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Effects of zinc supplementation on serum adiponectin concentration and glycemic control in patients with type 2 diabetes

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ABSTRACT

Background: Previous studies have suggested that zinc is involved in insulin homeostasis. Adiponectin is a well-known adipokine with anti-diabetic, anti-atherogenic, and anti-inflammatory properties. The aim of this study was to investigate the effect of zinc supplementation on glycemic control, and the potential mediating role of adiponectin, in patients with type 2 diabetes.

Methods: In this randomized double-blind placebo-controlled clinical trial, 60 patients with diabetes, 30-60 years, were randomized to receive either 30 mg/d zinc (as zinc gluconate) or placebo for 12 weeks. Circulating levels of adiponectin, zinc, glucose homeostasis parameters, and lipid profiles, as well as anthropometric parameters and dietary intakes, were assessed.

Results: About 53.3% of the patients had zinc insufficiency at baseline. Serum zinc levels improved significantly in the intervention than control group following 12 weeks supplementation ($P < 0.001$). Adiponectin (1.23 ± 2.23 µg/ml, $P = 0.006$) and insulin (3.6 ± 4.66 µIU/ml, $P = 0.001$) levels increased significantly compared to baseline in the zinc group; but this change was not significant compared with the control group. Following supplementation, there were no significant differences in glycemic control and anthropometric parameters between the two groups. Serum HDL levels increased significantly in the zinc (5.37 ± 14.8 mg/dl) compared to control (-1.53 ± 6.9 mg/dl) group following supplementation ($P = 0.039$).

Conclusion: Despite a significant increase in serum zinc level, no improvement was observed in glycemic control, following 12 weeks supplementation with 30 mg/d zinc (as zinc gluconate). Zinc supplementation restored adiponectin concentrations partly within the intervention group, and increased HDL levels compared to the control group. The current findings did not support improvement in glucose homeostasis following zinc supplementation in patients with type 2 diabetes under the present study design.

1. Introduction

The prevalence of diabetes has increased worldwide in recent decades predominantly due to obesity, unhealthy lifestyle and eating patterns [1]. Diabetes induces various disorders including cardiovascular disease and stroke, non-traumatic amputations, advanced organ failures, and neuropathies, which cause high mortality, morbidities and financial burden to health systems [2]. Available medications were developed to manage metabolic disorders and improve quality of life in diabetes. However, as they were not fully able to control diabetes associated complications, the potential benefits of complementary therapies have been considered progressively.

Zinc is one of the essential trace elements for human that exists in more than 300 metalloenzymes and 2500 translation factors and participates ubiquitously in many cellular functions and metabolic pathways involved in growth, immunity, reproduction, and neurological development [3]. It has been suggested that zinc is essential for the synthesis of insulin, the function of its receptors and associated kinases,

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and translocation of glucose transporter 4 (GLUT4) [4,5]. The membrane zinc transporter ZnT8 gene variants, which transports zinc to the secretory insulin and glucagon granules of pancreatic islet β and α cells, may be also correlated with diabetes risk [6,7]. The effects of zinc on glucose homeostasis is partly due to activating the insulin-signaling cascade via the phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt) pathways [8]. Additionally, zinc has an important role in the regulation of the transcription factor peroxisome proliferator activated receptor-γ (PPARγ) activity signaling [9]. PPARγ activation could improve insulin sensitivity and dyslipidemia that may be mediated, at least in part, by up-regulating adipose-derived insulin-sensitizing hormones like adiponectin [10].

Adiponectin is a well-recognized adipokine considering its anti-atherogenic, anti-inflammatory and anti-diabetic properties [11]. Thus, it has been considered as a novel therapeutic target in metabolic disorders. The effect of supplementation with zinc has been assessed in the regulation of glucose and insulin homeostasis. However, studies did not show conclusive results about the efficacy of this vital nutrient on glycemic control [12,13]. Besides, the probable role of adiponectin in mediating the effects of zinc on glycemic control has not been well studied in clinical studies so far. Experimental models have shown that daily oral administration of zinc compounds could improve glycemic control and restore suppressed levels of adiponectin in obesity-linked type 2 diabetic mice [14] and high-fat diet-fed streptozotocin induced diabetic rats [15]. Thus, the aim of this study was to investigate the role of zinc supplementation on glycemic control and lipid profile of patients with type 2 diabetes and the potential mediating role of adiponectin in this regard.

