Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

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ORIGINAL RESEARCH

Effects of zinc and multimineral vitamin supplementation on glycemic and lipid control in adult diabetes

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Aims: To evaluate the effects of zinc with or without other antioxidants on blood glucose, lipid profile, and serum creatinine in adult diabetics on long-term follow-up.

Materials and methods: Patients (n = 96) were randomly allocated to three groups: group A (n = 29) was supplemented with oral zinc sulfate (22 mg/day) and multivitamin/mineral (zinc+MVM) preparation; group B (n = 31) was given the same preparation without zinc (MVM); and group C (n = 36) was given a matching placebo for a period of 4 months in a single-blinded study. Blood samples were taken at baseline and after 4 months of supplementation to assess blood glucose (fasting and postprandial) and glycosylated hemoglobin (Hb_{A1C}%) and serum levels of zinc, creatinine, and lipids.

Results: The zinc+MVM group had a mean change of fasting blood sugar −0.33 mmol/L (standard error of the mean 0.21 mmol/L) and was significant ($P = 0.05$) when compared with the other two groups (mean change in the MVM group +0.19 (0.31) mmol/L and +0.43 (0.23) mmol/L in the control group, respectively). The Hb_{A1C}% level reduced significantly, irrespective of the baseline level, in zinc+MVM-supplemented individuals. In the other two groups, the change of Hb_{A1C}% level was not significant. Serum lipid levels reduced significantly in the zinc+MVM and MVM groups.

Conclusions: Zinc+MVM supplementation showed beneficial effects in the metabolic control of adult diabetics in addition to elevating their serum zinc level. Zinc supplementation improved glycemic control measured by Hb_{A1C}% and fasting and postprandial glucose. Furthermore, zinc supplementation lowered serum cholesterol and cholesterol/high-density lipoprotein ratio.

Keywords: zinc, multivitamin mineral supplementation, diabetes, glycemic control

Introduction

It has been known for decades that a physical–chemical relationship exists between insulin and zinc.[1] Zinc was added in vitro to make protamine zinc insulin and lente crystalline insulin in order to prolong the duration of action of insulin by delaying its absorption from the subcutaneous injection site, thus requiring fewer insulin injections. Previous studies have shown that serum zinc level is lower in diabetes patients than in nondiabetes subjects, increased urinary zinc excretion being the main reason.[2,3] There are studies where zinc supplementation in diabetic patients shows antioxidant properties.[4,5] In one study involving diabetics, zinc supplementation decreased lipid peroxidation.[6] However, there are no prospective studies in type 2 diabetes patients on the association between serum zinc level and cardiovascular complications.

Glycemic control and prevention of secondary complications are the important goals of pharmacological therapy of diabetes mellitus. The inadequate efficacy of oral

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hypoglycemic agents seen at times is attributed to inadequate postreceptor events associated with oxidative stress induced by long-term hyperglycemia. The administration of antioxidants such as zinc, magnesium, selenium, vitamin A, and vitamin E may improve the tissue response to insulin and increase the efficacy of drugs that act through this pathway. Elevated postprandial plasma levels of triglycerides (TG), free fatty acids, and cholesterol are common in type 2 diabetes.

To the best of our knowledge, there are no reports about the effects of zinc with or without other antioxidants (magnesium, selenium, vitamin A, and vitamin E) on blood sugar, serum insulin, lipid profile, and serum creatinine in adult type 2 diabetes patients already on standard medications. Coronary heart disease is a major cause of death in type 2 diabetes patients, and the risk of coronary heart disease is two- to four-fold higher among patients with type 2 diabetes than in nondiabetes subjects.[7] This enhanced risk is partly explained by traditional cardiovascular risk factors, eg, hypertension, plasma lipid and lipoprotein abnormalities, smoking, and obesity, but all of the excess risk cannot be explained by these conventional risk factors. Therefore, this study was designed to determine the effects of zinc with or without other antioxidant supplementation among type 2 diabetes patients who were being followed up in medical clinics for more than 2 years in a tertiary care hospital.

Research design and methods

The study received approval from the Ethical Review Committee of the Faculty of Medicine, University of Ruhuna, Galle, Sri Lanka. Previously diagnosed (for at least 2 years) patients with adult-onset (type 2) diabetes mellitus attending medical clinics of the teaching hospital in Karapitiya, Galle, were considered as the study population.

