Effect of Zinc Supplementation on Insulin Resistance, Lipid Profile, BMI in Type II Diabetic Patients

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Abstract

Background: Zinc is one of the most important essential trace metals in human nutrition and lifestyle with special role in diabetic patients mainly due to its involvement in insulin production, storage and secretion.-**Objectives**: to assess the effect of zinc supplementation on changing insulin resistance ,modifying lipid profile and body mass index(BMI) in type II diabetics.-**Design and Setting:** A randomized controlled clinical trial.-**Study participants:** the study was carried on 50 type II diabetic patients, both gender and followed for 6 weeks. the participants were randomly divided into intervention group who receives 50 mg/d elemental zinc and control group without zinc supplement.-**Materials**: S. zinc, fasting plasma glucose(FPG), fasting S. insulin, HbA1c, lipid profile, BMI were measured at the beginning(before supplementation and at the end of the 6 weeks duration.

Results: After 6 weeks of zinc supplementation, serum zinc levels improved significantly (P=0.0001). There was no significant difference in BMI (P=0.092). Insulin resistance (IR), HbA1c were significantly decreased (change mean -0.75 P=0.004 and -0.72, P=0.001) respectively. HDL-C was significantly increased (change mean 3.56 mg/dl P=0.022). TG and TC were significantly decreased (change mean-10.92mg/dl P=0.001 and – 3.52mg/dl P=0.009) respectively. There was significant positive correlation between zinc intake and serum zinc level (R^2=0.432).-***Conclusion:*** Our study results revealed that supplementation of 50 mg zinc sulphate improves insulin resistance and induces more healthy lipid profile, while it has no significant effect on BMI of type II diabetic patients after 6 weeks of supplementation.

Keywords: *Insulin Resistance; Supplementation; Zinc; Diabetics; health*

Introduction

The prevalence of Type 2 diabetes (T2D) in the world might reach 13.9% by 2030, while it was 9.1% in 2014[1] and the expected deaths from coronary heart disease (CHD) may reach 23.6 million per year by 2030 from 17.6 million deaths in 2016[2]. The most prevalent form of diabetes is T2D which accounting for over 90% of people with diabetes[3]. T2D is a chronic disease characterized by increased plasma glucose levels due to insulin secretion deficiencies (i.e., β-cell dysfunction) and insulin resistance (i.e., decreased target tissue capacity to react regularly to insulin. Insulin resistance considered as the greatest risk factor for the development of T2D[4]. Zinc plays important roles in DM, because it is involved in synthesis, secretion and storage of insulin and has antioxidant activity which makes zinc vital trace element in normalization of blood glucose level[5]. The end organ damage caused by diabetes is mainly due to oxidative stress. so many common complications of diabetes, such as cardiomyopathy, nephropathy and neuropathy will happen[6]. This organ damage that is caused by oxidative stress can be ceased by zinc which is considered as a powerful antioxidant[7].

High blood glucose level, leads to increased zinc loss in urine and a decrease in total body zinc. So zinc supplementation may qualify as a possible treatment

adjunct in T2D and prediabetes by promoting insulin signaling and euglycemia, especially in zinc deficient patients[8,6]. WHO reported that CHD is a primary cause of both men and women's mortality, which results in more than 7 million deaths annually[9].

Hyperglycemia, insulin resistance, and dyslipidemia are considered as risk factors contributed to diabetes-induced cardiovascular diseases[10]. Altered blood lipid is a common metabolic abnormality in T2D[11]. Overweight and obesity are related to micronutrient deficiencies more than normal weight[12]

Patients and Methods

***Study design*:**

A randomized, controlled clinical trial with a pre-post intervention design which conducted at the endocrine-diabetic clinic and was carried on type II diabetic patients (N=50) with less than 5 years duration of diabetes, male and female aged(25 - 60yrs).

Exclusion criteria

Taking zinc supplement, chronic (renal disease, liver disease, GI disease)or malabsorption, weight loss diets in the last 2 months, taking diuretics or multivitamin, on hormonal replacement therapy or birth control pill, on lipid lowering agent, smoker or alcohol drinker, concurrent acute illness, pregnancy and lactation were excluded from the study. Medical, surgical, drug and usual diet history were taken at the beginning of the trial. All participants were instructed to continue their usual dietary habits and physical activity during the study.