2. Material and methods

2.1. Participants

Patients with diabetes, age 30-60 years, and stable medication protocol within the past three months were recruited to the study from a diabetes management center affiliated to the Kashan University of Medical Sciences.

Non-inclusion criteria included pregnant, lactating and post-menopausal women, treatment with insulin, smoking, patients with history of acute or chronic renal failure, cardiovascular diseases, thyroid dysfunction, gastrointestinal and liver diseases, cancer, recent surgery and acute infections, people receiving trace element supplements in the previous three months, or medications that could affect body weight or interfere with zinc metabolism such as oral contraceptives, anti-depressants and anti-psychotics, hormones, glucocorticoids, diuretics and antibiotics. The sample size was determined based on adiponectin levels as the primary outcome. Considering a power of 80% to detect 2 unit change in adiponectin, a type I error of 0.05, and a drop-out rate of ˜10%, the sample size of 32 participants in each group was calculated. The study protocol was approved by the Ethics committee of the Tehran University of Medical Sciences and was conducted according to the Declaration of Helsinki. Patients were aware of the study purposes and signed an informed consent form.

2.2. Study design

In this randomized, double-blind, placebo-controlled, parallel-design trial, participants were randomly allocated to intervention and control groups using block randomization procedure of size 4. The random sequence was generated using random allocation software by the study statistician and assigning the participants to two groups was conducted by an independent person. Patients in the intervention group received a daily dose of 30 mg zinc as zinc gluconate (Nature Made Nutritional Products, Mission Hills, CA, USA) and the control group received identical-appearing placebo (manufactured by the Institute of Pharmaceutical Sciences, Tehran University of Medical Sciences, Tehran, Iran) for 12 weeks. The medication boxes were labeled as A and B and the researchers and participants were blinded to the allocation. All participants were instructed to continue their usual dietary habits and physical activity during the study. Patients were excluded if they did not consume more than 10% of the supplements. They were followed up every two weeks to check the compliance and probable side effects.

2.3. Biochemical analysis

Venous blood samples (10 cc) were collected after an overnight fast and centrifuged at 3500 rpm for 10 min. The plasma and serum fractions were stored at -80^{o}c until analyses were performed. Determination of serum zinc concentration was performed by atomic absorption spectrophotometry (Shimadzu, AA680 G, Japan). Serum adiponectin concentrations were determined using an enzyme-linked immunosorbent assay (ELISA) kit (Adipogen Inc., Seoul, Korea). Serum fasting blood glucose (FBG) concentration was determined by glucose oxidase enzymatic method (Pars Azmoon Inc., Iran) and plasma HbA1c measured using ion-exchange high pressure liquid chromatography (HPLC) method (Bio Systems SA, Barcelona, Spain). Serum lipid profiles, total cholesterol, triglyceride (TG), low density lipoprotein (LDL), and high density lipoprotein (HDL) were measured using standard biochemical methods (Pars Azmoon Inc., Iran). Serum insulin level was assessed using an immunoradiometric method (Biosource Europe SA, Belgium). Insulin resistance (IR) was calculated by the homeostasis model assessment for insulin resistance (HOMA-IR) model as fasting insulin (μU/ml) × fasting glucose (mmol/L) / 22.5.

2.4. Anthropometries and dietary intake

Anthropometric parameters including body weight, height, and waist circumference (WC) were measured using standard techniques, with light clothing and barefoot, at baseline and following 12 weeks intervention. Body mass index (BMI) was calculated by dividing weight (kg) by squared height (m^2). At the beginning and end of the study, a three-day 24-h dietary recall was obtained from all participants by a trained dietitian. Dietary data were analyzed by Nutritionist IV software (N Squared Computing, San Bruno, CA, USA) modified for local foods.

