Comparison of the Effects of Sodium metavanadate and Zinc Sulfate Supplementation on Lipid and Glucose in Patients with Type 2 Diabetes

Mohammad Afkhami-Ardekani*, Mahdi Karimi, Seyed Mohammad Mohammadi,
Forough Nourani, Sedigheh Soheilykhah

Yazd Diabetes Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

ABSTRACT

Type 2 diabetes mellitus is a chronic illness causing considerable morbidity and mortality. Enormous advances have been made in medical care but more people are still having tendency to use herbal or alternative remedies. This study is a randomized, controlled trial on type 2 diabetic patients. The subject consisted of 60 patients divided randomly into three groups and supplemented daily with 100 mg sodium metavanadate and 660 mg zinc sulfate or placebo for six weeks. The following were checked at baseline of the study and after six weeks: Body Mass Index (BMI), Blood Pressure (BP), Fasting Blood Sugar (FBS), 2-h postprandial glucose (2hpp), Glycated hemoglobin (HbA1c), Triglyceride (TG), Total Cholesterol (TC), Low-Density Lipoproteins, and High-Density Lipoproteins. Also HbA1c, BMI and BP were measured after 12 weeks to evaluate the long-term effects of drugs. Statistical analysis was performed using SPSS 11.5. Data of continuous variables are expressed as means ± standard deviation. Differences between groups were assessed by the paired T-test. Comparison between three groups was done by Post Hoc Tests. Mean age of patients was 51.39 ± 8.60 years. The results of this study show a significant decrease in TG ($P = 0.01$) and BMI ($P = 0.03$). After 12 weeks, there was a significant decrease in BMI ($P =0.01$) in Sodium metavanadate group. Due to zinc sulfate administration, significant decrease was seen in TG ($P =0.005$), TC ($P = 0.02$), LDL ($P = 0.01$) and systolic blood pressure ($P = 0.02$). After 12 weeks, there was a significant decrease in HbA1c ($P = 0.04$) with zinc sulfate consumption. Consumption of zinc sulfate in type 2 diabetic patients could be effective in lipid profile. It is recommended to use another vanadium compound to achieve better results.

KEY WORDS: Sodium metavanadate, Zinc sulfate, Type 2 diabetes mellitus.

INTRODUCTION

Type 2 diabetes mellitus is a polygenetic disorder resulting from interaction of both hereditary and environmental factors (1). It is a chronic, progressive illness that causes considerable morbidity and premature mortality (2). The worldwide prevalence of type 2 diabetes is high and increasing steadily (3). Approximately, 150 million people worldwide are affected by type 2 diabetes mellitus, and this figure is expected to double in the next 20 years (4). Diabetes significantly increases an individual's risk of developing multiple microvascular and cardiovascular intensive and comprehensive diabetes care (5). The cardiovascular events associated with type 2 diabetes and the high incidence of other macrovascular complications, such as strokes and amputations, are a major cause of illness and an enormous economic burden (6). Despite

*Correspondence: Mohammad Afkhami-Ardekani, Yazd Diabetes Research Center, Jomhouri Blvd., Yazd, Iran.
Tel: (+98) 351 522 3999. **Fax:** (+98) 351 525 8354. **E-mail:** afkhamiam@yahoo.com

impressive technical advances in diagnosis and treatment, many more people are using alternative therapies. Chronic conditions such as diabetes might be expected to foster the use of alternative medicines (7). Recently, two national surveys have examined the use of Complementary and Alternative Medicine (CAM) for diabetes. One study, using 1996 Medical Expenditure Panel Survey data, reported that ~8% of respondents with diabetes saw a CAM professional for care. A nationally representative survey conducted in 1997–1998 reported that about one third of respondents with diabetes used CAM to treat their condition (8). Supplements of micronutrients including the vitamins Niacin, C and E and the minerals zinc, chromium and vanadium have been studied (9).