The following exclusion criteria were applied in selecting them:

1. Those with renal or liver failure or any other chronic disease except essential hypertension and dyslipidemia
2. Those who were taking vitamin–mineral supplements or any hormone replacement therapy
3. Those with a history of recent surgery or acute infection
4. Pregnant or lactating women
5. Those who were receiving insulin preparations as a part of diabetes management.

All subjects (n = 96) were stratified by sex, age, and duration of treatment and randomly assigned to three treatment groups using the block randomization procedure. Group A (zinc+MVM) was supplemented with oral zinc sulfate (22 mg of elemental zinc/day) and a multivitamin/mineral preparation (vitamin A, vitamin D3, vitamin E, magnesium, manganese, copper, and selenium); group B (MVM) was supplemented with the same preparation but without zinc; and group C was supplemented with an identical placebo tablet. The study was registered at the Sri Lanka Clinical Trial Registry (SLCTR/2008/017) managed by the Sri Lanka Medical Association, linked to the Registry Network of the International Clinical Trials Registry Platform of the World Health Organization.

The composition of the supplement is given in Table 1. All subjects were instructed to take one tablet per day for a period of 4 months with their usual treatment regimen. The supplement and placebo tablets looked identical in color and shape. Because the reported mean daily intake of zinc in our population was low,[8] the supplemented zinc dose was set at the recommended dietary intake (20–25 mg/day) for the Sri Lankan population. All other minerals and vitamins that were included in the tablet were more or less equal to the dietary reference intake levels set by the Nutrition Coordination Division of the Ministry of Health, Sri Lanka.[9]

Once enrolled, all subjects were advised to attend a phlebotomy session at 08.00 after overnight fasting. A sample of 5 mL of venous blood was drawn before taking any oral hypoglycemic agent(s) or other drugs and before aliquots were made for fasting blood sugar (FBS) and glycosylated hemoglobin (Hb_{A1C}%) in sugar and EDTA

Table 1 Nutrient composition of the preparation[1]

Vitamins		
Vitamin A (as acetate)	BP	5000.0 IU
Vitamin D_3 (colecalciferol)	BP	400.0 IU
Vitamin E (tocopheryl acetate)	BP	151.0 IU
Thiamine nitrate	BP	10.0 mg
Riboflavine	BP	10.0 mg
Pyridoxine hydrochloride	BP	2.0 mg
Cyanocobalamin	BP	7.5 μg
Nicotinamide	BP	50.0 mg
Calcium pantothenate	BP	10.0 mg
Ascoribic acid	BP	75.0 mg
Minerals		
Magnesium oxide	BP	30 mg
Manganese sulfate	BP	2.8 mg
Copper sulfate	BP	2 mg
Zinc sulfate monohydrate[2]	USP	63 mg
Selenium dioxide	USP	70 μg

Notes: [1]Group 1 subjects get the tablets prepared with full formulae, whereas group 2 subjects get the same without zinc sulfate monohydrate, and group 3 subjects get the placebo tablet consisting of filling base magnesium stearate. [2]The elemental zinc content in the preparation was 22 mg.
Abbreviations: BP, British Pharmacopoeia; USP, United States Pharmacopeia.

bottles, respectively. The remaining portion of the blood sample was centrifuged at 5000 rpm for 10 minutes, and serum was separated and stored in acid-washed polystyrene tubes at −80°C until analysis for serum insulin, zinc, and creatinine was carried out. In addition, urine creatinine was measured from an aliquot of fresh urine sample obtained from each subject. Another portion of urine was stored at −80°C for analysis of urinary zinc. Following this, the patients were served with breakfast, and 2 hours later another blood sample (2 mL) was drawn for the assessment of postprandial blood sugar (PPBS). Another blood sample was collected on the next day after 14 hours of fasting for the assessment of lipid profile. Further, the patients' dietary intakes were assessed using a 24-hour dietary recall questionnaire at the study entry.