2.5. Statistical analysis

All statistical tests were performed using SPSS18 software (SPSS Inc., IL, Chicago, USA). Kolmogorov–Smirnov test was used to determine normality of the variables. Comparisons of baseline characteristics were performed using Student's t-tests (for normal variables) and Mann-Whitney test (for non-parametric variables). Paired t-test and Wilcoxon singed rank test were applied for within group comparisons (after supplementation compared to baseline). The effect of the intervention was investigated by ANCOVA test adjusting for baseline values and other potential confounders. $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. General characteristics

Among 64 patients who were included, 60 (30 in each group) completed the study. In each study group, 2 patients were reluctant to finish the study due to personal reasons (Fig. 1).

There were no significant differences in sex, age, type of hypoglycemic medications, hypertension, and duration of diabetes between two groups at baseline (Table 1). The mean reported dietary intakes demonstrated no significant differences in reported calorie, macro-nutrients, and zinc intakes between two groups at the beginning of the

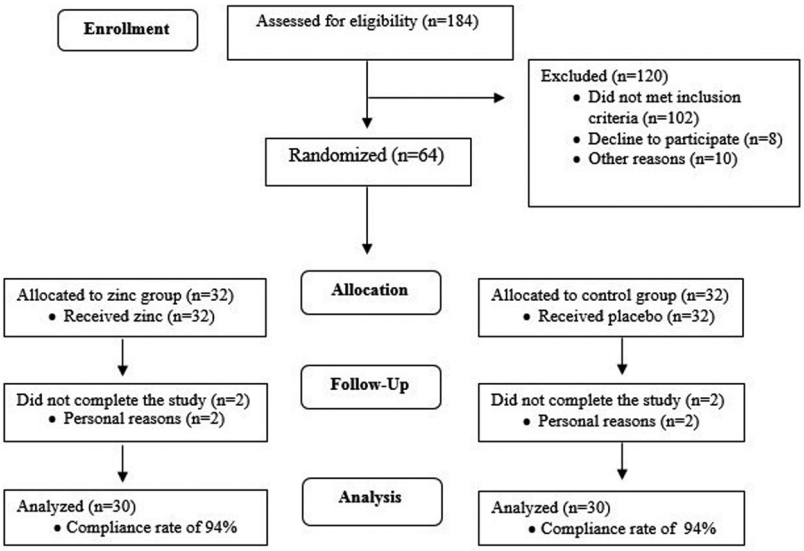

Fig. 1. CONSORT flow diagram of the study population.

Table 1
Baseline characteristics of the study population.

		Group		P
		Control (n = 30)	Zinc (n = 30)	
Age, years (Mean ± SD)		45.5 ± 5.4	46.2 ± 5.3	0.613†
Male, n (%)		15 (50)	17 (56.7)	0.796*
Diabetes duration, years (Mean ± SD)		9 ± 4.1	7.1 ± 3.5	0.065†
Drugs, n (%)	**Metformin**	2 (6.7)	6 (20.7)	0.356*
	Glibenclamide	6 (20)	5 (17.2)	
	Both	22 (73.3)	18 (62.1)	
Hypertension, n (%)		8 (26.7)	10 (33.3)	0.779*
Dietary intake (Mean ± SD)				
	Energy (kcal/d)	1217.4 ± 237.3	1362.6 ± 325	0.053†
	Carbohydrate (g/day)	161.4 ± 44.4	184.8 ± 58.5	0.087†
	Protein (g/day)	44.5 ± 13.4	50.2 ± 13	0.096†
	Fat (g/day)	47.5 ± 10.5	51.2 ± 11.3	0.203†
	Zinc (mg/day)	6.6 ± 2.3	7.5 ± 2	0.125†

† Based on t-test.
* Based on Chi-Square test.

study (Table 1). There was not also any difference in dietary intakes between the study groups at the end of the trial.

3.2. Serum adiponectin and zinc concentration

Our results showed that serum zinc levels were below the cut-off of 70 μg/dl in %53.3 of the participants (50% of the zinc and 56.7% of the control group). There was no significant difference in serum zinc value between two groups at baseline. Following 12 weeks supplementation, serum zinc levels were significantly higher in zinc than the control group (43.88 ± 18.55 vs. 2.55 ± 7.71 μg/dl, P < 0.001). The circulating levels of adiponectin increased significantly throughout the study, (1.23 ± 2.23 μg/ml change from baseline, P = 0.006) in the zinc group; but the difference was not statistically significant compared with the control group following the supplementation (Table 2).