Vanadium is a trace element believed to be important for normal cell function and development. It is present in all tissues, but its exact role in glucose homeostasis in man has yet to be established. Numerous *in vitro* and *in vivo* studies have shown that vanadium has insulin-like effects in liver, skeletal muscle, and adipose tissue (10, 11). Salts of vanadium interfere with an essential array of enzymatic systems such as different ATPases, protein kinases, ribonucleases and phosphatases, while vanadium deficiency accounts for several physiological malfunctioning including thyroid, glucose and lipid metabolism (12).

Zinc is known to be an essential trace mineral which is necessary for health and growth, and is also essential for the function and activity of over 200 metalloenzymes (13). The ability of zinc to retard oxidative processes has been recognized for many years (14). Zinc is an essential mineral that is required for various cellular functions. Its abnormal metabolism is related to certain disorders such as diabetic complications (15).

Abnormal zinc and lipid plasma levels occur more frequently in metabolically uncontrolled diabetic patients. Yet, zinc sulfate supplementation may be a therapeutical resource to recover some functioning and improve life span (16).

This article compares the effect of sodium metavanadate and zinc sulfate supplementation on lipid and glucose of patients with type 2 diabetes.

MATERIAL AND METHODS

This study is a randomized controlled trial. Subjects were enrolled from Diabetes Research Center. Inclusion criteria included type II diabetic patients with fixed drug dosage in past 6 months, fixed weight in past 3 months, without taking vitamins or mineral supplements in the previous 2 months and without clinical involvement of kidney, heart and lung. The subjects were fully informed of the purpose, procedures and hazards of trial and were free to leave the trial at any time desired. Written informed consent was obtained from all participants. The research protocol was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences.

The subjects consisted of 60 patients who were divided randomly into three groups and supplemented daily with 100mg sodium metavanadate and 660 mg zinc sulfate or placebo for six weeks. Zinc sulfate and sodium metavanadate capsules were provided by Alhavi and Merck Company, respectively.

Subjects were instructed not to modify diet or activity level; each individual maintained dietary records at intervals throughout the experiment. The following were checked before the beginning of the study: Body Mass Index (BMI), blood pressure and biochemical markers included Fasting Blood Sugar (FBS), 2-h postprandial glucose (2hpp), Glycated hemoglobin (HbA1c), Triglyceride (TG), Total Cholesterol (TC), Low-Density Lipoproteins (LDL), High-Density Lipoproteins (HDL), Blood Urea Nitrogen (BUN), Creatinin (Cr), Alanine aminotransferases (ALT), Aspartate aminotransferases (AST). BMI was calculated as the weight in kilograms per the square of height in meters, and blood pressure measured with the person in the sitting position after a 5-min rest.

All blood specimens were drawn at 8 A.M. after a period of 8 hours fasting. All patients were examined carefully and depending upon the treatment groups, each subject received capsules for a period of six weeks. Drugs in group I and III should be consumed with a large glass of water at the lunch meal and group II should eat capsules every eight hours by meal (220 mg TDS). BMI, blood pressure, AST, ALT and drug complications such as nausea, vomiting, abdominal pain,

diarrhea, constipation, reduction of appetite were checked after three weeks. Two patients in group I left the trial due to severe nausea and vomiting. At the end of 6 weeks all the indices were checked as before the beginning of the test and the drug complications were asked as well. HbA1c, BMI, blood pressure and complications were analyzed after 12 weeks to evaluate the long term effect of drugs.

Statistical Analysis: All statistical analyses were performed using SPSS 11.5. Data of continuous variables were expressed as means ±standard deviation. Differences between groups were assessed by the paired T-test. Comparison between three groups was done by Post Hoc Tests. Statistical significance was set at $P < 0.05$.