The patients were advised to take the trial medication once daily with other medication, and a monthly follow-up was arranged. Clinicians were blinded to the trial medication and they were allowed to continue the usual care given for diabetes subjects during the trial period. The study subjects were receiving either a single oral hypoglycemic agent (either sulfonylurea or metformin) or a combination of metformin and sulfonylurea (Table 2). The common sulfonylureas that were prescribed included tolbutamide, glibenclamide, glipizide, and gliclazide. No patient was on acarbose or glitazone. No changes in pharmacological or nonpharmacological management occurred during the trial period. Compliance on the supplementation was assessed by counting the remaining tablets at weeks 4, 8, and 12, and all side effects of trial medication were noted. After 4 months of supplementation, blood and urine samples were collected under the same conditions as described before for the same biochemical analyses.

Laboratory analysis

The zinc content in serum and urine was measured using an enzyme-linked immunosorbant assay (ELISA) kit from BioAssay Systems, Hayward, CA, USA, by the quantitative

Table 2 Baseline characteristics of the three study groups[1,2]

Parameter	Zinc+MVM (n = 29)	MVM (n = 31)	Control (n = 36)
Age (yrs)	54.1 (6.0)	51.2 (6.0)	54.8 (8.0)
Weight (kg)	57.51 (9.83)	58.92 (11.61)	54.81 (10.47)
Height (cm)	154.88 (8.34)	155.24 (8.69)	151.96 (8.06)
BMI (kg/m^2)	23.89 (3.5)	24.64 (4.0)	23.71 (4.1)
Blood pressure			
Systole (mm Hg)	122.96 (14.1)	121.92 (12.0)	123.33 (18.6)
Diastole (mm Hg)	76.67 (8.3)	74.69 (7.0)	77.00 (7.0)
Duration of treatment (yrs)	8.5 (2–24)	6.5 (2–25)	6.5 (2–25)
No. of hypoglycemic agents			
One	17 (59%)	19 (61%)	22 (61%)
Two	12 (41%)	12 (39%)	14 (39%)
On cholesterol-lowering agents (statins)			
Yes	15 (52%)	17 (55%)	19 (53%)
No	14 (48%)	14 (45%)	17 (47%)
On antihypertensive agents			
Yes	14 (48%)	12 (39%)	25 (69%)
No	15 (52%)	19 (61%)	11 (31%)
On cardioprotective agents			
Yes	22 (76%)	16 (52%)	26 (72%)
No	7 (24%)	15 (48%)	10 (28%)
Family history of diabetes			
Yes	16 (55%)	17 (55%)	19 (53%)
No	13 (45%)	14 (45%)	17 (47%)
Dietary intake of (mg/d)			
Energy (MJ/d)	5.24 (2.17)	5.18 (2.03)	5.21 (2.10)
Zinc	3.54 (0.24)	3.86 (0.33)	4.42 (0.30)
Retinol	191.86 (41.03)	147.30 (23.50)	161.61 (18.41)
Folate	77.30 (13.04)	69.24 (8.01)	75.10 (7.55)
Iron	18.74 (2.17)	18.83 (4.23)	22.19 (5.76)
Calcium	616.69 (58.17)	666.78 (51.06)	608.47 (40.82)

Notes: [1]Results presented as mean (standard deviation) except for the duration of treatment, which is given as mean (range). Treatment categories are given as number of subjects (%). [2]There were no significant differences in age and anthropometric parameters between groups at the study entry.
Abbreviations: BMI, body mass index; MVM, multivitamin/mineral.

colorimetric zinc determination at 425 nm.[10] Serum insulin level was measured by an ELISA kit provided by BioSource Europe SA, Nivelles, Belgium.[11] FBS and PPBS were enzymatically measured. Hb_{A1C}% was measured by chromatography method using a commercial kit (Sigma-Aldrich, St Louis, MO, USA). Serum TG and total cholesterol (TC) were enzymatically measured. High-density lipoprotein (HDL) cholesterol was determined after precipitation with phosphotungstate/magnesium and low-density lipoprotein (LDL) cholesterol after precipitation with heparin/sodium citrate. Intra- and interassay coefficient of variation was <5% for all laboratory tests.

Statistical analysis

The number of subjects per group was calculated based on the mean improvement in FBS (0.70 ± 1.10 mmol/L) shown by Farvid et al[12] when supplemented with multivitamin–mineral supplementation. Twenty-five subjects per group would provide adequate power (80%) at the α error of 5% to detect the treatment effect of zinc supplementation. The number of patients per group was increased by 3 in each group with an assumption of a 10% dropout rate.

