

Effect of Zinc Supplementation on Glycemic Control, Lipid Profile, and Renal Functions in Patients with Type II Diabetes: A Single Blinded, Randomized, Placebo-Controlled, Trial

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Abstract

This study was conducted to evaluate the effect of zinc supplementation on glycemic control, lipid profile, and kidney functions in patients with type 2 diabetes mellitus attending the diabetic centre of Alnoor, Specialized Hospital, in Makkah, Saudi Arabia .A single blinded, randomized, placebo-controlled, trial was conducted. Patients (n=60) were randomly allocated into two groups: zinc group, and placebo group, treatment was given for 8 weeks. Fasting blood glucose (FBG), glycated hemoglobin (HbA1c%), kidney functions and lipid profile were assessed at baseline and after 8 weeks. Results showed that FBG, HbA1c%, lipid profile, and kidney functions were significantly reduced in zinc group after 8 weeks compared to their levels before supplementation. Moreover, FBG, cholesterol, LDL, and LDL/ HDL ratio were significantly decreased, while HDL was significantly increased in zinc group compared to those in placebo group. Zinc may have supplementary benefits in the routine management of adult DM.

Keywords: type 2 diabetes, zinc, placebo, HbA1c%, lipids, kidney functions

1. Introduction

Diabetes mellitus (DM) is a major public health problem worldwide associated with great deal of morbidity and economic cost. It is expected that DM will affect 300 million worldwide persons by the year 2030 (Wahabi et al., 2010). The overall prevalence of diabetes in Saudi Arabia, 2009, is about 30% (Alqurashi et al., 2011).

Chronic hyperglycemia is believed to play a pivotal role in the development of diabetic complications. It was found that hyperglycemia triggered a number of mechanisms that evoke overproduction of reactive oxygen species (ROS). DM is associated with an increased level of free radicals, disturbances of the enzymatic antioxidant defense system. Consequently, these abnormalities lead to a redox imbalance called oxidative stress (Mrowicka et al., 2011).

Zinc is an essential trace element with a multitude of roles in human nutrition. Zinc's role as an important component of the body's antioxidant system in retarding the oxidative process is particularly related to diabetes. Specifically, zinc is required for the adequate formation and function of the antioxidant enzyme copper-zinc superoxide dismutase (CuZnSOD) and various metallothioneins. Chronic zinc deprivation generally results in an increased sensitivity to the effects of oxidative stress due to inadequate activity of these enzymes. In addition to its

antioxidant enzyme role, zinc is also believed to participate in cell membrane stabilization, protection against vitamin E depletion and restriction of endogenous free radical production (Andrews, 2005).

Since numerous studies demonstrated that oxidative stress, mediated mainly by hyperglycemia-induced generation of free radicals, contributes to the development and progression of diabetes and related complications, it became clear that ameliorating oxidative stress through treatment with antioxidants might be an effective strategy for reducing diabetic complications (Johansen et al., 2005).

The aim of this study was to evaluate the effect of zinc as an antioxidant on glycemic control, lipid profile, and kidney functions in patients with type 2 diabetes mellitus.

2. Material and Methods

2.1. Subjects

A single blinded randomized placebo-controlled clinical trial was performed on patients with adult-onset type 2 DM attending the diabetic centre of Alnoor, Specialized Hospital, in Makkah Governorate, Saudi Arabia between January and May, 2012. Permissions for the study were obtained from the authorities concerned, and patients were informed about the purpose of the study, and signed an informed consent before the beginning of this study.

2.1.1 Inclusion Criteria

Patients with type 2 DM, aged from 30 to 70 years, attending the clinic for a routine follow-up visit, on regular use of oral antidiabetic drugs (no insulin), with HbA1c concentrations of 8% or greater, not currently enrolled in a diabetes support or education program or participated in similar program in the last 6 months, and without taking vitamins or mineral supplements in the previous 2 months.