RESULTS

Fifty-eight of 60 subjects completed the study. The mean age of patients was 51.39 ± 8.60 (32 to 67 years) with male constituting 36.2% of patients (21 male and 37 female). Mean duration of diabetes was 6.65 ± 4.51 years. Of the study subjects, respectively 75.9% and 72.4% ate metformin and glybenclamide, but only 6.9% had acarbose consumption. Two patients in sodium metavanadate group withdrew because of side effects in the first week of the study. The characteristic and baseline biochemical marker of three groups are shown in Table 1.

Sodium metavanadate group:
As shown in Table 2, level of FBS and HbA1c decreased after six weeks treatment with sodium metavanadate but it was not statistically significant. Due to sodium metavanadate administration in diabetic patients, there was a significant decrease in TG ($P = 0.01$) and BMI ($P = 0.03$). Cholesterol and LDL was decreased but it was not significant. No statistically significant differences were found prior to and after vanadium treatment in systolic and diastolic blood pressure. Seventeen patients (94.4%) experienced nausea in the first three weeks which was tolerable and decreased. Eight patients (44.4%) had vomiting of whom two were excluded from the trial due to sever vomiting. Two patients (11.1%) experienced

loss of appetite. Complication rate decreased until 6 weeks and disappeared at the 12th week.

At the end of 12th week, no statistically significant decrease was found prior to and after 12 weeks in HbA1c, systolic and diastolic blood pressure but a significant decrease was seen in BMI ($P = 0.01$)

Zinc sulfate group:
As shown in Table 2, level of FBS, 2hpp and HbA1c decreased after six-week treatment with zinc sulfate but it was not statistically significant. Due to zinc sulfate administration in diabetic patients, a significant decrease occurred in TG ($P = 0.005$), TC ($P = 0.02$), LDL ($P = 0.01$) and systolic blood pressure ($P = 0.02$). HDL was increased but it was not significant ($P = 0.14$). No statistically significant differences were found prior to and after zinc treatment in BMI and diastolic blood pressure. Only two patients had mild abdominal pain. After 12 weeks, there was a significant decrease in HbA1c ($P = 0.04$) in group II but a significant decrease didn't occur in BMI and blood pressure.

Placebo group:
As shown in Table 2, no statistically significant differences were found prior to and after six weeks placebo treatment in different biomarkers.

Comparison between three groups:
Multiple comparisons between three groups by Post Hoc Tests clarified that there were no statistically differences in FBS, HbA1c and HDL prior to and after six weeks treatment in three groups. However, comparison of 2hpp, TG, TC, LDL, systolic and diastolic blood pressure between zinc sulfate group and sodium metavanadate showed significant decrease in zinc group ($P = 0.002$, $P = 0.001$, $P = 0.00$, $P = 0.00$, $P = 0.008$, $P = 0.00$) after six weeks.

Comparison between zinc sulfate group and placebo group showed significant decrease in 2hpp ($P = 0.007$), TC ($P = 0.001$), LDL ($P = 0.00$) and systolic blood pressure ($P = 0.00$) in zinc sulfate group after six weeks, but no significant decrease was seen in TG and diastolic blood pressure.

Comparison between sodium metavanadate group and placebo group showed no statistically changes in 2hpp, TG and Blood pressure but TC and LDL had significant decrease in sodium metavanadate group compared with placebo group ($P = 0.00$, $P = 0.007$) after six weeks.

Comparison between three groups showed no statistically effect on HbA1c and BMI after 12 weeks but systolic and diastolic blood pressure in zinc sulfate group had significant decrease compared with sodium metavanadate group ($P = 0.001$).

