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Effect of Sodium Metavanadate Supplementation on Lipid and Glucose Metabolism Biomarkers in Type 2 Diabetic Patients

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ABSTRACT

Type 2 diabetes mellitus is a chronic, progressive illness that causes considerable morbidity and premature mortality. Vanadium is a trace mineral that has been claimed to be effective in controlling blood glucose levels in diabetic patients. A randomised placebo-controlled study was conducted to evaluate the effect of sodium metavanadate on selected biochemical markers in type 2 diabetic patients. Forty patients were enrolled and half of them received 100 mg sodium metavanadate daily for 6 weeks while the other half were placebo subjects. The mean age of the patients was 53.1 ± 8.5 years. Body mass index (BMI), blood pressure(BP), fasting blood sugar (FBS), 2-h postprandial glucose, glycated hemoglobin (HbA1C), triglyceride(TG), total cholesterol (TC), low-density lipoproteins (LDL), high-density lipoproteins (HDL) were determined before the start and at the end of the study. Levels of FBS, HbA1C, TC and LDL in the diabetic subjects decreased after six weeks on sodium metavanadate, but the differences were not statistically significant on comparing between pre- and post-trial levels. Based on the results, this study did not find sodium metavanadate of beneficial use as a form of vanadium supplementation among patients with type 2 diabetes.

INTRODUCTION

Type 2 diabetes mellitus is a polygenetic disorder resulting from the interaction of both hereditary and environmental factors (Jinlin, Binyou & Terry, 2007). It is a chronic, progressive illness that causes considerable morbidity and premature mortality (Kleefstra *et al.*, 2007). Worldwide prevalence of type 2 diabetes is high and is increasing steadily (King, Aubert & Herman, 1998). Approximately, 150 million people worldwide are affected by type 2 diabetes mellitus, and this figure is expected to double in the next 20 years (Freeman & Cox, 2006).

Diabetes significantly increases risk of developing multiple micro-vascular and cardiovascular complications (Huang *et al.*, 2007). The cardiovascular events associated with type 2 diabetes and the high incidence of other macro-vascular complications, such as stroke and amputation, contribute to an enormous economic burden for the patient

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and country (Gaede *et al*., 2003). Despite impressive technical advances in diagnosis and therapy, many people resort to using alternative therapies for illnesses. Chronic conditions such as diabetes lend themselves to the use of alternative medicines (Ryan, Pick & Marceau, 2001). A survey in the United States on complementary and alternative medicine (CAM) use in diabetes, based on 1996 Medical Expenditure Panel Survey data, reported that 8% of respondents with diabetes use CAM professionals (Yeh *et al.*, 2003). The authors also reported that a nationally representative survey conducted in 1997–1998 in the United States found that one-third of the respondents with diabetes used CAM to treat their condition.

In the case of CAM care, patients often resort to the use of micronutrient supplements such as vitamins and minerals including zinc, chromium and vanadium (Cunningham, 1998). 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 humans has yet to be established. Several studies have shown that vanadium has insulin-like effects on liver, skeletal muscle, and adipose tissue (Shechter & Shisheva,1993; Verma, Cam & McNeill, 1998). Vanadium compounds have been shown to be associated with the pathogenesis of some human diseases and in maintaining normal body functions. Vanadium deficiency accounts for several physiological malfunctioning including thyroid hormone, glucose and lipid metabolism (Mukherjee *et al*., 2004). However, vanadium's effects are not all positive. Salts of vanadium interfere by blocking an array of enzymes including different ATPases, protein kinases, ribonucleases and phosphatases. This indiscriminate action renders vanadium to have the potential to be both positive and negative.

This article reports the effect of sodium metavanadate on lipid and glucose metabolism biomarkers in type 2 diabetes mellitus patients.

MATERIALS AND METHODS

Subjects

The study was caried out in the province of Yazd in Iran. The prevalence of type 2 diabetes in this province is high and is estimated to be 13.8% (Afkhami-Ardekani *et al*., 2001). The subjects were patients of Yazd Diabetes Research Center. Inclusion criteria included patients with type II diabetes who were on a fixed drug dosage for at least 6 months prior to the study, had been maintaining their body weight in the past 3 months, not taking vitamins or mineral supplements in the previous two months, and without kidney, heart and lung diseases. The subjects were informed of the purpose, procedures and hazards of the trial and were free to leave the trial at any time. Written informed consent was obtained from all the participants. The research protocol was approved by the Ethics Committee on Human Experimentation of Yazd University of Medical Sciences.

The patients (n=40) were divided randomly into two equal groups. One group was supplemented daily with 100 mg sodium metavanadate for 6 weeks, while the other was the placebo group. Sodium metavanadate capsules are manufactured by Merck, a pharmaceutical company. The subjects were instructed not to modify their diet and activity level, and to maintain dietary records at intervals throughout the experiment.

Body mass index(BMI), blood pressure (BP)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-cholesterol), high-density lipoproteins (HDL), blood urea nitrogen (BUN), creatinine (Cr), alanine aminotransferases (ALT), aspartate aminotransferases (AST) were determined at the beginning and the end of the study. BMI, blood pressure, AST, ALT and drug complications such as nausea, vomiting, abdominal pain, diarrhea, constipation, reduction of appetite were assessed after 3 weeks. Drug complications were also assessed at the end of the six week.