A one-sample Kolmogorov–Smirnov test was used to determine whether the baseline biochemical markers were normally distributed. Because the distributions of Hb_{A1C}%, serum TG, zinc, urine zinc, and creatinine values were skewed, they were log-transformed in all calculations. For presentation, these variables were transformed back to the original scale. The difference between the three groups at baseline was determined by one-way analysis of variance (ANOVA) for continuous data and the Chi-test for categorical data. Paired *t*-tests were used to study within-group treatment effects. The effect of intervention was determined by the univariate analysis repeated-measures design of the general linear model using SPSS Version 10.0 (SPSS Inc., Chicago, USA). Baseline values of respective parameters were also included in the analysis as a covariant for between-subject factors to correct for their possible confounding influence on the change in each parameter. Of the 96 subjects randomized, only 86 completed the study, and their data were included in the final analysis (per-protocol analysis). Spearman's rho correlation was used to analyze the mean change of treatment effect with the respective baseline parameter. Two-tailed $P < 0.05$ was considered to be statistically significant.

Results

Baseline characteristics

Ninety-six diabetic individuals (33 males and 63 females) were recruited for the study. The baseline characteristics of the three groups are given in Table 2. There was no difference in age distribution of patients in the three groups (males had a mean age of 54.6 ± 7.0 years whereas females had a mean age of 54.9 ± 9.0 years). Group A consisted of 29 subjects (12 males), group B 31 subjects (11 males), and group C 36 subjects (10 males). However, only 86 patients completed the study (28 out of 29 subjects from group A, all 31 subjects from group B, and 32 out of 36 from group C). Of the 10 patients who did not complete the trial, six were lost to follow-up, three did not take tablets for more than 2 weeks continuously, and diabetes treatment regimen was interrupted in the other individual. Those who completed the trial had drug compliance of >98%. The three groups were not different with regard to the use of lipid-lowering (statins) and other cardioprotective medications at the baseline or during the follow-up. Further, dietary intake of trace mineral and vitamins was not different, and dietary zinc intake was 3.96 mg/day (standard deviation [SD] 1.68 mg/day) (Table 2).

Effect on blood sugar levels

Compared with the baseline, the zinc+MVM group had a mean reduction of FBS of −0.33 mmol/L (standard error of the mean [SEM] 0.21 mmol/L) ($P = 0.05$). The FBS change observed in the MVM (+0.19 [0.31] mmol/L) and the control groups (+0.43 [0.23] mmol/L) was not statistically significant ($P = 0.89$). The PPBS level also reduced significantly ($P = 0.04$) in the zinc+MVM group with a mean change of −1.55 (0.56) mmol/L after the intervention. The MVM group had a significant increase ($P = 0.002$) in Hb_{A1C}% level (+1.28 [0.21]%) from the baseline, whereas in the zinc+MVM group a significant reduction of Hb_{A1C}% was seen (−0.01 [0.25]%, $P < 0.001$) following intervention (Table 3). The mean changes observed in FBS, PPBS, and Hb_{A1C}% after supplementation were found to be negatively correlated with their respective baseline values of FBS ($r = -0.46$, $P < 0.001$), PPBS ($r = -0.52$, $P < 0.001$), and Hb_{A1C}% concentration ($r = -0.48$, $P < 0.001$), raising the possibility of regression to mean effect in data. Data were reanalyzed using the "parameter estimate" function of univariate analysis of a general linear model where the final values were used as the dependent variable and the baseline values as a covariate. The observed β (mean difference) and the 95% confidence intervals for the three groups were more or less similar to the previous results.

Therefore, we categorized the subjects according to the degree of glycemic control (optimum control and partially controlled) based on their baseline levels of FBS, PPBS, and Hb_{A1C}, and the treatment effect was compared (Table 4). When the baseline FBS was <5.56 mmol/L (<100.0 mg/dL), there was

Table 3 Effect of supplementation on blood sugar and other serum/urine parameters[a]