Table 1- Characteristic and baseline biochemical markers of diabetic patients

Variables	Mean ± SD
FBS (mg/dl)	157.2 ± 42.3
2hpp (mg/dl)	235.7 ± 75.1
HbA1c (%)	7.7 ± 1.2
TG (mg/dl)	231.1 ± 90.9
TC (mg/dl)	190.2 ± 42.4
LDL (mg/dl)	102.4 ± 35.1
HDL (mg/dl)	52.4 ± 16.2
BMI (kg/m2)	27.1 ± 4.7
SBP (mmHg)	125.3 ± 22.2
DBP (mmHg)	75.4 ± 9.9

Body Mass Index (BMI), Fasting Blood Sugar (FBS), 2-h postprandial glucose (2hpp), Glycated hemoglobin (HbA1c), Triglyceride (TG), cholesterol (chol), Low-Density Lipoproteins (LDL), High- Density Lipoproteins (HDL), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP)

Table 2- Biochemical parameters before and after Sodium Metavanadate, Zinc Sulfate and Placebo consumption

Variables	Sodium metavanadate			Zinc sulfate			placebo		
	Pre-trial	Post-trial	P value	Pre-trial	Post-trial	P value	Pre-trial	Post-trial	P value
BMI (kg/m2)	30.2 ± 5.3	27.1 ± 7.1	0.03*	30.8 ± 5.1	27.7 ± 5.6	0.14	30.4 ± 4.8	28.9 ± 5.9	0.16
FBS (mg/dl)	175.5 ± 35.2	161.6±36.9	0.43	174.5 ± 59.2	134.2±57.8	0.09	157.60±31.08	159.5 ± 26.2	0.55
2hpp (mg/dl)	252.1 ± 48.8	253.4 ± 52.6	0.51	296.6 ± 77.5	168.8 ± 84	0.04*	250.5 ± 60.5	252.5 ± 59.9	0.26
HbA1c (%)	7.8 ± 0.9	7.8 ± 0.8	0.16	8.4 ± 1.2	7.0 ± 1.1	0.04*	7.5 ± 0.7	7.4 ± 0.8	0.62
TG (mg/dl)	282.6 ± 54.2	238.1 ± 57.2	0.01*	265.5±130.61	145.3±65.4	0.005*	266 ± 95.5	199.9 ± 99.5	0.21
Chol (mg/dl)	242.1 ± 42.4	239.2 ± 39.5	0.40	214.5 ± 47.8	136.4±33.2	0.02*	265.9 ± 42.2	274.5 ± 35.5	0.29
LDL (mg/dl)	128.5 ± 32.1	125.8 ± 26.5	0.29	145.5 ± 38.39	83.5 ± 21.6	0.01*	126.1 ± 25.5	129.7 ± 26.5	0.10
HDL (mg/dl)	57.2 ± 22.2	59.8 ± 2.7	0.80	48.4 ± 10.1	59.9 ± 11.8	0.14	46.5 ± 19.2	45.5 ± 19.5	0.51
SBP (mmHg)	139.5 ± 16.6	136.6 ± 11.9	0.67	135.2 ± 18.4	125.5±18.4	0.02*	132.5 ± 12.4	129.9 ± 11.5	0.26
DBP (mmHg)	75.5 ± 7.5	72.5 ± 8.4	0.10	77.7 ± 11.5	74.5 ± 9.3	0.10	77.5 ± 9.5	75.5 ± 9.3	0.10

*Statistical significance when p<0.05

DISCUSSION

Recently, diabetic patients have tendency to use complementary and alternative medicine beside routine therapies. Zinc is one of the minerals used by diabetic patients and vanadium is a well known anti-diabetic agent which mimics most of the actions of insulin on mature adipocytes (17). A little over one hundred years ago, a vanadium-containing compound was assessed clinically for using in treatment of human diabetic patients. The results were somewhat ambiguous, but nonetheless, intriguing. In 2000, the first Phase I clinical trial of a designed vanadium-based pharmaceutical agentbisoxovanadium was completed (18).

Effect of sodium metavanadate (100 mg/day for 6 weeks) was evaluated and revealed level of FBS and HbA1c, Cholesterol and LDL decreased after six-week treatment with sodium metavanadate but it was not statistically significant. A significant decrease occurred in TG ($P = 0.01$) and BMI ($P = 0.03$). No statistically significant differences were found prior to and after vanadium treatment in systolic and diastolic blood pressure. Due to zinc sulfate administration in diabetic patients, a significant decrease occurred in TG ($P = 0.005$), TC ($P = 0.02$), LDL ($P = 0.01$) and systolic blood pressure ($P = 0.02$). After 12 weeks, there was a significant decrease in HbA1c ($P = 0.04$) as well.