METHODOLOGY

Body mass index (BMI) was calculated by dividing body weight in kilograms by the square of height in meters. Blood pressure was measured in a sitting position after a 5-minute rest. All blood specimens were drawn in the morning after fasting for at least 8 hours. All patients had a general physical examination. Subjects in the treatment group were instructed on the taking of the mineral supplement. They were told to take the supplement during meals with a large amount of water.

Plasma glucose concentration was measured in duplicate using the glucose oxidase method with a Glucose Analyzer II (Beckman Coulter, Inc., Fullerton, California). HbA1C level was measured using a DCA 2000 (Bayer Corp., normal range, 4.0-6.0%). Triglyceride (TG), total cholesterol (TC), high-density lipoproteins (HDL) levels were measured by standardised enzymatic procedures using a Hitachi 917 autoanalyser (Roche Molecular Biochemical).

Statistical analysis

All statistical analysis was performed by using SPSS for Windows, version 11.50. Data of continuous variables are expressed as mean ± standard deviation. Differences of continuous variables between groups were assessed by the paired tests. Statistical significance was set at $p<0.05$.

RESULTS

Thirty-eight patients completed the study. Two patients in the treatment group left the study as they could not tolerate the side effect of vomiting. This left the treatment group with 18 men (47.4%) and 20 women. The mean age of patients was 53.1 ± 8.5 years. The mean duration of diabetes among the subjects was 7.5 ± 5.2 years. About one-quarter (26.3%) and almost half (44.7 %) of them had hypertension and hyperlipidemia respectively. The majority of the patients (81.6%) were taking metformin and glybenclamide while a small percentage (5.3%) was on acarbose.

The characteristic and baseline biochemical markers of subjects are shown in Table 1. On average, the subjects were overweight with BMI of 28.0 ± 5.2. After six weeks on sodium metavanadate, the levels of FBS and HbA1C decreased in the treatment group. However, the results were not statistically significant comparing pre- and post-trial levels. No statistically significant differences were found prior to and after vanadium treatment in TC, LDL-chol and blood pressure (systolic and diastolic blood pressure). A significant decrease was found, however, for TG ($p=0.01$) and BMI ($p=0.03$) among the treatment subjects. It is not clear whether these findings are due to the direct or in-direct effect of sodium metavanadate administration.

Seventeen of the treatment subjects (94.4%) experienced nausea in the first three weeks, but reported that the side effect was tolerable and became less with time. Eight

Table1. Characteristic and baseline biochemical markers of patients

Variables	*Mean ± SD*
Body mass index BMI (kg/m2)	28.0 ± 5.2
Fasting blood sugar FBS (mg/dl)	163.68 ± 33.61
2-h postprandial glucose 2hpp (mg/dl)	254.13 ± 60.94
Glycated hemoglobin HbA1C (%)	7.68 ± 0.81
Triglycerides (mg/dl)	232.73 ± 86.99
Total cholesterol (mg/dl)	207.02 ± 48.14
LDL-cholesterol (mg/dl)	112.07 ± 34.47
HDL-cholesterol (mg/dl)	52.47 ± 20.71
Systolic blood pressure (mmHg)	131.05 ± 18.16
Diastolic blood pressure (mmHg)	77.23 ± 12.23

of the patients (44.4%) had vomiting, and two of them were excluded from the trial as they experienced serious vomiting.

DISCUSSION

The use of vanadium as an anti-diabetic agent goes back a century when a vanadium-containing compound, bisoxovanadium, was assessed clinically for use in treatment of human diabetic patients. (Thompson & Orvig, 2007). Vanadium acts by improving the sensitivity of insulin in type 1 and type 2 diabetes (Garcia-Vicente *et al*., 2007). It has also been shown to reduce cholesterol levels and blood pressure.

Insulin mimetic action of vanadium on type 1 diabetes has been demonstrated in animal and short term human studies (Poucheret *et al*., 1998). The oral doses used to date in human trials are much lower than for animal studies out of concern for toxicity effects. Sodium vanadate supplementation at 125 mg daily for 2 weeks was found to lower the insulin requirement of five patients with type 1 diabetes, and their plasma cholesterol levels were also reduced (Goldfine *et al*., 1995). More dramatic improvements were observed in type II diabetic patients who displayed an improved insulin sensitivity attributed to an enhanced non-oxidative glucose disposal rates. Vanadium treatment did not affect hepatic glucose production (Goldfine *et al*., 1995). Concern for mild nausea and gastrointestinal upset may be overcome by the use of vanadyl sulfate (Cunningham, 1998).