Parameter	Zinc+MVM (n = 28)	MVM (n = 26)	Control (n = 32)
Fasting blood sugar (mmol/L)			
Baseline	6.24 (0.94)	6.31 (1.31)	5.92 (1.14)
Final	5.89 (1.07)	6.51 (1.13)	6.36 (1.69)
Mean change	–0.33 (0.21)[a]	0.19 (0.31)[b]	0.43 (0.23)[b]
Postprandial blood sugar (mmol/L)			
Baseline	10.13 (3.03)	9.64 (2.14)	9.58 (2.92)
Final	8.60 (1.93)	9.90 (2.18)	9.84 (3.20)
Mean change	–1.55 (0.56)[a]	0.43 (0.50)[b]	0.05 (0.39)[b]
Hemoglobin % (Hb_{A1C})			
Baseline	7.50 (1.30)	6.84 (1.18)	6.95 (1.20)
Final	6.64 (0.91)	8.20 (1.28)	7.32 (1.58)
Mean change	–0.91 (0.25)[a]	1.28 (0.21)[b]	0.25 (0.23)[c]
Serum creatinine (µmol/L)			
Baseline	114.90 (45.21)	102.38 (26.00)	118.15 (33.14)
Final	124.20 (42.59)	125.11 (36.04)	135.00 (34.87)
Mean change	8.18 (9.45)	22.69 (9.70)	15.94 (7.72)
Serum insulin (µmol/L)			
Baseline	57.90 (12.92)	52.88 (15.21)	55.18 (21.53)
Final	55.53 (13.20)[a]	52.52 (9.54)[a]	46.57 (18.15)[b]
Mean change	–2.01 (2.87)	–1.22 (1.87)	–8.11 (3.44)
Serum zinc (µmol/L)			
Baseline	9.33 (7.64)	9.77 (7.31)	11.51 (7.72)
Final	21.98 (9.99)[a]	10.99 (7.54)[b]	9.97 (7.11)[b]
Mean change	12.44 (1.30)[a]	0.45 (0.72)[b]	–1.86 (0.71)[b]
Urine creatinine (µmol/L)			
Baseline	89.72 (52.06)	84.42 (36.30)	91.72 (59.92)
Final	105.93 (71.11)	104.00 (61.65)	106.31 (48.20)
Mean change	16.41 (14.70)	19.00 (12.75)	15.63 (11.72)
Urinary zinc (µmol/L)			
Baseline	1.71 (1.29)	2.11 (1.97)	1.83 (1.47)
Final	1.89 (1.37)	1.70 (1.57)	2.01 (1.68)
Mean change	0.16 (0.41)	–0.62 (0.47)	0.08 (0.37)

Notes: [1]Results expressed as mean (standard deviation) except for mean change mean (standard error of the mean). Only those who had completed the trial (n = 86) were included in the analysis. [a,b,c]Superscripts within a row indicate significant difference ($P < 0.05$); univariate analysis with baseline value of the respective parameter was included as a cofactor.
Abbreviation: MVM, multivitamin/mineral.

Table 4 Effect of supplementation on blood sugar parameters[1]

Parameter	Zinc+MVM	MVM	Control
Fasting blood sugar			
Baseline < 100.0 mg/dL (<5.56 mmol/L)			
n	9	9	17
Baseline	5.09 (0.43)	5.11 (0.47)	4.99 (0.6.0)
Final	5.22 (1.22)	5.77 (1.28)	5.64 (1.25)
Baseline > 100.0 mg/dL (>5.56 mmol/L)			
n	19	17	15
Baseline	6.76 (0.58)	6.96 (1.20)	7.00 (0.66)
Final	6.21 (0.85)[a]	6.61 (1.07)[a]	7.17 (1.79)[b]
Postprandial blood sugar			
Baseline < 160.0 mg/dL (<8.89 mmol/L)			
n	5	8	10
Baseline	6.67 (1.00)	7.12 (0.66)	6.28 (1.22)
Final	7.10 (1.43)[a]	8.51 (2.94)[b]	7.54 (1.81)[c]
Baseline > 160.0 mg/dL (>8.89 mmol/L)			
n	23	18	22
Baseline	11.40 (1.81)	10.61 (1.42)	11.38 (2.07)
Final	9.17 (1.62)	10.03 (1.84)	10.88 (3.18)
Hemoglobin % (Hb_{A1C}%)			
Baseline < 6.0			
n	10	11	12
Baseline	5.63 (0.15)	5.81 (0.15)	5.81 (0.25)
Final	5.53 (1.27)[a]	7.55 (1.20)[b]	6.29 (0.77)[c]
Baseline > 6.0			
n	18	15	20
Baseline	7.79 (1.16)	7.75 (0.96)	7.49 (1.13)
Final	6.78 (0.79)[a]	8.68 (1.15)[b]	7.66 (1.64)[b]