Animal studies as well as short-term studies with type I diabetes mellitus showed insulinomimetic function of vanadium. The oral doses used to date in human trials are much lower than those for animal studies but an appreciable rise in serum vanadium is achieved. Sodium vanadate supplementation at 125 mg daily for 2 weeks lowered the insulin requirement in five patients with type I diabetes mellitus and also lowered their plasma cholesterol. Treatment lowered insulin requirements but had no effect on basal or C-peptide levels. Two of the five Type I diabetic patients showed improvements in glucose utilization. More dramatic improvements were observed in Type II diabetic patients who displayed an improved insulin sensitivity attributed to an enhancement of non-oxidative glucose disposal rates. Vanadium treatment did not affect hepatic glucose production (19). A concern for mild nausea and gastrointestinal upset may be overcome by the use of vanadyl sulfate (9).

Short-term clinical trials with vanadium have been performed in type II (noninsulin-dependent) diabetic patients, and the results suggest that vanadium may have a potential role in the adjunctive therapy of these patients (19,20,21,22). For example, Cohen examined the in vivo metabolic effects of vanadyl sulfate (VS) in type 2 diabetes mellitus patients. Six subjects treated with diet and/or sulfonylureas were examined at the end of three consecutive periods: placebo for 2 weeks, VS (100 mg/d) for 3 weeks and placebo for 2 weeks. Glycemic control at the baseline was poor (fasting plasma glucose 210± 19 mg/dl; HbA1c 9.6 +/- 0.6%) and improved after treatment (181 ± 14 mg/dl [$P<0.05$], 8.8 ± 0.6%, [$P<0.002$]). These effects were sustained for up to 2 weeks after discontinuation of VS (20). In our study mean of FBS was 165.72 ± 36.13 which was decreased to 162.66 ± 35.93 but it was not significant. It might be related to different type of vanadium used in this survey.

In 1994, Malabu et al. claimed that the decreases in plasma glucose levels observed after administration of vanadate were entirely attributable to a reduction in food intake (23).

In Cusi's study 11 type 2 diabetic patients were treated with Vanadyl sulfate (150 mg/day for 6 weeks). Fasting Plasma Glucose (FPG) decreased from 194 ± 16 to 155 ± 15 mg/dL ($P < 0.01$), HbA1c decreased from 8.1 ± 0.4 to 7.6 ± 0.4% ($P < 0.01$), without any change in body weight. Vanadyl sulfate treatment lowered the plasma TC (223 ±14 vs. 202 ± 16 mg/dL; $P < 0.01$) and low-density lipoprotein cholesterol (141 ± 14 vs. 129 ± 14 mg/dL; $P < 0.05$), whereas 24-h ambulatory blood pressure was unaltered. Cusi concluded that VOSO (4) at maximal tolerated doses for 6 weeks improves hepatic and muscle insulin sensitivity in type 2 diabetes mellitus (24). In the present study FBS, HbA1c, Cholesterol and LDL decreased but it was not significant.

In Goldfine's investigation, 16 type 2 diabetic patients were studied before and after 6 weeks for vanadyl sulfate (VOSO4) treatment at three doses. Fasting glucose and HbA1c decreased significantly in the 150- and 300-mg VOSO4 groups. At the highest dose, TC decreased, associated with a decrease in HDL. There was no change in systolic, diastolic, or mean arterial blood pressure on 24-hour ambulatory monitors at any dose. There was no apparent correlation between the clinical response and peak serum level of vanadium. The 150- and 300-mg vanadyl doses caused some gastrointestinal intolerance (25).