3.3. Glycemic control and lipid profile

HbA1c decreased marginally (-0.48 ± 1.33 % changes from baseline, P = 0.059) following supplementation; however, this decrease did not attain statistical significance and was not considerably different compared to the control group at the end of the study. Changes in fasting blood glucose were not statistically significant between the zinc and control groups. After the intervention, fasting insulin increased significantly in the zinc group (3.6 ± 4.66 μIU/ml compared to baseline, P = 0.001), but this change was not statistically different from the control group. HOMA-IR values increased at the end of the study in both the zinc (P = 0.003) and control (P = 0.021) groups compared to baseline. There was no significant difference in HOMA-IR between the two groups following the intervention (Table 3).

The findings showed a significant increase in serum concentrations of HDL in the intervention compared to the control group (5.37 ± 14.8 vs. -1.53 ± 6.9 mg/dl, P = 0.039). No other changes were observed in TG, cholesterol, and LDL levels following supplementation.

3.4. Anthropometric parameters

At baseline there were no statistically differences in weight (73.2 ± 9.5 vs. 72.2 ± 8.9 kg, P = 0.676), BMI (26.96 ± 2.9 vs. 26.9 ± 2.74 kg/m^2, P = 0.894), and WC (97.6 ± 8 vs. 95.5 ± 6.9 cm, P = 0.263) between the zinc and control groups, respectively. No significant differences were also seen in weight (P = 0.584), BMI (P = 0.695), or WC (P = 0.879), at the end of the study. Additionally, following supplementation, there were not significant differences in changes of weight (-0.4 ± 2.13 vs. -0.63 ± 1.7 kg, P = 0.641), BMI (-0.16 ± 0.8 vs. -0.22 ± 0.59 kg/m^2, P = 0.718), and WC (-1.12 ± 3.88 vs. -0.68 ± 3.08 cm, P = 0.634) between the zinc and control groups, respectively.

4. Discussion

The current study showed that following 12 weeks supplementation with 30 mg/d zinc in patients with diabetes, circulating adiponectin increased remarkably in the intervention group compared to baseline, which was not albeit significantly different from the control group at the end of the study. There was no significant improvement in glycemic control following supplementation with zinc. Zinc concentration increased considerably in the zinc compared to the control group following the study termination.

Table 2
Changes in adiponectin and zinc serum levels throughout the study.

		Control (n = 30)	Zinc (n = 30)	Diff	95% CI		P
		Mean ± SD	Mean ± SD		Lower	Upper	
Adiponectin (μg/ml)	Before	8.96 ± 4.47	7.66 ± 3.18	1.3	−0.704	3.304	0.115‡
	After	9.32 ± 3.45	8.89 ± 3.21	0.470	−0.576	1.516	0.372§
	Change	0.36 ± 2.39	1.23 ± 2.23	−0.87	−2.064	0.324	0.359‡
	P£	0.269	0.006				
Zinc (μg/dl)	Before	71.02 ± 24.56	70.68 ± 19.05	0.333	−11.027	11.693	0.442‡
	After	73.57 ± 20.84	114.57 ± 18.22	−41.229	−47.715	−34.743	< 0.001§
	Change	2.55 ± 7.71	43.88 ± 18.55	−41.333	−48.674	−33.993	< 0.001‡
	P£	0.012	< 0.001				

‡Based on Mann-Whitney test.
£Based on Wilcoxon singed rank test.
§Adjusted for baseline values based on ANCOVA.

Table 3
Changes in glucose homeostasis parameters and lipid profile throughout the study.