Notes: [1]Results expressed as mean (standard deviation). [a,b,c]Superscripts within a row indicate significant difference ($P < 0.05$); univariate analysis.
Abbreviation: MVM, multivitamin/mineral.

no significant treatment effect with the intervention. However, when FBS was >5.56 (>100 mg/dL), supplementation, with or without zinc, showed a significant effect on FBS. In the zinc+MVM group, the FBS level dropped to 6.21 (0.85) mmol/L from the baseline 6.76 (0.58) mmol/L, whereas in the MV group the baseline FBS level of 6.96 (1.20) mmol/L dropped to 6.61 (1.07) mmol/L. When the PPBS level was >8.89 mmol/L (>160.0 mg/dL), all the groups showed a reduction in mean PPBS with the intervention (Table 4). The Hb_{A1C}% level reduced irrespective of the baseline levels in zinc+MVM-supplemented individuals. When the baseline Hb_{A1C}% level was <6.0, the zinc+MVM group had a significant net reduction (mean level of 5.63 [0.15] at the baseline and 5.53 [1.27] after the intervention, $P < 0.05$).

Effect on serum insulin, zinc, and lipid profile

There was no significant effect on either serum or urine creatinine with the intervention (Table 3). There was a significant increase (mean change 12.44, SEM 1.3 µmol/L; $P < 0.001$) in serum zinc concentration in the zinc+MVM group, but there was no significant change in urinary zinc excretion, indicating that zinc supplementation improved only the body stores. Zinc+MVM and MVM supplementation had a significant effect on serum

lipids (Table 5). TC level in the zinc+MVM group dropped from 4.51 (0.99) mmol/L at baseline to 3.73 mmol/L after 4 months of intervention ($P < 0.05$). In the MVM group, TC level dropped from 4.36 mmol/L at the baseline to 4.22 (0.47) mmol/L ($P < 0.05$). Although a reduction in TG level was seen in all three groups, only in the MVM group did the change reach statistical significance (mean change of –0.07, SEM 0.08 mmol/L, $P < 0.05$). LDL cholesterol level also reduced in the zinc+MVM group from 2.60 (0.84) mmol/L to 2.54 (0.77) mmol/L ($P < 0.05$). Furthermore, cholesterol:HDL ratio reduced in both the zinc+MVM (from 3.39 to 3.21, $P < 0.05$) and MVM (from 3.37 to 3.20, $P < 0.05$) groups, whereas in the placebo group the baseline ratio of 3.42 increased to 3.92 ($P < 0.05$) after the intervention.

Discussion and conclusion

Previous research suggests that homeostasis of essential trace elements, especially zinc, can be disrupted by diabetes mellitus.[5,13] Our data showed that zinc supplementation causes an increase in serum zinc level, as reported in other studies.[14,15] Vitamins and minerals play diverse roles in the human body, not only in preventing deficiency diseases but also in regulating metabolism, gene expression, and influencing the development and progression of many chronic diseases. There is experimental and clinical evidence, especially in developed countries, supporting an alteration of zinc metabolism in patients with diabetes.[1,16] However, only a few studies have examined the relationship between zinc and diabetes in developing countries.[17] The mean serum zinc level in healthy individuals has varied from 11.4 µmol/L to 17.8 µmol/L.[18] A study in Iran by Al-Maroof and Al-Sharbatti[19] reported a lower mean serum zinc value (9.40 µmol/L) among diabetes patients. We observed a mean zinc level of 10.29 µmol/L (SD 7.50 µmol/L) in 96 diabetes patients who have been on treatment over a period ranging from 2 years to 22 years. This is lower than that (11.30 µmol/L) reported in a study of 110 Tunisian adult diabetics (both type 1 and type 2).[5] When the cutoff level of <10.7 µmol/L was used to define zinc deficiency, 65% (n = 63) of patients had serum zinc levels below this cutoff level in our study. However, we did not consider serum measurements of different antioxidants in the supplementation, as their effectiveness has already been proven.[4,5]