***Participants*:**

Study subjects were randomly divided into two groups, intervention group (n=25) receive zinc supplement and control group(n=25) without zinc supplement. Zinc supplement was given as 50 mg elemental zinc as zinc sulphate daily for 6 weeks. Compliance with taking zinc supplement has been made by examining the capsule containers.

Biochemical analysis-anthropometric measurements: FPG, S. insulin, HbA1c, S. zinc, and lipid profile, were measured and recorded at the beginning(before supplementation) and at the end of the study. Venous blood samples (7 cc) were collected after an overnight fast and 5 cc of it were centrifuged at 3500 rpm for 10 min. The serum fraction was stored at -25ºc until analyses were performed. The remaining (2cc) were put in an EDTA tube for the immediate measurement of HbA1c by Tosoh's G7 Automated HPLC Analyzer, Japan. Determination of serum zinc was done using a spectrophotometric method (Zinc PAPS LS inc. Standard. colorimetric end point method). Determination of lipids were done by (Dirui company end point method). Serum insulin was measured by electrochemiluminescence method on the cobas e411 analyzer. Determination of glucose was done by oxidase enzymatic method using Chromacast reagents.

Insulin resistance was calculated according to Homeostatic Model Assessment of Insulin Resistance formula : HOMA-IR = (Fasting serum glucose -mg/dL× Insulin(μU/L)]/405)[13] Measurement of weight was done by calibrated scale and for height by calibrated stadiometer. BMI was calculated by dividing weight (Kg) by squared height (m^2) at the beginning and at the end of the trial and categorized according to WHO criteria.

Statistical Analysis

IBM SPSS version 26 was used for statistical analysis. Participant characteristic data are presented as mean, SD and range. Paired sample t-test was used to compare the study group characteristics before and after intervention(P-value=0.05). Independent samples t-test was used to assess the difference between intervention and control group in the mean change of study group characteristics (P-value=0.05). in the mean change of study group characteristics (P-value=0.05). Pearson's correlation was used to assess the relation between daily dietary zinc intake and serum zinc levels (significant R $\geq \pm 0.3$).

Results:

-Demographic characteristics of study participants: There was no statistical difference between the intervention ad control group regarding age, gender, BMI, and other biochemical markers under study at baseline. Also there was significant positive

correlation between zinc intake and serum zinc level ($R^2 = 0.432$) as shown in(figure.1)

