Dyslipidaemia	DM+ Dyslipidaemia +CVD	Total population
3000 – 7000	0	0	0	0
Acute Zn intoxication (reported)				
1600 – 2990	0	0	0	0
Intoxication or secondary elevation due to excessive intake or hemodialysis				
840 – 1590	29(69.04%)	39(70.91%)	13(68.42%)	81(69.8%)
Normal range				
600 -830	10(23.80%)	11(20.00%)	5(26.31%)	26(22.41%)
Zinc Deficiency Physiological fluctuation variation caused by drugs, etc				
Below 590	3(7.14%)	5(9.09%)	1(5.26%)	9(7.75%)
Deficiency				

Evaluation of serum zinc levels and possible biological conditions showed that majority of female (76.00%) and male (65.15%) patients were within the normal range. This result was similar to the results showed by Yanagisawa ⁽²⁸⁾. As per the reference ranges for zinc in human serum published by Yanagisawa, none of the patients had the serum zinc levels higher than the upper limit of normal range⁽²⁸⁾.

Conclusions and Recommendations.

There were no difference in the mean serum zinc levels between diabetic subjects with and without dyslipidaemia and CVDs. Age, gender, BMI and duration of diabetes does not affect on the serum zinc concentration in type-2 diabetic patients. The role of serum zinc levels in T2DM and CVDs, factors predisposing zinc deficiency need to be examined further in long term longitudinal trials.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Conflict of interest:

The authors declare that they have no conflict of interest.

Limitations of the study

This is not a longitudinal study to study causation and the sample size is small.

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