We observed that group A had a mean change of –0.33 mmol/L in blood glucose level, whereas group C (placebo-controlled group) had a +0.43 mmolL change in blood glucose after 4 months of supplementation. Therefore, we can speculate that, overall, there is a 0.76 mmol/L (14 mg/100 mL) difference with zinc+MVM supplementation among diabetes patients. Further, we have shown that zinc supplementation (with or without other MVM) was effective in reducing FBS in partially controlled adult diabetics (FBS > 100 mg/dL) who were on long-term follow-up. Furthermore, supplementation significantly improved PPBS and Hb_{A1C}% levels when compared with placebo. This was similar to the results reported by Hussain et al[20] that showed a 25% reduction in FBS and a 17% reduction in Hb_{A1C}% with 3 months' supplementation with zinc and melatonin. In our analysis, the mean Hb_{A1C}% of the supplemented groups (zinc+MVM and MVM groups) reduced significantly by 0.3 ± 0.8% at the end of 4 months of follow up, whereas no significant change was found in the control group. The significant changes observed in the supplemented groups refer to the effective improvement in their glycemic control in response to zinc and other multivitamin and mineral supplementation. Our observations are consistent with the results of other trials that examined the effect of zinc supplementation on patients with type 2 diabetes.[5,19]

The significant negative correlation we observed between the change in serum zinc level after supplementation and the baseline serum zinc level suggests that zinc-deficient individuals had greater absorption of zinc than individuals with higher zinc levels at the baseline. This finding is

Table 5 Supplementary effects on lipid profile of study subjects[1]

Parameter	Zinc+MVM (n = 28)	MVM (n = 26)	Control (n = 32)
Total cholesterol (mmol/L)			
Baseline	4.51 (0.99)	4.36 (0.82)	4.48 (0.96)
Final	3.73 (0.88)[a]	4.22 (0.47)[a]	4.82 (0.98)[b]
Mean change	–0.79 (0.16)[a]	–0.17 (0.17)[b]	0.26 (0.18)[b]
Triglycerides (mmol/L)			
Baseline	1.06 (0.51)	1.34 (0.58)	1.24 (0.51)
Final	1.04 (0.31)[a]	1.30 (0.56)[b]	1.23 (0.43)[a]
Mean change	–0.02 (0.09)	–0.07 (0.08)	–0.02 (0.07)
High-density lipoprotein (mmol/L)			
Baseline	1.35 (0.22)	1.30 (0.19)	1.33 (0.19)
Final	1.45 (0.31)[a]	1.34 (0.24)[a]	1.25 (0.18)[b]
Mean change	0.10 (0.06)[a]	0.04 (0.06)[a]	–0.08 (0.05)[b]
Low-density lipoprotein (mmol/L)			
Baseline	2.60 (0.84)	2.45 (0.73)	2.63 (0.88)
Final	2.54 (0.77)[a]	2.53 (0.55)[b]	2.97 (0.87)
Mean change	–0.06 (0.13)	0.09 (0.16)	0.26 (0.13)
Ratio			
Baseline	3.39 (0.74)	3.37 (0.59)	3.42 (0.75)
Final	3.21 (0.50)[a]	3.20 (0.40)[a]	3.92 (0.93)[b]
Mean change	–0.72 (0.18)[a]	–0.20 (0.17)[b]	0.44 (0.18)[c]

Notes: [1]Results expressed as mean (standard deviation) except for mean change mean (standard error of the mean); ratio = cholesterol/high-density lipoprotein. [a,b,c]Superscripts within a row indicate significant difference ($P < 0.05$); univariate analysis.
Abbreviation: MVM, multivitamin/mineral.

consistent with the results of other studies, suggesting that zinc treatment will have a high chance of success in changing zinc status in zinc-deficient subjects.[21] In addition, we observed that baseline serum insulin levels were positively correlated with final serum insulin levels and negatively with mean change after the intervention (data not shown). Previous studies examining the effect of zinc supplementation on insulin level are sparse. Hussain et al[20] found no change in serum C-peptide level with zinc supplementation. However, we require studies with longer follow-up to see whether an increase in insulin secretion is sustained over a longer time period. Zinc treatment has also been shown to raise body defenses in immune-suppressed patients.[22] It is important to note that a large proportion of subjects in our study had a low serum zinc level at the baseline and that daily administration of zinc for 4 months resulted in almost double the baseline value (mean improvement + 12.44 μmol/L). We have not addressed issues related to immune status in the current study, and the clinical importance of the high prevalence of zinc deficiency among adult diabetics is not known to us.