2.1.2 Exclusion Criteria

Severe or uncontrolled cardiovascular disease (defined as a cardiovascular event within the last year), under hypolipidemic therapy, with proliferative retinopathy (defined as growth of new blood vessels on the retina and posterior surface of the vitreous), chronic foot ulcers or wounds, psychiatric disease or cognitive impairment interfering with treatment compliance, and Pregnant or lactating women. Sample size was calculated with power as 80% and level of significance at 0.05 based on a previously published study (Farvid et al., 2005). Patients (n : 60) were randomly allocated into two groups:

1. The intervention group: (zinc group)

The patients in this group (n: 30) were supplemented with oral zinc sulfate in addition to the oral anti diabetic drugs.

2. The control group: (placebo group)

The patients in this group (n: 30) were supplemented with oral placebo in addition to the oral anti diabetic drugs.

2.2 Methods

2.2.1 Interview Questionnaire

Information on age, sex, diabetic duration, drug usage, diabetic complications was obtained by an interview questionnaire.

2.2.2 Treatment scheme

Selection of chemical form, dose level, and duration of zinc supplementation in this study were based on the reports of other investigators (Roussel et al., 2003; Partida-Hernandez et al., 2006, and Oh and Yoon, 2008). Patients of both groups were instructed to take either 40 mg of zinc sulfate or cornstarch placebo once daily for a period of 8 weeks, both drugs were identical in formulation, shape, size, weight, texture, and packing. Subjects were also allowed to ask questions regarding any possible side effects and the degree of compliance was followed through a weekly telephone conversation.

2.2.3 Biochemical Assessment

Blood samples were collected from all patients (in both zinc and placebo groups) before starting treatment (zero time sample) and then after 8 weeks of treatment to monitor the changes in the studied parameters. A sample of 5 mL venous blood was drawn via venous puncture after an overnight fasting (10-14hours) between 8 and 10 a.m. before taking medications. The following biochemical markers were assessed:

- Indicators of glycemic control: fasting blood glucose (FBG), glycated hemoglobin (HbA1c)
- Lipid profile panel: triglyceride (TG), total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and the atherogenic index LDL/HDL ratio.
- Kidney function tests: blood urea nitrogen (BUN) and serum creatinine.

The blood samples were collected from each patient into two tubes: an Ethylenediaminetetraacetic acid (EDTA) tube and plain tube (without anticoagulant). Anticoagulated whole blood from EDTA tube was used for HbA1c analysis where, total haemoglobin was measured colourimetrically (Zander et al., 1984) while HbA1c was determined immunoturbidimetrically (Little et al., 1992). Using the values obtained for each of these two analytes, the percentage of total hemoglobin that is glycated is calculated and reported as % HbA1c. The ratio of both concentrations yields the final percent of HbA1c result (HbA1c %).

Serum was separated from the plain tube by centrifugation at 5000 rpm for 10 minutes and used for analysis of: FBG based on enzymatic hexokinase (Neely, 1972), total cholesterol based on enzymatic colorimetric method with cholesterol esterase, cholesterol oxidase, and 4-aminoantipyrine (Allain et al., 1974), HDL based on direct homogeneous enzymatic colorimetric assay (Sugiuchi et al., 1995), TG based on enzymatic colorimetric method with glycerol phosphate oxidase and 4-aminophenazone (Fossati and Prencipi, 1982; McGowan et al., 1983), and LDL based on Homogeneous enzymatic colorimetric assay (Sugiuchi et al., 1998), then the (LDL/HDL) ratio was calculated. Serum creatinine was determined based on buffered kinetic Jaffé reaction without deproteinization (Jaffé, 1886), and BUN was analysed by Kinetic test with urease and glutamate dehydrogenase (Sampson et al., 1980).

All biochemical tests were performed using an auto-analyzer (COBAS INTEGRA® 400 Roche Diagnostics, GmbH, Mannheim, Germany).