		Control (n = 30) Mean ± SD	Zinc (n = 30) Mean ± SD	P
HbA1c (%)	Before	9 ± 1.7	8.9 ± 1.7	0.704†
	After	8.6 ± 1.6	8.4 ± 1.3	0.58§
	Change	−0.4 ± 1.22	−0.48 ± 1.33	0.81†
	P¥	0.088	0.059	
Fasting Blood Glucose (mg/dl)	Before	179.7 ± 45.6	156.9 ± 46.9	0.064†
	After	183 ± 57.6	152.1 ± 45.2	0.201§
	Change	3.34 ± 31.75	−4.8 ± 41.03	0.398†
	P¥	0.575	0.527	
Insulin (μIU/ml)	Before	8.6 ± 5	8.01 ± 4.5	0.84‡
	After	10 ± 3.9	11.7 ± 6.3	0.068§
	Change	1.36 ± 4.31	3.6 ± 4.66	0.131‡
	P£	0.074	0.001	
HOMA-IR	Before	3.6 ± 2	3.2 ± 2.2	0.375‡
	After	4.5 ± 2.2	4.4 ± 3.2	0.811§
	Change	0.89 ± 2.21	1.15 ± 2.46	0.913‡
	P£	0.021	0.003	
Triglyceride (mg/dl)	Before	174.6 ± 79.2	187.5 ± 97.9	0.574‡
	After	156.3 ± 57.1	170.4 ± 76.4	0.567§
	Change	−18.3 ± 58	−17.2 ± 74.8	0.723‡
	P£	0.139	0.622	
HDL (mg/dl)	Before	33.2 ± 7.6	30.3 ± 6.39	0.064‡
	After	31.7 ± 7.4	35.6 ± 14.5	0.071§
	Change	−1.53 ± 6.9	5.37 ± 14.8	0.039‡
	P£	0.302	0.067	
LDL (mg/dl)	Before	103.4 ± 24.5	97.8 ± 22.8	0.206‡
	After	100.4 ± 26	96.9 ± 35.3	0.862§
	Change	−3 ± 23.4	−0.93 ± 25.2	0.446‡
	P£	0.504	0.719	
Cholesterol (mg/dl)	Before	181.6 ± 40.1	174.5 ± 37.19	0.183‡
	After	173.4 ± 46.3	171.67 ± 47.98	0.733§
	Change	−8.13 ± 45.12	−2.83 ± 32.17	0.308‡
	P£	0.099	0.627	

† Based on t-test.
‡ Based on Mann-Whitney test.
¥ Based on Paired Samples Test.
£ Based on Wilcoxon singed rank test.
§ Adjusted for baseline values based on ANCOVA.

The initial serum zinc concentrations were below the reference values (70 μg/dl) in nearly 50% of the patients of both groups. Many studies have reported decreased zinc concentration and increased urinary zinc excretion in patients with diabetes [16]. Despite the presence of only about 1% of the total body zinc in circulation, both plasma and serum zinc levels are considered valid biomarkers of zinc status [3]. In the current study, we used zinc gluconate for supplementation. The most common forms of zinc compounds are zinc sulfate, zinc gluconate, zinc acetate, and zinc oxide. Zinc sulfate and zinc gluconate were mentioned most frequently in previous studies. The published data has indicated high and comparable absorption of zinc gluconate, zinc citrate, and zinc sulfate, while zinc oxide is slightly less absorbed. Besides, zinc gluconate has better sensory properties and is odorless compared with zinc sulfate and zinc acetate that have strong metallic and bitter taste, which needs to be covered in supplements [17]. Supplementation with 30 mg zinc improved zinc deficiency significantly in the intervention group. However, there were no significant differences in HbA1c, FBG, insulin, and HOMA-IR between the two groups following 12 weeks supplementation with 30 mg zinc in this trial. Fasting insulin increased significantly compared to baseline in the zinc group. HOMA-IR changed considerably compared to the initial values in both groups.

Despite the suggested mechanisms involved in the relationship between zinc and glucose homeostasis, many clinical trials failed to show any advantageous effect in improving glycemic control in patients with diabetes following supplementation with 100 mg zinc sulfate for 12 weeks [18], 50 mg zinc gluconate for 4 weeks [19], or 40 mg elemental zinc for 12 weeks [20]. A meta-analysis showed a considerable reduction in FBG and postprandial blood glucose and no significant change in HbA1c. Insulin concentration and insulin resistance were not assessed in this meta-analysis and primary studies had a high heterogeneity [13]. In this trial, HbA1c decrease was marginally significant compared to baseline in the zinc group. Multiple studies have also shown a significant decrease in HbA1c only within the intervention groups compared to baseline, which did not statistically differ from the control groups following zinc supplementation [21–24]. Different supplementation protocols including 22 mg zinc as zinc sulfate for 4 months [22], 30 mg zinc as zinc sulfate for 3 months [21,23], and 660 mg zinc sulfate for 6 weeks [24] have been used in these studies. Similarly, positive changes in FBG and postprandial blood glucose (22 mg zinc as zinc sulfate for 4 months) [22], and serum levels of insulin and HOMA-IR (30 mg zinc aminochelate for 4 weeks) [25] in other studies were confined to post- vs. pre-values in the intervention groups, and were not different from the placebo groups at the end of trials. Thus, the accuracy of positive reported results in some previous studies needs to be reviewed to avoid biases and misinterpretations.