In the present study, vanadium salt and its dosage were different from Goldfine's study, so our results were different but gastrointestinal discomfort was seen with 100 mg of sodium metavanadate as well.

Other studies also mentioned the hypoglycemic and cholesterol lowering effects of vanadium (26,27) but they didn't discuss on TG level.

Reduction in BMI may be due to gastrointestinal discomfort such as nausea which leads to decrease in food intake.

Anderson's study on 110 patients with type 2 diabetes mellitus with HbA1c >7.5% revealed that more than 30% of the subjects may have been Zn deficient with plasma Zn values less than 10.7 mircomol/L (28). In present study, no statistically significant differences were found prior to and after 6 weeks zinc sulfate treatment in FBS, 2hpp, HbA1c, HDL, BMI and diastolic blood pressure. Due to zinc sulfate administration in diabetic patients, a significant decrease occurred in TG ($P = 0.005$), TC ($P = 0.02$), LDL

($P = 0.01$) and systolic blood pressure ($P = 0.02$). After 12 weeks, there was a significant decrease in HbA1c ($P = 0.04$). Some investigations indicated that a zinc-enriched diet has beneficial effects on basal and postprandial glycaemia and the content of cholesterol and triglycerides (29).

In Anne-Marie Roussel's study on 56 diabetic patients (divided to zinc gluconate and placebo group) treated with 30 mg zinc gluconate, HbA1c decreased from 8.9 ± 0.4 to $7.7 \pm 0.3\%$ following six months of zinc supplementation, but decreases were not significant at $P = 0.05$. No change was seen in FBS (30). The current study showed the same result about FBS and HBA1c.

Cunnane believed that zinc intimately affects many aspects of lipid metabolism through established enzymes, but also has modulatory effects whose mechanism is not obvious or established (31). There were decreased lipid peroxidation and improvement in antioxidant status in patients with type 1 diabetes mellitus who received 30mg of Zn as Zn gluconate for three months (32, 33).

In Partida-Hernandez's survey on type 2 diabetic patients who received 100 mg zinc sulfate, there were no statistically changes in FBS and HbA1c after 12 weeks (16). In the current survey HbA1c was statistically decreased after 12 weeks which may be related to the higher dosage of zinc sulfate in our study.

Diabetic patients had changes in their lipid profile after a 12-week zinc treatment as compared with placebo treatment in Partida-Hernandez's survey. The 100 mg zinc sulfate treatment was well tolerated, significantly reduced TC ($P = 0.01$) and triglyceride concentrations ($P = 0.02$), and increased those corresponding to zinc as well as HDL cholesterol in the bloodstream ($P = 0.002$) but decrease in LDL was not significant ($P = 0.22$). Differences with our study are related to drug dosage.

Results of randomized controlled trials of Suzanne Hughes show that LDL, TC and triglycerides in plasma are unaffected by supplementation with up to 150mg Zn/d. In contrast, HDL concentrations decline when zinc supplements provide a dose of >50 mg/d (34).

Higher dose of zinc sulfate is needed to decrease TG, TC and LDL. This was confirmed in the current study

Hooper's study examined the effect of zinc administration on serum lipoprotein values in man. Twelve healthy adult men ingested 440 mg of zinc sulfate per day for five weeks. High-density lipoprotein cholesterol concentration decreased 25% below baseline values (40.5 to 30.1 mg/dL). TC, triglyceride, and low-density lipoprotein cholesterol levels did not change throughout the study (35). Anne-Marie Roussel's study, as indicated previously no changes were seen in lipid profile (30).

In Freeland-Graves's study, four levels of zinc supplements (0, 15, 50 or 100 mg/day) were given to 32 women for 8 weeks. No significant differences were seen in HDL-cholesterol over 8 weeks except for the 100 mg group at week 4 when a transient decrease (57 to 48 mg/dl [P< 0.04]) was observed (36).

It seems that zinc is a proper mineral in diabetic patients due to their deficiency.