2.3 Statistical analysis

Statistical analysis was performed using The Statistical Package for Social Science (SPSS) version 16 (SPSS Inc., Chicago, IL, USA). For the quantitative variables, compliance with the normal distribution was assessed using the Kolmogorov-Smirnov test, Data were presented as mean \pm SD. Zinc or placebo effects for variables in the same individuals were analyzed by paired t test if the distribution was normal and Wilcoxon signed-rank test in case of non-parametric distribution. Data between the two groups were compared using student's t test if the distribution was normal, otherwise a non-parametric test was used (Mann-Whitney test). Pearson's Chi square (χ^2) test was used to compare qualitative variables between the two groups. P value of less than (0.05) was considered to indicate statistical significance.

3. Results

Out of 60 patients selected at the beginning of the study, 56 patients completed this research. Four patients in zinc group had withdrawn. The strategy of maintaining oral hypoglycemic therapy, along with taking either zinc or placebo once daily, depending on the case, prior to breakfast per day during 8 weeks was accepted in 100% of cases. Both groups were comparable regarding the base line characteristics and biochemical parameters as shown in Table 1 ($p > 0.05$).

3.1 Effect of zinc and placebo on FBG and HbA1C

After 8 weeks of zinc or placebo supplementation, FBG and HbA1c% were reduced significantly in zinc group ($p < 0.001$) while remained unaltered in placebo group ($p > 0.05$), when compared with those before treatment, Table (2,3). Moreover, after treatment, FBG was significantly lowered in zinc group compared to that in placebo group ($p < 0.001$) On the contrary, the reduction in the level of HbA1c in zinc group compared to that in placebo group was not significant ($p > 0.05$) (Table 4)

3.2 Effect of zinc and placebo on lipid profile

Zinc supplementation for 8 weeks had significant effects on all lipid parameters. Table (2) showed that total cholesterol, TG as well as LDL levels were significantly decreased, while HDL level was significantly increased after zinc therapy ($p < 0.001$). Furthermore, LDL / HDL ratio was significantly lowered in zinc treated group ($p < 0.001$). In patient treated with placebo, total cholesterol, TG, and LDL levels were increased with elevation in LDL / HDL ratio ($p < 0.001$) (Table 3). Total cholesterol, TG, HDL, LDL, and LDL / HDL ratio were significantly improved in cases treated with zinc compared to those treated with placebo ($p < 0.05$) (Table 4)

3.3 Effects of zinc and placebo on BUN and serum creatinine

In this study, zinc caused significant reduction in BUN and serum creatinine ($p < 0.001$) (table 2). Meanwhile, no significant changes occurred in both parameters in placebo group after treatment compared to those before treatment ($p > 0.05$) (Table 3).

4. Discussion

In the last two decades there has been an increase in diabetes occurrence attended with widespread associated metabolic disorders, for example, high blood pressure, atherogenic lipid profile or metabolic syndrome are found. These alterations lead patients to a highly elevated cardiovascular morbidity and mortality (Dakhale et al., 2011).

Development of diabetic complications has been hypothesized to be accelerated by generation of free radicals in cells and tissues. In diabetes, oxidative stress is in part due to an increased production of plasma free radical concentrations and a sharp reduction in antioxidant defenses. It may be postulated that oxidative stress represents the common pathway through which hyperglycemia and insulin resistance induce depressed insulin action (Gupta and Chari, 2006).

DM, insulin and zinc share complex relationship with both type 1 and type 2 DM patients often exhibiting lowered zinc status. The primary mechanism behind this typical reduced zinc status is increased urinary zinc losses as a consequence of hyperglycemia. Zinc is suspected as having a significant role in normal insulin metabolism. This includes the ability to regulate insulin receptor intracellular events and the ability to support normal pancreatic reaction to a glucose load (Andrews, 2005).

The main purpose of this study was to evaluate the effect of zinc as an antioxidant on glycemic control, lipid profile, and kidney functions in type 2 DM patients.