Insulin levels increased remarkably in the zinc group compared to baseline. This change was not accompanied with improvement in glycemic control. An experimental study in diabetes-prone BB Wistar rats showed that animals fed a diet containing 1000 ppm zinc, had higher serum and pancreatic insulin levels and lower serum glucose than those fed low zinc diets [26]. Zinc has also improved β cell function in patients with pre-diabetes [27]. Another clinical study did not confirm these findings; however, this trial has been done in healthy adolescence receiving low doses of zinc (9 mg zinc as zinc sulfate) for 4 weeks [28]. HOMA-IR did not differ between groups at the end of this study; although it has been elevated in both groups compared to baseline. This observation could not be completely justified in the current study as

diabetes is a complex and multifactorial disease, with different factors that affect its management and progression. The simultaneous increase in HOMA-IR in both the intervention and control groups indicates the involvement of unknown variables other than zinc supplement in exacerbating insulin resistance. Interestingly, few studies have reported changes in insulin resistance following zinc supplementation in diabetes and the available meta-analysis did not mention this important clinical outcome. The reference values of insulin are considered 2-25 μIU/ml [29]. In this study, the insulin level increased 3.6 μIU/ml (8.01 to 11.7 μIU/ml) in the zinc group. Although this increase was within statistically significance, no improvement was observed in glycemic control. The lack of improvement in insulin sensitivity following zinc supplementation, despite an increase in circulating insulin, might be due to the complex cellular mechanisms involved in insulin resistance. Several factors including the response of insulin receptor, the function of GLUT 4 especially in muscles and adipose tissue, disturbed fatty acids metabolism, inflammation, gut microbial dysbiosis and the level of other hormones [30,31] could have a determinant role, which were not probably improved with zinc supplementation. A review article has proposed that only trials with a significant number of patients with subnormal zinc status showed improvements in glycemic control following supplementation [32]. More than 50% of patients in this study had insufficient serum zinc status. Thus, the current study might be a counterexample and indicates the presence of more potential complicated determinants in zinc efficacy. The severity of metabolic disturbances and duration of supplementation might also play a role. In the current study, baseline HbA1c was more than 7.5 in 80%, and the duration of diabetes was more than five years in 85% of the participants. A recent clinical trial showed the efficacy of supplementation with 30 mg daily zinc sulfate for six months in improving glycemic control in patients with pre-diabetes [27] that had less metabolic complications and disease duration. Differences in other co-morbidities and protocol of medications in previous studies might also explain part of discrepancies in findings of zinc trials [32].