Treatment with MVM with or without zinc reduced TC, TG, and LDL plasma levels and increased HDL levels. These observations are consistent with those reported by Kadhim et al,[23] whereby a group of poorly controlled diabetes patients were supplemented with zinc and melatonin for a period of 3 months. In the current study, we observed a significant decrease in TG concentration (mean change of –0.07 mmol/L; $P < 0.05$) only in the MVM group. Partida-Hernández et al,[24] however, showed a significant decrease in TG concentration following 12-week supplementation with 100 mg zinc sulfate among diabetics who were not on cholesterol-lowering treatment. Furthermore, they showed a significant reduction in TC and an increase in HDL cholesterol, indicating that supplementation, in addition to improving glycemic indices, has favorable effects on other cardiovascular risk factors. Even though we have shown a similar trend, the reduction in TC and the effect on HDL levels were not as great as they reported. Most of our patients were already on cholesterol-lowering drugs and, as such, they may have achieved the "desired" lipid targets at the study entry.

Garber and Karlsson[25] showed that the treatment of dyslipidemia in diabetes must be focused on several targets involving glycemic control and reduction of LDL levels. The results of the present study are agreeable with these suggestions. There is evidence suggesting that zinc can act as an endogenous protective factor against atherosclerosis by inhibiting the oxidation of LDL in the presence of transition metals,[26] and that adequate zinc nutrition may protect against inflammatory diseases such as atherosclerosis by inhibiting the activation of oxidative stress responsive transcription factors as well as the expression of inflammatory cytokines.

The present intervention did not show any significant effect on renal functions measured by serum as well as urine creatinine, and our observations are similar to those of Khadim et al.[23] In contrast, a significant improvement in renal function has been observed in a previous study[27] after 60 days of supplementation. One limitation of our study is that we did not measure urinary microalbumin levels of the patients.

We performed this study in a single-blinded manner for logistical reasons, and this may have reduced the validity of data. This is one of the limitations in the study, as expectation bias or change in the behavior of the study subjects may have affected the results. However, only the FBS results were given to the clinicians at the follow-up sessions of their respective clinics. Secondly, we did not measure the change in physical activity and anthropometry because of the short duration (4 months) of follow-up. Therefore, we were unable to comment on the effect on anthropometry (ie, body mass index) with the intervention. Further, the small sample size may have contributed to inconclusive results seen in some analyses. To minimize the effects of disparity in baseline values between groups (ie, high Hb_{A1C}% levels in the zinc+MVM group over the other two groups), we included baseline measurements in each analysis as a cofactor (see Statistical analysis). Although physicians were free to make changes in the management of these patients, no changes in the major drugs such as antidiabetics, antihypertensives, or lipid-lowering therapy were made during the trial period. Apart from the trial drug, we inquired about the patients' compliance to their regular medication as well. However, there is still a possibility that patients may have changed their behavior (ie, diet and physical activity) during the trial period, but we expected it to be uniform in all three groups. This altered behavior can considerably limit the study outcome.

Data on dietary intake or serum zinc levels are limited to young children and adolescents[8,28] in Sri Lanka. Baines and Roberts[29] have reported that if the intake of zinc is marginal, it can have a major impact on food intake by reducing taste sensation. As taste is already impaired in the elderly, this can seriously affect food choice. Zinc is readily available in animal foods, especially red meat, liver, fish, and eggs. If this is not feasible, then the use of a multivitamin and minerals supplement may be a suitable alternative. However, multiple medication use is prevalent in this population, and another pill may add to the confusion.

In conclusion, the supplementation of zinc with other multimineral vitamins daily for a period of 4 months to adult

diabetes patients on standard diabetic care demonstrated favorable changes in metabolic profile, including better glycemic control and desirable changes in lipid profile. Based on the results presented in this report, it can be concluded that zinc, either alone or in combination with other known antioxidant minerals and vitamins, may have supplementary benefits in the routine management of adult diabetes.

Future applications

This study needs to be reproduced to examine the effect of zinc and other multimineral vitamins on long-term diabetic control, complications, and morbidity. Furthermore, the ability of zinc supplementation to reverse the components of metabolic syndrome should be examined.

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Disclosure

The authors report no conflicts of interest in this work.

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