The results of the current study showed that zinc supplementation in a dose of 40 mg/day orally for 8 weeks significantly decreases FBG and HbA1c in type 2 DM patients. These results are in agreement with previously published data that showed improvement in glycemic control with zinc supplementation (Hussain et., al 2006; Gunasekara et., al 2011). Meanwhile, , Oh and Yoon, 2008 analyzed the effect of zinc supplementation on glycemic control by the baseline HbA1c level of diabetes subjects (HbA1c <7.5% vs HbA1c ≥7.5%), and they found significant decrease of FPG and HbA1c in the higher HbA1c group (HbA1c ≥7.5%) after 4 weeks of supplementation.

On the other hand, Anderson et al., 2001, proved the potential beneficial antioxidant effects of zinc in people with type 2 DM. However, zinc supplementation in their study did not modify significantly HbA1c nor glucose homeostasis. The discrepancy of their results and the current may be explained on the basis that they used smaller dose (30 mg) and different preparation of zinc (zinc gluconate).

Some investigators have speculated that zinc supplementation could improve glucose tolerance as well as insulin sensitivity in type 2 DM through its antioxidant effects (Roussel et. al 2003). The potential antioxidant effects of zinc in diabetes could be related to several mechanisms. Zinc plays a structural role in the maintenance of CuZnSOD structural integrity. Zinc metallothionein complexes in the islet cells provide protection against immune-mediated free-radical attack, and zinc could act also in protecting sulfhydryl groups against oxidation and participate in the inhibition of the free radical production. Hence, zinc could reduce glucose toxicity and contributed in part to the prevention of a decrease of β cell mass and insulin content (Ohly et., al 2000).

The improvement of glycemic control was mainly initiated by a beneficial effect of antioxidant on β cells. However, we cannot totally deny the possibility that the antioxidant treatment could have exerted an influence on target tissues other than the β cells such as muscle and fat (Gunasekara et., al 2011).

Dyslipidemia is recognized to be one of the most important modifiable risk factors for cardiovascular disease in patients with diabetes even more than HbA1c, systolic blood pressure, and smoking (Shepherd, 2007). The dyslipidemia commonly observed in patients with diabetes is characterized by low plasma levels of HDL, increased levels of serum TG and elevated plasma levels of LDL (Tan, et al., 2002).

The present study indicated that zinc supplementation was effective in improvement of lipid profile in patient with type 2 DM. It caused significant decrease in total cholesterol, TG, and LDL with significant increase in HDL in zinc treated group compared to those in placebo treated group. These results are consistent with previous studies that examined the effect of zinc supplementation on lipid profile (Kadhim et al, 2006; Gunasekara et al, 2011). On the contrary, zinc in the study of Partida-Hernandez et al., 2006, showed no effect on LDL level.

Zinc can be involved in the modulation of plasma HDL as postulated by Lodovici et al, 2009, who found positive correlations between malondialdehyde, HDL, and antioxidants in diabetes patients. These correlations indicate that in the compensatory response to hyperglycemia-induced oxidative stress, HDL and antioxidants are involved. Additionally hyperglycemia increases glycation of lipoprotein, including LDL and HDL, associated with the elevation of TG levels in the blood through increased synthesis from glucose and impaired lipid metabolism

(Laakso and Letho, 1998). Moreover, glucose oxidizes itself and produces H₂O₂, ketoaldehydes and free radicals. These reactive substances subsequently react with proteins and produces LDL peroxidation which is inhibited by zinc (Roussel et al, 2003). Thus zinc supplementation could improves the lipid profile, either through the improvement of glycemic control or by decreasing the susceptibility of lipoproteins and other functionally essential proteins to oxidation by the elevated levels of damaging free radicals (Kadhim et. al, 2006).