Short-term clinical trials with vanadium have been performed in type II diabetic patients, and the results suggest that vanadium may have a potential role in the adjunctive therapy of these patients (Goldfine *et al*., 1995; Cohen *et al*., 1995; Boden *et al*., 1996). For example, Cohen *et al*., (1995) examined the *in vivo* metabolic effects of vanadyl sulfate in type 2 diabetic patients. Six type 2 diabetic subjects treated with diet and/or sulfonylurea were examined at the end of three consecutive periods: placebo for 2 weeks, vanadyl sulfate (100 mg/d) for 3 weeks, and placebo for 2 weeks. Glycemic control at baseline was poor (fasting plasma glucose 210 ± 19 mg/dl; HbA1c 9.6 ± 0.6%) but improved after treatment with vanadyl sulphate (181 ± 14 mg/dl [$p < 0.05$], 8.8 ± 0.6%, [$p < 0.002$]). These effects were sustained for up to 2 wks after discontinuation of vanadyl sulphate (Cohen *et al*., 1995). In the present study, the mean value for FBS was 165.72 ± 36.13, which was decreased to 162.66 ± 35.93 albeit not significantly. This may be due to different types of vanadium salt used.

Table 2. Biochemical parameters before and after sodium metavanadate supplementation compared to the placebo

Variables	*Sodium metavanadate*			*Placebo*		
	Pre-trial	*Post-trial*	*P-value*	*Pre-trial*	*Post-trial*	*P-value*
BMI (kg / m2)	29.27 ± 5.17	29.13 ± 17.76	0.03*	26.86± 5.15	26.75 ± 5.08	0.16
FBS (mg / dl)	165.72 ± 36.13	162.66 ± 35.93	0.43	157.60±31.08	159.50 ± 27.35	0.55
2hpp (mg / dl)	250.88 ± 49.92	261.44 ± 89.82	0.51	259.85±68.45	250.55 ± 60.85	0.05
HbA1C (%)	7.86 ± 0.90	7.85 ± 0.88	0.16	7.53± 0.71	7.46 ± 0.73	0.62
TG (mg / dl)	262.44 ± 65.33	244.05 ± 67.78	0.01*	206 ±96.58	197.15 ± 99.41	0.21
Chol (mg / dl)	236.05 ± 40.43	231.11 ± 49.39	0.40	80.90±39.16	177.85 ± 38.59	0.29
LDL (mg / dl)	126.55 ± 34.09	122.83 ± 28.85	0.29	99.05±29.95	95.80 ± 28.68	0.10
HDL (mg / dl)	59.27 ± 20.61	57.83 ± 17.76	0.80	46.35±19.28	46.55 ± 19.26	0.51
SBP (mmHg)	127.50 ± 17.67	125.83 ± 12.83	0.67	112.50± 6.38	106.10 ± 23.50	0.26
DBP (mmHg)	76.75 ± 13.79	71.5 ± 9.33	0.10	76.75±13.79	71.50 ± 9.33	0.10

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)

*Statistical significance at $p<0.05$

Malabu *et al*. (1994) reported that decreases in plasma glucose levels observed after administration of vanadate were entirely attributable to a reduction in food intake (Malabu *et al.*, 1994). In a study on 11 patients with type 2 diabetes treated with vanadyl sulphate (150 mg / day for 6 weeks), they found significant reductions in fasting plasma glucose (FPG), (194 ± 16 to 155 ± 15 mg / dL), HbA1c (8.1 ± 0.4 to 7.6 ± 0.4%), plasma TC (223 ± 14 to 202 ± 16 mg / dL) and LDL (141 ± 14 to 129 ± 14 mg / dL) (Cusi *et al.*, 2001). In this study FBS, HbA1C, TC and LDL decreased but did not show a significant difference. Other studies reported hypoglycemic and cholesterol lowering effects of vanadium (Beliaeva *et al*, 2000; Harland & Harden-Williams 1994).

In the study by Goldfine *et al.* (2000), 16 patients with type 2 diabetes were studied before and after 6 weeks of vanadyl sulfate treatment at three different dosages. The FBS and HbA1c levels decreased significantly in the 150- and 300-mg vanadyl sulphate groups. At the highest dose, total cholesterol 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 (Goldfine *et al.*, 2000). In the present study, the vanadium salt and its dosage was different from the study of Goldfine *et al.*, (2000), but gastrointestinal discomfort was seen with 100 mg of sodium metavanadate as well.

The present study evaluated the effect of sodium metavanadate, a vanadium supplement at 100 mg / day for 6 weeks on glucose and lipid biomarkers in type 2 diabetic patients. Levels of FBS, HbA1C, TC and LDL decreased but were not statistically significant between pre- and post-trials. No significant differences were also found in systolic and diastolic blood pressure prior

to and after vanadium intake. Sodium metavanadate administration in diabetic patients did bring about a significant decrease in TG and BMI (p=0.03). The reduction in BMI may be due to gastrointestinal discomfort such as nausea leading to a decrease in food intake.

Under normal human conditions, the body contains 20-25 mg of vanadium and the average diet supplies about 2 mg of vanadium daily (Walsh, 2007). Food sources rich in vanadium include pepper, dill, radishes, eggs, buckwheat and oats. The levels in food sources are believed to be safer than over the counter preparations.

CONCLUSION

Based on the findings, this study did not find a beneficial use of sodium metavanadate as a form of vanadium supplementation for patients with type 2 diabetes. More studies are needed to verify the effects of other forms and dosages of vanadium supplements in improving type 2 diabetes.

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