Although several studies have investigated the role of zinc on glucose and insulin homeostasis, little is known about the association between zinc function and adiponectin. Adiponectin production is increased by PPAR agonists such as the anti-diabetic medications thiazolidinediones [10]. Besides, it has been stated that zinc could regulate PPARγ signaling [9]. The PPARγ expression and activation reduced significantly in zinc deficiency and reversed with zinc supplementation [33,34]. Thus, in this study, it was hypothesized that improvement in zinc status following supplementation will lead to higher PPARγ and adiponectin levels and consequently better glycemic control. The findings have indicated considerable improvement in zinc status and a simultaneous increase in adiponectin concentration within the zinc group. However, this increase did not differ significantly from the control group and seems to be clinically inadequate to improve glycemic control. Different physiological concentrations of adiponectin have been suggested. In general, values between 2-30 μg/ml could be considered for normal population [35,36]. Comparing the values of adiponectin in this study with other trials showed notable variations in baseline values and changes following interventions, which restricts the possibility to recognize the clinically important changes in adiponectin concentration. Several variables including BMI, body fat percentage, metabolic status, diet, and medications could affect adiponectin levels. Besides, there is a heterogeneity in standards, laboratory techniques, type of adiponectin, unit of measurement and methodologies in previous studies. We have previously reported the efficacy of bariatric surgery [37] and nutritional supplements green tea extract [38] and quercetin [39] in improving adiponectin concentration and glycemic control in patients with insulin resistance. However, few clinical data are available investigating the effect of zinc on adiponectin levels. Twelve-week supplementation with 50 mg/day zinc as zinc sulfate in individuals with normal glucose tolerance test increased adiponectin levels significantly compared to the control group [40]. Supplementation with 30 mg/day zinc as zinc gluconate for 8 weeks in young obese women improved serum zinc status within the intervention group but did not affect insulin sensitivity or adiponectin concentration significantly [41]. Experimental studies in obesity-linked type 2 diabetic mice [14] and high-fat diet-fed streptozotocin induced diabetic rats [15] have reported an increase in adiponectin concentration and better glycemic control following 4-week oral administration of 5-15 mg/kg body weight zinc compounds. It has been shown that different zinc compounds could exert distinctive effects on glycemic control and adiponectin levels [42,43]. As adiponectin expression and concentration decline in diabetes, zinc supplementation in the current trial might just compensate for this decrease and probably different doses and durations are required to observe consequent clinical efficacy. Moreover, experimental models usually use active and highly absorbable complexes of zinc that could affect the results.

The findings of the current trial indicated a significant increase in HDL concentration, but not in TG, LDL, and total cholesterol, compared to the control group. Other studies showed controversial results. No significant changes were observed in lipid profile following three months supplementation with 30 mg/d zinc (as zinc sulfate) in patients with diabetes [23]. Other studies showed an increase in HDL levels in both patients supplemented with 100 mg zinc sulfate for 12 weeks and controls compared to baseline and a decrease in TG and cholesterol levels within the zinc group. These changes were not significantly different between intervention and control groups at the end of the study [18]. Besides, another trial in diabetes reported reductions in TG, TC, and LDL levels, but not HDL values, within the zinc group receiving 660 mg zinc sulfate for 6 weeks, which was not albeit different from the controls at the end of the study [24]. It should be considered that our patients did not have dyslipidemia, except for low HDL concentrations, at baseline, which could impact the efficacy of the intervention. In overall, despite significant improvement in HDL levels in the current trial, more studies are required to confirm the beneficial effect of zinc on lipid profiles and cardiovascular risk factors.

In the present study, there were no statistically significant changes in weight, BMI, waist circumference and dietary reported intakes between the two groups during the study. Thus, the changes in anthropometric measurements or dietary intakes could not be confounding factors in the interpretation of the observed results.

Despite sufficient evidence provided by cellular and experimental studies, many trials including the current study failed to show a remarkable advantage for zinc supplementation in diabetes. Additionally, many previous claimed positive results were interestingly limited to post- vs. pre-values in the intervention groups and did not actually differ significantly from controls. Thus, despite a long time investigating the role of zinc in glucose homeostasis, it seems premature to recommend zinc supplementation to improve glycemic control in diabetes.

There are some limitations to this study. Patients had a range of BMI from normal weight to obese. The potential effect of BMI has been considered in statistical analyses, however, investigating specific groups of patients in the future will better clarify the findings. Additionally, considering specific ranges of age, diabetes duration, and HbA1c control in future studies might lead to recognition of subgroups of diabetic patients that benefit from zinc supplementation.

5. Conclusion

The findings showed significant improvement in serum zinc status following 12 weeks supplementation with zinc in patients with diabetes. Serum adiponectin concentrations increased significantly and were probably partly restored compared to baseline in the intervention group. Similarly, serum insulin levels increased significantly in the zinc group; however, no improvement was observed in glycemic control at the end of the study. Serum HDL levels, but not other lipid profiles, improved considerably following supplementation. The findings of the

current study did not support zinc supplementation to improve glucose homeostasis in patients with diabetes.

Conflict of interest

None.

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