There was no similar study comparing the effects of vanadium and zinc.

CONCLUSION

Consumption of zinc sulfate in along with other nutritional and pharmacological treatments in type 2 diabetic patients could be effective in lipid profile. It is recommended to use another vanadium compound in type 2 diabetic patients to achieve better results.

ACKNOWLEDGEMENT

REFERENCES

1. Jinlin F, Binyou W, Terry C. A new approach to the study of diet and risk of type 2 diabetes. J Postgrad Med 2007;53(2):139-143.

2. Kleefstra N, Houweling ST, Bakker SJ, Verhoeven S, Gans RO, Meyboom-de Jong B, et al. Chromium treatment has no effect in patients with type 2 diabetes in a Western population: a randomized, double-blind, placebo-controlled trial. Diabetes Care 2007;30(5):1092-1096.

3. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care 1998;21(9):1414-1431.

4. Freeman H, Cox RD. Type-2 diabetes: a cocktail of genetic discovery. Hum Mol Genet 2006;15(2):202-209.

5. Huang ES, Brown SE, Ewigman BG, Foley EC, Meltzer DO. Patient Perceptions of Quality of Life With Diabetes-Related Complications and Treatments. Diabetes Care 2007;30:2478-2483.

6. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes. N Engl J Med 2003;348(5):383-393.

7. Ryan EA, Pick ME, Marceau C. Use of alternative medicines in diabetes mellitus. Diabet Med 2001;18(3):242-245.

8. Yeh G, Eisenberg DM, Kaptchuk TJ, Phillips RS. Systematic Review of Herbs and Dietary Supplements for Glycemic Control in Diabetes Diabetes Care 2003; 26(4):1277-1294.

9. Cunningham JJ. Micronutrients as nutriceutical interventions in diabetes mellitus. J Am Coll Nutr 1998;17(1):7-10.

10. Shechter Y, Shisheva A. Vanadium salts and the future treatment of diabetes. Endeavour 1993;17:27–31.

11. Verma S, Cam M, McNeill J. Nutritional factors that can favorably influence the glucose/insulin system: vanadium. J Am College Nutr 1998;17:11–18.

12. Mukherjee B, Patra B, Mahapatra S, Banerjee P, Tiwari A, Chatterjee M. Vanadiumùan element of atypical biological significance. Toxicology letters 2004;150(2):135-43.

13. Chen MD, Lin PY, Lin WH. Investigation of the relationships between zinc and obesity. Gaoxiong Yi Xue Ke Xue Za Zhi 1991;7(12):628-634.

14. Powell SR. The antioxidant properties of zinc. J Nutr 2000;130(5):1447S-1454S

15. Song Y, Wang J, Li XK, Cai L. Zinc and the diabetic heart. Biometals 2005;18(4):325-332.

16. Partida-Hernandez G, Arreola F, Fenton B, Cabeza M, Roman-Ramos R, Revilla-Monsalve MC. Effect of zinc replacement on lipids and lipoproteins in type 2-diabetic patients. Biomed Pharmacother 2006;60(4):161-168.

17. García-Vicente S, Yraola F, Marti L, González-Muñoz E, García-Barrado MJ, Cantó C, et al. Oral insulin-mimetic compounds that act independently of insulin. Diabetes 2007;56(2):486-493.

18. Thompson KH, Orvig C. Vanadium in diabetes: 100 years from Phase 0 to Phase I. J Inorg Biochem 2006;100(12):1925-1935.

19. Goldfine A, Simonson D, Folli F, Patti M-E, Kahn R. Metabolic effects of sodium metavanadate in humans with insulin-dependent and noninsulin-dependent diabetes mellitus in vivo and in vitro studies. J Clin Endocrinol Metab 1995;80:3311–3320.

20. Cohen N, Halberstam M, Shlimovich P, Chang CJ, Shamoon H, Rossetti L. Oral vanadyl sulfate improves hepatic and peripheral insulin sensitivity in patients with non-insulin-dependent diabetes mellitus. J Clin Invest 1995;95(6):2501-2509.