Additionally, zinc in the present study caused significant reduction in LDL / HDL ratio (3.31±0.46 before treatment versus 1.98±0.36 after treatment). Packard et al., 2005, and Indumati et al., 2011, have found the LDL /HDL ratio to be an excellent marker of diabetic dyslipidemia and coronary heart disease risk than the individual levels of LDL or HDL, they suggested that antihyperlipidemic therapy could be targeted to those with an LDL/HDL ratio of 3.3 and coronary deaths spiked when the LDL /HDL ratio reached between 3.7 and 4.3. Therefore zinc supplementation in diabetes can act as protective factor against atherosclerosis by lowering LDL /HDL ratio through inhibiting the oxidation of LDL by ROS (Hennig et al., 2001).

The present trial showed significant improvement in renal functions as measured by serum creatinine and BUN. Similar results were observed by Garg and Bakris, 2002, while, Khadim et al., 2006, found no significant effect of zinc on renal functions as measured by serum as well as urine creatinine. Since hyperlipidemia is a risk factor for the progression of nephropathy in patients with type 2 DM therefore, the beneficial renal effects of zinc found in the current trial may be through the reduction of hyperlipidemia . Moreover, zinc may have renoprotective effect via its antioxidant property (Parham et al, 2008).

5. Conclusion

Supplementation of zinc to type II DM patients demonstrated better glycemic control and desirable changes in lipid profile as well as improvement in kidney functions. , so Zinc may have supplementary benefits in the routine management of adult DM., and could be a feasible strategy favoring the life quality of those who have risk factors for other diseases in addition to diabetes.

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Table 1. Baseline Characteristics and Biochemical Parameters of Patients in Placebo and Zinc Groups

Variables	Zinc group (n = 26)	Placebo group (n = 30)	P value	95% CI
Age (years)	48.46 ± 4.61	48.20 ± 4.09	0.823	-2.07: 2.59
Male (%)	12 (46.2)	16 (53.3)	0.592	
Female (%)	14 (53.8)	14 (46.7)		
Duration of diabetes (years)	5.92 ± 1.35	5.93 ± 1.60	0.980	-0.81: 0.79
FBG (mg/dl)	172.23 ± 23.83	181.73 ± 29.22	0.192	-23.93: 4.93
HbA1c (%)	9.56 ± 0.71	9.36 ± 1.13	0.422	-0.30: 0.70
Cholesterol (mg/dl)	203.00 ± 16.36	193.80 ± 36.32	0.219	-5.67: 24.07
TG (mg/dl)	166.08 ± 31.93	154.03 ± 30.64	0.156	-4.74: 28.83
HDL (mg/dl)	40.62 ± 4.79	42.07 ± 4.20	0.232	-3.86: 0.96
LDL (mg/dl)	132.85 ± 14.11	133.33 ± 13.53	0.896	-7.90: 6.93
LDL/ HDL ratio	3.31 ± 0.46	3.01 ± 0.77	0.082	-0.04: 0.63
BUN (mg/dl)	24.15 ± 6.28	24.33 ± 6.14	0.914	-3.52: 3.16
Serum creatinine (mg/dl)	0.90 ± 0.42	0.79 ± 0.28	0.239	-0.08: 0.31

Values are mean ± SD, FBG: fasting blood glucose, HbA1c: glycated hemoglobin, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TG: triglyceride, BUN: blood urea nitrogen.

Table 2. Comparison of Biochemical Parameters in Type 2 Diabetic Patients Before and After Treatment with Zinc.