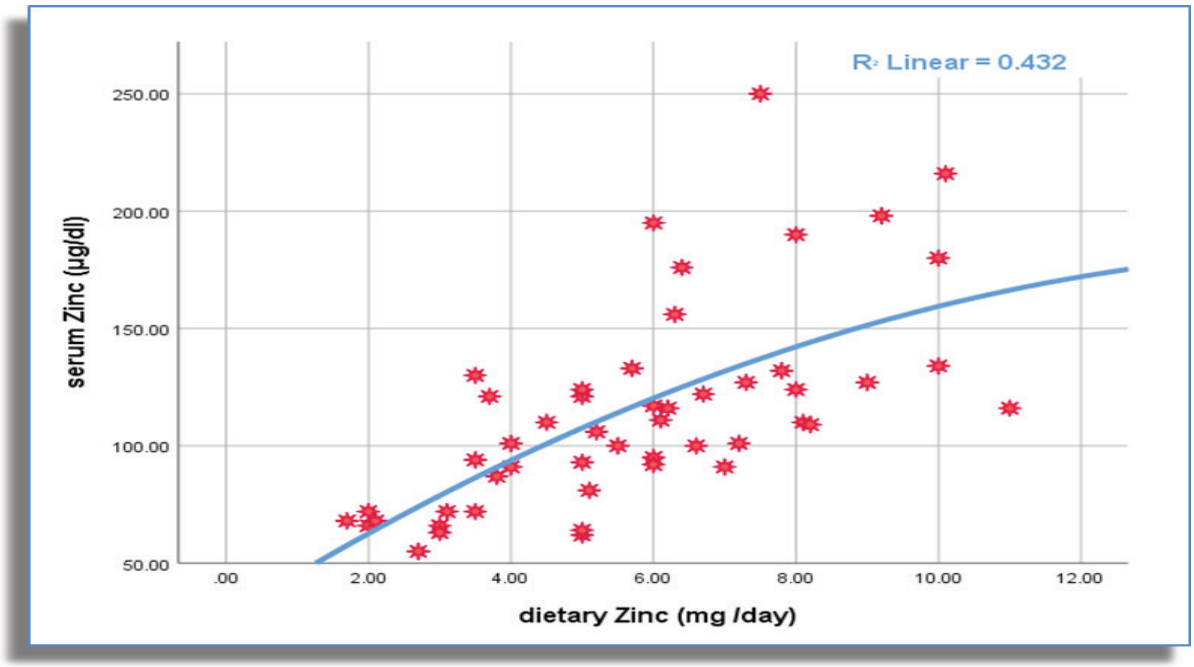

Figure.1 Pearson's correlations between s. zinc level and daily dietary zinc intake

-The change in the intervention group characteristics after 6 weeks*(table.1):*

-Difference between Intervention and control group in the mean change of study group characteristics*(table.2)*: No significant difference in BMI (P=0.092). Insulin resistance (IR) was significantly decreased in intervention group (change mean-0.75 P=0.004).Serum zinc level was significantly higher(change mean 7.72µg/dl P=0.0001). HbA1c was decreased significantly (change mean-0.72 P=0.001). TG and cholesterol were significantly decreased (change mean -10.92mg/dl P=0.001 and – 3.52mg/dl P=0.009) respectively. While HDL-C was increased significantly (change mean 3.56 mg/dl P=0.022).

Table.1 Comparisons of the study group characteristics before and after intervention

N=25		Study Group					
		Intervention group Mean			Control group Mean		
		before	after	P-Value	before	after	P-Value
Anthropometric measurements	Weight (kg)	87.78	85.90	0.004*	83.72	83.50	0.735
	BMI (kg/m^2)	31.46	30.77	0.004*	30.22	30.15	0.763

Cont... **Table.1 Comparisons of the study group characteristics before and after intervention**

Glucose homeostasis & Serum Zinc	FPG (mg/dl)	133.36	119.68	0.026*	124.52	124.00	0.727
	serum Insulin µU/mL	16.99	16.42	0.443	15.50	16.23	0.034*
	Insulin Resistance	5.72	4.97	0.082	4.67	4.93	0.053
	Serum zinc(µg/dl)	123.64	131.36	0.053	104.56	103.48	0.155
	HbA1c	8.14	7.42	0.007*	7.92	7.88	0.544
Lipid Profile	VLDL (mg/dl)	34.67	28.40	0.237	28.92	29.40	0.083
	LDL (mg/dl)	103.40	98.32	0.390	77.44	80.64	0.008*
	HDL (mg/dl)	49.20	52.76	0.099	51.64	51.44	0.821
	TG (mg/dl)	154.44	143.52	0.158	146.28	147.68	0.026*
	Total Cholesterol (mg/dl)	183.08	179.56	0.645	160.24	162.40	0.012*
*significant P< 0.05							

Table.2 Difference between Intervention and control group in the mean change of study group characteristics

N=25		**Study Group**		**P-Value**
		Intervention group	**Control group**	
		Mean ±SD	**Mean ±SD**	
Anthropometric measurements	BMI change (kg/m2)	-0.69 ±1.08	-0.07 ±1.12	0.092
Glucose homeostasis & Serum Zinc	IR change	-0.75 ±2.08	0.25 ±0.62	0.004*
	s. zinc Change (µg/dl)	7.72 ±18.97	-1.08 ±3.67	0.0001*
	HBA1c change	-0.72 ±1.22	-0.05 ±0.39	0.001*
Lipid Profile	VLDL change (mg/dl)	-6.27 ±25.83	0.48 ±1.33	0.052
	LDL change (mg/dl)	-5.08 ±28.99	3.20 ±5.51	0.078
	HDL change (mg/dl)	3.56 ±10.37	-0.20 ±4.37	0.022*
	TG Change (mg/dl)	-10.92 ±37.50	1.40 ±2.94	0.001*
	Cholesterol change (mg/dl)	-3.52 ±37.75	2.16 ±4.00	0.009*
*significant P< 0.05				

Discussion

Most of the diabetic patients tend to consume alternative medicines to control their blood sugar, zinc is the most commonly one. There is no consensus on optimal dose and duration for zinc supplementation in diabetic patients to improve their health status. In this study we aimed to evaluate the effect of supplementation of 50 mg zinc sulphate for 6 weeks on IR, lipid profile, BMI, we found a statistical significant improvement in serum zinc Level, IR, HbA1c, HDL-C, TG, TC and no statistical significant difference in BMI.