21. Boden G, Chen X, Ruiz J, van Rossum GD, Turco S. Effects of vanadyl sulfate on carbohydrate and lipid metabolism in patients with non-insulin-dependent diabetes mellitus. Metabolism 1996;45:1130–1135.

22. Thompson KH, Orvig C. Design of vanadium compounds as insulin enhancing agents. Journal of the Chemical Society, Dalton Transactions 2000;2000(17):2885-2892.

23. Malabu US, Dryden S, McCarthy HD, Kilpatrick A, Williams G. Effects of chronic vanadate administration in the STZ-diabetic rat. The antihyperglycemic action of vanadate is attributable entirely to its suppression of feeding. Diabetes 1994;43:9–15.

24. Cusi K, Cukier S, DeFronzo RA, Torres M, Puchulu FM, Redondo JC. Vanadyl sulfate improves hepatic and muscle insulin sensitivity in type 2 diabetes. J Clin Endocrinol Metab 2001;86(3):1410-1417.

25. Goldfine AB, Patti ME, Zuberi L, Goldstein BJ, LeBlanc R, Landaker EJ, et al. Metabolic effects of vanadyl sulfate in humans with non-insulin-dependent diabetes mellitus: in vivo and in vitro studies. Metabolism 2000;49(3):400-410.

26. Beliaeva NF, Gorodetskiĭ VK, Tochilkin AI, Golubev MA, Semenova NV, Kovel'man IR. Vanadium compounds--a new class of thera-

peutic agents for the treatment of diabetes mellitus. Vopr Med Khim 2000;46(4):344-360.

27. Harland B, Harden-Williams BA. Is vanadium of human nutritional importance yet? J Am Diet Assoc 1994;94(8):891-894

28. Anderson RA, Roussel AM, Zouari N, Mahjoub S, Matheau JM, Kerkeni A. Potential antioxidant effects of zinc and chromium supplementation in people with type 2 diabetes mellitus. J Am Coll Nutr 2001;20(3):212-218.

29. Ghayour-Mobarhan M, Taylor A, New SA, Lamb DJ, Ferns GA. Determinants of serum copper, zinc and selenium in healthy subjects. Ann Clin Biochem 2005;42(5):364-375.

30. Roussel AM, Kerkeni A, Zouari N, Mahjoub S, Matheau JM, Anderson RA. Antioxidant effects of zinc supplementation in Tunisians with type 2 diabetes mellitus. J Am Coll Nutr 2003;22(4):316-321.

31. Cunnane SC. Role of zinc in lipid and fatty acid metabolism and in membranes. Prog Food Nutr Sci 1988;12(2):151-188.

32. Faure P, Benhamou PY, Perard A, Halimi S, Roussel AM . Lipid peroxidation in insulin-dependent diabetic patients with early retina degenerative lesions: effects of an oral zinc supplementation. Eur J Clin Nutr 1995;49(4):282-288.

33. Faure P, Corticelli P, Richard MJ, Arnaud J, Coudray C, Halimi S et al. Lipid peroxidation and trace element status in diabetic ketotic patients: influence of insulin therapy. Clin Chem 1993;39(5):789-793.

34. Hughes S, Samman S. The Effect of Zinc Supplementation in Humans on Plasma Lipids, Antioxidant Status and Thrombogenesis. Journal of the American College of Nutrition 2006;25(4):285-291.

35. Hooper PL, Visconti L, Garry PJ , Johnson GE. Zinc lowers high-density lipoprotein-cholesterol levels. JAMA 1980;244(17):1960-1961.

36. Freeland-Graves JH, Friedman BJ , Han WH, Shorey RL, Young R. Effect of zinc supplementation on plasma high-density lipoprotein cholesterol and zinc. American Journal of Clinical Nutrition 1982;35:988-992.