Parameters	Zinc (n = 26)		P value	95% CI
	Before treatment	After treatment		
FBG (mg/dl)	172.23 ± 23.83	117.62 ± 17.34	<0.001	41.25: 67.98
HbA1c (%)	9.56 ± 0.71	8.85 ± 0.69	<0.001	0.62: 0.81
Cholesterol (mg/dl)	203.00 ± 16.36	167.31 ± 14.41	<0.001	29.82: 41.57
TG (mg/dl)	166.08 ± 31.93	144.23 ± 32.16	<0.001	16.34: 27.35
HDL (mg/dl)	40.62 ± 4.79	51.15 ± 6.76	<0.001	-12.51: -8.57
LDL (mg/dl)	132.85 ± 14.11	99.08 ± 10.18	<0.001	30.31: 37.23
LDL/ HDL ratio	3.31 ± 0.46	1.98 ± 0.36	<0.001	1.21: 1.46
BUN (mg/dl)	24.15 ± 6.28	21.15 ± 6.04	<0.001	2.54: 3.46
Serum creatinine (mg/dl)	0.90 ± 0.42	0.82 ± 0.42	<0.001	0.06: 0.10

Values are mean ± SD, FBG: fasting blood glucose, HbA1c: glycated hemoglobin, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TG: triglyceride, BUN: blood urea nitrogen.

Table 3. Comparison of Biochemical Parameters in Type 2 Diabetic Patients Before and After Treatment with Placebo.

Parameters	Placebo (n = 30)		P value	95% CI
	Before treatment	After treatment		
FBG (mg/dl)	181.73 ± 29.22	185.07 ± 30.09	0.078	-7.07: 0.40
HbA1c (%)	9.36 ± 1.13	9.26 ± 0.99	0.203	-0.06: 0.27
Cholesterol (mg/dl)	193.80 ± 36.32	210.53 ± 34.59	<0.001	-21.22: -12.25
TG (mg/dl)	154.03 ± 30.64	168.53 ± 45.78	0.019	-26.42: -2.58
HDL (mg/dl)	42.07 ± 4.20	39.80 ± 9.90	0.137	-0.76: 5.30
LDL (mg/dl)	133.33 ± 13.53	138.68 ± 15.30	<0.001	-7.64: -3.05
LDL/ HDL ratio	3.01 ± 0.77	3.68 ± 0.94	<0.001	-0.78: -0.56
BUN (mg/dl)	24.33 ± 6.14	23.97 ± 5.22	0.458	-0.63: 1.36
Serum creatinine (mg/dl)	0.79 ± 0.28	0.80 ± 0.18	0.814	-0.08: 0.07

Values are mean ± SD, FBG: fasting blood glucose, HbA1c: glycated hemoglobin, TG: triglyceride, HDL: high-density lipoprotein, LDL: low-density lipoprotein, BUN: blood urea nitrogen.

Table 4. Comparison of Biochemical Parameters after Treatment with Zinc or Placebo in Patients with Type II DM.

Parameters	Zinc group (n = 26)	Placebo group (n = 30)	P value	95% CI
FBG (mg/dL)	117.62 ± 17.34	185.07 ± 30.09	<0.001	-80.45 : -54.46
HbA1c (%)	8.85 ± 0.69	9.26 ± 0.99	0.078	-0.87 : 0.05
Cholesterol (mg/dL)	167.31 ± 14.41	210.53 ± 34.59	<0.001	-57.21 : -29.24
TG (mg/dL)	144.23 ± 32.16	168.53 ± 45.78	0.024	-45.32 : -3.29
HDL (mg/dL)	51.15 ± 6.76	39.80 ± 9.90	<0.001	6.74 : 15.97
LDL (mg/dL)	99.08 ± 10.18	138.68 ± 15.30	<0.001	-46.68 : -32.52
LDL/ HDL ratio	1.98 ± 0.36	3.68 ± 0.94	<0.001	-2.08 : -1.33
BUN (mg/dL)	21.15 ± 6.04	23.97 ± 5.22	0.067	-5.83 : 0.20
Serum creatinine (mg/dL)	0.82 ± 0.42	0.80 ± 0.18	0.781	-0.15 : 0.20

Values are mean ± SD, FBG: fasting blood glucose, HbA1c: glycated hemoglobin, TG: triglyceride, HDL: high-density lipoprotein, LDL: low-density lipoprotein, BUN: blood urea nitrogen

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