Effect on glucose control and IR:

Similar to our result, in a clinical trial on 40 obese patient, Zn supplementation has a favorable effect in reducing IR after 15 weeks of 30mg zinc/d, and may play an effective role in the treatment of obesity [13]. Another trial performed 30mg of zinc supplementation for 30 days in 28 obese women, found a reduction in serum insulin and HOMA-IR values[14]. Also our result come in line with 2 recent systematic reviews concluded that Zn supplementation improves insulin resistance in obese individuals [15,16].The difference from finding of another trial[17], might due to the severity of metabolic disturbances, the dose and type of supplementation .

Effect on Serum zinc: serum zinc concentration increased notably in our study after intervention in comparison to the control group. Similar to this result, several clinical trials observed that 30 mg /d of zinc for (12ws, 4ws, 12ws, 15ws) respectively were increased S. zinc concentration[17,13]. In contrast to the former trials, our study showed that mean S. zinc level of the intervention and control group at baseline was within normal reference level (123.64 ±53.79 and 104.56 ±26.73 µg/dl) respectively according to reference lab value (normal value=50-150mg/dl) and this could be due to 3 reasons: 1) Duration of diabetes < 5yrs in our study participants[18]2) The biochemical markers under study including zinc, have been measured in fasting state that increase serum zinc level [19].

3) Serum zinc level do not reflect cellular Zn status precisely due to highly regulated homeostatic control mechanisms[8]. One meta-analysis conclusion was comparable to our finding [20].

Effect on lipid profile

According to a Meta-analysis investigation results, regarding the effect of zinc supplementation on lipid profiles were inconsistent[20],

Our results agree with a clinical trial which concluded that 100 mg zinc sulfate, significantly reduced TC,TG concentrations, and increased those corresponding to zinc and HDL-C in the bloodstream[21,22,17].

In contrast to our results, a clinical trial showed no significant change in lipid parameter, that is might be explained by small dose (10mg/d)of zinc[23]. Or larger dose in other study(660mg zinc/d)[24].

Baseline lipid levels of the study participants, low doses of zinc over short periods might be the reason behind this difference from other studies. while several systematic reviews were agree with us [25,7]. In a recent systematic review of randomized controlled trials, combining 9 effect sizes from 9 RCTs, resulting in a significant decrease in TG, TC a non-significant effect on serum LDL-C and HDL-C, but the overall effect size of zinc supplementation on serum HDL-C concentrations became significant[26].

Effects on BMI: The reduction in weight and BMI in our trial was only in zinc group post supplementation, but No statistical significant difference was found in BMI in comparison to control group and this result was in agreement with a clinical trial that conducted on 40 subjects after 6 weeks of 660 mg zinc sulphate supplementation[24]. Parallel to our results, in a systematic review and dose response meta-analysis, 27 trials (n=1438 participants) were included[27], while a clinical trial conducted on 80 obese person concluded significant BMI reduction[28]. Larger sample size, longer duration in this trial may result in this diversity from our study.

The strength in this trial was the wide range of exclusion criteria, specific range of age, limited duration of diabetes, but there was limitations in our study such as short period of follow-up.

However, we cannot generalize our study results on whole Iraqi diabetic patients because of small sample size and short duration of supplementation. This trial could be considered as a reference study to the future

similar trial that could take into consideration our trial limitation. It can be suggested that increasing the period of intervention and determining the safety and effectiveness of doses of zinc supplementation be considered in future studies.

Conclusion

Our study results revealed that daily dose of 50 mg zinc improves insulin resistance and induces more healthy lipid profile, while it has no significant effect on BMI of type II diabetic patients after 6 weeks of supplementation. Hence zinc could play an essential role in delaying or preventing the progression of T2D.

Ethical Clearance: The Research Ethical Committee at scientific research by ethical approval of both MOH and MOHSER in Iraq

Conflict of Interest: None

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